UPPSALA UNIVERSITET

Department of Medical Sciences

Annual Report 2014

Fastställd av Lars Rönnblom 2015-04-29

Introduction

Following the trend from recent years, 2014 was also a positive year for the Department of Medical Sciences. The Department has continued to grow, both in staff and in revenues. The staff is now 210, and the Department has more than 300 associated co-workers at the Uppsala University Hospital, working in more than 20 different clinical specialities. The turnover has increased to 250 MSEK, and the external research funding to 170 MSEK which can be attributed to the sustained ability of the researchers at the Department to attract grants from e.g. the Swedish Research council, the Cancer Society, the Swedish Heart & Lung Foundation and from the EU. As two examples of large grants awarded, I would like to mention the 300 MSEK grant from the Heart &Lung foundation and Knut and Alice Wallenberg Foundation.to Swedish CardioPulmonary bioImage Study (SCAPIS), coordinated by professors Lars Lind and Johan Sundström, and the 35MSEK grant to professor Agneta Siegbahn for "Biomarkers for Cardiovascular disease" from the Swedish Foundation for Strategic Research. In this context I also would like to mention the excellent services provided by the platforms hosted by the Department; the SNP&SEQ Technology platform and the Array and Analysis facility, and the two new platforms, Clinical Biomarkers, and In Vitro and Systems Pharmacology]

The performance of the Department's research groups is also shown by the close to 650 peer reviewed publications during 2014, an increase with 10% from 2013, and by the 11theses produced during 2014. The theses presented represent all six research programs at the Department, namely Cancer, Cardiology and Clinical physiology, Diabetes and Metabolic Diseases, Epidemiology, Inflammation and autoimmunity, and Microbiology and Infectious diseases. Major research findings achieved during 2014 by researchers at the Department will be presented on the following pages.

Teachers at our department are very active in many of the undergraduate programs at the Faculty of Medicine. Some 2000 students pass courses for which we are responsible every year. The department aims to provide a good environment for learning combined with education given at a high academic level. During 2014 a few persons retired after long and very successful careers. On behalf of the Department I would like to thank professor Eva Vingård for her many important contributions As a new head of the Department, I would like to thank my predecessor Eva Tiensuu Janson for performing such an excellent job during her years as head of IMV, which has been handled over to me in very good condition! Finally, I would like to conclude by thanking all personnel at the Department for their dedicated work during 2014.

Lars Rönnblom
Head of department

Contents

Organization of the Department of Medical Sciences

Chair, head of department

Lars Rönnblom

Deputy head of department

Johan Sundström

Assistant heads of department

Jan Sjölin, responsible for graduate studies

Christer Janson, responsible for undergraduate studies

Department board

Lars Rönnblom	chair
Lars Lind	teacher
Håkan Melhus	teacher
Erik Ingelsson	teacher
Eva Lindberg	teacher
Birgitta Sembrant	technical staff
Juliana Imgenberg Kreuz	PhD student
Sandra Porath	student representative
Vacant	student representative

Deputies

Johan Sundström	teacher
Martin Wohlin	teacher
Jan Eriksson	teacher
Per Hellström	teacher
Karin Eriksson	technical staff
Henning Karlsson	PhD student
Vacant	student representative
Vacant	student representative

Employees 2014

Adolfsson Sofia
Alassaad Anna
Alexsson Andrei
Alfredsson Jenny
Ali Ahmed Abir
Almlöf Jonas
Andersson Claes
Axelsson Tomas
Backlin Carin
Bandaru Kumar Manoj
Berggren Olof
Berglund Eva
Berglund Malin
Bergquist Maria
Berne Berit
Billing Ewa
Björnerfeldt Susanne
Björnerfeldt Susanne
Blomström Lundqvist Carina
Bryon Kristin
Brännvall Mathias
Bäcklin Christofer
Bäckström Lars
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Carlsson Elin
Carlsson Ingmarie
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Cars Otto
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Castillejo-Lopez Casimiro
Christersson Christina
Chu Xia
Collin Sofie
Dahl Staffan
Dahlberg Johan
Dalin Frida
Den Hoed Marcel
di Lorenzo Sebastian
Diaz Hetzel
Dubois Louise
Edén Desirée
Edlund Hanna
Ekberg Sara
Ellström Patrik
Eloranta Maija-Leena
Elvingson Veronika
Emami Khoonsari Payam
Emmanouilidou Anastasia
Englund Edvard
Engvall Karin
Enström Camilla
Eriksson Barbro
Eriksson Jan
Eriksson Karin
Eriksson Oskar
Eriksson Per
Fall Tove
Fellström Bengt
Flachskampf Frank
Floderus Gustaf
Foyer Anna
Freyhult Eva
Fryknäs Mårten
Fuxler Lisbeth
Fällmar Helena
Ghaffari Mostafa
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Grönberg Malin
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Gustafsson Stefan
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Hagberg Niklas
Hagforsen Eva Christina
Haglund Caroline
Halim Muhammad Abdul

Halin Lejonklou Margareta
Hall Jan
Hallböök Helene
Hartman Anna
Hasan Badrul
Haukkala Anna
Hedman Åsa
Helgesson Magnus
Helgesson Magnus
Hellström Per
Henriksson Karin
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Holloway Bronwen
Hägg Sara
Hägglund Maria
Högman Marieann
Ilbäck Nils-Gunnar
Imgenberg-Kreuz Juliana
Ingelsson Erik
Jacobson Rasmusson Annica
Jakobsson Charlotta
James Stefan
Janson Carolina
Janson Christer
Jarvius Malin
Jasovsky Dusan
Joelsson Martin
Jonasson Katarina
Kamble Prasad
Kashif Muhammad
Kask Lena
Kjeldgård Eva
Klingström Tiffany
Kriegholm Cecilia
Kultima Kim
Lagensjö Johanna
Lagerbäck Pernilla
Lampinen Maria
Landegren Nils
Larsson Anders
Larsson Gunnel
Larsson Kristina
Larsson Pontus
Larsson Rolf
Laxman Navya
Leek Christina
Lehmann Sören
Lenhammar Lena
Li Su-Chen
Liedén Martina
Liljedahl Ulrika
Liljegren Andersson Ulrik
Lind Lars
Lind Monica
Lindahl Bertil
Lindberg Eva
Lindell Magnus
Linder Stig
Lindersson Marie
Lindgren Komp Patricia
Lindqvist Mårten
Lindqvist Ulla
Lindström Elisabeth
Ljunggren Östen
Loftsdottir Heidur
Lundmark Anders
Lundmark Per
Manninen Johanna
Marincevic-Zuniga Yanara
Marklund Elisabeth
Marzouka Nour Al-Dain
Mcloughlin Anette
Melhus Håkan
Melhus Åsa
Moberg Lena
Mokhtari Dariush
Monazzam Azita
Mubanga Mwenya
Munir Muhammad
Muntlin Athlin Åsa
Najafi Nasrin
Nilsson Anna
Nisser Katarina
Nordlund Jessica

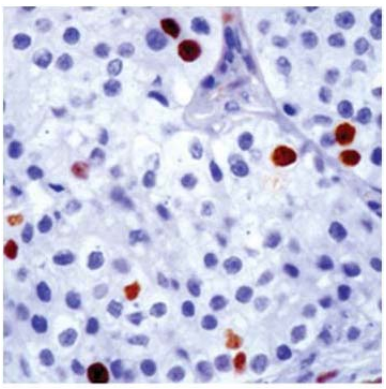
Nordstedt Michael
Norsted Hanna
Nowak Christoph
Nykvist Marie
Nystedt Sara
Oldgren Jonas
Olofsson Caroline
Olsen Björn
Omar Shumi
Parrow Vendela
Pereira Maria
Pränting Maria
Quarfordt Pernilla
Raine Amanda
Ramqvist Ulrica
Ramsell Jon
Rask-Andersen Anna
Rautelin Hilpi Iiris
Rebello Lisa
Rollman Ola
Ronquist Göran
Rosenfeld Daniel
Rydåker Maria Sonja
Rönnblom Lars
Rönnerblad Michelle
Salihovic Samira
Sandling Johanna
Schedin Johan
Sembrant Birgitta
Senkowski Wojciech
Sidibeh Cherno
Siegbahn Agneta
Signér Linnéa
Sjölin Jan
Skarp Astrid
Skogseid Britt
Smeds Patrik
Sollander Karin
Stenemo Markus
Stenemo Markus
Storm Marianne
Strese Sara
Stålberg Kjell
Sundelin Johan
Sundström Johan
Svartengren Magnus
Svensson Johanna
Syvänen Ann-Christine
Tandre Karolina
Tano Eva
Tao Lingjie
Thulin Åsa
Tiensuu Janson Eva
Tängdén Thomas
Törmä Hans
Törnros Christel
Uusitalo Pia
Wadelius Mia
Wahlberg Per
Wallentin Lars
Wallmenius Katarina
Wang Juan
Webb Dominic-Luc
Vega Enrique
Westholm Susanne
Weström Simone
Widell Mikael
Wiman Ann-Christin
Wohlin Martin
von Kartaschew Anna
Vretman Helena
Zhang Hanqian
Zorzet Anna
Åberg Mikael
Ånnhagen Eva
Åslin Matilda
Åström Paulsson Sofia
Ärnlöv Johan
Örn Thorsteinsson Ingvar
Öst Torbjörn
Övernäs Elin

Funding 2014

GRANTS	
SWEDISH RESEARCH COUNCIL	39 MSEK
SIDA	10,5 MSEK
THE SWEDISH RESEARCH COUNCIL FORMAS	13 MSEK
THE SWEDISH HEART-LUNG FOUNDATION	5 MSEK
EU	5,4 MSEK
ERC	4,6 MSEK
WALLENBERG FOUNDATIONS	7,6 MSEK
VINNOVA	1,4 MSEK
SWEDISH FOUNDATION FOR STRATEGIC RESEARCH	8,7 MSEK
THE SWEDISH CANCER FOUNDATION	4,3 MSEK
GOVERNMENT FOR CLINICAL RESEARCH (ALF) - FUNDING	50 MSEK
GOVERNMENT OFFICE	1,7 MSEK
OTHER FUNDINGS	17 MSEK
SUBTOTAL	**168 MSEK**
CONTRACT RESEARCH	
VARIOUS COMMISSIONING AGENTS	3,4 MSEK
TOTAL	**171,4 MSEK**

Scientific Reports

Cancer



Cancer research at the Department of Medical Sciences is carried out by several independent research groups, and spans all the way from basic studies of carcinogenesis, detection and monitoring of cancers, development and characterization of cancer drugs, and to clinical trials. There are three groups working in the area of neuroendocrine tumours, studying carcinogenesis, development of biomarkers, exploring new treatment concepts and conducting clinical trials. Research on haematological malignancies is focused on development and testing of new drugs and development of registers for malignant haematological disorders. The cancer pharmacology and computational medicine research program acts at the intersection of clinical pharmacology, oncology and medical bioinformatics. Key issues are related to drug resistance and improved multi-compound therapies.

Endocrine Oncology

Eva Tiensuu Janson and Kjell Öberg

Neuroendocrine tumours (NETs) are life-threatening diseases that have been the subject of investigation for more than a century. NETs derive from cells that have the unique ability to synthesize, store and secrete a variety of metabolic active products including peptides, and amines, which cause specific clinical syndromes in different parts of the body. The majority of neuroendocrine tumour patients are usually diagnosed late, and surgery for neuroendocrine tumour patients with metastasis is seldom curative. Although new powerful medical treatments are available, the need of identifying novel diagnostic, prognostic and predictive biomarkers to broader the knowledge about disease course and response to therapy are clearly warranted.

The research group with Eva Tiensuu Janson as principal investigator focuses on research concerning neuroendocrine tumours with a special emphasis on tumours derived from the gastric mucosa and small intestine, as well as a new line of research including neuroendocrine differentiation in breast cancer. The research group of Kjell Öberg has two main objectives; the first is to develop new potential biomarkers for small intestinal and lung neuroendocrine tumours, and the second is to develop new NET-therapies.

Genetics in familial and sporadic neuroendocrine tumours

Eva Tiensuu Janson, Abir Ali and Staffan Welin

Small intestinal NETs (SI-NETs) are a clinically distinct endocrine tumour that has generally been considered a sporadic disease. We have now, however, identified a large number of families with an inherited variant of SI-NETs. Through comprehensive clinical and molecular studies we have shown that familial tumours are clinically indistinguishable from sporadic tumours and that the genetic changes involves chromosome 18. We have performed exome and whole genome sequencing of familial patients' tumours and blood in order to define the specific genetic events which lead to tumour development. This work is performed in collaboration with researchers at the department of genetics and pathology at Uppsala University (professor Jan Dumanski) and Karolinska Institutet. We have recently identified genes coding for a family of proteins which are potentially interesting as possible disease causing proteins and we are now working to confirm this possible genetic change in our SI-NET families. We are currently expanding our material with new families from Norway and Denmark.

In a different genetic study of SI-NETs we have performed the first study to investigate the role of constitutional genetic polymorphisms predisposing individuals to this disease. Our genome-wide association study (GWAS) of 239 cases and 110 controls identified four copy-number variants (CNVs) in multiple cases that were absent in the controls. The obtained results will provide a valuable resource for future work and they

warrant for a replication study in an independent cohort.

Expression of neuroendocrine markers in tumours

Malin Grönberg, Ylva Naeser, Clary Georgantzi, Sandra Irenaeus, Abir Ali, Staffan Welin and Eva Tiensuu Janson

One of our main objectives is to identify the expression of tumour markers in neuroendocrine tumours in order to predict response to treatment and prognosis. An area of interest is the expression of ghrelin and obestatin in normal tissues and tumours. We have shown that these two peptides are expressed in normal breast tissue and more recently in the majority of breast cancer specimens collected from a cohort at the university hospital in Malmö. Ghrelin expression was significantly correlated to better recurrence-free survival and breast cancer-specific survival. These studies have expanded into new cohorts and we are also investigating the significance of the expression of other neuroendocrine markers in breastcancer. In related projects we have studied the expression of somatostatin receptors on neuroblastomas, and found frequent expression of these receptors, suggesting that treatment with somatostatin analogs should be further explored in neuroblastomas. Further studies of neuroendocrine markers in neuroblastomas are ongoing and the possible use of chromogranin A as a biomarker in blood in neuroblastoma patients is under investigation.

Studies of neuroendocrine carcinomas (NEC)

Staffan Welin, Abir Ali, Ylva Naeser and Eva Tiensuu Janson

As a collaborative project between the Nordic countries we are studying NECs which are tumours with neuroendocrine differentiation with a Ki67 index >20%. These highly malignant tumours are becoming more and more frequently diagnosed, probably as a result of increased awareness among clinicians and pathologists. In the recently published Nordic NEC study we could show that performance status, location of primary tumour, and Ki67 were predictive markers for survival. In our study we could show that NEC patients with a Ki67 <55% respond less well to established chemotherapy treatment but have a longer survival than those with Ki67 >55%. In our ongoing collaboration we have a Nordic registry which now includes more than 500 NEC patients and we are currently evaluating new markers in tumour tissue in order to try to find factors which may be used to make a new, clinically relevant classification for this tumour group. A clinical trial with a new combination of drugs (temozolomide and everolimus) for the subgroup of patients with a lower Ki67 has started and is recruiting patients from Sweden, Norway and Denmark. Further studies on this patient group are ongoing to evaluate the expression of tumor markers in tissue and to evaluate the use of surgery for this patient group.

Novel biomarkers for small intestine and lung neuroendocrine tumors

Valeria Giandomenico, Tao Cui, Su-Chen Li, Kjell Öberg

We continue to investigate novel potentials biomarkers for small intestine (SI-) and lung-neuroendocrine tumours (NETs). In separate projects we are investigating microRNAs as novel biomarkers for SI-NETs, and analyzing specific genes and proteins expressed by SI-NETs and lung-NETs.

MicroRNAs during early tumourigenesis and tumour progression

MicroRNAs have a significant impact on the tumourigenesis of many malignancies so it is reasonable to believe that they play a role in NETs as well. A growing number of potential oncogenic or tumour suppressor miRNAs have been identified in SI-NETs and lung NETs and recent evidences support the use of specific miRNA signatures to predict clinical outcome. We therefore genome-wide profiled miRNA expression and could identify more than 30 miRNAs that could classify SI-NET at different stages. Among these we selected 9 miRNAs for QRT-PCR analyses and verified that 5 miRNAs are significantly upregulated and 4 significantly down regulated. We will now try to clarify whether they have a role in early tumorigenesis and tumour progression of SI-NETs and lung NETs, and also to investigate their usefulness as biomarkers.

Targeted treatment of neuroendocrine tumours

Kjell Öberg

A majority of NETs express somatostatin receptors which consequently might be targets for new therapies. Since almost 30 years back alpha interferon has been applied for treatment of small intestinal NETs with significant clinical benefit, however with significant side effects. If the side effects could be prevented significantly higher doses, and better efficacy, of alpha interferon could be achieved. In a collaboration with Profs. Katarina Edwards and Lars Gedda we try to solve the problem by using interferon-loaded nanoparticles, coated with somatostatin to target the particles to NETs. In a related project, together with Prof. Magnus Essand, we are employing oncolytic adenoviruses modified with somatostatin motifs for selective infection of neuroendocrine tumour cells.

Members of the group 2014

Eva Tiensuu Janson, Professor of Medicine
Staffan Welin, MD, PhD
Malin Grönberg, PhD
Abir Ali, PhD student
Ylva Naeser MD, PhD-student
Sandra Irenaeus, MD, PhD-student
Anthoula Koliadi, MD, PhD-student
Clary Georgantzi MD, PhD-student
Ieva Lase MD, PhD-student
Kjell Öberg, Professor, MD, PhD
Valeria Giandomenico, PhD
Dan Granberg, MD, PhD
Su-Chen Li, PhD
Xia Chu, PhD-student

Funding

Swedish Cancer foundation:	600 kSEK,
Söderbergs foundation	320 kSEK
Selanders foundation	300 kSEK
ALF:	1000 kSEK
Lions foundation for Cancer research	200 kSEK

Publications 2012-2014

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Reviews

1. Öberg K. Neuroendocrine tumors of the digestive tract : impact of new classifications and new agents on therapeutic approaches. Current Opinion in Oncology. 2012 Jul;24(4):433-40.

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Books

1. Öberg K E. Tumores Neuroendocrinos Gastrointestinais: In: Aparhelho Digestivo Clinica e Cirurgia. Vol 1 Brazilien: Atheneu; 2012. p. 337-.

Dissertations

Su-Chen Li: Small Intestinal Neuroendocrine Tumor Analyses : Somatostatin Analog Effects and MicroRNA Profiling

Anthoula Koliadi: The Prognostic Impact of Proliferation Markers in Breast Cancer with Emphasis on Cyclin B1 and PPH3.

Haematology

We perform research on all the major fields of haematology with the following focus areas:

- Preclinical development and clinical trials of new drugs and therapy strategies in malignant haematological diseases, in particular acute myeloid leukaemia
- Studies based on data from national population based registries (e.g. CML, AML, ALL, MDS)
- Studies on CML, AL-amyloidosis and infectious complications in the immunocompromised host

An important part of the activities of the Haematology group is also leadership and participation in national and international research groups for initiating international studies, for guidelines and for development of centres of clinical excellence. We participate actively in the U-CAN project (structured biobanking at diagnosis, follow-up and relapse). In Janury 2015. Sören Lehmann joined our group as full professor in Haematology and leader of the research group. Sörens main research interest is translational studies in malignant haematology, in particular studies of epigenetics in leukemia.

Preclinical drug development in acute myeloid leukaemia (AML)

Anna Eriksson, Martin Höglund

In close collaboration with the Pharmacology Cancer group (prof Rolf Larsson) our focus is preclinical development of new drugs in AML. In particular, we are interested in investigating signal transduction inhibitors, "intelligent" drug combinations and in exploring the anti-leukemic efficacy of drugs previously used outside the cancer filed ("repositioning"). Key elements in this research are the application of information-rich compound libraries, clinically relevant tumour model systems (including primary tumour cells from well characterised patients) and high-throughput analytical capabilities in combination with bioinformatics expertise. Uppsala is leading centre in the first-in-man Phase I trial AKN-001, which is based preclinical work in our research group.

Acute lymphoblastic leukaemia – national studies of toxicity, prognostic factors and treatment protocols

Emma Bergfelt, Helene Hallböök and Bengt Smedmyr

The Swedish Adult Lymphoblastic Leukaemia Group (SVALL), chairperson Hallböök, is a working group with responsibility for national guidelines and studies. We are evaluating the outcome of national treatment protocols in younger and elderly adults with ALL as well as the prognostic value of minimal residual disease (MRD) as analysed by advanced flow cytometry.

Studies on prognostication and resistance mechanisms in chronic lymphocytic leukemia (CLL)

Mattias Mattsson, Karin Larson and Martin Höglund

In close collaboration with professor Richard Rosenquist (Dept of Immunology, Genetics and Pathology), we are presently performing studies in CLL on prognostic and prediciive biomarkers, clonal evolution and resistance in patients with advanced disease treated with the BCR inhibitors ibrutinib or idealisib. In another project, we aim to clinically and genetically characterise subsets of CLL with very good prognosis.

Population-based registry studies in CML, MDS, AML and ALL

Emma Bergfelt, Elisabeth Ejerblad, Martin Höglund, Helene Hallböök, Hans Hägglund and Gunnar Larfors

The Swedish population based registries in patients with haematological malignancies are internationally unique. Presently, more than 1000 patients with CMLand more than 6000 patients with acute leukaemia are included. In a recent publication (Hoglund ta al, Blood 2013, 122, p 1284), we have shown that the estimated 5 yrs. survival for patients with CML is 80% and in certain diagnostic subgroups 95%. At

present, our studies focus on the outcome of patients with secondary leukaemia, relapsed AML, patient related outcome measures (PROM) and the association of CML with other types of cancer.. Using the Nordic Registry for Hematopoietic Stem Cell Donors (NRHSD) and linking it other national registries, we are studying short-term and possible long-term complications following donation of hematopoietic stem cells.

Chronic myelogenous leukaemia (CML)

Stina Söderlund, Ulla Olsson-Strömberg, and Bengt Simonsson

In collaboration with Dept. of Clinical Immunity we are investigating pre-existing and developing anti-tumour immunity during treatment with tyrosine kinase inhibitors (TKIs). Patients enrolled in clinical trials within a Nordic network are evaluated for immunological phenotype and function. Different TKIs are investigated, and the results are then correlated to TKI efficacy. We have investigated for the presence of immune escape mechanisms such as myeloid-derived suppressor cells and T regulatory cells. These results may aid the understanding of which patients that can benefit from TKI discontinuation.

Plasma cell disorders

Sara Rosengren, Torbjörn Karlsson and Kristina Carlson

Clinical studies on plasma cell disorders are performed in collaboration with the Nordic Myeloma Study Group and the Swedish Group for plasma cell disorders. In collaboration with the PET-imaging centre and cardiologic an imaging study of cardiac AL-amyloidosis has recently been performed.

Clinical and laboratory studies on infectious and haemorrhagic complications in patients treated for haematological malignancies

Tobias Svensson, Honar Cherif

We have recently conducted or are presently conducting several clinical and laboratory studies aiming to improve the diagnosis and management of these complications in patients receiving treatment for haematological cancers. These studies include for example: assessing the impact of IgG subgroup deficiency in patients with Chronic Lymphocytic Leukaemia (CLL); conjugated påneumococcal vaccination in patients with CLL; the use of the thrombopoietin receptor agonist eltrombopag in patients with high risk MDS with thrombocytopenia who are treated with azacitidine and a retrospective survey aiming to evaluate the clinical value of Bronhio-Alveolar-Lavage (BAL) in patients with haematological malignancies

Myeloproliferative neoplasms (MPN), cancer anaemia and supportive care

Elisabeth Ejerblad, Torbjörn Karlsson, Gunnar Birgegård, and Anncarin Svanberg

In MPN and cancer anaemia we are involved in several clinical trials including a large European multicentre study for long term follow-up of platelet-reducing therapy in essential thrombocythemia (ET), a 7-year prospective follow-up of ET patients treated with anagrelide, and a randomised phase II trial investigating the effect of IV iron alone in cancer patients with functional iron deficiency. As regards supportive care, we have previously shown that cryotherapy significantly reduces mucositis after high dose chemotherapy, and in two recently performed studies investigated the physiological mucosal effects on oral mucosa and the protective effect of a new saturated calcium-phosphate solution in addition to cryotherapy during chemotherapy.

