UPPSALA
UNIVERSITET

Department of Medical Sciences

Annual Report 2013

Fastställd av Eva Tiensuu Jansson 2013-05-09

Introduction

Following the trend from recent years, 2013 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 are 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 revenues increased with 5 % to 244 MSEK, which can be attributed to the ability of the researchers at the Department to attract grants from e.g. the Swedish Research council, the Cancer Society, the Swedish Heart&Lung Fondation and from the EU, from which for example professor Erik Ingelsson was awarded the prestigious ERC starting grant. Last year professor Lars Rönnblom together with coinvestigators also were awarded 28 million SEK from AstraZeneca/SciLife for a five-year project aiming to dissect disease mechanisms in three systemic inflammatory autoimmune diseases with an interferon signature. 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.

The performance of the Department's research groups is also shown by the close to 600 peer reviewed publications during 2013, an increase with 10% from 2012, and by the 14 theses produced during 2013. 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 2013 by researchers at the Department will be presented on the following pages.

During the year much effort has been spent on the planning of moving from the outdated laboratory premises at the University Hospital. The first to move were the Molecular Medicine group and the two platforms which relocated to the new Science for Life Laboratory at BMC. This year other research groups will move to the Rudbeck laboratory, and in 2015 additional group will follow after completion of the new building at Rudbeck. Although there will be clear benefits with moving to new modern laboratory facilities, the increased physical distance to the hospital will become a disadvantage for all scientists performing clinical work.

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 2013 a few persons retired after long and very successful careers. On behalf of the Department I would like to thank professor Anders Vahlquist and professor Kjell Öberg, our former chairman and dean, for their long services and many important contributions. I also would like to welcome Jan Eriksson as new professor and group leader for Clinical Diabetology and Metabolism. Finally, I would like to conclude by thanking all personnel at the Department for their dedicated work during 2013.

Eva Tiensuu Janson
Head of department

Contents

Organization of the Department of Medical Sciences

Chair, head of department

Eva Tiensuu Janson

Deputy head of department

Lars Lind

Assistant heads of department

Jan Sjölin, responsible for graduate studies

Christer Janson, responsible for undergraduate studies

Department board

Eva Tiensuu Janson	chair
Jan Sjölin	teacher
Håkan Melhus	teacher
Johan Sundström	teacher
Lars Rönnblom	teacher
Birgitta Sembrant	technical staff
Markus Mayrhofer	PhD student
Sandra Porath	student representative
Vacant	student representative

Deputies

Marie Thörn	teacher
Torbjörn Linde	teacher
Christer Janson	teacher
Hans Törmä	teacher
Karin Eriksson	technical staff
Oskar Eriksson	PhD student
Vacant	student representative
Vacant	student representative

Group leaders 2013

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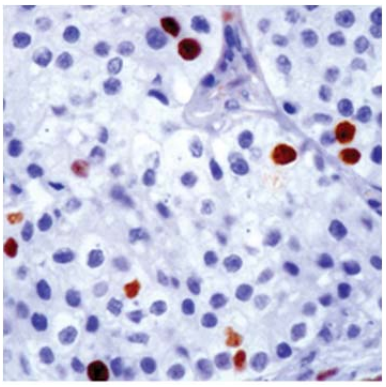
Funding 2013

GRANTS	
SWEDISH RESEARCH COUNCIL	24,5 MSEK
SIDA *(Swedish International Development Cooperation Agency)*	11 MSEK
THE SWEDISH RESEARCH COUNCIL FORMAS	8,6 MSEK
THE SWEDISH HEART-LUNG FOUNDATION	6,4 MSEK
EU (7^{th} FRAME PROGRAMS)	9,8 MSEK
VINNOVA	3,2 MSEK
SWEDISH FOUNDATION FOR STRATEGIC RESEARCH	9,5 MSEK
THE SWEDISH CANCER FOUNDATION	3,6 MSEK
SWEDISH RESEARCH COUNCIL FOR HEALTH, WORKING LIFE AND WELFARE (FORTE)	4,2 MSEK
RAGNAR SÖDERBERG'S FOUNDATION	7,1 MSEK
OTHER FUNDINGS	20,5 MSEK
GOVERNMENT FOR RESEARCH (ALF) - FUNDING	48 MSEK
GOVERNMENT OFFICE	2,6 MSEK
SUBTOTAL	**159 MSEK**
CONTRACT RESEARCH	
VARIOUS COMMISSIONING AGENTS	6,8 MSEK
TOTAL	**166 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 comput-ational 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

Abir Ali, Staffan Welin and Eva Tiensuu Janson

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.

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 Naesser, Clary Georganzi, Sandra Irenaeus 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. We have a special focus on the proliferation marker Ki67, and have shown that even very small increases of proliferation in SI-NETs may have an impact on the survival of patients. This is further investigated in larger cohorts to confirm our previous results. Another 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. In related projects we have e.g. 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.