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Swedish Cancer foundation:	100 kSEK,
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Publications 2012-2014

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Cancer Pharmacology and Computational Medicine

Rolf Larsson, Mats Gustafsson and Peter Nygren

Cancer Pharmacology and Computational Medicine is a research program that combines areas of pharmacology, toxicology, oncology, biomedical engineering, and computational informatics with high throughput experimental techniques to discover novel and improve existing therapies for cancer and other complex diseases. We are addressing key issues related to drug resistance and improved multi-compound therapies. Our multi-disciplinary research is organized it into four mutually reinforcing activities:

I. Drug and multi-compound therapy discovery

This activity is aimed at discovering novel drugs and multi-compound treatments for problems associated with drug resistance and toxicity in cancer therapy. In-house compound libraries, information-rich model systems, high-throughput technologies for drug screening, and the most recent methods for systemic molecular and phenotypic profiling (spectroscopy, arrays, sequencing, and microscopy) are available for this purpose together with required theory and algorithms for quantitative bioinformatics systems analysis. Among several novel assays we have established is a 3D (spheroid) forming assay, and a proximity ligation-based assay for high content screening of drug effects on signalling pathways.In collaboration with Stig Linder, KI we have recently demonstrated that the specific interference with mitochondrial function was identified as a novel principle for selective killing of hypoxic tumor cells found deep in solid tumors using the small molecule VLX 600 as a prototype inhibitor. During the past years we have systematically screened several innovative model systems with focus on colorectal carcinoma (CRC) and acute myelocytic leukemia (AML) using our library of annotated and clinically tested drugs. In this effort we have identified several potentially useful candidates for repositioning (finding new indications for old drugs) including the anti-parasitic drugs quinacrine, mebendazole, and nitazoxanide.

In the area of multi-compound therapies we have recently refined an integrated bioinformatic+experimental infrastructure, including novel search algorithms and tailored programming of liquid handling robots/systems, which makes it possible to search for promising drug combinations by means of a semi-automated loop. In this context we have also developed and implemented novel theory and algorithms suitable for discovery of multi-compound therapies that have a therapeutic window in the in vitro model systems employed. We have also developed computational tools for improved single compound as well as multi-compound analyses of the Connectivity Map database downloaded from Broad Institute (http://www.broadinstitute.org/cmap/).

II. Characterization and refinement of drug therapy candidates

Given a promising drug, combination of drugs or treatment protocol, it is important to gain an improved pharmacological understanding about the properties of the new treatment. For example what systemic effects does it cause and does it meet basic requirements to be advanced to further preclinical and clinical testing? For a set of already established drug therapies, are there patient subpopulations that should benefit from changing the currently employed therapy to others that are more potent with less adverse side effect? Here we employ modern experimental and bioinformatics tools for addressing this kind of questions while at the same time developing beyond state-of-the-art alternatives. The main issues of current interest are determination and prediction of (1) mechanism of action, (2) toxicity and other adverse side effects, (3) combination activity, and (4) in vivo proof-of-concept. The core of this evaluation program meets European regulatory requirements for documentation of primary pharmacology prior to clinical phase I trials in patients but also allow additional analyses. One recent development is an automated version of our QuantMap network bioinformatics algorithm making it possible to translate a pre-defined (perturbed) protein list into a protein-protein network based on publicly available protein-protein interaction data. Recently we also developed two algorithms for computational processing of label free time-lapse

microscopy movies making it possible to detect intracellular bubbles (often associated with autophagy) as well as cells being in the state of apoptosis.

III. Systems Pathology

In order to gain new insights about molecular disease mechanisms and for diagnostic and prognostic purposes, including therapy selection, systemic profiling is performed and/or analyzed at different molecular levels: mDNA, mRNA, proteins, peptides and metabolites. The resulting measurements are analyzed by means of standard bio-statistical methods as well as using multivariate machine learning methods in order to obtain successful and easily interpretable predictors for therapy response. Ideally, the most successful prediction models obtained this way are easy to interpret in terms of a small subset of all the system wide variables measured (for example mRNA gene expression levels or morphological changes at the cellular level). Recently we have mainly been working with Leukemia patient samples profiled at the mDNA and mRNA levels as well as samples from humans and mice related to pain and neuro-degenerative diseases profiled at the levels of peptides and proteins.

IV. Algorithmic biosystems analysis & control

To be able to achieve robust measurements using the many different measurement technologies emerging for molecular and phenotypic profiling, one needs tailor made algorithms that perform different forms of low-level instrument bio-signal processing such as noise suppression, as well as, algorithms for systems analysis that e.g. can give ideas about the underlying biochemical mechanism associated with the disease and treatment. This requires tailor made analytic tools as well as generic beyond state-of-the-art algorithms for multivariate and temporal data analysis. In particular, there is a great need for semi-automated discovery algorithms that can detect and model clinically important multivariate patterns hidden in complex data sets that may consist of a mixture of standard patient journal information together with different molecular and phenotypic profiling results of varying quality. Moreover, there is great potential in interactive closed-loop learning algorithms that are able to propose a set of maximally informative experiments, analyze the results obtained from the experiments, refine the current models/hypotheses based on the analysis and propose a new batch of informative experiments for the next iteration in the loop. During the last year we have initiated new efforts to further refine our network bioinformatics algorithms and we have launched a new PhD project aimed at high-throughput mass spectrometry data analysis.

For more information, please see;
http://www.medsci.uu.se/forskning/Cancer/Cancerfarmakologi+och+ber%C3%A4kningsmedicin/

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Swedish Cancer Foundation	800 tSEK	KAW	1000 kSEK
Swedish Strategic Foundation	2400 tSEK	VR	500 tSEK
Proactive EU project	900 tSEK	FORMAS	1100 kSEK
Oncopeptides	240 tSEK	NordForsk	250 tSEK
Akinion AB	300 tSEK	ENABLE	600 tSEK
ALF	1300 tSEK		

Publications 2012-2014

1. Norberg M, Lindhagen E, Kanduri M, et al. Screening for Cytotoxic Compounds in Poor-prognostic Chronic Lymphocytic Leukemia. Anticancer Research. 2012;32(8):3125-3136.
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Dissertations:

Obaid Aftab: Towards High-Throughput Phenotypic and Systemic Profiling of *in vitro* Growing Cell Populations using Label-Free Microscopy and Spectroscopy: Applications in Cancer Pharmacology

Endocrine tumor biology

Britt Skogseid

Researchers in our translational group represent various disciplines, *e.g.* endocrinology, oncology, endocrine surgery, molecular biology, and perform basic science as well as clinical studies. We focus primarily on ***tumorigenesis of the endocrine pancreas and adrenal,*** but we also run **clinical studies on adrenocortical carcinoma** and a project on genetics of ***serous ovarian cancer.*** Group members are also tightly connected with the clinics, i.e. Endocrine oncology and Endocrine surgery, and thus have the opportunity to perform clinical trials and work on the comprehensive patient and tumor material that have been collected since more than 30 years.

Tumors of the endocrine pancreas and the adrenal

Neuroendocrine tumors of the pancreas are rare, and most have a more indolent behavior than exocrine pancreatic cancers. The tumors may produce bioactive amines or peptides that can give rise to characteristic endocrine symptoms/syndromes *e.g.* insulinoma syndrome with hypoglycemia, but the majority are silent and therefore described as non-functioning. Eighty-five percent occur sporadically but the rest develop in the context of an inherited trait; multiple endocrine neoplasia type 1 (MEN1) or von Hipple Lindau.

MEN1 is an autosomal dominantly inherited disease, and gene carriers develop multiple tumors in many endocrine organs but also some non-endocrine tissue. Our research group has long focused on MEN1 and explored pre-clinical and clinical aspects of the syndrome, especially with regard to the pancreatic and adrenal lesions and molecular effects of MEN1 gene inactivation.

Apart from our continuous work to evaluate and refine our management strategies for patients with MEN1 as well as applied treatment protocols for patients with advanced sporadic neuroendocrine tumors of the pancreas, we have during the last year focused on three lines of investigations;

MEN1 tumorogenesis and haploinsufficiency

Our hypothesis is that the MEN1 gene is a haploinsufficient suppressor resulting in growth advantage in endocrine cells of carriers of the MEN1 trait (heterozygous), but also alterations of the phenotype of the non-tumorous surrounding tissue. In a recent study supporting our hypothesis we used five-week-old conventional MEN1 knock-out mice to show that Ki67 proliferation index in heterozygous islets of Langerhans was indeed twice as high compared to that found in islets of wild type littermates. Furthermore, numerous genes were differentially expressed in these islets, *e.g.* up-regulated genes ontogenetically belonged to growth factor families, mitochondrial membrane transport, apoptosis inhibition and transcriptional regulation, and down-regulated genes involved cell structure and chromatin modification. In order to further understand the very onset of transformation, *i.e.* the effect of MEN1 heterozygosity per se, we now performing proteomics as well as microRNA array on heterozygous MEN1 mouse adrenals compared to that of wild type littermates.

Angiogenesis and pre-clinical PET

In an earlier project, aiming to identify vascular and endothelial alterations in the MEN1 pancreatic endocrine tumors, we could show increased PDGF-BB and PDGF receptor beta in heterozygous islets and tumors as well as increased VEGFR2, FGFR, Ang2/Tie2 and HIF1-alpha. Interestingly, pericyte content was increased and distribution was altered already in young heterozygous islets, whereas in tumors glomerular-like structures of pericytes were noted. The increased blood flow observed even in small pancreatic mouse lesions, but also the macro-tumors of MEN1 patients, indicates that PET technique applying an agiogenesis-detecting tracer could be of value to visualize the tumors as well treatment response. We have therefore started to assess various potentially relevant PET tracers by performing autoradiography as well as micro-PET/CT of our MEN1 mouse model. Furthermore, micro-PET-MR is now available in house, and we are currently planning a project applying this new technique in our MEN1 mouse model.

The PI3K/Akt/mTOR pathway in MEN1 tissue

Inhibitors of the PI3K/Akt/mTOR pathway have entered the oncological arsenal of targeted therapies. Data on tumorigenesis and signal transduction in neuroendocrine tumor are however limited, so we aim at recognizing how menin interacts with the PI3K pathway and how mTOR and PI3K inhibitors function in the complete absence of menin as well as in MEN1 heterozygous cells. In these ongoing studies we use various drugs inhibiting this pathway as well as our MEN1 mouse model treated with these inhibitors.

Adrenocortical carcinoma

Adrenocortical carcinoma (ACC) is a rare disease with an extremely poor prognosis. The median survival for patients with metastatic disease is 25 weeks. We have performed an investigator-initiated initiated academic international phase III trial (the FIRM-ACT study) which has established a benchmark therapy; *cisplatin, etoposide, doxorubicin in combination with mitotane (EDP+M)* as first line therapy in advanced ACC. Currently several new studies are being launched within the efficient ACC-network already established during the years of fruitful FIRM-ACT cooperation:

- Participate in the second round of clinical studies of treatment of ACC, together with the FIRM-ACT investigator-network, in order to compare efficacy of new treatments to the results of the treatments studied in FIRM-ACT
- Participate in studies of adjuvant therapy, *e.g.* a randomized study of mitotane vs expectancy in patients radically operated for ACC with low or medium Ki67 index (Adiuvo I study). A second adjuvant study will soon start; Adiuvo II where adjuvant mitotane is randomized vs cisplatin in patients radically operated for tumors with high Ki67 index.
- Launch a phase II trial for treatment of advanced ACC.

Serous ovarian cancer

Malignant epithelial tumors make up for approx. 75% of ovarian cancers, and are the most lethal of the gynaecological malignancies. Overall 5 year survival is 40% Poorly-differentiated serous tumors have the worst prognosis, and are believed to arise from the surface of the ovary or in the tubar epithelium. Maximum tumor debulking surgery combined with platinum/taxanes is the mainstay of treatment today. Most poorly-differentiated serous cancers initially respond well to therapy, however, a majority will relapse within two years. When matched for stage, histopathological differentiation, and surgical outcome there is a high degree of uncertainty regarding what impacts survival, indicating that there are unknown factors involved.

Novel tumor markers, and novel pathways for drug-interaction may improve personalized treatment of these patients, and we aim therefore to

- Identify genetic aberrations in serous ovarian cancer using SNP-genotyping, as well as Exome-sequencing.
- Identify markers for long-term survival (>5 years)
- Identify potential therapeutic targets/pathways in serous ovarian cancer

We have collected samples from a group of patients treated for serous ovarian cancer as well as matched controls, and SNP-genotyping has been performed. After deep-sequencing we intend to verify the results in a larger cohort of patients.

Members of the group 2014

Britt Skogseid, MD, professor
Barbro Eriksson, MD, professor
Peter Stålberg, MD, assoc. professor
Mikael Björk, research nurse, system developer
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Funding

The Swedish Cancer foundation	800 kSEK
Swedish research council	500 kSEK
ALF	650 kSEK

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Biochemical endocrinology

Mats Stridsberg

There are currently three major research areas; the first is focus on Chromogranins and Secrotogranins as biomarkers for neuroendocrine tumours, the second focus on Chromogranins and Secrotogranins as biomarkers for other diseases and the third focus on biomarkers for endocrine responses to stress exercise and food intake**.**

Biomarkers for neuroendocrine tumours and neuroendocrine-related diseases

Mats Stridsberg

This project focuses on biomarkers for patients with neuroendocrine diseases. These diseases include patients with malignant tumours, such as carcinoid tumours, endocrine pancreatic tumours, pheochromocytomas and neuroblastomas. A large number of antibodies against neuroendocrine associated proteins have been raised. These antibodies are used for developments of Radioimmunoassays and Elisas for quantitative measurements in different biological fluids, mainly plasma and serum. The antibodies are also used in Immuno-Histochemical applications. Neuroendocrine proteins of special interest are Chromogranin A (CgA), Chromogranin B (CgB), Secretogranin II, Secretogranin III, Secretoneurin, Proconvertases, Somatostatin receptors, Secretin receptors and Synatophysin. During the last year I have been working with further developments of assays for measurements of Chromogranins and Secretogranins, including new and enhanced methods for CgA and CgB and further developments of the assays for Secretogranins. Measurements of CgA and CgB are still the most important tools for the management of patients with neuroendocrine tumours.

Biomarkers for cardiac diseases and gastrointestinal diseases

Mats Stridsberg

This project focuses on biomarkers for patients with non-neuroendocrine diseases. These diseases include non-malignant diseases where neuroendocrine properties are of interest, such as ischemic coronar disease, cardiac failure, inflammatory bowel disease (IBD) and non-inflammatory bowel disease (IBS). In my studies, I have shown that Chromogranins and Secrotgranins are useful biomarkers for heart failure and I have shown that they also can be used as a biomarker for congestive heart failure and gives additional information compared to previously used markers. The use of Chromogranins and Secrotgranins as diagnostic aid for IBD and IBS has not been assessed before. Preliminary results show that Chromogranins and Secrotgranins can be used as biomarkers for at least IBS.

Endocrine responses to stress exercise and food intake:

Mats Stridsberg, Torbjörn Åkerfeldt

The hormonal responses elicited by nutrition and exercise are an area of interest. Both over-feeding and starvation involve hormonal responses. This project focuses on improvement and development of biochemical methods to monitor changes in body composition in relation to food intake and also in relation to stress and exercise. Hormones of special interest are IGF-1, IGF-binding proteins, Adiponectin, Obestatin, Leptin, Melatonin, and other peptide hormones.

Members of the group during 2014

Mats Stridsberg, MD, PhD, Assoc. Prof.

Torbjörn Åkerfeldt, MD, PhD student

Funding

ALF

Lions Research Foundation

Publications 2012-2014

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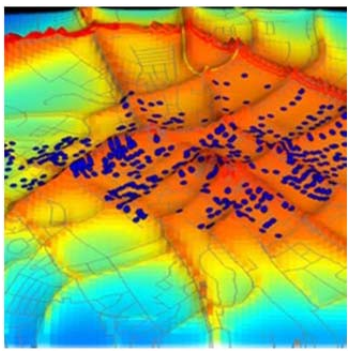
Epidemiology



Epidemiology research is carried out by several individual research groups working in five different areas; cardiovascular (CV) disease, pulmonary disorders, osteoporosis, occupational and environmental medicine and clinical pharmacogenetics. One mutual strategy for these research groups is to study genetic and environmental risk factors aiming to understand the pathophysiology of atherosclerosis mediated CV-disorders, osteoporosis, and chronic respiratory diseases, respectively. Risk factor analysis is also employed by the environmental medicine group to assess the impact of occupational and environmental exposures. The common goals for the research groups are to develop better risk classifications, and to improve both prevention and treatment strategies for the above mentioned common disorders.

Cardiovascular epidemiology

Lars Lind

The major uniting aim in the research group is to understand the pathophysiology behind the atherosclerosis mediated CV disorders myocardial infarction and stroke for an improved risk classification in the population and improved treatment strategies.

Besides our ongoing studies on established cohorts (see below) we have lately initiated two new, major projects. The first project, led by Johan Sundström, MetaHealth, is a collaboration network of existing cohorts in Sweden designed for individual participant data meta-analyses of uncommon diseases, for which very large samples are needed. Currently, a study on subarachnoida heammorrage is on-going.

The second project is a new cohort study, the EpiHealth cohort. The plan is to enrol 300,000 Swedes in the age-groups 45 to 75 years to study the interplay between genes and life-style factors on the development of common disorders seen in the elderly, such as myocardial infarction, stroke, bone fractures, dementia, chronic obstructive pulmonary disease, cancer arthrosis. Data on life-style exposures will be collected by a web-based questionnaire and serum/plasma/DNA will be biobanked at a visit to a test centre where also physiological measures, such as blood pressure, lung function, cognitive function, anthropometry and ECG will be recorded. A test centre in Uppsala was started up in April 2011 and in Malmö in Jan 2012. By the end of 2013, abound 11,000 individuals had been enrolled in the study.

In addition, we are in the planning phase for the SCAPIS study, a nation-wide cohort study engaging 6 universities in Sweden with the aim to collect data in 30,000 individuals regarding athosclerosis and lund function, including CT coronary angiography, ultrasound of the carotid arteries, a lung function test and CT of lungs.

The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study

Lars Lind

The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study is a population-based longitudinal cohort study, started in 2001, of men and women aged 70. A number of cardiovascular characteristics have been collected, e.g. measurements of intima-media thickness, three different tests of endothelial function, and a large number of biochemical biomarkers

A reinvestigation of the cohort at age 75 was performed between March 2006 and Sep 2009, and a reinvestigation at age 80 was started during the spring of 2011 and will continue to the summer 2014. Apart from analyses of classical risk factors, ultrasound of the carotid arteries and the heart will be performed together with 2 cognitive function tests.

The Uppsala Longitudinal Study of Adult Men (ULSAM)

Johan Sundström, Lars Lind, Johan Ärnlöv and Lars Lannfelt (PI)

The ULSAM study was started in 1970, when 2 322 men at the age of 50 participated in a health survey. The men have thereafter been investigated again at ages 60, 70, 77, 82 and 88 years, respectively. The focus in the ULSAM cohort is on cardiovascular disease and metabolic links, but several other research areas have also been explored, such as nutrition, osteoporosis, and dementia. The follow-up time for morbidity and mortality through national registers is now >40 years. The major research aims in the ULSAM study are: to investigate the impact of life-time exposures of risk factors using updated covariates on the major CV diseases MI, Stroke and heart failure, to explore new risk factors, and to evaluate the risk associated with different genotypes on CV outcomes.

The Prospective investigation of Obesity, Energy production and Metabolism (POEM) longitudinal study

Lars Lind

A randomized sample of more than 1000 individuals selected from the inhabitants of the Uppsala County aged 50 have been invited for the baseline examination. In addition, by use of a health screening project, another 300-400 obese middle-aged subjects with a mean age of 50 will be subjected to the same baseline examination. These subjects will then be examined every 10th year regarding hypertension, obesity, diabetes and dyslipidemia. The development of CV disorders will be followed throughout life by means of the Swedish national registers of hospital care and mortality. The first patient was included in the study in Sep 2010.

Management and outcome of stroke using Riks-Stroke

Anders Terent

Stroke is the most common clinical manifestation of vascular disease in the brain. The onset of symptoms is sudden and the consequences long-lasting. Bleeding (15%) or infarction in the brain parenchyma (85%) causes stroke. In Sweden about 30 000 people suffer strokes every year. We perform a cohort study of 105 034 patients, registered in Riks-Stroke (Swedish National Quality Register for Stroke Care) during 2001 through 2005. Cross-linking to the Hospital Discharge and Cause of Death Registers has been done to achieve data on previous hospitalisations, death dates and causes of death. The objectives are to assess co-morbidity, functionality and drug treatment in stroke patients before and after the stroke. Of particular interest is the use of anti-thrombotic treatment at onset of acute stroke and at discharge from hospital. Risk and risk factors for fatal and non-fatal recurrent stroke are analysed.

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Publications 2012-2014

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Respiratory medicine and allergology

Christer Janson

The research in our group focuses on three principal areas: COPD, asthma and allergy, sleep-disordered breathing and rehabilitation and physical activity. The group is also involved in projects concerning other respiratory diseases such as lung cancer and tuberculosis.

Epidemiology of asthma and COPD: risk factors, systemic and local inflammation and co-morbidity

Christer Jansson

In 2005, four million persons died from chronic respiratory diseases: asthma and chronic obstructive pulmonary disease (COPD) which makes this one of the globally leading causes of mortality. The prevalence of asthma and COPD has increased rapidly in most countries and in Sweden one out of every ten person has asthma and 10% of those above 45 years have COPD. The general aim is to study risk factors and co-morbidity in asthma and COPD with special emphasis on systemic and local inflammation, and the analyses are performed using data from several population studies.

During 2008 and 2009 our group coordinated a large epidemiological study in asthma and COPD through the GA2LEN network. In the study we have now completed a clinical phase were about 1600 subjects were investigated with allergy testing, spirometry, inflammatory markers etc.

In 2010 we began the follow up our large asthma cohort (RHINE II and ECRHS III). The clinical phase of ECRHS III started in 2011 and was completed during the spring 2013. Our next phase is to contact children from the RHINE cohort through a web based survey which was done in February 2015..

The MIDAS study includes children and young adults and is a project done in cooperation with a research group at the Department of Women's and Children's Health, Phadia (Thermo Fisher Scientific) and Aerocrine. In the study we have included 400 asthmatics and 100 controls that have been carefully phenotyped. A follow up of the MIDAS study started in 2014 and will be completed in 2015..

The ECRHS III, GA2LEN and MIDAS populations are part of a national consortium aimed at finding better biomarkers for asthma – the ChAMP project.

The PRAXIS study is a study of COPD patients and asthma patients from Primary Care Health Centres (PCHCs) and Hospital outpatient clinics in the Uppsala Örebro Region. The study includes questionnaires to patients and Health care centres as well as structured reviews of patient records. The first phase include approximately 2000 patients with asthma and COPD, these patients were followed up 2012. In 2014 a new sample of patients was included in order to study change in management of asthma and COPD. The PATHOS study is a study of 21,000 COPD patients from PCHCs in different part of Sweden. The study uses patients record data merged with data from national registries.

The CHROMED study is a EU funded study of the use of telemedicine in COPD, this study is conducted in cooperation with the research group of Clinical Physiology. Our research group is also involved in the planning of the SCAPIS study a large cardiopulmonary imaging study that will begin recruiting patients in Uppsala during the autumn of 2015.

Sleep and Health

Eva Lindberg

About 4% of men and 2% of women are diagnosed and treated for obstructive sleep apnea syndrome (OSAS). We have recently reported that the occurrence of sleep apnea, i.e. at least 5 respiratory pauses per hour of sleep is far more common and up to 50% females in the population fulfil these crieteria. However, the knowledge about long-time evolution and consequences of this are sparse especially in women. The

major aims are to understand the consequences of sleep-disordered breathing (SDB) to health and to understand the underlying pathophysiology. Our research is mainly epidemiological in design and we follow two unique population-based cohorts (one male and one female) prospectively who were investigated for sleep disorders at baseline and followed for health outcomes. Subsamples have been clinically investigated including polysomnography, blood sampling and oral glucose tolerance test. During 2013-15 we have been working on a unique 10-year follow-up of a community-based cohort of women including repeated full-night polysomnography. In recent years we have focused also on the impact of sleep architecture on metabolism and health. In addition, in a randomised, controlled trial we study the effect of physical training on sleep-disordered breathing. In the same clinical cohort we analyse the effect on metabolism and systemic inflammation when the sleep-disordered breathing is effectively treated. Since 2013 we are running a clinical trial in obese patients with and without sleep-disordered breathing. The main purpose is to analyse effects on glucose metabolism and lung function by treatment of sleep-disordered breathing and by rapid weight loss by surgery. Ongoing clinical trials also include a study to evaluate the role of measuring nose resistance to predict treatment compliance and also to validate questionnaires used to select patients at high risk of sleep apnea syndrome.