Studies of neuroendocrine carcinomas (NEC)

Staffan Welin, Abir Ali, Ylva Naesser 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. We are also initiating a clinical trial with a new combination of drugs for the subgroup of patients with a lower Ki67.

Members of the group during 2013

Eva Tiensuu Janson, Professor of Medicine
Staffan Welin, MD, PhD
Malin Grönberg, PhD
Abir Ali, PhD student
Ylva Naesser MD, PhD-student
Sandra Irenaeus, MD, PhD-student
Anthoula Koliadi, MD, PhD-student
Clary Georgantzi MD, PhD-student

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.

OR51E1 as a novel therapeutic target

OR51E1 (olfactory receptor family 51subfamily E, member 1) is a G-protein couples receptor that has been detected at the transcriptional level in normal EC cells and SI-NET cells. We have characterized the expression of OR51E1 in more detail, using Q-RT-PCR and immunohistochemistry analyses on tumour slides. OR51E1 is expressed in approximately 50 % of SI-NET tumour cells, and over 25% of liver metastasis, but not in normal hepatocytes. Thus, high expression in a subgroup of patients might render OR51E1 a novel tissue marker and may be developed as a radiological diagnostic tool and/or a therapeutic target.

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 2013

Kjell Öberg, Professor, MD, PhD
Valeria Giandomenico, PhD
Dan Granberg, MD, PhD
Tao Cui, PhD student
Su-Chen Li, PhD student

Funding

Eva Tiensuu Janson

Swedish Cancer foundation:	600 kSEK,
ALF:	650 kSEK
Lions Cancer Foundation	100 kSEK

Malin Grönberg

Selanders:	70 kSEK

Kjell Öberg

Novartis:	750 kSEK
ALF:	800 kSEK

Valeria Giandomenico

Novartis:	300 kSEK
Selanders foundation:	100 kSEK

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Reviews

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Dissertations

Tao Cui: Novel Circulating and Tissue Biomarkers for Small Intestine Neuroendocrine Tumors and Lung Carcinoids

Haematology

Martin Höglund

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

- Development and testing 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)

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.

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.

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

Gunnar Larfors, Emma Bergfelt, Elisabeth Ejerblad, Martin Höglund, Helene Hallböök,

The Swedish population based registries in patients with haematological malignancies are internationally unique. Presently, more than 1000 patients with CMLand more than 5000 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 on the pharmacoepidemiology in CML.

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. Before treatment and at different time-points the patients donate blood for research purposes. 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. At Uppsala University Hospital clinical trials on myeloma patients are ongoing in collaboration with e.g. Dept. of Radiology. In collaboration with the PET-imaging centre and cardiologic expertise a pilot 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

Gunnar Birgegård, Elisabeth Ejerblad, 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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Publications 2011-2013

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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, 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 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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Funding 2013

Swedish Cancer Foundation	1000 tSEK	ALF	1300 tSEK
Swedish Strategic Foundation	2400 tSEK	KAW	1000 tSEK
Proactive EU project	900 tSEK	VR	360 tSEK
Oncopeptides	350 tSEK	FORMAS	1100 tSEK
Akinion AB	300 tSEK	NordForsk	250 tSEK

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Endocrine tumour biology

Britt Skogseid

Researchers in our translational group, the Endocrine Tumor Biology 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 the clinics, i.e. Endocrine oncology and Endocrine surgery, and thus have the opportunity run clinical trials and work on the comprehensive patient and tumor material that have been collected since more than 30 years. We also have a multiple endocrine neoplasia type 1 (MEN1) conventional knock-out mouse strain that mimic the human disease (below) very well. During 2013 the group has included two new researchers; a specialist of pre-clinical PET-technique, and one with experience of studies of signal transduction in cancer.

MEN1 is an autosomal dominant disease caused by a mutation in a tumor suppressor gene (MEN1). Gene carriers develop multiple tumors of the parathyroids, endocrine pancreas and pituitary. We have developed biochemical screening programs for early detection of lesions, performed longitudinal studies of large MEN 1 families, and instituted early interventions allowing unique possibilities to prospectively observe tumorigenesis in endocrine tissues. The MEN 1 gene was cloned in 1997 and now more than 1000 disease related mutations have been identified, though no obvious genotype-phenotype correlation has yet been revealed. The protein is called menin and is ubiquitously expressed. Why MEN1 gene inactivation leads to tumor formation only in some organs is unclear. The main death cause is the pancreatic endocrine tumors. Seemingly, the MEN1 gene is involved in the endocrine differentiation of the pancreas and may be a haploinsufficient tumor suppressor gene.