Physical training and physical activity

Margareta Emtner

The level of physical activity and capacity is low in the general population and especially low in subjects with chronic lung diseases. A low physical activity and capacity is associated to decreased health-related quality of life in subjects with lung diseases and increases the risk of mortality and morbidity in healthy subjects and in subjects with all type of diseases. Our main focus is on clinical research with the aims of identifying physical activity and physical capacity in subjects with pulmonary diseases; investigate reasons for exercise-induced breathing problems, investigating reasons for physical inactivity and physical limitations, investigating fall prevention interventions, identifying simple tests to measure physical capacity, and evaluating rehabilitation interventions.

Since 2011 our group is coordinating a multicenter study investigating the long-term benefits (2 years) of a behaviour medicine intervention in chronic obstructive pulmonary disease (COPD) patients. Patients who have participated in exercise training twice a week for 8-12 weeks are eligible to take part in the study. They are randomised to a maintenance behaviour medicine intervention for six months or usual care. The intervention includes telephone calls, initially every week, and thereafter more seldom, focusing on improving physical active level in everyday life. Forty-two patients out of 100 have been included and three sites are participating. The study is ongoing.

In 2012 we started a Nordic multicenter study, the AMBOX study (Ambulatory oxygen), aiming at investigating the benefits of supplemental oxygen to patients with COPD, who do not have long-term oxygen therapy, but desaturate during exercise. Six sites are now including patients and a total number of 52 out of 144 patients have been included and followed for a year. The study is ongoing.
In 2013 we started collaboration with the Departments of Women's and Children's Health and Surgical Sciences investigating the prevalence of exercise-induced breathing problems in adolescents in Uppsala and reasons for exercise-induced breathing problems. A population based survey has been performed, and a manuscript was published in 2014. Exercise provocation tests to investigate bronchial and laryngeal obstruction have been performed in 150 subjects, and physical activity during seven days has been measured with an accelerometer in all subjects. In addition, analyses of blood samples have been performed.

The TRIAD study including 100 COPD patients from the lung clinics in Uppsala and Gothenburg aiming at identifying physical capacity, physical activity, nutrition status and inflammatorty markers has during 2014 completed the 4-year follow-up of all patients.

In collaboration with researchers in Umeå we have in population-based cohorts within the Obstructive Lung disease In Northern Sweden (OLIN) study, evaluated if factors as concomitant heart disease and fatigue were related to lower levels of physical activity in subjects with COPD and control subjects. Further evaluations are ongoing.

Members of the group during 2014

Christer Janson, MD, PhD, professor
Eva Lindberg, MD, PhD, professor
Margareta Emtner, PT, PhD, assoc prof
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Christer Jansson

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Eva Lindberg

Heart and Lung Foundation	700 kSEK
Swedish Society of Heart and Lung diseases	180kSEK,
Uppsala-Örebro Regional Research Council	350 kSEK

Margareta Emtner

Uppsala university	400 kSEK
Astma- and Allergy Foundation	200 kSEK

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Clinical Pharmacogenetics and Osteoporosis

Håkan Melhus, Mia Wadelius, Pär Hallberg and Gabriella Scordo

Genetic and dietary risk factors for osteoporosis

Thomas Lind, Annica Jacobson, Håkan Melhus

We aim to identify and study genetic and environmental risk factors that can help us explain why Sweden and Norway have the world's highest incidence of osteoporotic fractures, and to develop new treatments for osteoporosis. We have primarily studied genetic and dietary factors, especially vitamin A and D.

Mechanistic studies on Vitamin A-induced bone toxicity

Thomas Lind, Annica Jacobson, Håkan Melhus

Vitamin A is the only known substance that can induce spontaneous fractures in laboratory animals. We have previously shown that excessive doses lead to a reduced diameter of the long bones without affecting the bone mineral density in rodents. To try to clarify the molecular mechanisms behind this vitamin A-induced bone toxicity, we have continued these animal studies as well as our studies of the effects in bone cells in vitro.

Warfarin pharmacogenetics and pharmacometrics

Niclas Eriksson, Anna-Karin Hamberg, Hugo Kohnke, Mia Wadelius

There have been significant advances in the pharmacogenetics of warfarin, but also controversies. In 2014, we explored reasons for discordant results in randomised clinical trials comparing pharmacogenetic dosing of warfarin with standard dosing. We further characterised the variability in warfarin dose requirements in children by using pharmacometric modelling and simulation. The International Warfarin Pharmacogenetics Consortium (IWPC) genome-wide association study (GWAS) meta-analysis is continuing.

Genetics of serious adverse drug reactions

Pär Hallberg, Håkan Melhus, Mia Wadelius

SWEDEGENE (www.swedegene.se) is a national study of genetic susceptibility to adverse drug reactions led by our group. We currently have clinical data and DNA from over 2000 cases. We collaborate internationally concerning rare serious reactions and are partners of the EU FP7 funded study PREDICTION-ADR. Genotyping or exome sequencing is performed at the Uppsala SciLife SNP&SEQ platform. Around 6000 non-related Swedes with genome-wide data are used as population controls.

Improving the Quality and Safety of Drug Use in Hospitalized Elderly

Anna Alassaad, Håkan Melhus

Elderly people admitted to hospital are at high risk for rehospitalisation and medication errors. We have in aprevious randomized controlled trial (RCT) shown that a clinical pharmacist intervention reduces the number of revisits to hospital for patients 80 years or older acutely admitted to hospital. Our continued work have suggested appropriate targets for these interventions.

Bisphosphonate-Associated Atypical Fractures and osteoporosis

Pär Hallberg, Mohammad Kharazmi

We aim to increase the knowledge about the adverse effects of bisphosphonates, manifesting as atypical fractures in the skeleton and osteonecrosis of the jaw. Specifically, we have studied the relative risks of atypical fractures associated with different bisphosphonates, whether gender is a risk factor, described the characteristics of prodromal symptoms, and published case reports of bisphosphonate-related osteonecrosis of the jaw. We are currently investigating whether or not atypical fractures are associated with an increased mortality compared with ordinary low-trauma fractures of the femoral shaft. These studies are partly based on data from SWEDEGENE.

Pharmacogenetics and therapeutic outcome

Gabriella Scordo

We investigate, by an integrated pharmacokinetic-pharmacodynamic approach, the contribution of allelic variability in genes coding for proteins involved in drug metabolism, transport and effects to the clinical outcome of the drugs used in neuropsychiatry (with focus on the therapy of schizophrenia, depression and Alzheimer's disease) and cardiology. The aim is to identify genetic markers of treatment outcome, quantify their predictive value, and evaluate how this information can be used to design genotype-based dosing schedules for improved pharmacotherapy. Furthermore we evaluate the frequencies of these polymorphisms in different ethnic groups, in order to identify differences in the distribution patterns underlying the need for different dose recommendations in different populations.

Clinical consequences of polymorphisms in xenobiotics metabolising enzymes

Gabriella Scordo

We collaborate in an international, multicenter project that aims to identify and clarify the role of the genetic polymorphism in the enzymes that metabolize xenobiotics in the susceptibility to develop Multiple Chemical Sensitivity (MCS), a multi-systemic syndrome characterized by intolerance to environmental chemicals.

Members of the group during 2014

Håkan Melhus, Professor
Mia Wadelius, MD Lecturer
Pär Hallberg, MD PhD
Gabriella Scordo, MD PhD
Thomas Lind, Researcher, PhD
Annica Jacobson Rasmusson, Researcher, PhD
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Ulrica Ramqvist, Research nurse
Elisabet Stjernberg, Research nurse
Hugo Kohnke, Biomedical analyst MSc
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Funding 2014

Håkan Melhus:

VR	1000 kSEK
ALF	900 kSEK
Formas	430 kSEK

Mia Wadelius:

Heart & Lung foundation	300 kSEK
Swedish Research Council	1600 kSEK
ALF	465 kSEK
EU FP7 (PREDICTION-ADR)	1400 kSEK
Thuréus' foundation	100 kSEK

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Dissertations

Anna Alassaad: Improving the Quality and Safety of Drug Use in Hospitalized Elderly: Assessing the Effects of Clinical Pharmacist Interventions and Identifying Patients at Risk of Drug-related Morbidity and Mortality

Occupational and environmental medicine

Eva Vingård

Occupational and environmental medicine is a research area studying the significance of environmental factors and exposure on human health in a wide context, covering all age groups. The environmental factors can be from the workplace, the indoor environment, or the outdoor environment. The type of exposures can be physical, chemical, biological, psychosocial or organizational. The research methodology mainly includes epidemiological methods, either in specific groups or in the general population, as well as experimental animal studies and intervention field studies.

One focus in our research group is health effects of the environment with respect to asthma, ocular and respiratory symptoms, rhinitis and allergic symptoms. The indoor studies have covered schools, day care centers, hospitals, dwelling, stables and the cabins in aircraft. Another focus is health and work environment in health care and education. Studies investigating health, work environment, life style and socioeconomic factors are conducted. Some multi-disciplinary studies investigating how building construction and property management together with energy use are associated and affects indoor environment, health and well-being are conducted. Organizational factors for the good work environment are studied as well as musculoskeletal and psychiatric disorders in relation to work. Return to work, rehabilitation causes for and consequences of sick listing are other focus of research for the group. Another new and promising area for research is exposure to endocrine disrupting chemicals and the potential progression of major common diseases like obesity, cardiovascular disease and osteoporosis. The research group are using epidemiological studies as well as experimental laboratory studies in a translational way. To study and develop methods for occupational health services are another research group within OEM.

The research at the department is interconnected with the Occupational and Environmental department at Uppsala Akademiska Hospital serving three county councils (Uppsala, Gävleborg and Dalarna) and many of the members in the research group have their position at that county council department.

The overall aims of the research group are to;

- discover, explore, assess, analyze and report health and risk factors for occupational and environmental exposures.
- develop new methods for research in occupational and environmental medicine
- develop and evaluate prevention strategies at work and in the general environment.

Below is a selected list of current research projects. For a more complete list, and more detailed information, please see http://www.medsci.uu.se/fogrupp/occupmed/occupmedicine.htm.

Health and future in the public sector – an investigation of the healthy organization

Hospitalization due to common potentially work related disorders, disability pension and mortality among native and foreign-born residents in Sweden during1990-2008.

Exposure to endocrine disrupting chemicals and the potential progression of major common diseases like obesity, cardiovascular disease and osteoporosis.

Persistent organic pollutants and CVD from a gender perspective.

Health effects of exposure to Bisphenol A.

Does Developmental Exposure to Bisphenol A Induce Bone and Adipose Tissue Disturbances?

Healthy sustainable houses and energy use

Asthma, risk factors, prevention and quality of life for the affected person.

Horse stable environment, health effects on stable workers and horses and the impact of horse on community planning.

Characterisation, exposure levels and health effects of particles in dwellings.

Experimental early intervention of Swedish Social Insurance Agency to reduce sickness absence at work.

Psychiatric symptoms, psychiatric disorders and its associations with factors in childhood, sociodemographic factors, life style and work. Follow up of two cohorts; 50000 conscripts during 40 years and 10 000 inhabitants of Stockholm county.

Balanced communication, leadership and health.

Funding

Eva Vingård

FORTE	1.0 MSEK

Dan Norbäck

Astma och allergiförb.	240 kSEK
VR	350 kSEK

Karin Engvall

FORMAS	850 kSEK

Monica Lind

FORMAS	2.5MSEK

Margareta Torgén

FORTE	400 kSEK

Magnus Svartengren

FORTE	2.6 MSEK
AFA	2.4 MSEK

Members of the group during 2014

Eva Vingård, Professor, MD

Anna Rask Andersen, Professor, MD

Peter Westerholm, Professor emeritus, MD

Dan Norbäck, Assoc professor

Magnus Svartengren, Adj. Professor, MD

Gunilla Wieslander, Assoc professor, MD

Robert Wålinder, Assoc professor, MD

Monica Lind, Assoc professor

Lena Elfman, Assoc professor

Malin Josephson, Assoc professor

Greta Smedje, Assoc professor

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Guihong, Cai, PhD

Mostafa Ghaffari, PhD

Hans Goine, PhD

Eva Bergsten PhD-student

Margareta Halin Lejonklou, Postdoc

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Bjarne Lembke, PhD-student

Erik Lampa, PhD-student

Camilla Lodin, PhD-student

Peter Palm, PhD-student

Susanne Victor, PhD-student

Juan Wang, PhD-student

Sofia Åström Paulsson, PhD-student, MD

Publications 2012-2014

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Dissertations 2014

Monica Rönn: Environmental Contaminants and Obesity.

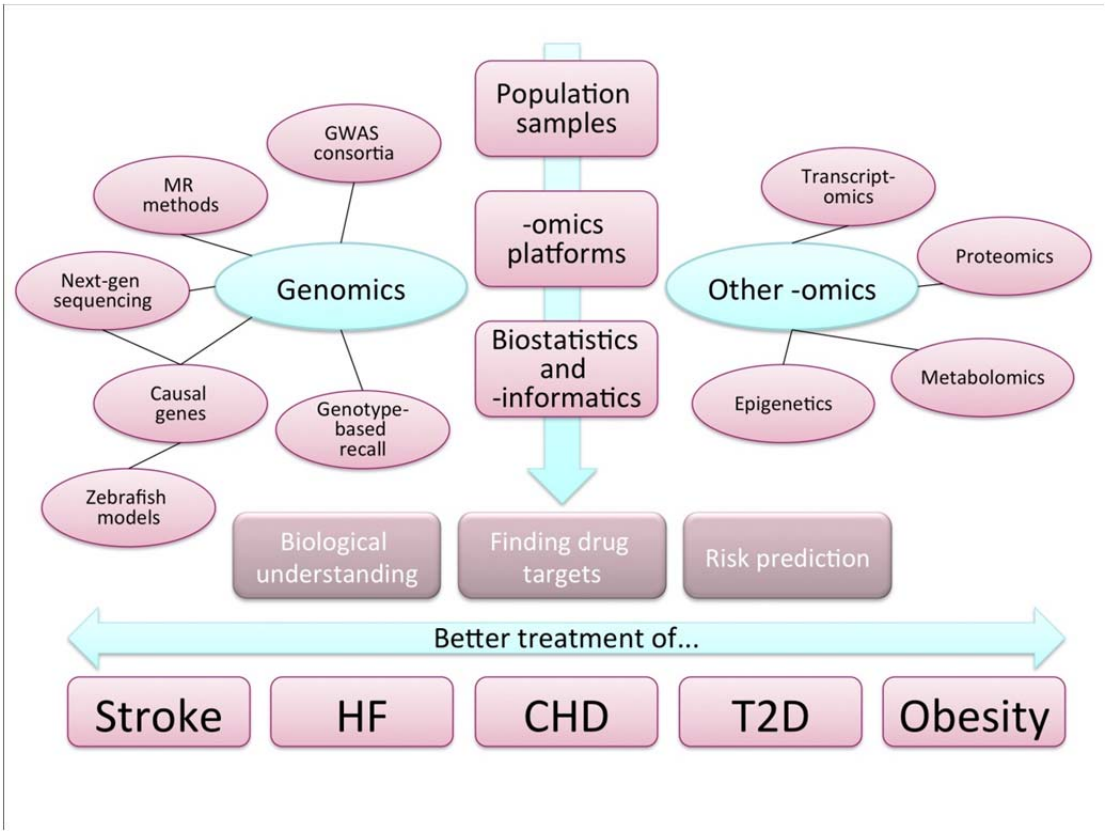
Guihong Cai: Fungal DNA, Mould, Dampness and Allergens in Schools and Day Care Centers and Respiratory Health

Molecular epidemiology

Erik Ingelsson, Tove Fall, Marcel den Hoed

Summary of ongoing projects

Our research area is cardiovascular medicine with a special focus on metabolic disturbances, such as obesity and insulin resistance and their role in the development of subclinical and clinical cardiovascular disease. The methods used are primarily from the molecular epidemiology field where we use -omics studies of how cardiovascular disease and related conditions varies with DNA variation, RNA expression, and circulating biomarkers such as proteins and metabolites. We are also working with functional characterization of candidate genes using zebrafish models and cell-based techniques. Our research is translational, trying to bridge molecular biology and clinical medicine to reach new important insights into the pathophysiology of cardiovascular diseases, identification of new biomarkers for improved risk prediction, and discovery of novel targets for drug development (see **Figure**).



Genomics

Our research group has been taking a very active part in the various ongoing large-scale international genetics projects within the area of cardiovascular and metabolic disorders in the past five years. The work within these consortia has led to landmark papers dissecting the genetic architecture of complex traits, as well as to one of the first examples of detailed characterization of GWAS findings, by using refined physiological measures of glucose metabolism in humans. Prof. Ingelsson has been the corresponding author of several of these large consortia papers, which were published in leading journals, while in others we have had an important role in the writing group. As a whole, these papers have not only identified hundreds of novel genetic loci associated with cardiovascular traits, but also dramatically increased the understanding of the genetic architecture of complex traits and the biology underlying these conditions.

Over the past 3-4 years, we have also been working with Mendelian randomization (MR) as a method to address causality - a key concept in clinical medicine and epidemiology. The first examples of such projects that we have led have now been published in high-impact journals, and we have several additional projects using this methodology in the pipeline.

Based on findings from the characterization of loci in human studies, we prioritize the best candidate genes for mechanistic studies using model systems. We use CRISPR-Cas9 techniques to generate functional gene knockouts in adipocytes, myocytes, and zebrafish, to study glucose, insulin and lipid metabolism, atherosclerosis and other related phenotypes. This in-depth characterization of genes will provide further evidence towards causality and the mechanisms of action, as well as a first evaluation of which could be viable drug targets.

For *in vivo* studies, we use a zebrafish (Danio rerio) model system. Due to the short reproductive cycle, high proportion of orthologous genes, similarities to human physiology, and low costs for maintaining and phenotyping, we believe that the zebrafish model system is ideal for characterization of candidate genes for involvement in obesity, lipid metabolism and atherosclerosis. We use the CRISPR-Cas9 system, which allows for efficient, targeted, permanent mutagenesis of our candidate genes, and we have set up a highly multiplexed approach to target many genes simultaneously. Phenotyping of the zebrafish is done using the Vertebrate Automated Screening Technology (VAST) BioImager (http://www.unionbio.com/vast/), in combination with a fluorescence microscope. This setup enables the processing of multiple animals simultaneously, with fully automated manipulation, positioning and orienting of zebrafish larvae. The throughput of all handling and imaging steps is in the order of minutes per larva, which together with the characteristics of zebrafish and the CRISPR-Cas system, allows for unprecedented opportunities of genetic screening in an *in vivo* system.

For *in vitro* studies, we use human SGBS adipocytes and HepG2 hepatocytes. For knockdown and overexpression experiments, we transfect cells using CRISPR-Cas9 constructs and lentivirus. We assess the effect of knockout or overexpression of candidate genes on basal and insulin-stimulated glucose uptake (using 14C-labeled deoxyglucose) and lipolysis (measuring glycerol after insulin and/or isoprenalin exposure), as well as insulin signaling proteins and adipogenesis. We address downstream effects of gene knockdown or overexpression using transcriptomic and metabolomic profiling on cell lysates.

Other -omics

We have had a strong interest in studies of circulating biomarkers in the past decade, and have been working extensively with prediction of cardiovascular disease by use of both traditional and more novel biomarkers and by use of different statistical metrics for prediction.

From 2011 and on, we have changed focus, going from analyses of one or a few biomarkers at a time to analyses of hundreds, or more often, thousands of markers in the same experiment using -omics methods. We have a range of ongoing projects using transcriptomics, epigenomics, proteomics and metabolomics - all aiming at increase the biological knowledge of cardiovascular diseases and to identify new biomarkers and drug targets. In transcriptomics, we are both using in silico data from the GEO database, and de novo RNA sequencing of almost 700 skeletal muscle biopsies from the ULSAM study. In epigenomics, we are working with a set of DNA methylation projects aiming to identify sites with differential methylation patterns associated with various cardiovascular traits. Towards this end, we have run the Illumina Infinium HumanMethylation450 BeadChip Kit Array in 998 samples from the PIVUS study. In proteomics, we are working with two different methodologies in parallel. Both methods are affinity-based (i.e. using antibodies), but whereas one allows for screening of thousands of antibodies from the Human Protein Atlas in an untargeted manner, the other targets 90 proteins, but with higher sensitivity and specificity. The methods are complementary, have different advantages, and we use them for different projects and purposes. In metabolomics, we are using liquid chromatography (LC)-tandem mass spectrometry (MS/MS) methods, and we have run analyses in about 5,500 samples from several longitudinal cohort studies. Over the next few years, we plan to continue to analyze new samples using these methods, combine data across studies and data types, and to use -omics to improve knowledge about cardiometabolic diseases. We are also setting up a pipeline for analysing the microbiome from saliva and fecal samples.

Significance and novelty

Our research program combines comprehensive characterization in humans using both -omics methods and detailed phenotyping, with experiments in both in vitro and in vivo model systems in an integrative fashion providing a translation-back translation framework. We have access to unique study materials, state-of-the art methods, and a strong track record of successful projects in this field. Few other groups are able to combine -omics methods to elucidate the whole chain from DNA variation to clinical phenotypes in such

large and well-characterized study samples, and to combine that with functional models to screen for and characterize causal genes at this scale. Our work is anticipated to lead to new important insights into the pathophysiology of obesity, lipid metabolism, type 2 diabetes and cardiovascular diseases, and to new approaches to prevention and treatment that could have a huge impact on public health.

Read more at our home page: www.ingelsson.org

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Major external funding

Project title	PI	Funding agency	Year	Total (SEK)
Cardiomics: Use of -omics methods in large populations for identification of novel drug targets and clinical biomarkers for coronary heart disease	Ingelsson	Knut och Alice Wallenberg Foundation	2014-2018	7 500 000
		European Research Council (ERC Starting Grant)	2013-2017	13 007 876
Metabolomic profiling of large human populations with dynamic measures of glucose homeostasis for exploration of the diabetic continuum	Ingelsson	Swedish Diabetes Foundation (Diabetesfonden)	2014-2016	975 000
Establishing a Swedish node in European Advanced Translational Research InfraStructure in Medicine (EATRIS.se)	Ingelsson	Swedish Research Council (2014-6361)	2015-2017	13 395 000
Cardiomics: Integration of -omics methods for identification of novel drug targets and clinical biomarkers for coronary heart disease	Ingelsson	Swedish Heart-Lung Foundation (20120197)	2013-2014	1 200 000
		Swedish Research Council (2012-1397)	2013-2015	4 500 000

Beyond GWAS of obesity: An integrated approach to translate genetic association to function	Ingelsson	Swedish Heart-Lung Foundation (20140422)	2015-2017	1 800 000
Identifying targets and compounds for the therapeutic intervention of coronary heart disease using a zebrafish model system	den Hoed	Swedish Heart-Lung Foundation (20140543)	2015-2017	1 800 000
The role of risk factors related to early life microbial exposure in Type 1 diabetes etiology - a national cohort study using sibling design	Fall	Diabetesfonden (2014026)	2015	150 000
Genetics of diabetic heart disease	Fall	Borgströms stiftelse	2015	250 000
Unika register och innovativa metoder möjliggör bättre förståelse för orsak och konsekvenser av sjukdomar hos barn och ungdomar	Almqvist (Fall co-PI)	Swedish Research Council (2013-5867)	2014-2018	19 600 000
Cardiovascular and metabolic disease in companion animals and their owners: A unique nationwide cohort study	Fall	Formas	2014-2016	2 800 000
		Agria	2013-2015	450 000

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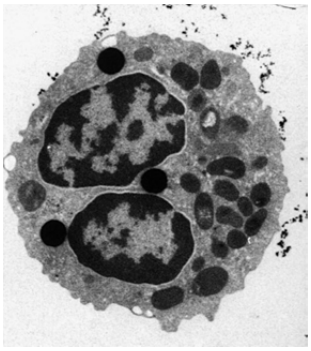
Dissertations in 2014

Ci Song, Lipid-related genes and their association with coronary heart disease (Karolinska Institutet=)

Elisabeth Jobs, Cathepsin S as a biomarker of Low-grade Inflammation, Insulin Resistance, and Cardiometabolic Disease Risk .