Studies of the endocrine pancreas and adrenal gland

- Molecular events in pancreatic endocrine transformation, apart from inactivation of the MEN1 gene, remain poorly characterized. We study down-stream effects of altered MEN1 gene expression by transfections and RNA interference using expression microarrays, quantitative PCR and proteomics.
- In order to prolong survival and ameliorate suffering we continue to evaluate and refine our management strategies for patients with MEN1 as well as applied treatment protocols for patients with advanced neuroendocrine tumors of the pancreas
- Molecular events in pancreatic endocrine transformation, apart from inactivation of the MEN1 gene, remain poorly characterized. We proceed with efforts to determine the physiological role of the MEN1 gene in tumorigenesis by studying its molecular effects in endocrine tissue
- Characterize the early events in transformation of endocrine pancreatic cells and adrenals by means of proteomic analysis and studies of angiogenesis, thus pursuing indications of MEN1 being a haploinsufficient suppressor gene
- 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..

FIRM-ACT study

Adrenocortical carcinoma (ACC) is a rare disease with an extremely poor prognosis. The incidence has been estimated to 1-2 per million per year. The median survival for patients with metastatic disease is 25 weeks. Due to low incidence, single centers or even single countries have been unable to collect sufficient number of patients to conduct a reliable evaluation of treatment options. Thus, choice of therapy is vastly based on local experience and data from uncontrolled trials. In 2004 we started an investigator-initiated initiated academic (not sponsored by pharmaceutical companies) international phase III trial (the FIRM-ACT study) comparing 2 chemotherapeutical regimens for treatment of advanced ACC. The study ran in 12 counties. It has been finalized and the results are published in N Engl J Med 2012; 3662189-2197. The clinical impact following the publication is substantial; The study established a benchmark therapy;

cisplatin, etoposide, doxorubicin in combination with mitotane (EDP+M) as first line therapy in advanced ACC. A study of mitotane pharmacokinetics in ACC patients have also recently been published. 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; High dose cisplatin (metronomic) vs EDP+M within the FIRM-ACT investigator network. Initiative for this study comes from our group and Prof Tito Fojo at NIH. Study chair and webmaster service as well as data collection will be run from Uppsala. Writing of study protocol, ethical considerations/application and the eCRF construction is ongoing.
- Participate in a EU-financed study of the role of different PET tracers for diagnosis of ACC, the FAMIAN study. PI Prof Bruno Allolio, Wurtzburg, Germany.
  ongoing, but preliminary data indicate that first line treatment with EDP/M is beneficial for the patient.

Members of the group 2013

Britt Skogseid, professor

Peter Stålberg, MD, assoc. professor

Barbro Eriksson, professor

Mikael Björk, research nurse and system developer

Andreea Barbu, senior researcher, PhD

Azita Monazzam, PhD, researcher

Margareta Halin Lejonklou, PhD

Mårten Santesson, MD, PhD student

Monica Hurtig, research nurse

Masoud Razmara, PhD, technician

Pantelis Antonodimitrakis, MD

Xia Chu, PhD-student

Örjan Linde, researcher, PhD

Lillebil Andersson, secretary

Publications 2011-2013

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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 2013

Mats Stridsberg, MD, PhD, Assoc. Prof.

Torbjörn Åkerfeldt, MD, PhD student

Funding

ALF

Lions Research Foundation

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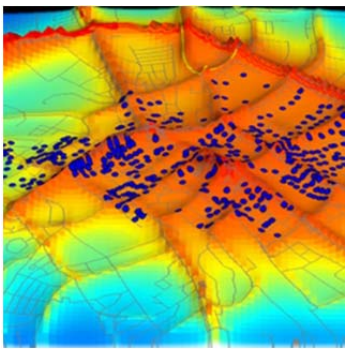
Epidemiology



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 Malmö/Lund and Uppsala 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.

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, 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.

Members of the group during 2013

Lars Lind, MD, professor
Andreas Terént, MD, professor
Johan Sundström, MD, assoc professor
Anders Holmlund, PhD
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Jessika Andersson, MD, PhD-student
Gabriel Arefalk, PhD-student
Tomas Cars, PhD-student
Said Mashia, MD, PhD-student
Kasper Andersen, MD, PhD-student

Funding

Lars Lind

Swedish Research Council	1.0 MSEK
ALF	2.0 MSEK
Hjärt-Lungfonden	2.3 MSEK
EpiHealth	3.0 MSEK

Johan Sundström

Swedish Research Council	0.7 MSEK
ALF	0.2 M SEK
Heart & Lung Foundation	0.3 MSEK

Publications 2011-2013

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2. Barbier C, Nylander R, Themudo R, et al. Prevalence of unrecognized myocardial infarction detected with magnetic resonance imaging and its relationship to cerebral ischemic lesions in both sexes. Journal of the American College of Cardiology. 2011;58(13):1372-1377.
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4. Debette S, Visvikis-Siest S, Chen M, et al. Identification of cis- and trans-Acting Genetic Variants Explaining Up to Half the Variation in Circulating Vascular Endothelial Growth Factor Levels. Circulation Research. 2011;109(5):554-563.
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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 during the spring 2013. Our next phase is to contact children from the RHINE cohort through a web based survey which will be done in the autumn this year.