Inflammation and autoimmunity



Inflammation and autoimmunity are important aspects of several diseases of major importance for morbidity and mortality, including e.g. cardiovascular diseases, autoimmune diseases, renal diseases, inflammatory bowel disease and many skin diseases. The long Swedish tradition of biobanking and the ready access to patient records, together with the strong clinical and molecular expertise accumulated in Uppsala for these areas, have resulted in both innovative approaches and several successful projects. The goals for the independent research groups working in this area are to develop new biomarkers for disease classification, define targets for improved diagnostics, create new insights into disease mechanisms and develop novel therapeutic strategies.

Biological structure and function

Anders Larsson

The researchers within the research group are working within the field of laboratory technology with independent and collaborative projects. The research group explore several research areas.

Studies of the role of prostasome in fertility and prostate cancer

Göran Ronquist, Lena Carlsson, Louise Dubois, Gunnar Ronquist, Anders Larsson

We discovered the prostasomes more than 35 years ago and named them. The prostasome was the first described member of the exosome family. The prostasomes with their complex membrane architecture have been assigned multifunctional features in the normal reproductive process. What is more, evidence has accumulated pointing to a role of prostasomes in the propagation of prostate cancer, based on the findings that also malignant prostate cells are able to produce and export prostasomes to the extracellular environment. Furthermore, the abilities favouring prostate metastatic tumour cell survival and motility in an otherwise hostile environment are upregulated in prostasomes deriving from prostate cancer cells compared to prostasomes from normal secretory prostate cells. We demonstrated, by using an extremely sensitive and specific method, that prostasomes can function as new biomarkers for prostate cancer in blood plasma. Hence, our assay seemed to discriminate between blood samples representing low Gleason scores (indolent prostate cancer) from those representing medium and high Gleason scores (aggressive prostate cancer). Louise Dubois (PhD student) is working with the characterization of surface membrane antigens on prostasomes. Of special interest is our recent finding of an ATP-forming capacity of prostasomes, which has opened up studies on purinergic receptors of different types in seminal prostasomes and prostasomes derived from malignant cell lines. We have also been able to purify prostasomal lipid rafts whose protein content has been examined by mass spectrometry. The lipid rafts are essential for intercellular communication. We have mapped the content of prostasomal chromogranins in detail. We plan to do the same with cardiosomes once we have scaled up the production of cardiosomes. Cardiosomal and prostasomal DNA sequencing is ongoing and results are expected in Q2, 2015. We recently obtained results on prostasome DNA being mostly single stranded (unpublished data) and this will be confirmed in cardiosomal DNA. The finding of single-stranded genomic DNA is contrary to earlier findings using a less reliable technique. We are internationally leading on the use of avian antibodies for diagnostic and therapeutic purposes and we have developed techniques for successful production of high quality antibodies to exosomes/prostasomes.

Oral immunotherapy with IgY for the prevention of bacterial and viral infections in humans

Johan Stålberg, Per-Erik Wejåker, Anders Larsson

Cystic fibrosis (CF) is a hereditary life-shortening disorder with repeated respiratory infections and malnutrition as main clinical manifestations. Chronic lung infections with Pseudomonas aeruginosa (PA) are major causes of morbidity and mortality. We have shown that we can reduce the number of pseudomonas infections in CF patients by oral immunotherapy with anti-pseudomonas IgY. The study includes more than 50.000 daily patient doses and is the world's largest study with IgY. We have received an orphan drug designation from EMEA. We also have initiated development of therapies against candida albicans and ESBL-klebsiella. We are currently performing a Phase III, placebo-controlled randomized double blind study supported by an EU grant (EUR 5.35 million over a 4 year period) for a clinical study to prevent pseudomonas infections in CF patients. We have now randomized 151 patients in nine European countries and we expect to include the last patient in the study Q2 2015. The maximum treatment period is 2 years so the study will be ended in 2017. This is one of a very few ongoing phase III studies that focus on antibiotics resistance and alternatives to antibiotics.

Serum half-life of pituitary gonadotropins is decreased by sulfonation and increased by sialylation in women

Leif Wide and Karin Eriksson

The gonadotropins are secreted from the human pituitary as spectra of isoforms with different degrees of sulfonation and sialylation of the oligosaccharides, modifications suspected to determine their half-lives in the circulation. We found that the decline in LH and FSH during GnRH receptor blockade is associated with a decrease in sulfonated and increase in sialylated residues. The results indicate that both sulfonation and sialylation of the gonadotropins regulate their half-life in the circulation. The rapid disappearance of LH isoforms with two and three SO3-GalNAc residues suggests their removal by hepatic SO3-GalNAc-receptors similar to those in rodents. Episodic secretion of spectra of isoforms with different half-lives is expected to lead to continuous changes in gonadotropin isoform compositions in blood.

Studies of F-calprotectin and S-calprotectin

Tom Nilsen, Anders Larsson

Calprotectin is found in neutrophil and the protein is released when the neutrophils are activated. Faeces calprotectin is widely used as a marker for inflammatory bowel disorder while S-calprotectin could be used as a marker for neutrophil activation. We are currently, together with Gentian and Buhlmann, developing a turbidimetric calprotectin assay. The project is supported by EU through Eurostar. The aim of the project is to develop calibrators and reagents for F-calprotectin and S-calprotectin and evaluated them with clinical materials.

Urinary biomarkers for tubular kidney damage, cardiovascular disease and mortality

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Estimation of the glomerular filtration rate (eGFR) is essential for the diagnosis and monitoring of patients with kidney disease and for correct dosage of drugs that are eliminated from the circulation by the kidneys. Cystatin C has been shown in several studies to be superior to creatinine for estimation of eGFR and as a cardiovascular risk marker. We are one of the leading groups in cystatin C research and have been involved in the new international calibrator for cystatin C and the new CAPA equation. We have shown that cystatin C-estimated GFR has a very good correlation with iohexol-estimated GFR both in patients with slight and severe kidney disease. Cystatin C also has a low diurnal variability, which facilitates the use of the marker. Cystatin C is also a promising risk marker for cardiovascular morbidity and mortality and is significantly correlated with HbA1c, diabetes and inflammation in elderly males. A natural step is to expand the research field to other types of kidney damage (glomerular and tubular damage). We have in our laboratory set up

new tubular biomarkers for kidney damage urinary neutrophil gelatinase-associated lipocalin (U-NGAL), urinary kidney injury molecule (U-KIM-1) and urinary cystatin C (U-cystatin C). We are currently evaluating them as biomarkers of acute kidney injury in intensive care units. Recently it was shown that mild to moderate increases of these biomarkers may also reflect chronic kidney damage and subsequently cardiovascular risk. Increased concentrations of U-NGAL, U-KIM-1 and U-Cystatin C are independently associated with cardiovascular morbidity and mortality in prospective studies of elderly men. During the last three years we have been involved in a number of publications in JAMA, Lancet and New Engl J Med on mortality and GFR markers.

Members of the group during 2014

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Coagulation and Inflammation Science

Agneta Siegbahn

Cells within arteriosclerotic tissue express high levels of tissue factor (TF), the principal activator of blood coagulation. Uncontrolled activation of the coagulation process following plaque rupture with assembly of the TF/FVIIa complex on cellular surfaces leads to fast thrombus formation eventually with a total occlusion of the vessel and myocardial infarction. Circulating procoagulant cellular aggregates and microparticles contribute to the systemic responses in this syndrome. TF/FVIIa also supports several non-coagulant functions, including cell migration, apoptosis and inflammation by activation of intracellular pathways. The molecular mechanisms leading to activation of these path-ways and the biological significance remain elusive. Our research focuses on characterization of TF expression and procoagulant activity, and signalling mechanisms to find ways for pharmacological interventions and possible defects in signalling as a mechanism of cardiovascular disease. The research group is furthermore engaged in genomic and proteomic analyses and functional studies in a number of global clinical trials in acute coronary syndromes and arterial fibrillation using the new generation of antithrombotic and antiplatelet drugs. The underlying theme of our research is thus the integrated approach from molecular basic science to patients treatment, ultimately personalized.

TF expression and procoagulant activity

Individual variations of TF expression and activity in monocytes have been established, but still little is known of cellular and genetic factors regulating the magnitudes of TF expression and activity. We identified the novel 5466 A>G SNP in the TF gene, coding for increased TF expression and activity in monocytes. This SNP was subsequently shown to be associated with myocardial infarct and cardiovascular death in acute coronary syndrome. Very recently, thrombin formation following vascular injury and thrombin-lowering effect of statins in patients with CAD were found to be genetically determined by the TF 5466A>G polymorphism. We are continuing our studies how the tissue factor gene is regulated on the molecular level. During 2014 we have started a collaboration with Professor Johann Wojtas research group in Vienna concerning different subsets of monocytes and found that a subset of monocytes, CD14+ and CD16+, express higher levels of TF induced by LPS and the cytokine IL-33. The ultimate goal being to identify novel mechanisms, genetic, epigenetic and microRNAs, governing tissue factor gene regulation.

A cocktail of cytokines was shown to express TF in pancreatic islets. TF/FVIIa signalling was also demonstrated to augment beta-cell death in response to cytokines.

Microparticles; methods and biological functions

Upon activation platelets, leukocytes and endothelial cells form MPs. Circulating platelet MPs have been found in inflammatory diseases and are related to the severity of disease. We have during the year developed a new flow cytometry method to calculate the amount of MPs with different cellular origin in whole blood. The new method is superior to earlier used methods, and is now implemented in a number of new clinical studies in patients with CAD and pulmonary arterial hypertension. Characterization of the biological effects induced by purified platelet MPs upon interaction with a number of human cells and whether new antiplatelet/antithrombotic drugs can interfere with this interaction are a subject of our ongoing experimental studies.

TF non-coagulant, signalling and biological funcions

The TF-induced signalling events eventually changes cell fate and behaviour, rendering cells and tissues pro-migratory, resistant to apoptosis and proliferative. This experimental work is paralleled by clinical observations of increased TF expression in conditions such as metastatic cancers and the atherosclerotic plaque, where cell survival, migration and proliferation are paramount to the pathological process. We reported for the first time that TF/FVIIa induces the transactivation of receptor tyrosine kinases, i.e the PDGFRβ, and thereby identified a new signalling pathway involved in cell migration.

We have continued our work on TF/FVIIa-induced signaling and biological consequences. We showed that IGF-1R is a key player in TF/FVIIa-induced cell survival. TF/FVIIa induces transactivation of the IGF-1 receptor, which then translocates to the nucleus, and binds to chromatin and induces generegulation.

We have also shown that Eph RTKs are novel proteolytical targets of TF/FVIIa and cleaved in their ectodomains by TF/FVIIa. We have identified the exact cleavage site in the receptors. The cleavage controls EphB2-mediated cell segregation. Cleavage of EpHA2 by TF/FVIIa complex leads to potentiation of EphA2-ligand induced cytoskeleton reorganization. Moreover, we have demontsrated that TF/FVIIa phosporylates serine 897 in the cytoplasmic domain of EphA2. EphA2/ephrinA1 pathway is a novel proinflammatory mediator and one regulator of atherosclerotic plaque development.

MicroRNA: TF regulation and arrays for clinical studies

Not much is known about the molecular regulation of the human TF gene. We have recorded 211 differentially expressed microRNAs during TF down-regulation. One of these, was identified to regulate the transcription of the human TF gene by directly binding to its target sequence in the 3'UTR. In a patient cohort with ACS, we found that expression of this microRNA is reduced one year after the acute event, and this reduction correlates with an increase in TF on the surface of platelets and circulating platelet microparticles.

A novel high-throughput and cost effective qPCR-method for measuring relative microRNA expression levels is currently being established using the BioMark HD at the Clinical Biomarkers facility, SciLifelab (headed by me). So far 34 miRNAs have been successfully amplified using this system. This method will be used for screening microRNAs in our large studies on ACS and AF.

Identification of biomarkers in atherothromboembolic diseases

The purpose is to identify new biomarkers and establish new tools with higher sensitivity to be used in the understanding of pathophysiologic mechanisms, diagnosis and for estimation of prognosis and treatment efficacy in these diseases.

Plasma samples from our well-characterized patients with CAD have been analysed with a new plasma proteomic multiplex assay, the proximity extension assay, where 90 samples and 92 biomarkers in each sample are analysed simultaneously. A case control study of 400 patients with MI included in the PLATO study has been analyzed with the multiplex PEA. Using this assay and also conventional assays a number of the new biomarkers of importance for new events have been identified, among others the stem cell factor, SCF. GDF-15 has been demonstrated to be an excellent prognostic biomarker for bleeding in patients with AF and NOAC treatment.

We have been actively involved in the design of the substudy programs of biomarkers, genome wide association studies and the analyses of the plasma samples and to translate candidate genes and proteins into functional studies. During the last year we have in close collaboration with the Cardiology research group at IMV been very actively involved in establishing new clinical tools for improving the identification of risk of stroke, MI and bleeding during anticoagulant treatment. These tools are based on age, biomarkers and previous cardiovascular events, and therefore called ABC-risk scores. The first version of three different scores, based on biomarker results analysed in our large trials in ACS and AF, have recently been presented.

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Heart and Lung Foundation:	800 kSEK
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Christina Christersson

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Dermatology and Venereology

Hans Törmä

Our research embraces several projects related to the biology and treatment of skin diseases, especially keratinisation disorders. Epithelial differentiation is a complex process, which can be modulated by vitamin A and its analogs (retinoids), also used therapeutically in keratinizing disorders. We try to identify new gene mutations and pathogenetic mechanisms underlying several types of congenital keratinizing disorders, such as ichthyosis and epidermolysis bullosa (EB). The skin barrier failure in these disorders, as well as in atopic dermatitis, is studied aiming at finding new therapies.

The role of mast cells in psoriasis is investigated in vivo and in vitro. Skin biopsies and experimental skin models are utilized to discover new strategies for treating psoriasis based on interference with HER signalling and mast cell-mediated inflammation. Clinical characteristics and serologic markers are also studied in autoimmune disorders of the skin.

During 2014 we have focused on the following projects;

Etiologies and new therapies for monogenetic epidermal diseases

Hans Törmä, Marie Virtanen, Berit Berne, Anders Vahlquist

New keratin mutations underlying various epidermolytic skin disorders are continuously searched for. Immortalized cells from epidermolytic ichthyosis (EI) and EB patients have been established and characterized in our lab. These cells are now used for screening of chemical libraries in the search novel therapies using automated fluorescence microscopy. Compounds affecting keratin filament structure will be tested in cell and organotypic cultures in vitro.

Using transgene mouse models for epidermolytic disorders (collaboration with Irwin McLean et al, Dundee), we explore the effects of substances that in our cell culture experiments on keratinocytes have shown the most promising results as stabilizers (chaperons) of mutated cytoskeleton. Provided these animal experiments continue to show promising results on inducible EB/EI and no toxicity is observed, then a next step will be to plan phase I trials in humans.

In other projects, the genetic causes of autosomal recessive congenital ichthyosis (ARCI) other rare keratinisation disorders, which are currently diagnosed at the Genodermatosis Centre in Uppsala (a national referral centre), are investigated. This has already resulted in new knowledge about the pathoetiology of these diseases. The analyses are performed within the framework of a EU-sponsored network (GeneSkin).

In order to find new targets for treatment of ARCI and hyperkeratinisation, the interplay between known ARCI-associated gene products is studied in patients´ skin and keratinocytes and in siRNA knock-down keratinocytes exposed to retinoids and other drug candidates.

HER deregulation in psoriatic skin

Ola Rollman, Hans Törmä

Psoriatic skin displays chronic inflammation and hyperplasia associated with incomplete maturation of epithelial cells. The initiating and driving forces in this disease are not fully understood although several hallmarks of psoriatic skin suggest that aberrant cell signalling via human epidermal growth factor receptors (HERs) may add to the characteristic phenotype. Gene and protein expression of HER members and their ligands are investigated in diseased vs. normal skin using PCR, proximity ligation, Western blot and IHC assays. These studies have shown that HER1-ligands are overexpressed while HER4 is markedly downregulated in psoriatic plaques. Ongoing research focuses at more detailed mapping of epidermal HER4 as potential target for antipsoriatic therapy.

Mast cell apoptosis in psoriatic skin

Ola Rollman, Eva Hagforsen

Mast cells are major effector cells in allergic reactions such as atopic asthma and urticaria. These effects are mainly due to release of histamine from cytoplasmatic granules. More diverse and complex functions of

cutaneous mast cells have recently been recognized in non-allergic diseases such as psoriasis. This inflammatory skin disorder is considered to be partly driven by several proteases and other mediators released from dermal mast cells. We are studying if apoptosis-inducing drugs may be applied to reduce the influence of mast cells in psoriatic skin. Preliminary experiments in collaboration with prof G Pejler (SLU, Uppsala) indicate that such drugs will indeed reduce the number of dermal mast cells and the expression of pro-inflammatory mediators in cultured biopsies of lesional and non-lesional psoriatic skin. Our results support the idea that cutaneous mast cells contribute to the inflammatory process in psoriasis, and that lysosomotropic drugs should be evaluated as pro-apoptotic agents in mast cell-mediated dermatoses.

Immunologic mechanisms in idiopathic inflammatory skin diseases

Mohammad Alimohammadi

One of the major challenges in care of patients with skin disorders is to manage disease symptoms in a disease-specific manner. The majority of dermatologic disorders are today considered as idiopathic although in most of them, a role of the immune system can be observed. For example histological examination of most of skin disorders involve lymphocytic infiltration. Although, the underlying molecular reason for this immune action is rarely contemplated in the routine clinical work.
The overall purpose of this project is to elucidate and understand underlying disease mechanisms and determine biomarkers for diseases that may have autoimmune components. This could lead to better diagnosis and better treatment strategies for these patients. We collect tissue samples, including serum, PBMC and skin biopsies from clinically well characterized patients and use the samples. The collected samples are later examined for signs of autoimmune mechanisms using different autoantibody detection methods such as SEREX, candidate autoantigen approach, cytokine profiling, western blotting and T cell activation experiments.

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Gastroenterology and hepatology

Per M. Hellström

Research in gastroenterology and hepatology is focused on inflammatory reactions in the gastrointestinal tract and liver. From a patient registry (SWIBREG), special attention is given to inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis) and microscopic colitides (collagenous colitis, lymphocytic colitis) as well as sclerosing cholangitis as complication of IBD. Epidemiologic and etiopathogenic perspectives of disease are covered through studies on the commensal microflora and inflammatory reaction in the gut mucosa. Plasma and fecal biomarkers of inflammation are studied and evaluated as regards their usefulness as predictors of disease progression in IBD and sclerosing cholangitis. Special attention is given to the inflammatory aerocrine biomarkers nitric oxide (NO) in rectal gas, circulating biomarkers tumour necrosis factor (TNF), interleukin-1beta, and interferon gamma, as well as interleukin-2 and interleukin-17, metalloproteinases and CXCL2; and fecal eosinophil cationic protein and eosinophil protein X all of which known drivers of an inflammatory process. To this end, regulatory gut peptide functions are studied in IBD as compared to irritable bowel syndrome (IBS). As an extension, diagnostic procedures for prediction of development of malignant liver disease in sclerosing cholangitis are being developed.

A developmental research branch emanating from the IBD concept is *gut permeability* for diagnosis of the "leaky gut syndrome". Exploratory research is focused on a basic methodology to enable rapid and feasible detection of biomarkers for permeability by use of a light emission de-quenching technique to substitute for conventional HPLC, as well as the detection of endotoxin and zonulin in plasma as promoters of IBD and autoinflammatory reactions in the gut.

Metabolic interactions with inflammation are studied focusing on gastric emptying and enteric dysmotility as primary steps in the endocrine cascade after food intake. In broad collaborations, work has been carried out to study the importance of gastric emptying in obesity, bariatric surgery and diabetes, as well as diabetic complications, such as gastroparesis and enteropathy where our experimental studies conclude that the gut peptide hormones ghrelin and motilin and their receptors are ideal for drug development through stimulation of gastrointestinal motility and improvement of metabolic control.

The composite work includes epidemiological, experimental, and clinical studies aiming at delineating events at the molecular and subcellular level leading to relevant clinical research of disease, and identifying diagnostic and predictive markers of gastrointestinal and liver disease.

The aim is to build a gastroenterological research facility with modern immunoassay and molecular biology-based analytical detection systems branching into:

- Clinical research unit for academic and industry-sponsored clinical trials
- Gastroenterology lab unit with basic chemistry and physiology for clinical and investigational studies of pathophysiology in gastrointestinal disease

Select projects

- Epidemiology of IBD and microscopic colitides and complications of disease
- Incidence cohort of patients with IBD for studies of inflammatory mechanisms, microbiota, proteomics and biomarkers
- Nitric oxide, nitrite and nitrate in the inflammatory IBD response
- Fecal microbiota transplantation in IBD and IBS
- Eosinophilic granulocyte activation in IBD.
- The leaky gut syndrome in the context of celiac, IBD and IBS
- Diagnostic and predictive markers of malignant progression in IBD with sclerosing cholangitis

- Regulatory peptide hormones and drug development in gastroparesis and enteric dysmotility
- Regulatory peptide hormones in obesity and metabolic disorders
- Fecal eosinophil inflammatory markers in IBD and sclerosing cholingitis
- Optimized treatment of liver disease with portal hypertension using transjugular intrahepatic portosystemic shunt (TIPSS)
- Optimized detection, treatment and prognostic markers of biliary cancer in sclerosing cholangitis.

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Marie Carlson

ALF	450 kSEK
Bengt Ihre fund	150 kSEK
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Fredrik Rorsman

ALF	150 kSEK

Anders Rönnblom and Mari Thörn

ALF	200 kSEK

Publications 2012-2014

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Molecular Medicine

Ann-Christine Syvänen

The research group in Molecular Medicine headed by Professor Ann-Christine Syvänen was established in 1998 to introduce modern genomic methods into clinical and medical research. Since its start the group has worked towards this goal by creating close collaborations with clinical scientists at Uppsala University and University Hospital and by hosting the SNP&SEQ Technology Platform in Uppsala that offers genotyping and "next generation sequencing" services and training to academic researchers. The Molecular Medicine group is interested in methods for large-scale genomic analyses and applies them to human diseases, with a focus on acute pediatric leukemia and autoimmune diseases. A-C Syvänen also heads the SNP&SEQ Technology Platform, which is part of the National Genomics Infrastructure (NGI) at Science for Life Laboratory. In the beginning of 2014 the Molecular Medicine group and the SNP&SEQ Platform moved from the Research Department at the Academic Hospital to excellent facilities at the Uppsala University Biomedical Centre (BMC).

Epigenetics and genomics of acute leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer in the Western world. Although there has been great progress in treatment protocols for ALL during the past decade, about 20% of the patients do not respond to drug treatment for unknown reasons. In the research project on ALL, the Molecular Medicine group uses genome-wide genotyping and “next generation” sequencing for detection of somatic mutations, analysis of gene expression, DNA methylation and regulatory genomic sequence variation in primary cells from patients with ALL. The aim of the project is to identify genetic and epigenetic signatures that may be used as biomarkers for prognosis of the disease progression and response to treatment in individual patients. The group is also involved in similar research in pediatric acute myeloid leukemia (AML). A second objective of the project is to gain in-sights into mechanisms by which DNA methylation transforms normal hematopoietic cells into leukemic cells, and how DNA-methylation affects treatment responses in acute leukemia. In this project the group is analyzing a unique collection of bone marrow and blood samples from children with acute leukemia, collected in the Nordic countries by the Nordic Society for Pediatric Hematology and Oncology (NOPHO). The project involves a close collaboration with pediatric oncologists at the Children's Hospital in Uppsala. During 2014 the project was funded by the Swedish Foundation for Strategic Research (SSF), the Swedish Cancer Foundation and the Pediatric Cancer Foundation.

From genes to function in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is regarded as the prototype for autoimmune diseases because it involves most immune cells and can affect all organs of the human body. SLE has a strong heritable component. There are about 50 confirmed genetic risk loci for SLE that have been identified by genome-wide association studies and subsequent follow-up studies. By analysis of well characterized Swedish SLE patients, collected by the Swedish Lupus Network, the Molecular Medicine group has contributed to the identification of about half of these loci. The genes at the SLE-associated loci belong to the type I interferon (IFN), B-cell and T-cell signalling pathways. To identify the actual functional, disease-causing alleles in the risk loci for SLE, the Molecular Medicine group uses new technology for second generation DNA sequencing in combination with functional analysis of fractionated human blood cells. The group is also performing epigenetic analysis of DNA methylation and of chemical modifications of histone proteins in immune cells from healthy individuals and patients to elucidate the role of epigenetics in SLE and Sjögren’s syndrome. The project involves a close collaboration with the research group in Rheumatology and the Rheumatology Clinic at Uppsala University Hospital. The project is funded by the Knut and Alice Wallenberg Foundation, the Swedish Research Council for Medicine & Health (VR MH) and the Swedish Research Council for Science &Technology (VR NT).

Large collaborative projects

The Molecular Medicine group participates in collaborative projects, in which its competence in genomic technology is combined with the capacity of the SNP&SEQ Technology Platform for large-scale SNP genotyping and "next generation" sequencing (NGS). The Molecular Medicine group participates in the International ImmunoSeq consortium that studies regulation of gene expression by NGS of regulatory genomic regions in patients with immunological diseases. As partner in the "European Sequencing and Genotyping Infrastructure (ESGI)", the Molecular Medicine group and the SNP&SEQ Technology Platform work together with five other leading European centers to establish and develop "best practice" protocols for NGS. The Molecular Medicine group contributes to ESGI by laboratory protocols for epigenetic analyses and bioinformatics tools for allele-specific gene expression analysis, while the SNP&SEQ Platform offers transnational access to SNP genotyping and NGS to European scientist. The Molecular Medicine group and the SNP&SEQ Platform also contribute to the EU FP7 project Prediction ADR, by NGS to detect genetic variants that cause adverse drug reactions (ADR) in samples from Sweden, the Netherlands and the UK. In 2014 the Molecular Medicine group was invited to join the EU FP7 – funded Blueprint project as an associate partner. Blueprint studies genetic and epigenetic regulation of gene expression in human blood cells. In addition to the EU projects, technology development activities in the Molecular Medicine group are funded by the Swedish Research Council for Science & Technology (VR NT).

For more information see **www.molmed.medsci.uu.se**

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Funding 2014

Swedish Research Council for Science and Technology (VR NT)	0.9 Mkr
Swedish Research Council for Medicine and Health (VR MH)	1.2 Mkr
Swedish Foundation for Strategic Research (SSF) (3 groups)	4.0 Mkr
The Knut and Alice Wallenberg Foundation (KAW) (2 groups)	4.8 Mkr
Swedish Foundation for Cancer Research	1.0 Mkr
Swedish Foundation for Pediatric Cancer Research	0.9 Mkr
European Commission, FP7	2.8 Mkr

Publications 2012-2014

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Renal Medicine

Bengt Fellström

The overall objective of the research is to investigate means and methods for prevention of renal failure, and treatment of complications in renal failure. Our research program involves studies on cardio-vascular complications in chronic kidney disease and renal transplantation, studies on FGF-23 in renal failure, clinical studies on chronic kidney disease and haemodialysis as well as studies on new biomarkers for renal failure. Recently we have also finalized new approaches with regard to pathogenesis and treatment of IgA nephropathy, and commenced new joint venture with the research group in Nanotechnology and Functional Surfaces. A substantial research grant has been approved for development of a new generation of dialysers and new devices for extracorporeal blood treatment. It is our firm belief that the outcome of this research will lead to an improved medical and social rehabilitation of patients with renal failure.

Cardio Vascular Complications in Chronic Kidney Disease and Renal Transplantation

Bengt Fellström, Hans Furuland, Inga Soveri, Eva Carlsson, Hilde Kloster, Liina Vassil

Cardiovascular disease (CVD) is extremely common in patients with renal insufficiency, which includes dialysis and renal transplant patients. Our efforts are targeting the importance of e.g. endothelial dysfunction, oxidative stress, and inflammation as contributing factors to the high rate of CVD. An important part of our efforts is treatment studies,often initiated from our own unit. Such studies include the ALERT trial in renal transplant patients, the AURORA trial in haemodialysis patients, and the SHARP trial in preuremic and dialysis patients. In a new study we are investigating if a low-dose aldosterone blockade by Spironolactone may have a positive effect on cardiovascular morbidity and mortality in haemodialysis patients. We have also initiated a CV study in renal transplant patients studying CV biomarkers while switching from CNI based immunosuppression to a belatacept based regimen. Other trials involve e.g. studies in patients with early IgA nephropathy using a corticosteroid compound acting primarily in the gut (budesonide)

A new line of research in CVD in renal failure includes studies of complement activation, formation of microparticles and screening of inflammatory markers using the multiplex PLA technology. In addition we are also collecting samples such as plasma and vascular tissue for proteomics analysis in collaboration with Prof. J Bergqvist at SciLifeLab. No results are available as yet, but awaiting a substantial amount of data within Q2 2015.

Superb biobanks have been collected with genomic materials from patients participating in the MIMICK , AURORA and ALERT trials, which we have used to analyze genomic aberrations in inflammation-related genes as well as telomere length in DNA material, and shown a striking relationship to the degree of inflammation, oxidative stress, fetuin levels and patient survival in the MIMICK trial.

The role of FGF-23 in phosphate regulation and calcium/phosphate homeostasis in chronic kidney disease

Torbjörn Linde, PerAnton Westerberg

FGF-23 is a secreted growth factor that is produced in bone and circulates in the bloodstream to ultimately regulate phosphate handling and vitamin D production in the kidney. An important pathophysiological role of FGF23 has been implicated in several hereditary and acquired disorders.

Our studies, aiming to understand the molecular mechanisms and the endocrine action of FGF-23, are important for several reasons. Identification of FGF23 down-stream targets within the kidney proximal tubule as well as the parathyroid glands will be critical for understanding the molecular mechanisms of FGF-23 on Pi and vitamin D metabolism. Furthermore, it will provide opportunities to modify FGF-23 signalling and consequently to develop novel drug targets for disorders of calcium and Pi homeostasis.

Biomarkers of renal injury

Jan Melin, Per Venge, Per Sangfelt, Fredrik Rorsman, Bengt Fellström

Acute kidney injury is an increasing problem, and there are many conditions and procedures that put the kidneys at risk. Current markers of renal injury, such as creatine, are unspecific, but new biomarkers that show the actual degree of renal injury are now emerging; e.g. Human Neutrophil Lipocalin/Neutrophil gelatinase-associated lipocalin (HNL/NGAL), Kidney injury molecule (KIM-1), and Cystatin. We are currently evaluating several of these new biomarkers of renal injury in different clinical settings. The ability to identify parenchymal renal injury at a much earlier time than today would be beneficial for the patient, and would allow the physicians to customize the treatment.

Polycystic kidney disease (PKD)

Jan Melin, Hans Furuland, Inga Soveri, Bengt Fellström

A novel research path includes studies of biomarkers for progression of PKD , as well as initiation of a treatment study using Tolvaptan, which was just recently started .

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Publication 2012-2014

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Reviews

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Rheumatology

Lars Rönnblom

Rheumatic diseases are a major cause of morbidity and affect a large proportion of the population. Our research group is organized in three major project groups, which study several aspects of autoimmune rheumatic diseases. The research areas encompass the genetic background to systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS), the regulation of the immune system and mechanisms for loss of tolerance, the clinical picture of psoriatic arthritis and the connection between chronic inflammation and development of lymphoma. Our studies will clarify central autoimmune mechanisms and our ultimate goal is to contribute to the development of improved diagnostic tools and new therapeutic strategies in rheumatic diseases. Members of our group coordinate the Swedish SLE network, the Scandinavian Sjögren's syndrome research network and the national auto-lymphoma study.

Project group Systemic Autoimmunity

Lars Rönnblom, Maija-Leena Eloranta, Gunnel Nordmark.

Identification and functional analysis of risk genes that contribute to loss of immunological tolerance

We have continued to identify new risk loci for SLE and primary Sjögren's syndrome. The work on SLE susceptibility genes has been done in collaboration with Prof. Syvänen's and Prof. Lindblad-Toh's research groups and with the contribution of the Swedish SLE network..

In March 2014 we launched a collaborative project, for which Lars Rönnblom is the PI, between AstraZeneca and SciLifeLab. The project is entitled "Dissecting disease mechanisms in three systemic inflammatory autoimmune diseases with an interferon signature –DISSECT". The overall aim of the study is to identify molecular pathways in sub phenotypes of three systemic inflammatory autoimmune diseases which share the type I interferon signature in blood and target organs. This will be achieved by combining genetic studies with functional cellular studies in well characterized cohorts. In DISSECT we aim to perform targeted sequencing of 1900 genes in 1000 patients each for the diseases SLE, Sjögren's syndrome and myositis, as well as 1000 common control individuals. This is being done together with the Swedish SLE network, the Scandinavian Sjögren's syndrome network, the European myositis network, the Lindblad-Toh research group and the SciLifeLab National Genomics Infrastructure Uppsala node. During 2014 targeted sequencing was completed in DNA from 2000 patients and healthy control individuals.

We have participated in the first genome wide association study (GWAS) in primary Sjögren's syndrome in collaboration with K. Sivils, USA. A strong association with HLA was established, together with six non-HLA loci at genome wide significance level ($p<5x10-8$). We have continued our collaboration including additional patients and controls as well as collected phenotype data for a follow up GWAS study. Epigenetic studies of whole genome DNA methylation in different cell types and tissues from patients with primary Sjögren's syndrome have been performed. A distinct hypomethylation of interferon-induced genes has been found in multiple cell types.

Regulation of the type I interferon response by immune cells

We have continued to characterize autoantibodies to NKG2A and NKG2C in patients with SLE, and investigated the prevalence of these autoantibodies in large SLE, pSS and systemic sclerosis cohorts. The anti-NKG2A and anti-NKG2C autoantibodies impaired the NKG2A-mediated inhibition and NKG2C-mediated activation of NK cell activation, respectively. These autoantibodies could also deplete NKG2A or NKG2C expressing target cells through antibody-dependent cellular cytotoxicity. The presence of anti-NKG2A autoantibodies was associated with high SLE disease activity and damage index, as well as

increased serum IFN-α levels in SLE patients (Hagberg, Rheumatology, 2013 and Hagberg, Arthritis and Rheumatology, 2014). Taken together these studies highlight the importance of NK cells and their interaction with pDC in regulation of immune response in patients with SLE and other autoimmune diseases.

Bioresource of healthy blood donor samples

Uppsala Bioresource is a permanent resource of 2000 genotyped (200K Immunochip, Illumina) healthy blood donors visiting the Uppsala Blood Transfusion Center, Uppsala University Hospital. An imputation pipeline for genotype beyond the SNPs analyzed is established and has been applied, as well as physically verified in the laboratory, for the HLA gene region. Genetic risk for several of the autoimmune diseases has been shown to depend heavily on the HLA region, making this bioinformatic achievement a major advantage when choosing appropriate donors of fresh leukocytes for functional studies of the immune system. Blood, DNA, serum and for individuals with selected genotypes also cryopreserved cells are the biological samples collected, forming a sample collection within Uppsala Biobank. Fresh buffy coats of relevant genotypes are achieved upon demand. Sex, year of birth and data on past and present smoking habits are available data for the participants.

In a study by Berggren et al (submitted 2014) we investigated whether SNPs associated with SLE and other autoimmune diseases affect the IFN-α production in healthy individuals. The isolated pDCs were stimulated with RNA-containing immune complexes and the IFN-α levels were correlated with the individuals' genotype. The study showed several associations between SLE-risk alleles and the IFN-α levels. In Temporal Change Project, a collaborative effort with McGill University, Montreal: *Variability and stability of the epigenome and transcriptome within and between individuals over time* our permit for repeated sampling of selected individuals has been taken advantage of. Cells dedicated for DNA sequencing, epigenome analysis, transcriptome studies and chromatin analysis are collected up to four times for each individual, enabling conclusions on stability versus variation over time in the molecular setups of the blood cells of healthy individuals.

Project group Eva Baecklund

Studies of associations between inflammatory rheumatic diseases and malignant lymphomas

Clinical, immunological and genetic studies of granulomatosis with polyangiitis

Studies of anemia and liver complications in patients with rheumatoid arthritis

Eva Baecklund, Ann Knight, Carin Backlin, Lilian Vasaitis, Karin Hellgren, Amelie Kinch, Karin Hjorton, Johan Back, Johanna Sundbaum

We have continued the studies of associations between inflammatory diseases and lymphoma development with focus on RA, Sjögren's syndrome and safety follow-ups of new biologic drugs used in rheumatic diseases. A comparative study of patients with lymphoma after organ transplantation has been published. The AUTO-LYMPHOMA study has continued successfully during 2014 and now includes more than 100 patients with an autoimmune/inflammatory disease and an incident lymphoma and follow-up with collection of blood and lymphoma tissue for immunological and genetic studies.

In addition, our research group has ongoing projects covering some common clinical problems in rheumatology. We have finished a study of efficacy and safety of rituximab as maintenance therapy for relapsing granulomatosis with polyangiitis. A detailed study of anemia in patients with RA is ongoing as is a study of liver complications in RA patients treated with methotrexate which includes genetic studies in cooperation with the SWEDE-GENE study and comparisons with psoriatic patients. Furthermore our group participates in a national vasculitis project with the aim is to study clinical therapeutical and genetic

implications of small-vessel vasculitis. For the genetic part of the project, where Uppsala has a leading role, the collection of blood samples from other participating centers is accomplished and analysis ongoing.

Project group Ulla Lindqvist

Psoriatic arthritis; pathophysiological and clinical studies in early and manifest disease

Ulla Lindqvist, Peter Matt, Sandra Kleinau, Dan Henrohn

The background for the clinical and experimental scientific work is our 10 years old cohort of early PsA, the early Swedish Psoriatic Arthritis Register (SwePsA) consisting of 360 patients. Clinical data, outcome and results of 5 years follow up has been published 2013 in Ann Rheum Dis as an extended report. We recently published a study on inflammation in skin present in different PsA classification groups and could show that there is a gross pathology of hyaluronan (HA) in both involved and non-involved psoriatic skin. Our future work is focusing on the inflammatory effect of low molecular mass of HA in different sites of inflammation in active polyarticular PsA. There are signs of autoimmunity in PsA with existing low titres of autoantibodies to rheumatoid factor and ANA which has led to ongoing studies on fc receptors in polyarticular PsA by Peter Matt. Within a Nordic research group, the most destructive form of PsA, arthritis mutilans, is being studied with focus on genetics and phenotype of this classification group. We have so far reported the prevalence in the Nordic countries to be 3.69 per 1,000,000 inhabitants. PAM in the Nordic countries has a low prevalence. The majority of the patients present with mild skin disease compared to poly-deformed joints.

Members of Rheumatology research group during 2014

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Maija-Leena Eloranta
King Gustav V 80 year foundation 100 kSEK
Swedish Rheumatism Society 100 kSEK

Eva Baecklund/Ann Knight
ALF grant 310 kSEK

Eva Baecklund
Swedish Cancer Society 500 kSEK
Selanders foundation 100 kSEK
Swedish Rheumatism Society 150 kSEK

Ulla Lindqvist
SIDA 560 kSEK
ALF grant 100 kSEK
Wyeth 50 kSEK

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Dissertations 2014

Dag Leonard: Cardiovascular Disease and Immune Mechanisms in Systemic Lupus Erythematosus

Niklas Hagberg: The Role of Plasmacytoid Dendritic Cells and Natural Killer Cells in Systemic Lupus Erythematosus

Clinical Microbiology and Infection Medicine

The section for Clinical Microbiology and Infection medicine consists of several individual groups with the common overall aim to combat emerging and re-emerging infectious diseases. The challenge of infection is quite unlike any other disciplines in medicine, as it goes beyond the boundaries of knowledge about mankind, requiring a broad perspective on human in relation to nature, an insight in the biology of the microorganism, a deep understanding of the host parasite interactions as well as a humanistic approach on the individual patient. The profile of the research groups has this plethora with the wide spectrum from the individual patient at one end, to the infectious diseases in a changing world at the other.

Clinical Microbiology

Hilpi Rautelin

Clinical Microbiology consists of five independent research groups that work with different pathogens, both bacteria such as *Campylobacter* and *Chlamydia*, and viruses such as retroviruses and Hepatitis C virus. The main goals are to understand the epidemiology and the pathogenicity of these pathogens, and to improve both diagnosis and treatment of these infections as well as to focus on preventive measures.

Campylobacter infections and intestinal microbiota

Hilpi Rautelin, Patrik Ellström, René Kaden, Christian Kampmann, David Lennebratt, Akofa MacKwashie, Anna Nilsson, Anders Lannergård, Astrid Skarp, Erik Torell, Lars Engstrand,

Our research strategy is based on three approaches to study human campylobacteriosis. Firstly, for bacterial characteristics, a genetic approach is used to search for virulence and pathogenicity mechanisms of *Campylobacter* and a phenotypic approach to study the role of them. Modern molecular methods including whole genome sequencing are used. Secondly, for human host characteristics, the role of the human intestinal microbiota is studied with emphasis on the colonization resistance to *Campylobacter* infection, on one hand, and the impact of *Campylobacter* infection on the intestinal microbiota, on the other hand, along with human host response parameters. Thirdly, the molecular mechanisms and the connection between the defined bacterial and host characteristics are studied in an *in vitro* infection model. Our approach increases understanding of the pathogenicity of Campylobacter at a molecular level and helps to direct preventive measures. We recently showed, for the first time in humans that, the fecal microbiota composition was associated with susceptibility for *Campylobacter* infection and that *Campylobacter* infection had long-term effects on the fecal microbiota composition.

Exo- och endogenous retroviruses, and development of new diagnostics

Jonas Blomberg, Christina Öhrmalm, Amal Elfaitouri, Vidar Blikstad, Anna Sjösten, Agnes Bölin-Wiener

We study the occurrence of both exo- and endogenous retroviruses, develop new diagnostics, and are engaged in the safety issues during blood transfusions and transplantation. We have a unique database of retroviruses, as well as unique bioinformatics tools, so we are well positioned to develop diagnostic tests for these viruses. We investigate if some of them are associated with the chronic fatigues syndrome. We have continued to work with our, now patented, multiplex nucleic acid based assay Variation tolerant Capture Multiplex Assay; VOCMA. In addition, a new type of multiplex serological test for IgG and IgM antibodies has been developed and used on sera from blood donors and patients suffering from the chronic fatigue syndrome.

Chlamydial infections in humans and birds

Björn Herrmann, Jenny Isaksson, Kristoffer Strålin, Guma Abdeldaim.

Our group has developed a high-resolution typing system that enables epidemiological investigations of the spread of *Chlamydia trachomatis* in sexual networks and populations. The method is now applied in many countries and increases the knowledge of distribution mechanisms as well as evaluation of antibiotic mass-treatment of trachoma. The spread of *Chlamydia psittaci*, a high-risk pathogen, from wild birds to humans is not well understood. In collaboration with the group of Björn Olsen, *C. psittaci* infections in birds and their role for zoonotic disease are investigated. An additional research topic in our group is the detection and identification of bacteria causing respiratory tract infections.

Antiviral treatment and resistance

Johan Lennerstrand, Assar Bergfors, Bhavya Kolli, Dennis Leenheer, Anders Lannergård

In collaboration with many local and international scientists, our group focuses on the following themes:

1. Prevalence of natural Hepatitis C virus resistance to protease-NS3 and NS5A inhibitor drugs in untreated patients. 2. Ultra deep-sequencing detection of Hepatitis C virus resistance to NS5A and NS5B non-nucleoside inhibitors. 3. Tracing Hepatitis C virus transmission in the Uppsala region. 4. Novel technology platform for measuring various deoxynucleoside kinase activities in drug resistance monitoring of acute myeloid leukemia (AML). 5. Novel Dengue and TBE virus drug screening assays. 6. Biochemical mechanism of HIV RT resistance to nucleoside analogs.

Infection Prevention and Control

Birgitta Lytsy, Anna Hambraeus, Ulrika Ransjö

Our group focuses on clinical microbiological diagnostics and surveillance of resistant bacteria, infection prevention and control, and antibiotic use. In different projects, local and international collaborators and networks are involved.

Members of the groups during 2014

Guma Abdeldaim, scientist
Assar Bergfors, scientist
Vidar Blikstad, PhD-student
Jonas Blomberg, prof. emer.
Sabine Gravelsina, scientist
Lars Engstrand, professor
Anna Hambreus, Senior advisor
Björn Herrmann, assoc. prof.
Jenny Isaksson, research engineer
Magnus Jobs, scientist
René Kaden, scientist
Christian Kampmann, PhD-student
Johan Lennerstrand, assoc. prof
Birgitta Lytsy, scientist
Anna Nilsson, PhD-student
Ulrika Ransjö, senior advisor
Hilpi Rautelin, professor
Bengt Rönnberg, scientist
Astrid Skarp, scientist
Hongyan Xia, scientist
Christina Öhrmalm, scientist

Funding 2014

FORMAS	1.9 MSEK
VR	0.5 MSEK
ALF	1.2 MSEK

Publications 2012-2014

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Infectious diseases

Jan Sjölin and Otto Cars

The principal research fields of the group are the host response to infection and antibiotic treatment, especially the treatment of resistant bacteria

Interplay between antibacterial and antifungal treatment and innate and specific immunological responses in severe infections

Mia Furebring, Elisabeth Löwdin, Miklos Lipcsey, Markus Castegren, Eva Söderberg, Paul Skorup, Magnus von Seth, Jesper Sperber. Axel Nyberg, Anna Hedberg, Siri Kurland, Frida Wilske, Katja Hanslin, Eva Tano, Jan Sjölin

The overall aim is to study the interplay between treatment and innate and specific immunological responses in severe sepsis and septic shock as well as in bacterial infections in the central nervous system. Translational projects involving clinical studies, in vitro experiments and intensive care animal models as clinically relevant as possible with the use of sedation, mechanical ventilation, vasopressors all known to influence the inflammatory response. Animal experiments focus mainly on clinical issues that cannot be solved by randomized clinical trials.

During 2014 the antibiotic-induced endotoxin release in septic shock has been studied in our intensive care porcine primary septic shock model using healthy animals in order to investigate the subsequent effect on the inflammatory response. In vitro a substantial endotoxin release is observed after treatment with beta-lactam antibiotics and this is reduced after the addition of an aminoglycoside. However, these data were not reproduced when investigated in vivo because of a rapid elimination of bacteria. In spite of this, cephalosporin treatment was associated with a larger increase in the inflammatory response. In another study that was completed during the year labelled albumin was given either as a bolus or a short infusion to previously healthy animals with septic shock and the effect on clinical parameters as well as the extravasation of albumin which was measured by the use of microdialysis.
To more closely mimic the clinical situation in the intensive care unit we have also developed a secondary sepsis model by using the biological effects of endotoxin tolerance. Using this model we found an impaired ex vivo bacterial clearance in comparison to animals with primary sepsis. Despite this, clinical symptoms seem to be less intensive but this is further investigated in an ongoing study. We have also initiated the development of a tertiary sepsis model, in which the inflammatory response is blunted by an endotoxin-induced anti-inflammatory response in combination with steroid treatment, thus even enabling the establishment of candidemia. In addition, we are now in the possession of a model of ventilator-associated pneumonia. In order to better understand the negative results of clinical trials on immunomodulating therapy for the adjunctive treatment in septic shock, the temporal development of the inflammatory response seems to be important to take into consideration. The present models will increase our knowledge and ability to conduct clinical trials. In addition, a retrospective study on sepsis in intensive care patients looking at the clinical definitions of primary, secondary and tertiary sepsis has been analyzed and submitted for publication.
In clinical studies the effect of the systemic inflammatory response on pharmacokinetics of antibiotics and antifungals has been initiated in 2014. In other studies that have been published in 2015 or accepted for publication, we have in 2014 studied 1) the effect of tigecycline, an important antibiotic in the treatment of resistant bacteria, on the inflammatory response (Shock) and 2) organ specific cytokine production after protective and traditional ventilation in experimental primary sepsis (Pulmonary Medicine). Furthermore, in a clinical study we have investigated 3) the effect of neurosurgical trauma and the innate immune response on the specific immunity by vaccination of patients with T-cell dependent and T-cell independent vaccines (Infection); and in registry studies 4) the effect on antibiotic treatment and outcome by early recognition of the inflammatory response in the treatment of community-acquired meningitis (Clinical Infectius Diseases and 5) the effect of the qualification of the first line physician (Clin Microbiol Infect).
Clinical studies evaluating the effect of the systemic inflammatory response on pharmacokinetics of antibiotics and antifungals change has been initiated during the year. Furthermore, the work with the development of a new pharmacodynamic biofilm in vitro model has continued.