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. Participants from the MIDAS and GA2LEN study are also being included in a genetical project lead by Prof Dumanski at the Department of Genetics and Pathology which has been sponsored as a pilot project in the Science for Life initiative. A follow up of the MIDAS study will start during this year.

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. This year a new sample of patients will be 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.

Sleep and Health

Eva Lindberg

About 18% of men and 9% of women suffer from obstructive sleep apnea and every fourth of them display severe daytime symptoms requiring treatment. Despite that, the knowledge about long-time evolution and consequences 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 we have been working on a unique 10-year follow-up of a

community-based cohort of women including repeated full-night polysomnography that will be ongoing until 2014.

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. During 2013 we started 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.

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 obstructive pulmonary disease (COPD). A low physical activity and capacity 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 of a behaviour medicine intervention in COPD patients, who have participated in a rehabilitation program. Two cites in primary care have been included in 2013 and 2014 in order to recruit more patients.

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 desaturate during exercise. Recruiting is still ongoing.

In 2013 we started collaboration with the Departments of Women's and Children's Health and Surgical Sciences investigating reasons for exercise-induced breathing problems in adolescents. A population based survey has been performed. Exercise provocation tests to investigate bronchial and laryngeal obstruction have been performed in 150 subjects. Further analyses of blood samples and accelerometers to assess physical activity will start this semester.

The TRIAD study including 100 COPD patients performed together with the University of Gothenburg are now investigating 4-year follow-up results.

Members of the group during 2013

Christer Janson, MD, PhD, professor
Eva Lindberg, MD, PhD, professor
Margareta Emtner, PT, PhD, assoc prof
Agneta Markström, MD, PhD, assoc professor
Jan-Erik Broman, RN, PhD, assoc professor
Gunnar Boman, MD, PhD, prof emeritus
María Gunnbjörnsdottir, MD, PhD
Inger Dahlén, MD PhD
Mary Kämpe MD, PhD
Inga Sif Olafsdottir MD, PhD
Andrei Malinovschi, MD, PhD
Jenny Theorell Haglöw RN, PhD
Malin Svensson, MD, PhD
Robert Moverare PhD
Rain Jögi, MD, PhD
Harpa Arnardottir PT, PhD
Mats Arne, PT, PhD
Martin Sandelin MD, PhD student
Mirjam Lunggren MD, PhD student
Antonis Patelis MD, PhD student
Carina Hagman PT, PhD student
Guihong Cai, PhD student
Fredrik Sundbom, PhD student
Michael Smith, PhD student
Sören Spörndly-Nees, PhD student
Andreas Palm, PhD student
Caroline Bengtsson, PhD student
Helena Igelström PT, PhD student

Mikael Andersson PT, PhD student
Henrik Johansson PT, PhD student
Kristina Lamberg MD, Clinician
Carl-Axel Karlsson MD, Clinician
Katarina Nisser, RN
Ulrike Spetz-Nyström, RN
Gunilla Hägg, NA
Birgitta Andersson, RN
Shumi Omar RN
Gun-Marie Bodman Lund, secretary

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Christer Jansson

Heart and Lung Foundation	700 kSEK
Astma- and Allergy Foundation	200 kSEK

Eva Lindberg

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Swe Soc. of Heart&Lung diseases	180 kSEK
Uppsala-Örebro RRC	350 kSEK

Margareta Emtner

Uppsala University	800 kSEK

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Clinical Pharmacogenetics and Osteoporosis

Håkan Melhus, Mia Wadelius, Pär Hallberg and GabrielllaScordo

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

In 2013 we published the EU FP7 funded randomised clinical trial comparing pharmacogenetic dosing of warfarin with standard dosing (EU-PACT). In her thesis Anna-Karin Hamberg presented a clinically useful PKPD-based pharmacometric model for warfarin that is applicable to both adults and children. We have also continued our collaboration with the International Warfarin Pharmacogenetics Consortium (IWPC) and are doing a meta-analysis of GWAS on warfarin dose requirements.

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 1700 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. Over 6000 non-related Swedes with genome-wide data are used as population controls.

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.

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 chemical

Members of the group during 2013

Håkan Melhus, Professor
Mia Wadelius, MD Lecturer
Pär Hallberg, MD PhD
Gabriella Scordo, MD PhD
Thomas Lind, Researcher, PhD
Annica Jacobson Rasmussen, Researcher, PhD
Fredrik Stiger, PhD student
Anna-Alassaad, PhD student
Gabriela Rosén, Research engineer
Anna-Karin Hamberg, Pharmacist PhD
Niclas Eriksson, Statistician PhD
Sofie Collin, Research assistant
Eva Prado, Research assistant
Ulrica Ramqvist, Research nurse
Elisabet Stjernberg, Research nurse
Jenny Thunberg, Research nurse
Maria Röjstad, Research nurse
Victoria Wallin, Research nurse
Hugo Kohnke, Biomedical analyst MSc