Improved antibiotic therapy for multidrug-resistant bacteria

Otto Cars, Thomas Tängdén, Pernilla Lagerbäck, Anna Hallgren, Hanna Montelin

The increasing prevalence of multidrug-resistant Gram-negative bacteria is of great clinical concern. Due to the dry pharmaceutical pipeline, efforts are urgently needed to optimize the use of existing antibiotics that might still be active against these bacteria. The overall purpose of the project is to improve the antibiotic treatment of infected patients. A multicenter, observational, clinical study of urinary tract infections caused by ESBL-producing Enterobacteriaceae is conducted in collaboration with 20 infectious diseases clinics in Sweden. Clinical outcome include clinical cure, microbiological cure and relapse. Isolated strains will phenotypically and genotypically characterized, and further explored for antibiotic susceptibility in vitro.

Bacterial killing of single antibiotics as well as combinations of two or three antibiotics are evaluated in vitro with the standard time-kill method as well as the automated systems oCelloScope and BioscreenC. In these experiments, multidrug-resistant strains are exposed to clinically relevant static or dynamic antibiotic concentrations. Bacterial killing and emergence of resistance during antibiotic exposure are evaluated. Further, the in vitro data are used to create mathematical models (in collaboration with the pharmacometrics groups at Uppsala University) that can predict the antibacterial effects of alternative dosage regimens. A large-scale screening for effective antibiotic combinations against carbapenem-resistant Enterobacteriaceae, Pseudomonas and Acinetobacter is ongoing.

Recent studies have demonstrated synergistic and bactericidal effects of combinations including colistin, meropenem, rifampicin, aztreonam, tigecycline and other antibiotics against carbapenem-resistant strains, despite that the bacteria are often highly resistant to the single antibiotics. Resistant mutated subpopulations emerged frequently in ESBL-producing E. coli and K. pneumonia during exposure to ertapenem in time-kill experiments, and new PK/PD targets as well as alternative dosage regimens were suggested based on the results of mathematical modeling. These findings have clinical implications in the treatment of patients infected with multidrug-resistant bacteria for which there are few or no effective therapeutic options.

Cytomegalovirus infections

Britt-Marie Eriksson, Fredrik Sund, Gabriel Westman

CMV specific and general T-cell immunity has been studied in healthy immunocompetent persons, in infants with congenital or postnatal infection, in renal transplant patients and in patients with Alzheimer´s disease.

In our latest studies on Alzheimer´s disease, which also involve antibody responses towards different viruses in the Herpes group and amyloid-beta, CMV specific and general T-cell immunity was studied in 50 patients with Alzheimer´s disease and in 50 age-matched controls. Our hypothesis was that persons with Alzheimer´s disease have an aged immune system with an immune profile corresponding to that seen in the very old with an inversed CD4:CD8 ratio and a shift from naive T-cells to memory T-cells. Unexpectedly a decreased proportion of Cytomegalovirus specific CD8 T-Cells but no signs of general immunosenescence were seen in Alzheimer's Disease.

The incidence of primary CMV-infection and clinical outcome was evaluated over a 10-year period in 104 CMV high-risk renal transplant recipients with low-dose valacyclovit prophylaxis. The risk of severe CMV disease, graft loss or mortality was not higher in this group compared to a large number of patients in an European data-base. In an ongoing study on pancreas transplant recipients, protocol biopsies of duodenum connected to the transplant are examined regarding CMV infection. The results will be related to different kinds of antiviral prophylaxis.

In another ongoing collaborative study, enteric biopsies have been collected from patients with newly diagnosed inflammatory bowel disease (IBD). Patients with irritable bowel syndrome serve as controls. The purpose is to find out if CMV has a pathogenic role in IBD from start or is reactivated in patients treated with immunosuppression. Also, viral presence in biopsies is compared to the amount of viral DNA in faeces.

Study of the innate and adaptive immune defense in elderly and patients with cancer, post allogeneic stem cell transplantation and solid organ transplantation and New biomarkers for diagnostics of bacterial and viral infections.

Karlis Pauksens, Amelie Kinch, Gunilla Enblad, Eva Bäcklund, Daniel Molin, Åke Berglund, Helene Hallböök, Honar Cherif, Daniel Garwitz, Per Venge, Lena Douhan-Håkansson

Special interests are focused on the role of Ebstein-Barr virus (EBV) and the development of post-transplant lymphoproliferative diseases (PTLD). In a large nationwide case series of PTLD following solid organ transplantation, we are investigating if the tumor cell derives from the recipient or the donor and how they differ in PTLD subtype, clinical characteristics and survival. The PTLD specimens will either be analyzed by fluorescence in situ hybridization (FISH) for the X and Y chromosome or by HLA typing of the tumor tissue. Tumor-infiltrating regulatory T-cells (Tregs) are associated with better prognosis for certain lymphoma entities, but knowledge on their role in PTLD is limited. We have investigated the association between the expression of the Treg marker FoxP3 (forkhead box protein 3) in biopsies of PTLD and survival, PTLD subtype, and clinical characteristics in a nationwide case series of 74 PTLD after solid organ transplantation in Sweden. We found that intratumoral FoxP3+ Tregs are rare in PTLD, possibly because of heavy immunosuppression, and that the frequency of FoxP3+ cells did not influence overall survival. Further, we are investigating the frequency of Tregs in T-cell lymphomas gathered from Sweden and Denmark. The material has previously been analyzed regarding presence of EBV in lymphoma tissue and blood.

Human neutrophil lipocalin (HNL) is released from neutrophils upon activation. As measured in blood, HNL was previously shown to have a great potential as a diagnostic means to distinguish acute infections caused by bacteria or virus. A distinction that could guide in the treatment of the infection with antibiotics or not. The current project was conducted to confirm these results in larger cohorts of patients and also to test new test procedures that might be even more specific. The results showed a distinction between bacterial and viral infections that was superior to any other contemporary biomarker and should be clinically useful when developed as a point-of-care assay. Hitherto approximately 700 subjects have been included.

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Dissertations

Amelie Kinch: Posttransplant Lymphoproliferative Disorders : Studies of Epstein-Barr Virus, Regulatory T Cells and Tumor Origin

Infection medicine

Björn Olsen

During 2014 Professor Björn Olsen, Professor Åke Lundkvist, MD, PhD Erik Salaneck and MD, PhD Josef Järhult have been instrumental in building up "The Zoonosis Science Center" at BMC, IMBIM. This joint venture has created an arena for theoretical and practical research in all aspects of zoonotic infections. Therefore, we have associated researchers from a plethora of disciplines such as human and veterinary medicine, ecology, and molecular biology and virology. From the first initiative taken in early spring 2014 we are now an established part of the high diversity of research within the medical faculty in particular and Uppsala University in general. By generous support partly by the medical faculty we are increasing our strength with a high security laboratory (BSL 3) that will be working from the autumn 2015. There we will be able to conduct high quality research on pathogens as haemorrhagic fever virus, influenza virus of higher pathogenicity and particular hazardous bacteria.

We have also created an online forum www.onehealth.se and an open access journal (www.InfectionEcologyandEpidemiology.net), under the same name, to publish papers, share ideas and raise awareness of its work among politicians, industry and to the wider public. The journal is open access and publication has been free of charge for the first three years. We are searchable via pubmed and will receive the impact factor beginning of 2015. The preliminary and unofficial impact today is 2.34. Since we are a One Health journal we are encouraging scientific reports from low income countries.

Influenza

Josef Järhult, Neus Latorre-Margalef, Conny Tolf, Anna Gillman, Jonas Waldenström, Per Eriksson and Björn Olsen

During the last century, Influenza A virus (IAV) caused three pandemics. In 1918-1920, the Spanish Flu killed at least 50 million people. All pandemic viruses contain avian genetic material achieved through a reassortment process. There are two different strategies used in treatment and prophylaxis of IAV: 1) Vaccines are effective but the production of vaccines is slow, 2) antiviral drugs like the neuramidase inhibitors oseltamivir (OC) (Tamiflu) and zanamivir (ZA) (Relenza) are the options in the early phase of a pandemic. OC is stable in water and not removed or degraded in sewage treatment plants. In the downstream water ducks, the natural reservoir of IAV, are exposed to OC resulting in resistance induction of viruses in their gastrointestinal tract. With mallards as an animal model and by virological, chemical and molecular techniques we have detected induction of resistance in IAV and retention of resistance mutations in repeated replications and transmission without drug pressure. Our results will be of value for organizations and authorities working with strategic pandemic preparedness planning, like WHO.

Campylobacter and other gastrointestinal pathogens

Patrik Ellström, Petra Griekspoor, Jenny Olofsson, Jonas Waldenström, Björn Olsen

Epidemiologically, Campylobacter bacterium is still a conundrum. On one hand the bacterium is considered as sensitive to environmental stress, while on the other hand it is widely distributed in several host species. Furthermore, despite efforts we have not found efficient ways of reducing prevalence of the bacteria in our farm animals and not fully understood re-colonization after stock rotations. Together with continuing studies of Campylobacter in the natural reservoirs we have taken a new grip on the epidemiology of Campylobacter. Further, by collaboration with British researchers we have conducted whole genome sequencing of C. jejuni to get information of the genetic thresholds behind the different infectivity of certain genotypes in different vertebrate species. Building on the knowledge gained, we will use our own novel epidemiological tools, and some of the latest state of the art techniques to explore a very promising unresolved epidemiological pathway – the role of protozoan as intermediate hosts for survival in the environment. This pathway will be complemented with a population genetic characterization of campylobacters from humans, farm animals, wild birds and water using the technique of multilocus sequence typing on a unique collection of strains.

Spotted fever rickettsiosis; diagnostic procedures, prevalence in vector and mammal hosts and association to clinical disease

Karin Elfving, Katarina Wallmenius, Anders Lindblom, Carl Påhlson, Kenneth Nilsson

The spotted fever group of rickettisae has a world-wide distribution and different species are established depending on the geographic area. Migrating birds may however contribute to a long-distance dispersion of bacteria, and also to an inflow of novel and potentially pathogenic rickettsia species into countries. In Sweden, Rickettsia felis and Rickettsia helvetica have been reported. R. felis is usually transmitted by fleas while R. helvetica is the only tick-transmitted rickettsia found free in nature where the tick Ixodes ricinus represents the most important potential vector and natural reservoir. Several studies have shown that patients may present a flu-like self-limiting mild febrile disease sometimes with prolonged fever as well as subacute meningitis or perimyocarditis, The pathogenic role of the organism has to be further studied, as well as the pathways of transmission, natural hosts and it´s relation to clinical disease. One study describes rickettsial species in ticks from 29 different areas in Sweden. R. helvetica is the most prevalent and is found endemic in tick populations and there is a need to consider infections when investigating disease after a tick bite. Growth characteristics and morphology of R. helvetica were also studied to better understand invasiveness and virulence. The findings indicate that the invasiveness is comparable with other rickettsia, though R. helvetica seems to have a stable but slightly slower growth.

Tick borne infections

Erik Salaneck, Göran Günther, Mats Lindeborg, Tove Hoffaman, Björn Olsen

Birds fly. This fact makes them extremely important as vehicle and transmitters of various parasites and potential carriers of pathogenic microorganisms. The new concept ”ornithological-medicine” is a research area that will give new insights into the ecology, epidemiology and infection biology of vector borne infections in general and tick born infections in particular. A basic knowledge on the mechanisms of the spread of and occurrence of zoonoses will be very important for agriculture and veterinary medicine. Borrelia spp and Ehrlichia spp. can cause serious infections in animals and humans and therefore basic research on the biology, pathogenicity and virulence of tick borne zoonoses is important. We will study the importance of seabirds and terrestrial birds in the dispersal of the tick borne pathogens. Further, by developing infection models we can study the interaction, virulence, pathology and infection biology between host, vector and microorganism.

Antibiotic Resistance

Karin Bergström, Jonas Bonnedahl, Badrul Hasan, Johan Kaarme, Birgitta Lytsy, Johan Stedt, Susanne Sütterlin, Åsa Melhus, Eva Tano, Björn Olsen, Johan Kaarme

The main force behind emergence of antibiotic resistance is the use of antimicrobial agents in human and veterinary medicine and domestic animal husbandry, providing a strong selection pressure for bacteria to acquire resistance. However, there is also evidence that epidemic spread of drug-resistant bacteria and horizontal transfer of resistance genes are contributing factors to resistance emergence. It is important to realize that there are no closed systems – the bacteria we select for in environments close to humans will, back and forth, find their way to bacterial communities in nature and vice versa. In recent studies, we have shown the presence of antibiotic resistant bacteria in areas lacking antibiotic usage. This strongly indicates that the resistance emergence in countries like Sweden, are not only governed by national concerns but also by what happens in a larger context. The knowledge of antibiotic resistance in the environment is limited and we need to explore this field and link it to consumption of antibiotics in our societies. We have brought together experts in different fields to evaluate how bacterial resistance is transferred and maintained within all potential reservoirs, including humans, domestic animals, wildlife and the environment. Our strengths complement each other in terms of methodological and practical skills, and in our joint team we have physicians, veterinarians, ecologists, micro- and molecular biologists, and chemists. Further, we harbour valuable sets of bacterial collections from different reservoirs that are a good foundation for comparative studies.

Members of the groups during 2014

Anders Lannergård, MD, PhD
David Lennebratt MD PhD student
Björn Olsen, MD PhD, Professor
Åsa Melhus, PhD, MD, Assoc. Professor
Anders Bergqvist, PhD
Kåre Bondeson, MD PhD
Marie Edvinsson MD, PhD
Christian Ehrenborg MD, PhD
Patrik Ellström PhD, Assoc. Professor
Katarina Engdahl, PhD-student
Anna Gillman, PhD-student
Karolina Gullsby, PhD-student
Badrul Hasan, PhD
Eva Haxton coordinator, Ph Lic
Jorge Hernandez, PhD
Jenny Isaksson, Research engineer
Eva Tano, PhD student
Tove Hoffman, PhD student 2015
Per Eriksson PhD student 2015
Göran Gûnther, MD, PhD
Josef Järhult, MD, PhD
Johan Kaarme, MD, PhD-student
Lisa Labbé Sandelin, PhD student
Anders Lannergård, MD, PhD
Heidi Lindbäck, PhD-student
Mats Lindeborg, MD, PhD student
Carl-Johan Neiderud, MD, PhD-student
Kenneth Nilsson, MD, PhD, Assoc. Professor
Christina Nyström-Rosander MD, PhD
Arsene Nzobandora, MD, PhD-student
Jenny Olofsson, PhD student
Gustaf Starlander, PhD-student
Susanne Sütterlin, MD, PhD student
Eva Tano, BMA
Erik Torell, MD, PhD
Katharina Wallménius, PhD student

Funding 2014

VR	2.3 MSEK
FORMAS	3 MSEK
ALF	1.4 MSEK
Karin Korsner Foundation	0.15 MSEK
Olle Engkvist Foundation	3 MSEK

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Dissertations 2014

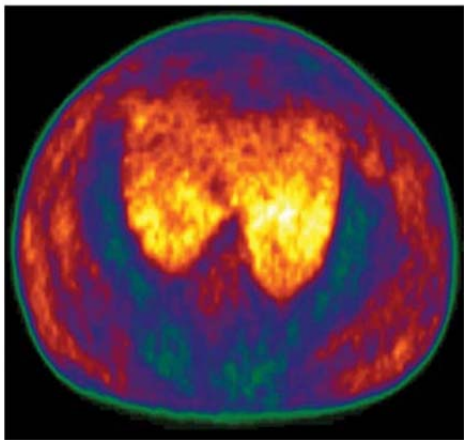
Jorge Hernández: Human Pathogens and Antibiotic Resistant Bacteria in Polar Regions

Johan Stedt,. Antibiotic resistance markers in different environmental matrices. (Linnaeus University)

Petra Griekspoor,. Phylogenetic studies of Campylobacter jejuni. (Linnaeus University).

Cardiology and Clinical physiology

The organization consists of three separate groups performing research in ischemic heart disease and heart failure, arrhythmia and cardio-pulmonary aspects in acute and chronic lung disease, respectively. In ischemic heart disease the focus is on Acute Coronary Syndromes, heart failure and atherothrombotic disease in general. A major part of the work is the evaluation of treatments by performing large clinical trials and by quality registry based evaluation of treatments in clinical routine. In cardiac arrhythmia there are two main research projects: Atrial Fibrillation - assessment of Mechanism and novel Interventional Therapies, and Molecular investigation of Inherited Cardiac Arrhythmogenic Syndromes. In the area of clinical physiology focus is on impeded lung function during anaesthesia and in acute respiratory failure, with an increasing orientation towards lung inflammation.



Cardiology

Bertil Lindahl

The research group has three main lines of research: ischemic heart disease and especially acute coronary syndromes; atrial fibrillation and stroke prevention and heart failure, including pulmonary hypertension. In each of these three areas we are working on different levels in order to be able to ultimately improve the treatment and management of the individual patient. The research group participates in several national and international research collaborations and have leading positions in several of those.

Below are some examples of research group published in 2014.

Understanding the disease(-s) and the unmet needs

In 2014 we published in Heart the so far largest study of type 2 myocardial infarctions . Among 20.138 hospitalizations of acute myocardial infarction in Sweden, 7.1% of the infarctions were classified as type 2 AMI. These patients were older, predominantly women and had more comorbidities. Invasive treatment strategies and cardioprotective medications were less used. Patients with type 2 AMI had higher crude mortality compared with type 1 patients with MI. However, after adjustment, the 1-year mortality was similar.

In a study published in American Heart Journal elderly (80 years or older) patients with ST-elevation myocardial infarction (STEMI) were studied. The use of primary percutaneous coronary intervention (PCI) in this high-risk population remains poorly investigated. Using the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), 4,876 consecutive patients with STEMI 80 years or older undergoing primary PCI during a 10-year period were identified. The prognosis was relatively unchanged during the 10-year inclusion period, despite changes in patient characteristics and treatment. Advanced age increased the risk of adverse events, but survivors of the early phase after PCI had a slightly improved prognosis compared with the general population.

Diagnosis, risk assessment and tailoring of treatment

High-sensitivity troponin-I (hs-TnI) measurement improves risk assessment for cardiovascular events in many clinical settings, but the added value in atrial fibrillation patients has not been described. Therefore, troponin I was measured in 14 821 atrial fibrillation patients in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. The study published in Circulation showed that Troponin-I was detected in 98.5% and elevated in 9.2% of atrial fibrillation

patients. The hs-TnI level was independently associated with a raised risk of stroke, cardiac death, and major bleeding and improves risk stratification beyond the CHA2DS2VASc score.

The unique study, “Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data”, was published in Lancet. The aim was to investigate whether the benefits of blood pressure-lowering drugs are proportional to baseline cardiovascular risk, to establish whether absolute risk could be used to inform treatment decisions for blood pressure-lowering therapy, as is recommended for lipid-lowering therapy. The results showed that lowering blood pressure provides similar relative protection at all levels of baseline cardiovascular risk, but progressively greater absolute risk reductions as baseline risk increases. The results support the use of predicted baseline cardiovascular disease risk equations to inform blood pressure-lowering treatment decisions.

Evaluation of treatments and other interventions

The innovative Register based randomized clinical trial, Taste, was presented 2013 and the concept of registry-RCT got world wide attention. The one-year results of the Taste study was published in New Englan Journal of Medicine 2014. The study randomly assigned 7244 patients with STEMI to undergo manual thrombus aspiration followed by PCI or to undergo PCI alone. Routine thrombus aspiration before PCI in patients with STEMI did not reduce the rate of death from any cause or the composite of death from any cause, rehospitalization for myocardial infarction, or stent thrombosis at 1 year. The results were consistent across all the major subgroups, including grade of thrombus burden and coronary flow before PCI.

A study evaluating the effect of quitting snus after myocardial infarction was published in Circulation. After adjustment snus quitters had half the mortality risk of post-MI continuing snus users (hazard ratio, 0.57; 95% confidence interval, 0.32-1.02). Thus, discontinuation of snus use after an MI was associated with a nearly halved mortality risk, similar to the benefit associated with smoking cessation.

Miscellaneous

Members of the group have also participated in work with national and international clinical guidelines and published educational articles and reviews (see below).

Members of the group during 2014

Bertil Lindahl, Professor

Lars Wallentin, Professor emeritus

Stefan James, Associate professor

Jonas Oldgren, Associate professor

Claes Held, Associate professor

Gerhard Wikström, Associate professor

Bo Lagerqvist, Ph.D.

Erik Björklund, Ph.D.

Christina Christersson, Ph.D.

Emil Hagström, Ph.D.

Nina Johnston, Ph.D.

Kai Eggers, Associate professor

Gunnar Frostfeldt, Ph.D.

Christoph Varenhorst, Ph.D.

Mohammamd Kavianipour, Ph.D.

Axel Åkerblom, Ph.D.

Ziad Hijazi, Ph.D.

Cathrin Henriksson, Ph.D. R.N.

Birgitta Jönelid, Ph.D student

Gorav Batra, Ph.D student

Gabriel Arefalk, , Ph.D student

Daniel Lindholm, Ph.D student

Julia Aulin, MD

Ola Vedin, Ph.D student

Daniel Lind, Ph.D student

Kasper Andersen, Ph.D.

Thomasz Baron, Ph.D.

Funding

Swedish Heart-Lung foundation: Stefan James 1,200,000 + 1,100,000 SEK.

Swedish Foundation for Strategic Research: Bertil Lindahl 4,100,000 SEK; Lars Wallentin and Jonas Oldgren co-applicants in a large grant 7,000,000 SEK.

ALF: 2,800,000 SEK

Selanders foundation: Kai Eggers 100,000 SEK; Christina Christersson 100,000 SEK

Swedish Society of Medicine: Kai Eggers 106,000 SEK; Christina Christersson 250,000 SEK

"1.6 milj klubben": Christoph Varenhorst 300,000 SEK

In addition have members of the research group received several industrial grants.

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Dissertations

Karin Hambræus: From Stenting to Preventing : Invasive and Long-term Treatment for Coronary Artery Disease in Sweden. Superviser: Bertil Lindahl

Cardiology-Arrhythmia

Carina Blomström-Lundqvist

The research group focuses on two different areas, atrial fibrillation (AF) and inherited heart diseases. AF is associated with decreased quality of life, increased morbidity and mortality. Anti-arrhythmic agents have poor long term effects for AF control, and may contribute to the observed higher death rate in AF populations. Our aim is therefore to assess the mechanism of AF, develop novel surgical and catheter based ablation techniques for the elimination of AF. We further aim to identify predictors for AF recurrences.

Atrial Fibrillation – assessment of arrhythmia mechanism, predictors of AF recurrence and development of novel non-pharmacological therapies

There are three ongoing projects evaluating non-pharmacological treatment strategies for AF:

The Nordic Multicenter and randomised **CAPTAF trial** (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation), an intention to treat study, aims to compare the effects of two treatment strategies, catheter ablation of atrial fibrillation versus optimized conventional pharmacological therapy, in patients with symptomatic AF. The primary hypothesis is that early intervention with catheter ablation of AF is superior to optimized conventional drug therapy, in improving general health-related quality of life (QoL) at 12 months follow-up, in patients with symptomatic AF. Secondary end-points are AF burden, a composite of morbidity end-points, symptoms, left atrial and ventricular function, physical capacity, cardiovascular hospitalisation, health economy and complications evaluated at 12, 24, 26, and 48 months of follow up. The study includes centers from Umeå, Stockholm, Uppsala (co-ordinating center), Gothenburg and Finland, and is supported by SBU and Swedish Heart and Lung Foundation and by Vetenskapsrådet. The inclusion period ended in January 2013. Patients will be followed for 4 years and the last follow up will be in January 2018. Patients are evaluated for the Quality of Life parameter General Health (Medical Outcomes Study Short Form-36 (SF-36)) as primary endpoint. The study is unique in that it will demonstrate long term treatment effects and freedom from AF confirmed by continuous rhythm monitoring using an implantable device. The main analysis will be performed on the Intention to treat (ITT) population including all randomized patients.