Funding 2013

Håkan Melhus:

VR	1000 kSEK
ALF	400 kSEK

Pär Hallberg:

Swedish Society of Medicine	166 kSEK
Medical Products Agency	150 kSEK

Mia Wadelius:

Heart & Lung foundation	600 kSEK
Swedish Research Council	1250 kSEK
ALF	540 kSEK
EU FP7 (EU-PACT 2012-2013)	925 kSEK
EU FP7 (PREDICTION-ADR)	1378 kSEK
Selander's foundation	100 kSEK
Thuréus' foundation	130 kSEK

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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. 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 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

FAS	1.0 MSEK

Dan Norbäck

Astma och allergiförb.	240 kSEK
SIDA	250 kSEK

Karin Engvall

FORMAS	850 kSEK
NCC	100 kSEK

Monica Lind

FORMAS	2.5MSEK

Margareta Torgén

FAS	250 kSEK

Magnus Svartengren

FAS	2.6 MSEK
AFA	2.4 MSEK

Members of the group during 2013

Eva Vingård, Professor, MD

Ingvar Lundberg, 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

Helena Anundi, PhD

Roma Runeson Broberg, PhD

Margareta Torgén, PhD, MD

Karin Engvall, PhD

Xi Fu, PhD

Kristina Gunnarsson, PhD

Bo Sahlberg, PhD

Guihong, Cai, PhD

Mostafa Ghaffari, PhD

Hans Goine, PhD

Margareta Halin Lejonklou, Postdoc

Bo Johansson, Researcher

Johanna Penell, Researcher

Pia Rehfisch, Researcher, MD

Martin Toldel, Researcher, MD

Zhuohui Zhao, Researcher

Monica Rönn, PhD

Åsa Stöllman, Psychologist

Hassan Alinaghizadeh, Statistician

Kaj Elgstrand, Adminsitrator

Tomas Eriksson, Investigator

Miles Goldstick Web editor

Magnus Helgesson, Med.lic

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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 2011-2013

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Dissertations 2013

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

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 (**Figure**).

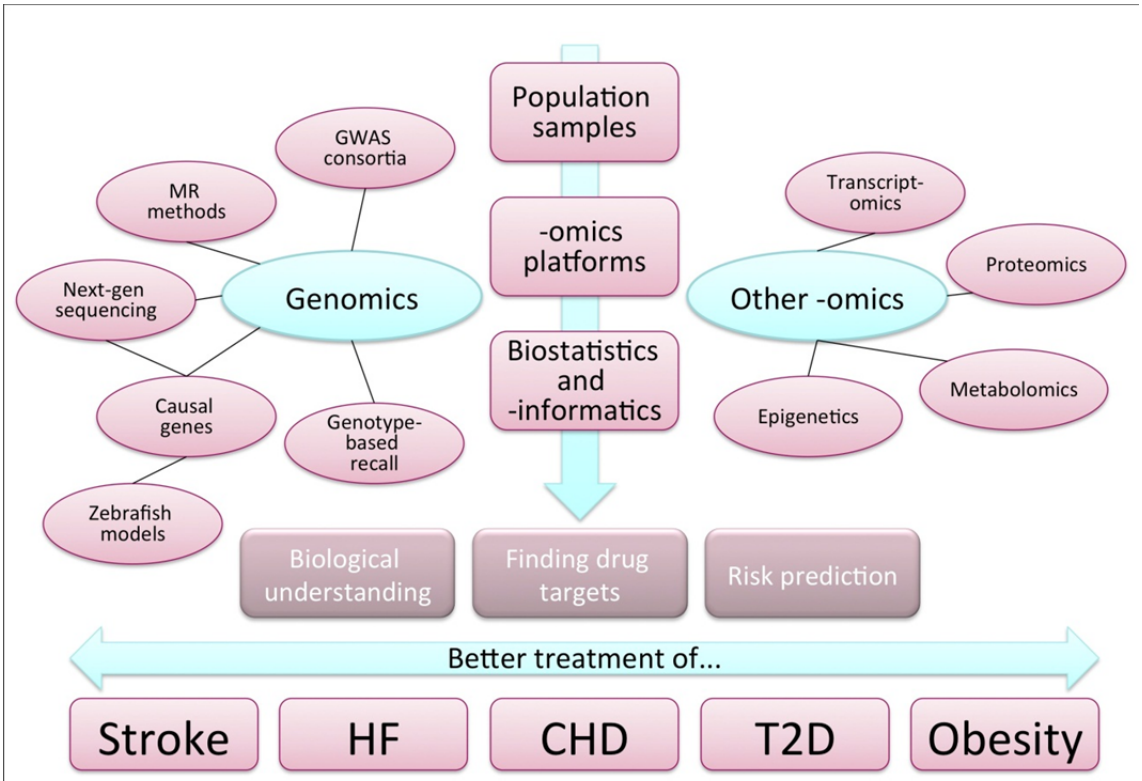

Figure. Overview of our current research program

There is a large need for revitalization of the research on cardiovascular diseases and related conditions including: a) improved risk prediction and more adequate individually-tailored treatment; and b) new targets for drug development based on pathways previously unknown to be involved in CHD pathophysiology.