The objective of the **CryoLPAF** study, an exploratory study, is to assess whether pulmonary vein isolation (PVI) using a cryoballoon is sufficient to achieve clinical efficacious outcome in at least 50% of patients with longstanding persistent AF at one year follow up after 1-2 procedures. The primary objective of the study is to determine the clinical success of catheter ablation, defined as either freedom from AF related symptoms irrespective of the presence of asymptomatic AF on Holter provided AF is absent or only paroxysmal in nature, or presence of AF related symptoms but significant symptomatic improvement. Secondary objectives are complete freedom from AF without drugs, rhythm, AF burden, Quality of Life, symptoms, atrial size and function, biomarkers including nTproBNP and troponin I, extent of atrial scar tissue, safety, cardiovascular hospitalization, and health economics at 12 months. Prediction of freedom from AF by risk variables including left atrial volume – contractility - intracardiac pressures - and dPdT, atrial electrical signal amplitude analysis during AF prior ablation, extent of scar tissue as assessed by a voltage mapping, and demographic variable, will be performed. It is hypothesized that PVI achieved by the new cryoballoon will be associated with a clinically successful outcome in at least 50% of patients with longstanding persistent AF at one year follow up after 1-2 procedures. A total of 40 patients will be treated and restudied at 12 months follow-up irrespective of symptoms, to assess whether the cause of AF recurrence is reconduction in the vast majority of long standing persistent AF patients. Arrhythmia monitoring during follow up will be performed by a 7 day Holter monitoring (or a Reveal XT) every third month at 6, 9 and 12 months follow up, including a 12 lead ECG. A CT and transthoracic echocardiography will be repeated at 12 months follow up to assess LA volume and contractility. All patients will be reinvestigated for assessment of PV re-conduction using a circular mapping catheter, irrespective of symptoms. Patients with symptomatic recurrence requiring a redo ablation procedure will be re-studied after 8-12 months while asymptomatic patients will be studied at 12 months follow up.

The aim of the **ECAF star trial** is to assess the effects of electrical cardioversion in patients with recent onset AF with regard to new silent cerebral thrombo-embolic lesions and cognitive function. The hypothesis defined is that acute electrical cardioversion will result in a 20 % increase in incidence of new asymptomatic cerebral ischemic lesions as detected by nuclear magnetic resonance imaging (MRI) of the brain directly after and at 7 days after cardioversion. In a 1st study the risk for silent embolism after electrical cardioversion of recent onset AF will be assessed by MR scan before, immediately after and 7 day after the cardioversion. Patients who present to the emergency department with recent onset AF are eligible for the study. A total of 70 patients will be screened to ensure that 40 patients will remain in sinus rhythm at least 7 days after cardioversion. The secondary endpoints analysed directly after cardioversion, at day 7 and at day 30 will be compared with baseline and include plasma markers for thrombin activity and measures of coagulation activity, left and right atrial volumes, while global left atrial ejection fraction and P wave duration / amplitude, as measures of atrial electrical remodeling parameters will be used to assess timing and degree of reverse remodeling; left ventricular ejection fraction and left ventricular diastolic function (transmitral velocities, E/E' index), neurohormonal, inflammatory, specific cardiac biomarkers, and a vasoactive peptide will all be analysed and compared with baseline. A minimental test will be analysed comparing number of points at 7 and 30 days versus baseline. In a 2nd study we will compare electrical cardioversion with pharmacological cardioversion (PhCV) by randomizing patients between the 2 treatments. The Primary end-point is new silent cerebral ischemic events detected on MRI after electrical cardioversion and secondary end-points are electrical and functional/structural remodeling parameters as stated above and including time to AF recurrence, and AF burden. Health economic comparisons will be conducted for electrical cardioversion and PhCV. We will also assess whether cardioversion with vernakalant leads to less AF recurrences as compared with electrical cardioversion during a 12 months follow up period. The study will be conducted at the department of Cardiology in Uppsala and SÖS and possibly in Västerås, Gävle hospital and to Malmö hospital. The project is in collaboration with the department of Radiology in Uppsala and Professor Elna Marie Larsson.

Project evaluating the role of inflammation and pre-thrombotic state for the initiation and perpetuation of atrial fibrillation. Collaborative research with the Department of Pathology has been initiated. Atrial tissues from patients undergoing Maze-surgery have been analyzed with regard to the presence of inflammation and fibrosis. The on-going histological studies of excised atria will be finalized. A second step is to analyse inflammatory parameters from frozen left atrial appendages obtained from Maze-surgery, and compare those with the changes observed in an age- and sex-matched population.

Underlying aetiology and predictors of sudden cardiac death and ventricular tachycardia in young patients – genetic screening and pheno-type characteristics.

The most common cause of sudden cardiac death in patients under the age of 35 years are congenital heart diseases, such as hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (ARVC). The diagnosis of ARVC is difficult and freqeuntly relies on findings from several types of investigations. The patient suffers from ventricular tachycardia related to fat and fibrous tissue in the right ventricular myocardium. Several genes have been identified and reported in the literature, but up to now there is no genetic testing available for routine clinical use in the Nordic countries.

We have in collaboration with the clinical genetics, department of pathology and BMC, collaboration for identifying a genetic and clnical risk marker in patients with ARVC. We also intend to develop a screening test for phenotype characterisation using echocardiography, signal averaged ECG, and MR/CT, and to identify clinical risk factors for sudden cardiac death in combination with genetic testing, by a systematic long term follow-up of patients. The study is conducted in collaboration with the Institution of Genetic and Pathology.

Members of the group during 2014

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Swedish research council	1 800 k SEK
Swedish Heart-Lung foundation	300 kSEK

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Dissertations:

Helena Malmborg, Catheter ablation of Atrial Fibrillation and Atrial Flutter : A Comparison of Cryo and Radiofrequency Techniques.

Clinical physiology

Hans Hedenström

Cardio-pulmonary aspects in acute and chronic lung disease

The research program is based on the results that we have gained during previous years that have focused on atelectais formation and impeded lung function during anesthesia and in acute respiratory failure, with an increasing orientation towards lung inflammation.

New techniques for ventilatory support

A number of studies have been conducted comparing fully controlled mechanical ventilation (MV) and spontaneous breathing combined with a basic mechanical support (APRV or BIPAP). A consistent finding has been that spontaneous breaths improve lung aeration and function by recruiting lung tissue and increasing respiratory compliance and gas exchange compared to mechanical ventilation. The advantages and even superiority of spontaneous breathing are important findings that guide in the development of improved ventilatory techniques. It has focused our interest in another Swedish invention, neurally adjusted ventilatory assist, NAVA. This technique is based on the recording of the diaphragm EMG to guide the ventilator in tailoring the breath according to the demand by the patient (i.e. the respiratory centre of the brain).

Ventilator-induced lung injury

When using conventional mechanical ventilation an optimal ventilator setting is critical, an issue that has been intensely discussed during the last 10 or 15 years. A desire is to provide “protective ventilation”. However, it still remains to define what “protective” really is. Our own studies have focused on the application of suitable positive end expiratory pressure, PEEP. Low PEEP will allow collapse of lung tissue, and more importantly, cyclic recruitment and collapse of airways and alveoli. Studies how to find optimum PEEP levels have been performed. They have also stimulated us to do studies using PET and inflammatory markers together with CT to detect onset of inflammatory responses to ventilatory support and relate inflammation to morphological changes as assessed by CT.

Asthma disease phenotyping and natural history of asthma disease

MIDAS is a VINNOVA-sponsored consortium (2008-2012) for research on minimally invasive diagnostics in allergies and hypersensitivities with main focus on respiratory diseases. Within these projects, an asthma cohort of 411 subjects (schoolchildren and young adults) was formed between March 2010 and February 2012. A total of 119 matched controls were recruited in parallel. All subjects answered a broad questionnaire on asthma, rhinitis and eczema symptoms, allergic symptoms, asthma control, asthma quality of life, use of medication etc. Measurements of exhaled NO at different flow-rates, nasal NO, exhaled carbon monoxide, lung function and methacholine reactivity are performed. Blood samples were taken for analysis of IgE sensitisation to important aeroallergens and food allergens, inflammatory markers and cytokines. Nasopharyngeal aspirate was collected in order to assess presence of virus via RT-PCR. The overall aim of the baseline study of asthma cohort was to map asthma disease with emphasis on inflammation and allergic sensitisation pattern as a basis for future therapeutic interventions. At the present moment, four PhD students are working with results from the MIDAS study and several manuscripts are being prepared. A follow-up of the MIDAS study was started in April 2013 and it is going to continue under 2014. The main aim with the follow-up study is to understand the natural follow-up of the disease, with focus on different asthma phenotypes as well as predictive value of some of the baseline characteristics. A special focus will be on the role of the mast cell with measurements of mast cell progenitors and bronchial reactivity to mannitol in a subgroup of subjects. Further focus will be on characterizing small airways involvement, as described below.

Importance of lung function characterization and lung function monitoring in COPD – a series of prospective studies

Spirometry is used to define COPD and has been used to grade severity of COPD. However it becomes more recognized that FEV1 is not an optimal correlate of the exercise capacity and has limited value even in disease prognosis. In a prospective study, we have investigated the value of a complete lung function characterization (including DLCO measurements and lung volumes) for prognosing exercise capacity decline. The main finding was that DLCO was the only predictor of a decline in exercise capacity over a 5-year period. COPD exacerbations have big socio-economic impact and therefore it is important to understand its predictors in order to prevent exacerbations. In an ongoing, multicentre study we assess the value of lung function (complete lung function characterization), exercise ability, inflammation markers for predicting exacerbations in COPD patients from primary and tertiary care. (Tools for Indicating Exacerbations study) – the study has started August 2014 and is planned to continue until 2017). Forced oscillation technique (FOT) and impulse oscillometry (IOS) are relatively new methods which have a potential to detect changes in small peripheral airways. FOT and IOS require minimal cooperation from the patients, in contrast to conventional measurements of pulmonary function, and therefore these methods can also be used in children and old persons. Nitrogen washout test can also be used to detect small airway disease and new, user-friendly devices are now available. These methods will be used in patients with cystic fibrosis and in patient with esophagusatresia in order to early identify obstruction of peripheral airways and to predict which patients are at higher risk.

Evaluation of new information in echocardiography

Comparison of echocardiographic measurements with pressure from the right ventricle and systolic pulmonary pressure and correlation of these findings with actual pressure measurements from right heart catheterization (RHC). The possibility for right ventricular pressure estimation in the absence of tricuspid regurgitation (TR) was of particular interest. This was evaluated by measuring acceleration time (AT) from the forward flow in the pulmonary valve. In addition correlation of estimated pressure from the right atrium (RA) by echocardiography and catheterization was evaluated. Last, calculations of pulmonary resistance (PVR) with a previously suggested formula was compared to PVR from catheterization in a group with high incidence of pulmonary hypertension and an alternative way of presenting echocardiographic PVR was evaluated. Patients with cardiac amyloidosis were evaluated using echocardiography, ECG and right heart catheterization to find out a echocardiographic pattern in these patients. Patients with asymptomatic severe aortic stenosis and preserved ejection fraction were evaluated according to European guidelines to determine the impact of new combinations of echocardiographic variables.
Studies of patients with aortic or mitral regurgitation (LV-regurge) has been started and will go on for the next years. The studies involve a lot of different investigation techniques such as PET, MR, echocardiography and cardio-pulmonary exercise test. These methods will be used for early identification of changes that can lead to severe heart failure.
As an evaluation of 3-dimential echocardiographic imaging, studies have been done to find out if 3-Dimensional echocardiographic area strain is diagnostically superior to longitudinal and circumferential Strain.

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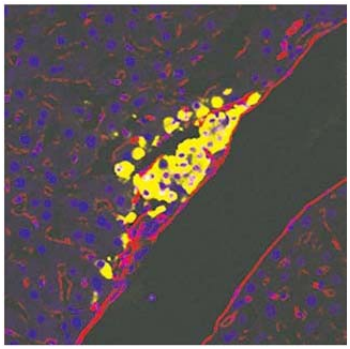
Dissertations

Maria Bergquist: Glucocorticoid receptors in severe inflammation: Experimental and clinical studies

Joao Batista Borges: Ventilator-induced lung injury; experimental PET studies

Diabetes and Metabolic diseases

Research in the field of diabetes and metabolic diseases is focused on strategies for treatment of diabetes and obesity. The overall aim of the research on islet transplantation and beta-cell regenerative medicine is to develop means to intervene with the development of type 1 diabetes mellitus and find treatment strategies to restore glucose homeostasis in patients with type 1 diabetes mellitus using cell therapy. Studies are also undertaken to investigate gastrointestinal physiology of patients subjected to bariatric surgery with the aim to increase our understanding of metabolic events induced by the surgery. The research group on diabetes self care investigates diabetes self management and the balancing act between rigorous blood glucose control and quality of life.



Clinical diabetology and metabolism

Jan Eriksson

A main focus of our research is to increase the understanding of factors related to adipose tissue that drive insulin resistance and other types of metabolic dysregulation. This can in turn promote the development of diabetes and its complications. Adiposity is of critical importance in type 2 diabetes, which is strongly associated with abdominal obesity. But it appears to be of relevance also in type 1 diabetes. The factors of interest include biomolecules that are produced by the adipose tissue, such as hormones and cytokines, but the role of the cellular and tissue morphology, nervous regulation and nutritional status of adipose is also explored. A major aim of the research is to identify novel pharmacological mechanisms as well as biomarkers, that can improve prevention, treatment and monitoring of diabetes and its complications.

Within the group there is also a separate program involving diabetes nursing research that aims to identify factors of importance for diabetic patients' self-care, evaluate diabetes care interventions and test psychometric properties for the evaluation of patient centered care.

Hormonal and metabolic mechanisms in human adipose tissue – importance for the development of type 2 diabetes

Maria Joao Pereira, Joey Lau, Cherno Sidibeh, Prasad Kamble, Petros Katsogiannos, Monika Gelotte, Jan Eriksson

The project focuses on metabolic dysregulation in human adipose tissue and its importance for insulin resistance, type 2 diabetes and their complications.

The primary objective is to increase understanding of mechanisms in human adipose tissue that play a role in the development of insulin resistance and type 2 diabetes. An important long-term aim is to identify new therapeutic principles for prevention and treatment of type 2 diabetes.

We perform exploratory studies of e.g. hormones and appetite peptides, body composition and energy balance post-surgery, lipid stores examined by magnetic resonance tomography and spectroscopy, vascular reactivity examined by ultrasound, very low calorie diet prior to surgery evaluated biochemically and by MRI/MRS.

Effects of gastric by-pass surgery on glucose and lipid metabolism

Niclas Abrahamsson, Anders Karlsson, Magnus Sundbom, Petros Katsogiannos, Maria Joao Pereira, Jan Hall, Jan Eriksson

The project is run in collaboration with the Dept of Surgery, and it focuses on the profound changes seen in glucose and lipid metabolism following bariatric surgery. Obese patients undergoing gastric by-pass (GBP) markedly improve their insulin sensitivity and glucose tolerance. According to most available data, these

effects are much greater that what the weight loss itself can explain. Thus, it is believed that there are important factors induced by the rearrangement of intestinal anatomy that influence metabolism in various organs.

We investigate metabolic effects of GBP in comparison to similar weight loss achieved with very low-calorie diet on glucose and fatty acid turnover as well as insulin sensitivity in specific tissues. In addition, we perform functional assessments of the insulin-producing beta cells. Both type 2 diabetic and non-diabetic patients with obesity are enrolled, and a specific aim is to address mechanisms explaining the remission of diabetes that is often seen following GBP. We utilize a broad range of investigations such as glucose clamps, meal tests, imaging (PET and MRI), autonomic nerve activity and also in vitro assessments of tissue material obtained by biopsies.

The main purpose is to identify novel mechanisms following GBP that improve glucose and lipid metabolism. In the long-term perspective, this could support bariatric/metabolic surgery as a first-line treatment of some type 2-diabetes patients. The findings could potentially also deliver new pharmacological targets of interest in diabetes and obesity.

Insulin resistance caused by immunosuppressive drugs.

Joey Lau, Maria Joao Pereira, Cherno Sidibeh, Prasad Kamble Petros Katsogiannos, Jan Hall, Jan Eriksson

Glucocorticoids and other immunosuppressive agents (IA) are used to prevent graft rejection after organ transplantation and to treat autoimmune diseases. In addition to suppression of the immune system, these drugs also have adverse effects on nutrient metabolism and they can increase the risk for dyslipidemia, diabetes, central adiposity and cardiovascular disease. NODAT (new-onset diabetes after transplantation) is a serious and common complication in patients that have been transplanted for various reasons.

Our recent studies suggest that glucocorticoids and the IAs rapamycin, cyclosporin A and tacrolimus cause insulin resistance and alter glucose and lipid metabolism in adipose tissue. However, the mechanisms by which they affect nutrient handling are not well characterized. Therefore, we explore the cellular pathways, including regulation of key genes and proteins that lead to metabolic dysregulation following IA treatment. The adipose tissue is believed to be an important site mediating these adverse metabolic effects, and we investigate effects of the drugs in experiments on human adipose samples obtained by biopsies.

The main aim of this project is to increase our understanding of the molecular mechanisms underlying the development of insulin resistance during immunosuppressive therapy. This may point to novel pharmacological concepts that can mitigate the adverse effects caused by IAs. Such findings can also be of relevance for the development of future treatments for other forms of diabetes including type 2.

Metabolic and hormonal effects of SGLT2 inhibition.

Per Lundkvist, Sam Amini, Joey Lau, Maria Joao Pereira, Jan Eriksson

We currently perform several studies exploring the potential for novel indiciations for antidiabetic drugs in the class of SGLT2 inhibitors, in particular dapagliflozin. We do clinical trials as well as mechanistic human studies. They focus on energy balance and obesity, effects on fatty liver disease and hormonal effects relating to pancreatic islets in particular. In addition, we address novel combination therapies as well as adjuvant use of SGLT2 inhibition in type 1 diabetes.

Team- and Person-centered care in the context of diabetes.

Karin Wikblad, Janeth Leksell, Anna Lindholm Olinder, Veronika Elvingson, Violeta Armijo del Valle, Therese Granström, Maria Svedbo Engström.

We have since almost 30 years prospectively followed a group of type 1 diabetic patients and have been able to identify important factors for the management of diabetes. As part of this larger study we have recently examined the long-term effects of glycaemic control and treatment satisfaction in people with Type1 diabetes mellitus who changed from multiple daily insulin injections to insulin pump therapy. The aim of the study was through deep interviews describe experiences of the impact of insulin pump therapy in

adults with Type1 diabetes mellitus after >5years' use of an insulin pump. The performed analysis revealed that insulin pump therapy was experienced as both a shackle and a lifeline. Sub-themes emerged that could be used by physicians and diabetes specialist nurses to support self-management among people with insulin pump treatment.

In a separate study we perform a randomized intervention study, which aims to evaluate the effect of an intervention with GSD-Y in groups of adolescents starting on insulin pumps and their parents on diabetes-related family conflicts, perceived health and quality of life (QoL), and metabolic control.

In another study we carry out a randomized controlled study called: Acceptance and commitment therapy intervention. The aim is to test the effects of an ACT group intervention for patients with unsatisfactory blood glucose level, consisting of seven sessions and three follow-up sessions on blood glucose control and well-being.

Evaluate the patient perspective on diabetes care

A new questionnaire is needed, as there is no measurement that meets the ambition of a comprehensive diabetes-specific measure based on the capability approach. Within a pilot study, a first version of the questionnaire (the Diabetes Capabilities Questionnaire I) has been developed. The pilot questionnaire, based on and inspired by literature, established questionnaires and clinical experiences, covers domains such as self-management skills and emotional aspects, feeling of safety, experienced service, access, involvement, and social and work activities. The revised questionnaire has been successfully tested among 2000 patients with diabetes. The final questionnaire will be implemented in National Diabetes Registry (NDR) during 2015. A comprehensive evaluation of diabetes and diabetes care from the patient's perspective will enable the NDR to meet the ambition to follow up, improve and develop diabetes care based upon the individual's situation.

Damage to the eye is the most feared complications of diabetes and one of the most common causes of vision loss is diabetic macular edema (DME). In January 2011 a new treatment for DME, called anti-VEGF treatment was approved. This study is focused on patients experience in relation to need for information in connection with the named treatment. The treatment involves an injection into the vitreous of the eye and begins with three injections every four weeks (monthly) for the first 12 weeks. The treatment places increasing demands on the patient with more visits and a stressful treatment. The aim is to evaluate the new treatment, anti-VEGF, using both qualitative and quantitative evaluation, by describing the patients experience and measuring their health-related quality of life as well as medical endpoint. During 2015 some of the results will be presented.

Members of the group during 2014

Jan Eriksson, Professor
Anders Karlsson, Professor emeritus
Christian Berne, Professor emeritus
Karin Wikblad, Professor emerita
Ewa Billing, Assoc prof
Janeth Leksell, Assoc Prof
Anna Lindholm Olinder, PhD
Maria João Pereira, Researcher, PhD
Joey Lau Börjesson, Researcher, PhD
Petros Katsogiannis, Physician
Sam Amini, Physician
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Margareta Ericson, Research engineer
Caroline Moberg, Research nurse
Lovisa Nordlinder, Research nurse
Violeta Armijo del Valle, specialist nurse
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Moawia Abdelgadir Ali, PhD-student
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Cherno Sidibeh, PhD-student
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Maria Svedbo Engström PhD student

Funding

AstraZeneca	4 100 kSEK
Diabetesförbundet	180 kSEK
Diabetesförbundet	200 kSEK
Vårdvetenskap, UU	300 kSEK

Publications 2012-2014

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Endocrinology and mineral metabolism

Östen Ljunggren

The projects within the research group are based on clinical samples from a specialised osteoporosis outpatient unit. In that setting individual patients with metabolic bone diseases are investigated. Also clinical trials and gathering of clinical cohorts are performed. Samples from patients, as well as genetic analyses and experimental work on human bone cells are conducted at the Centre for clinical and medical research at Uppsala University. Focus of the research is on three main areas. Male osteoporosis, osteogenesis imperfecta and phosphate homeostasis.

Male osteoporosis

These investigations are based on the clinical cohort, Mr OS. This is a collaboration between Sweden, US and Hong Kong. In total 11 000 elderly men are followed prospectively to fracture. In Uppsala 1000 men are gathered. The baseline sampling of the cohort and 5 year follow up is now completed. Current research is mostly on regulation of calcium and phosphate, influence of sex hormones and genetic determinants for fracture.

Osteogenesis Imperfecta

In collaboration with the children's hospital in Stockholm a cohort of patients with OI is collected. The mutations causing OI are determined, and at present large amount of clinical data are gathered to investigate genotype-phenotype interaction in this disease. Also, individual patients with new sorts of mutations causing defect collagen are investigated. Finally in this project we are investigating the possibility to use gene silencing to interrupt dominant negative mutations in the genes for collagen type I.

Phosphate homeostasis

In collaboration with nephrologists at Uppsala hospital, hormonal regulation of serum phosphate is investigated. Focus is on the recently discovered putative hormone FGF-23. Again the research is based on clinical cases or groups of patients. To date most interest has been on studies in patients with oncogenic phosphate wasting osteomalacia, and in patient groups with renal impairment.

Members of the group during 2014-2015

Östen Ljunggren, Professor

Hans Mallmin, Professor

Andreas Kindmark, Associate professor

Elin Carlsson, Research engineer

Navya Laxman, PhD student

Anne Björk, MD, Phd student

Selwan Khamisi, MD, PhD student

Publications 2012-2014

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Transplantation and regenerative medicine

Per-Ola Carlsson

The overall aim of the research group on islet transplantation and beta-cell regenerative medicine is to develop means to intervene with the development of type 1 diabetes mellitus and find treatment strategies to restore glucose homeostasis in patients with type 1 diabetes mellitus using cell therapy. The dual role of the P.I. as experimental and clinical scientist simplifies translational approaches, and the research group is active both at the Department of Medical Cell Biology and the Department of Medical Sciences. Studies are conducted to elucidate the importance of islet endothelial, neural or their progenitor cells for beta-cell regeneration and function, and investigate the concept of islet heterogeneity. Other studies investigate the adaptation of pancreatic islets to the implantation organ, i.e. the so called engraftment process, following transplantation, and develop bioengineering strategies (coating of islets with supporting stem cells, oxygen carriers and growth factors, as well as with use of scaffolds) to improve results of pancreatic islet transplantation by enhancement of engraftment e.g. by improved revascularization. Human islets are tested in these experimental systems with a focus to produce clinically applicable protocols. We also perform research to develop safe and effective means to generate new human beta-cells by stimulating adult beta-cell proliferation, e.g. by stem cell stimulation, or by stem cell differentiation in vivo. Clinical studies are performed to prevent development of type 1 diabetes in patients, e.g. by autologous mesenchymal stem cell transplantation, and to develop means for beta-cell imaging by positron emission tomography. We also conduct studies to improve the results of clinical islet transplantation, e.g. by encapsulation in order to avoid immune suppression of the patients.