Our ambition is to be an international, vibrant and creative research environment with many exciting projects within large-scale genetic and biomarker projects. Our research is projected to lead to new important insights of disease mechanisms, which in turn can facilitate development of new treatments of these diseases, as well as to new biomarkers of disease for improved risk prediction and prognostication.

Members of the group during 2013

Erik Ingelsson, MD, professor
Tove Fall, associate professor
Marcel den Hoed, scientist
Sara Hägg, scientist
Jitender Kumar, postdoc
Åsa Hedman, postdoc
Samira Salihovic, postdoc
Stefan Gustafsson, bioinformatician
Andrea Ganna, PhD-student
Ci Song, PhD-student
Anastasia Emmanouilidou, research engineer
Tiffany Klingström, research assistant
Manoj Bandaru, research assistant
Åsa Michelgård Palmquist, research coordinator

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
Planning of a Swedish node in European Advanced Translational Research InfraStructure in Medicine (EATRIS.se)	Ingelsson	Swedish Research Council	2014-2015	200 000
Cardiomics: Integration of -omics methods for identification of novel drug targets and clinical biomarkers for coronary heart disease	Ingelsson	Swedish Heart-Lung Foundation	2013-2014	1 200 000
		Swedish Research Council	2013-2015	4 500 000
		KI fonder	2012	152 500
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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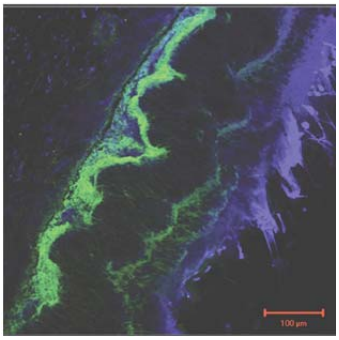
Dissertations 2013

Stefan Gustafsson: Adiponectin: Genetic determinants and relations with subclinical cardiovascular disease (Karolinska Institutet)

He Gao: Genetic predisposition and dietary factors in relation to adiponectin and insulin resistance (Karolinska Institutet)

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.



Autoimmunity

Olle Kämpe

Autoimmune disorders account for one third of morbidity and mortality in the Western world. It is thus of great clinical interest to better understand the underlying factors and develop better diagnostic tools.

Using Addison's disease and Autoimmune Polyendocrine Syndrome type 1 (APS 1) as model disorders, our research group has improved the diagnostic methods in autoimmune disorders and identified a number of autoantigens, e.g. 21 hydroxylase in Addison's disease (Winqvist, Lancet 1992), tryptophan hydroxylase in malabsorption associated with APS-1 (Ekwall, Lancet 1998), SOX10 in vitiligo (Hedstrand, J Biol Chem 2001), TDRD6 in lymphocytic hypophysitis (Bensing, Proc Natl Acad Sci USA 2009), and more recently NALP5 in hypoparathyroidism (AliMohammadi, N Engl J Med 2008) and KCNRG in a severe form of lung disease (AliMohammadi, Proc Natl Acad Sci USA 2009).

In recent years, the research has expanded to include epidemiologic investigations of endocrine autoimmune disorders and genetic studies using the dog and the chicken as tools to better understand human autoimmune disease.

Olle Kämpe was the principal coordinator of a recently finished EU-project (www.apeced.net) and is the work-package coordinator of two ongoing EU-projects (www.euradrenal.org and www.eurolupa.org).

Immunological studies of target structures for T- and B-cells using Addison's disease and APS I as models

Olle Kämpe, Mohammad AliMohammadi, Sophie Bensing, Åsa Hallgren, Håkan Hedstrand, Eva Landgren, Thomas Nilsson, Filip Sköldberg

a) Identification of a pulmonary autoantigen

b) Identification of autoantigens in uvea and cornea

c) Identification of autoantigens in the kidney

d) Identification of autoantigens in paraneoplastic disorders

Epidemiology of autoimmune polyendocrine syndromes

Olle Kämpe, Sophie Bensing, Sigridur Björnsdottir, Beatrice Kennedy, Tove Fall, Katja Fall, Lena Brandt, Nancy Pedersen, Paul Blomqvist, Anders Ekbom

a) Continuation of the nation-wide registry and biobank for Addison's disease

b) Risk of prematurity in children of mothers with Addison's disease

c) Risk of fractures in patients with autoimmune Addison's disease

d) Heritability between twins of different autoimmune disorders

e) Combining human and canine epidemiology to investigate if there are any relations between diseases in the dog and in the dog-owner's family