Communication between endothelial or neural cells and beta-cells

Liza Grapensparr, Svitlana Vasylovska, Carl Johan Drott, Monica Sandberg, Per-Ola Carlsson

We have observed an importance for endothelial-beta-cell communication to maintain beta-cell proliferation, differentiation and function. An important mediator of these effects seems to be basement membrane components, predominantly the beta1 chain of laminin secreted by the islet endothelial cells. We have also shown that the glycoprotein thrombospondin-1 (TSP-1) is highly expressed in the endothelium of islets, and that TSP-1 deficient mice were markedly glucose intolerant, despite having an increased beta-cell mass. Reconstitution experiments supported that the beta-cell defects occurring in TSP-1 deficient islets reflected postnatal loss of the glycoprotein in the islet endothelial cells. Treatment of TSP-1 deficient mice with the transforming growth factor beta-1 (TGFβ-1) activating sequence of TSP-1 showed that reconstitution of TGFβ-1 activation prevented development of decreased glucose tolerance in these mice. Thus, endothelial derived TSP-1 activates islet TGFβ-1 of importance for beta-cells. In other experiments, the possibility for endothelial progenitor cells, neural crest stem cells and Schwann cells to stimulate human beta-cell proliferation and function are investigated. These cell types may be used for co-transplantation with islets, or used to regenerate the endogenous endocrine pancreas.

Heterogeneity of pancreatic islets in health and disease

Sara Ullsten, Joey Lau, Per-Ola Carlsson

We have identified a functional reserve of islet endocrine cells in rodents. Normally 20-25% of islets are low oxygenated and with low protein biosynthesis, but these cells may be activated upon need during increased functional demands. On the other hand, more islets become down-regulated when beta-cell mass is increased. We have also observed that the most blood perfused islets, having a higher vascular density, have a superior beta-cell function, proliferation and gene expression. Noteworthy, these islets also seem more prone to develop amyloid deposits, as well as are more prone to cellular death when stressed by hyoxia or cytokines in vivo and in vitro.

Engraftment of intraportally transplanted islets

Joey Lau, Per-Ola Carlsson

We have developed a technique to quantify the blood perfusion of islets experimentally transplanted intraportally into the liver by combining fluorescent islets for transplantation with a fluorescent microsphere technique. One month post transplantation the blood perfusion of the intrahepatically transplanted islets was found to be only 5% of that in native islets. Most interestingly, a six fold higher blood perfusion was observed in the intrahepatic grafts composed of islets transplanted after overnight incubation when compared to islets transplanted after four days of culture. By the use of the biochemical marker pimonidazole the low revascularization and blood perfusion of intraportally transplanted islets were found to correlate to impaired oxygenation of the tissue. The accumulation of pimonidazole correlated to an increased apoptosis frequency in the intraportally transplanted islets, and correlated negatively to islet function and (pro)insulin biosynthesis in the islets. Co-transplantation of islets with neural and endothelial progenitor cells can be performed to promote early survival, revascularization and beta-cell proliferation in the grafts.

Transplanting islets into striated muscle and omentum

Daniel Espes, Monica Sandberg, Per-Ola Carlsson

We have previously observed that transplantation of pancreatic islets to their normal micro-environment, the pancreas, almost restored the islet vascular network and beta-cell function, in contrast to islets implanted to the liver. We have evaluated the intramuscular site for islet transplantation and found that mouse and human islets experimentally transplanted into muscle within 14 days the islet vascular network is fully restored with functional capillaries. Moreover, the oxygenation of intramuscularly transplanted islets was almost restored. The function of islets transplanted into muscle was proven by curing diabetic mice, 300 islets implanted to striated muscle fully restored glucose tolerance in recipient diabetic mice. The experimental data on islet revascularization at the intramuscular site were confirmed by high resolution magnetic resonance imaging studies of pancreatectomized patients autotransplanted with islets to forearm muscle. Such grafts showed high plasma volumes indicating normalized vascular density. In other research projects we compare outcome to another promising site, the omentum, and have developed means to improve also early survival of the islet grafts by e.g. bioengineering with polymerized hemoglobins.

Amyloid formation

Sara Bohman, Hanna Liljebäck, Arne Andersson, Per-Ola Carlsson

Isolated and microencapsulated human islets are found to rapidly accumulate much larger amounts of amyloid than free native and transplanted islets, suggesting an importance of vascular drainage to prevent amyloid formation. We are presently investigating the possible correlation between vascularisation, blood perfusion and tendency for amyloid formation in human islets and native and transplanted rhIAPP overexpressing islets. Of particular relevance for islet transplantation may be our comparison between different implantation sites with regard to amyloid accumulation and long-term graft function and failure, when considering the marked differences in revascularization and blood perfusion of islets implanted to the liver, striated muscle, omentum or pancreas

Intervention strategies to preserve residual beta-cell mass in newly developed type 1 diabetes

Daniel Espes, Per-Ola Carlsson

Possibilities to save residual beta-cell mass in newly diagnosed patients with type 1 diabetes by autologous transplantation with mesenchymal stem cells are tested. Patients are followed up to five years after diagnosis, and residual insulin production is investigated in response to metabolic load. New techniques to visualise beta-cell mass are in parallel developed by positron emission technology using the PET ligand [^{11}C]-5-hydroxy-tryptophane. In a first study, we have been able to preserve beta-cell function for at least a

year after debut of type 1 diabetes by mesenchymal stem cell treatment. Based on this, we are now conducting a larger, blinded, phase 2 efficacy trial with the same concept.

Encapsulation of pancreatic islets for clinical transplantation

Daniel Espes, Per-Ola Carlsson

Clinical islet transplantation is hampered by the need of chronic immune suppression of the recipients. In a collaborative effort with Beta-O_2, a newly developed oxygenized chamber to harbour the human islets is tested in an ongoing investigator-initiated phase 1/2a trial in type 1 diabetes patients. The macrodevice protect the islets from immune rejection, whereas oxygen is supplied daily into a refillable oxygen tank. The trial included the first patient during autumn 2014. A follow up study is planned with instead transplantation of human embryonic stem cells derived to insulin producing cells within the same device.

Members of the group 2014

Per-Ola Carlsson, M.D., Ph.D, Professor
Arne Andersson, MD, Professor em
Joey Lau, post-doc
Monica Sandberg, post-doc
Sara Bohman, post-doc
José Caballero, post-doc
Svitlana Vasylovska, post-doc
Daniel Espes, M.D., PhD student
Carl Johan Drott, M.D., PhD student
Liza Grapensparr, PhD student
Sara Ullsten, PhD student
Astrid Nordin, laboratory engineer
Ing-Britt Hallgren, laboratory engineer
My Quach, laboratory engineer
Lisbeth Sagulin, laboratory engineer
Eva Törnelius, laboratory technician
Violeta Armijo Del Valle, research nurse
Rebecca Hilmius, research nurse
Hanna Liljebäck. MD/PhD student
Zhanchun Li, laboratory engineer

Funding for 2014

Swedish Research Council -Clinical Treatment Research grant	8.4 MSEK
Juvenile Diabetes Research Foundation USA	2.0 MSEK
Novo Nordisk Foundation DK 2014	0.7 MSEK
Swedish Research Council -Regular grant	1.7 MSEK
Torsten Söderbergs Stiftelse	2.0 MSEK
Swedish Diabetes Association	0.4 MSEK
AFA	1.0 MSEK
The Swedish Juvenile Diabetes Foundation	1.0 MSEK
Strategic funding, Exodiab	0.6 MSEK
Diabetes Wellness	0.4 MSEK
Regional Research Council	0.6 MSEK

Publications 2012- 2014

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20. Espes D, Lau J and Carlsson P-O. Increased circulating levels of betatrophin in individuals with long-standing type 1 diabetes. Diabetologia 57:50-53, 2014
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Undergraduate Teaching 2014

Medicine Programme;	**Approx. students**
Clinical Medicine I 28,5 hp	215
Clinical Medicine III 30 hp	180
Clinical Medicine IV 19,5 hp	150
Occupational and Environmental Medicine	150
Physiotherapy Programme:	
Internal Medicine 3 hp	76
Physiology 9 hp	46
Nursing Programme:	
Pharmacology 6 hp	200
Clinical Microbiology 4,5 hp	200
Pharmacology and microbiology 10,5 hp	5
Nursing and Medical Sciences within Medical Care 15 hp	200
Biomedicial Laboratory Science Programme:	
Medical Microbiology 10,5 hp	45
Medical Laboratory Data Analysis	28
Projectic 9 hp	28
Clinical Chemistry and Hematology, Toxicology and Pharmacology 13 hp	39
Clinical Physiology 7,0 hp	46
Practical Tuition I	35
Practical Tuition II	29
Biomedicine Programme:	
Biomedical Data Analysis	40
Diseases – Clinical Survey	
Single Subject Courses	
Advanced Course in Medical Sciences, 15 hp	1
Diabetes Care I 15 hp	36
Diabetes Care II 7,5 hp	8
Diabetes Adult Learning 7,5 hp	17
Diabetes Care, Scientific Methodology and Essay 15 hp, Basic Course	1
Diabetes Care, Scientific Methodology and Essay 15 hp, Advanced Course	1
Clinical Drug Development 30 hp	30
Methodology in Clinical Trials 3 hp	18
Treatment and Nursing in Ischemic Heart Disease 7,5 hp	40
Advanced Course in Cardiatic Care	10
Clinical Clerkship	13
Work Environment in the New Working Life 7,5	14
Occupational Physician Ed	29
TOTAL:	**2 000 students**

Core Facilities

The SNP&SEQ Technology Platform in Uppsala

Director: Professor Ann-Christine Syvänen

Providing access to genotyping and sequencing on all scales

The objective of SNP&SEQ Technology Platform in Uppsala is to make large-scale SNP genotyping and "next generation" DNA sequencing of high quality available to academic researchers in Sweden and other countries at the lowest possible costs. The SNP&SEQ Platform has a professional staff of ~25 FTEs, including laboratory heads, research engineers/laboratory technicians, bioinformatics and database specialists, IT-staff and managers for project coordination and technology development. To assure a high quality of the data produced, the SNP&SEQ Platform works according to the ISO/IEC 17025:2005 quality standard, and the genotyping and sequencing process are accredited by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC). Genome-wide SNP panels facilitate association studies in human complex diseases and traits, determination of copy number alterations and DNA-methylation across the genome. "Next generation" sequencing is applied to sequence large and small genomes, discovery of SNPs in targeted regions of large genomes, functional analyses of gene regulation by analysis of chromatin immunoprecipitated DNA and transcriptome sequencing. The SNP&SEQ Technology Platform constitutes a major part of the National Genomics Infrastructure (NGI) hosted by Science for Life Laboratory. Since 2009, the SNP&SEQ Platform has been supported as a national research infrastructure by the Swedish Council for Research Infrastructures (VR RFI). The SNP&SEQ Platform also participates in large collaborative EU projects, including the FP7 project European Sequencing and Genotyping Infrastructure (ESGI) that provides transnational access to genotyping and sequencing to scientist in Europe. The SNP&SEQ Technology Platform is well equipped for assisting academic research projects over a broad size range, with four genotyping instrument and 10 sequencing instruments, including 5 HiSeqX instruments for large-scale human whole genome sequencing, for which the Knut and Alice Wallenberg granted funding in 2014.

Projects

The users of the services of the SNP&SEQ Technology Platform are affiliated with the Faculties for Medicine and Pharmacy, Academic Hospital and the Faculty for Science and Technology at Uppsala University. In accordance with the status of the SNP&SEQ Platform as a national infrastructure, 53% of the users of the SNP genotyping services, and 30% of the users of the sequencing services are affiliated with other universities than Uppsala University. During 2014, 60 genotyping projects including a total of 27600 DNA samples and 141 sequencing projects of 9260 DNA or RNA samples were completed. Many projects study human diseases or populations, but genotyping and sequencing in numerous other organisms, like birds, domestic animals, plants, insects, fungi and bacteria were also performed. So far the SNP&SEQ Platform has contributed to several hundred publications in respectable scientific journals, of which 61 appeared in 2014. Of the 61 publications that appeared in 2014, as many as 16 were published in journals with an impact factor > 9, including 6 publications in top journals like Science, Nature and Nature Genetics. The large number of publications in high-impact journal illustrates that the services offered by the SNP&SEQ Platform contribute to research of a high international standard in Sweden.

For a complete list of publications and for more information see

www.genotyping.se or www.sequencing.se

Staff of the SNP&SEQ Technology Platform during 2014

Tomas Axelsson, PhD, head of SNP unit
Ulrika Liljedahl, PhD, head of SEQ unit
Pontus Larsson, PhD, head of bioinformatics unit
Jesscia Nordlund, head of R&D
Lars Bäckström, computer systems manager
Sofia Adolfsson, engineer
Susanne Björnerfeldt, research engineer
Johan Dahlberg, bioinformatician
Sara Ekberg, research engineer
Edvard Englund, PhD, database systems developer
Camilla Enström, research engineer
Susanne Forsberg, technician
Helena Fällmar, PhD, research engineer
Anna Haukkala, research engineer
Maria Hägglund, PhD, research engineer
Katarina Jonasson, administrator
Johanna Lagensjö, research engineer
Kristina Larsson, senior research engineer
Ulrika Liljegren, research engineer
Magnus Lindell, PhD, research engineer
Heidur Loftisdottir, research engineer
Per Lundmark, PhD, bioinformatician
Johanna Manninen, research engineer
Amanda Raine, PhD, senior research engineer
Jon Ramsell, PhD, research engineer
Patrik Smeds, bioinformatician
Karin Sollander, research engineer
Kjell Stålberg, PhD, research engineer
Olof Wadell, research engineer
Ann-Christine Wiman, research engineer
Ingvar Örn Thorsteinsson, research engineer
Matilda Åslin, bioinformatician
Torbjörn Öst, research engineer

Array and Analysis Facility – microarray-based analyses and bioinformatics for research and health care

Director: Associate Professor Anders Isaksson

The facility provides access to large-scale technologies for research and health care and is supported by Uppsala University and Uppsala University Hospital. We provide microarray related services based on the Affymetrix Gene Chip 3000 and Gene Titan systems, which includes analysis of mRNA levels, miRNA levels, DNA copy measurements and whole genome SNP genotyping etc. In addition we provide bioinformatic support and develop algorithms for problems that many user face. For more information see the platform home page: http://www.medsci.uu.se/plattformar/Array+and+Analysis+Facility/

Doubled demand for platform services during 2014

Introduction of the Axiom platform for flexible genotyping has led to an increase in the total number of analysed samples from 1348 in 2013 to 3124 in 2014. By providing a diverse set of array-based analyses and bioinformatics support continues to provide services to a large number of projects. The analyses mainly come from UU (81%), Akademiska sjukhuset (13%), other Swedish Universities (5%) and companies (1%). The platform has a staff of 6 full-time positions. The platform has contributed to 28 publications in high ranking international journals during 2012-2014 (see list below).

Array-based analyses for improved health care

Our vision is to continue to develop the platform and offer a wide variety of array-based analyses. In particular we want to focus on developing clinical analyses that can become an important part of individualized treatments in Uppsala. Together with Clinical Genetics we have since 2008 offered array-based diagnostics of children with suspected mental retardation of as a routine clinical analysis. We analysed 359 patients during 2014. In December of 2013 these analyses were extended also to pre-natal testing and 61 samples were analysed during 2014.

Our focus is on developing clinically useful diagnostic and predictive tests based on array analyses. One example is an array-based method for routine diagnosis of ALL that uses a data analysis method we developed at the facility.

Future

Array and Analysis facility is planning to further develop our support for array analyses and bioinformatics.

Staff of Array and Analysis Facility during 2014

Anders Isaksson, director

Hanna Göransson Kultima Bioinformatician

Markus Mayrhofer, Bioinformatician

Malin Olsson, Research engineer

Maria Rydåker, Research engineer

Belinda Fridman, Bioinformatician

Björn Viklund, Bioinformatician

Publications 2012-2014

Uppsala array platform has contributed to 28 published articles during 2012- 2014. Fourteen of them are published without platform employees as co-authors and 14 with co-authors from the platform.

Publications without platform employees as co-authors

1. Calcif Tissue Int. 2012 Mar;90(3):219-29.. Microarray profiling of diaphyseal bone of rats suffering from hypervitaminosis A. Lind T, Hu L, Lind PM, et al.
2. Oncoimmunology. 2012 Jan 1;1(1):18-27. Lymphoblastoid cell line with B1 cell characteristics established from a chronic lymphocytic leukemia clone by in vitro EBV infection. Rosén A, Bergh AC, Gogok P, et al.
3. Clin Cancer Res. 2013 Jan 1;19(1):194-204. Biomarker discovery in non-small cell lung cancer: integrating gene expression profiling, meta-analysis, and tissue microarray validation. Botling J, Edlund K, Lohr M, Hellwig B, Holmberg L, et al.
4. Endocrinology. 2012 Jun;153(6):2588-98. Accelerated proliferation and differential global gene expression in pancreatic islets of five-week-old heterozygous Men1 mice: Men1 is a haploinsufficient suppressor. Lejonklou MH, Barbu A, Stålberg P, Skogseid B.
5. Mol Immunol. 2012 Apr;50(4):210-9. Tumor-mast cell interactions: induction of pro-tumorigenic genes and anti-tumorigenic 4-1BB in MCs in response to Lewis Lung Carcinoma. Wensman H, Kamgari N, Johansson A, et al.
6. Physiol Genomics. 2012 Sep 18;44(18):865-77. Role of sepsis in the development of limb muscle weakness in a porcine intensive care unit model. Aare S, Radell P, Eriksson LI et al.
7. Horm Behav. 2012 May;61(5):711-8. Transgenerational effects of early experience on behavioral, hormonal and gene expression responses to acute stress in the precocial chicken. Goerlich VC, Nätt D, Elfwing M, Macdonald B, Jensen P.
8. BMC Genomics. 2012 Feb 4;13:59..Heritable genome-wide variation of gene expression and promoter methylation between wild and domesticated chickens. Nätt D, Rubin CJ, Wright D, et al.
9. Dev Comp Immunol. 2012 Sep;38(1):17-26. Global transcriptional response to ISCOM-Matrix adjuvant at the site of administration and in the draining lymph node early after intramuscular injection in pigs. Ahlberg V, Lövgren Bengtsson K, Wallgren P, Fossum C.
10. J Pathol. 2012 Nov;228(3):378-90. Transcriptional profiling of human glioblastoma vessels indicates a key role of VEGF-A and TGFβ2 in vascular abnormalization. Dieterich LC, Mellberg S, Langenkamp E, et al.
11. Eur J Cardiothorac Surg. 2013 Mar;43(3):612-8. doi: 10.1093/ejcts/ezs386. A modified Glenn shunt improves haemodynamics in acute right ventricular failure in an experimental model. Vikholm P, Schiller P, Johansson J, Hellgren L.
12. Invest New Drugs. 2012 Nov 20. Gambogic acid is cytotoxic to cancer cells through inhibition of the ubiquitin-proteasome system. Felth J, Lesiak-Mieczkowska K, D'Arcy P, et al.
13. Exp Cell Res. 2012 Aug 1;318(13):1577-85. Loss of cancer drug activity in colon cancer HCT-116 cells during spheroid formation in a new 3-D spheroid cell culture system. Karlsson H, Fryknäs M, Larsson R, Nygren P.
14. Oncogene 32(47): 5409–5420. 2013. Snail depletes the tumorigenic potential of glioblastoma. Savary K, Caglayan D, Caja L, Tzavlaki, Bin Nayeem K S, Bergström T, Jiang Y, Uhrbom L, Forsberg-Nilsson K, Westermark B, Heldin C-H, Ferletta M, Moustakas A.

Publications with platform employees as co-authors

15. BMC Cancer 14(1):872. 2014. 1p36 deletion is a marker for tumour dissemination in microsatellite stable stage II-III colon cancer. Mayrhofer M, Göransson Kultima H, Birgisson H, Sundström M, Mathot L, Edlund K, Viklund B, Sjöblom T, Botling J, Micke P, Påhlman L, Glimelius B, Isaksson A.
16. Genome Biol. 2013 Mar 25;14(3):R24. Patchwork: allele-specific copy number analysis of whole genome sequenced tumor tissue. Mayrhofer M, DiLorenzo S, Isaksson A.
17. Physiol Genomics. 2011,16;43:1334-50. Mechanisms underlying the sparing of masticatory versus limb muscle function in an experimental critical illness model. Aare S, Ochala J, Norman HS, et al.

18. BMC Cancer. 2012 Sep 12;12:407. Loss-of-heterozygosity on chromosome 19q in early-stage serous ovarian cancer is associated with recurrent disease. Skirnisdottir I, Mayrhofer M, Rydåker M, Akerud H, Isaksson A.
19. Genes Brain Behav. 2012 Nov 12.. Brain gene expression differences are associated with abnormal tail biting behavior in pigs. Brunberg E, Jensen P, Isaksson A, Keeling LJ.
20. Epigenetics 2012. Dec 1; 7(12):1435-42. Distinct transcriptional control in major immunogenetic subsets of chronic lymphocytic leukemia exhibiting subset-biased global DNA methylation profiles. Kanduri M, Marincevic M, Halldórsdóttir AM, et al.
21. Int J Cancer. 2012 131(10):2264-73. CD99 is a novel prognostic stromal marker in non-small cell lung cancer Edlund K, Lindskog C, Saito A, et al.
22. Am J Hematol 2012 Apr;87(4):361-7. Mantle cell lymphoma displays a homogenous methylation profile: A comparative analysis with chronic lymphocytic leukemia. Halldórsdóttir AM, Kanduri M, Marincevic M, et al.
23. Clin Cancer Res. 2012 May 1;18(9):2695-703.. A comprehensive analysis of human gene expression profiles identifies stromal immunoglobulin kappa C as a compatible prognostic marker in human solid tumors. Schmidt M, Hellwig B, Hammad et al.
24. Virology. 2012 Mar 15;424(2):115-28. The transcriptome of the adenovirus infected cell. Zhao H, Dahlö M, Isaksson A, Syvänen AC, Pettersson U.
25. Leukemia. 2013 Jan;27(1):150-8. 450K-array analysis of chronic lymphocytic leukemia cells reveals global DNA methylation to be relatively stable over time and similar in resting and proliferative compartments. Cahill N, Bergh AC, Kanduri M, Göransson-Kultima H, Mansouri L, Isaksson A, Ryan F, Smedby KE, Juliusson G, Sundström C, Rosén A, Rosenquist R.
26. PLoS ONE. 2013 Jun 18; 8(6):e66513. Behavioural and Brain Gene Expression Profiling in Pigs During Tail Biting Outbreaks - Evidence of a Tail Biting Resistant Phenotype Brunberg E, Jensen P, Isaksson A, Keeling L.
27. Sooman, L.; Ekman, S.; Andersson, C.; Johansson, F.; Goransson-Kultima, H.; Isaksson, A.; Bergqvist, M.; Blomquist, E.; Lennartsson, J.; Gullbo, J. 2012. 1012 Synergistic Effects of PI3K or P38 MAPK Inhibition in Combination With Vandetanib Treatment in Glioblastoma Cells. *European Journal of Cancer* vol. 48 July, 2012. p. S244
28. Cancer Chemotherapy and Pharmacology Aug;72(2):329-40. 2013. Synergistic interactions between camptothecin and EGFR or RAC1 inhibitors and between imatinib and Notch signaling or RAC1 inhibitors in glioblastoma cell lines. Sooman L, Ekman S, Andersson C, et al.

Awards and Appointments 2014

Ann-Christine Syvänen - the Rudbeck Medal for 2014, for her prominent scientific achievements at Uppsala University.

Erik Ingelsson – Recipient of ERC Starting Grant, European Research Council, and Academy Fellow, Knut och Alice Wallenberg Foundation.

Björn Olsen - The Linnaeus Medal, Uppsala The gold medal is conferred "for truly outstanding scientific achievement, especially in the Linnaean subject areas but also for meritorious furtherance of the legacy of Linnaeus or Uppsala University.

Per-Ola Carlsson - The 2014 DPLU/LUDC Nordic prize for an Outstanding Young Diabetes Investigator.

Åsa Hedman – Winner of Linnéus Foundation for Medical Research.