Comparative genomics

Olle Kämpe, Kerstin Ahlgren, Göran Andersson, Leif Andersson, Örjan Carlborg, Lucy Crooks, Olov Ekwall, Tove Fall, Katarina Sundberg, Åsa Hallgren, Anna Lobell, Hélène Hamlin, Susanne Kerje, Åke Hedhammar, Kerstin Lindblad-Toh, Anna-Stina Sahlqvist, Katarina Tengvall and others.

a) Linkage analysis in three chicken models for spontaneous autoimmune disorders, namely the OS-line for thyroiditis, the Smyth line for vitiligo and the UCD 200-line for scleroderma.

b) GWAS for autoimmune disorders in different breeds of dogs, namely Addison's disease, Canine diabetes mellitus, and lymphocytic thyroiditis

For more information:

http://www.medsci.uu.se/fogrupp/autoimmun/autoimmun.htm

Members of the group during 2013

Olle Kämpe, MD, PhD, professor
Susanne Kerje, PhD
Sophie Bensing, MD, PhD
Mohammad AliMohammadi, MD, PhD
Håkan Hedstrand, MD, PhD
Eva Landgren, MD, PhD
Thomas Nilsson, MD, PhD
Åsa Hallgren, first research engineer
Anna-Stina Sahlqvist, PhD-student
Kerstin Ahlgren, PhD-student
Magnus Isacsson, MD, PhD-student
Frida Dahlin, PhD-student
Beatrice Kennedy, MD, PhD-student
Nils Landegren, MD, PhD-student

Funding

Swedish Research Council	0.7 MSEK
Nordic research Committee	0.8 MSEK
ALF	1.8 MSEK

Publications 2011-2013

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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.

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

Johan Stålberg, Elin Nilsson, 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 have received a grant from Uppsala Bio to conduct a clinical study on ESBL-carriers in Uppland and an EU grant (EUR 5.35 million over a 4 year period) for a clinical multicenter study to prevent pseudomonas infections in CF patients.

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 the role of prostasome in fertility and prostate cancer

Göran Ronquist, Lena Carlsson, Gunnar Ronquist, Anders Larsson

We discovered the prostasomes more than 30 years ago and named them. 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).

Studies of cystatin C and inflammation markers

Mats Flodin, Lars-Olof Hansson, Anders Larsson

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. 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.

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

Johanna Helmersson Karlqvist, Anders Larsson

The 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) are mainly evaluated 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.

Members of the group during 2013

Anders Larsson, professor/consultant

Lena Carlsson, post doc

Karin Eriksson, laboratory engineer

Mats Flodin, laboratory engineer

Tom Nilsen, PhD student

Peter Ridefelt, associate professor/consultant

Gunnar Ronquist, professor em.

Göran Ronquist, post doc

Ingvar Ryden, post doc

Leif Wide, professor em

Johanna Helmersson-Karlqvist, post doc/consultant

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Impactt, FP7	2 000 kSEK
Swedish Research Council	350 kSEK
Eurostar	380 kSEK

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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. The ultimate goal being to identify novel mechanisms, genetic, epigenetic and microRNAs, governing tissue factor gene regulation.

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 roles

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 recently reported that TF/FVIIa induces the transactivation of the PDGFRβ, and thereby identified a new signalling pathway involved in cell migration. We continue to investigate how TF interacts with PDGFRβ and other growth factor receptors. We hypothesize that several of the non-haemostatic functions of TF are dependent on growth factor activity and aim to clarify what role growth factor receptor signalling play in these functions of TF.

During the year we have also focused on I) connections between TF cytoplasmic domain and the cytoskeleton and II) mechanism involved in TF-dependent antiapoptotic effects. Using a peptide microarray we have characterized the interaction of TF with the actin-crosslinking protein Filamin A, and shown for the first time that TF-signalling reduces activation of caspase-8 through a reduction of the “death associated protein kinase 1 (DAPK1).

Identification of biomarkers in atherothromboembolic diseases

We have established individual responses to drug treatment with an oral thrombin inhibitor (DTI) and that treatment can be monitored in ACS by measurements of biomarkers, such as D-dimer. We now report a persistent elevation of platelet activity in a myocardial infarction population after the cessation of the acute antithrombotic treatment and that the addition of an oral DTI diminishes the platelet activity. In contrast, long-term treatment with a DTI increased several markers of inflammation.

Biobanks from international prospective clinical trials have been established at the UCR-laboratory during the last 2 years. DNA and plasma samples from patient materials (including around 70.000 patients) in acute and chronic CAD and AF have been accumulated from a large number of trials, e.g. PLATO - on new P2Y12 inhibitor ticagrelor in ACS (n=18000), and ARISTOTLE - on new oral factor Xa inhibitor apixaban in AF (n=18000). 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, performed at the UCR-laboratory and to translate candidate genes and proteins into functional studies. Based on these studies we will establish sensitive and rapid tests for clinical purposes.

Collaborations with several groups within the SciLife laboratory have started during the year. Plasma samples from our well-characterized patients with CAD are used in a new plasma proteomic multiplex assay and with Professor Ulf Landegren using proximity ligation assay. The purpose is to identify new biomarkers and establish methods with higher sensitivity to be used in the understanding of pathophysiologic mechanisms, diagnosis and for estimation of prognosis and treatment efficacy in these diseases.

Members of the group during 2013

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Christina Christersson

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Dariush Mokhtari

Göran Gustafsson's stift.	850 kSEK
Anér's stiftelse:	100 kSEK

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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 inflammatory process in psoriasis and palmo-plantar pustulosis (PPP) is investigated in vivo and in vitro. Experimental models have been established to discover new strategies for treating psoriasis based on inhibition of EGF signalling. Clinical characteristics and serologic markers are also studied in autoimmune disorders of the skin. The treatment of hyperhidrosis using botulinum toxin is also being developed.

During 2013 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 in siRNA knock-down keratinocytes exposed to retinoids and other drug candidates.

The skin barrier function and mRNA expression profile is examined *in vivo* after topical application of moisturizers with various compositions in patients with mutations in profilaggrin (atopic dermatitis and ichthyosis vulgaris) or steroid sulfatase (X-linked ichthyosis). Huge differences in the expression of barrier repair genes have been noted between the two types of ichthyosis, which may explain an association between dermatitis and ichthyosis in the former case.

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.

Pathogenic mechanisms in palmo-plantar pustulosis

Eva Hagforsen

Palmo-plantar pustulosis (PPP) is a complex autoimmune disease precipated by smoking. PPP is characterized by redness, scaling and pustules on the palms / soles. The disease mainly affects women who smoke and are very resistant to treatment. Immunohistochemical studies are performed to understand the inflammation in PPP, which mainly affects the outer portion of the sweat ducts (the acrosyringium

Members of the group during 2013

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Swedish Research Council	600 kSEK
Foundation of Ichthyosis and Related Skin Types	500 kSEK
Dermatology fund (total)	1325 kSEK
Psoriasis Foundation	100 kSEK
ALF (Vahlquist, Berne, Rollman)	1100 kSEK
Other funds	625 kSEK

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Dissertations 2013

Torborg Sturesdotter Hoppe - Skin Barrier Function and mRNA Expression Profiles in Patients with Atopic Dermatitis, Ichthyosis Vulgaris, and X-linked Recessive Ichthyosis : Aetiopathogenic Differences and the Impact of Moisturizing Treatment

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, special attention is given to inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis) and microscopic colitides (collagenous colitis, lymphocytic colitis) as well as inflammatory liver disease and anemia as complications of IBD. Etiopathogenic perspectives of disease are covered through studies on the commensal microflora, cytomegalovirus infections and eosinophilic granulocyte invasion in IBD. Different biomarkers of inflammation are studied and evaluated as regards their usefulness as predictors of disease progression. Special attention is given to the biomarkers nitric oxide (NO), tumour necrosis factor (TNF), interleukin-1beta, and interferon gamma, as well as interleukin-2 and interleukin-17, metalloproteinases and CXCL2; all of which indicative of an inflammatory process. In addition, regulatory gut peptide functions are studied in IBD as compared to irritable bowel syndrome (IBS). In IBD, biomarkers elaborated in close proximity to the site of inflammation, such as eosinophil cationic protein and eosinophil protein X are studied in relation to the gut inflammatory process mirrored by fecal calprotectin, myeloperoxidase, tryptase and C-reactive protein (CRP). Parallel research programs with their basis in epidemiology, biochemistry, immunology and pathophysiology are conjoined to focus on mechanisms underlying IBD and biomarkers of inflammatory reactions primarily in the liver and colon, causing primary sclerosing cholangitis and malignant disease. Specifically, diagnostic procedures for prediction of malignant liver disease in primary 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 autoinflammatory reactions in the gut.

In addition, metabolic research focusing on gastric emptying and enteric dysmotility as the primary steps in the endocrine cascade after food intake is studied. In broad collaboration, work has been carried out to study the importance of gastric emptying in obesity 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
- Genes encoding inflammatory marker proteins in IBD
- Cytomegalovirus and commensal gut microflora as pathogen in IBD
- Nitric oxide, nitrite and nitrate in the inflammatory response of the gut
- Pathogenic mechanisms in microscopic colitis
- Eosinophilic granulocyte activation, macrophage infiltration and apoptosis in IBD.
- Gastrointestinal permeability ("leaky gut") and endotoxemia in IBD and IBS
- Diagnostic and predictive markers of malignant development in IBD with primary sclerosing cholangitis

- Regulatory peptides hormones and drug development in gastroparesis, enteric dysmotility and metabolism
- Fecal inflammatory markers for diagnosis and monitoring of bowel graft-vs-host disease in allogenic bone marrow transplant
- Diagnosis and treatment of portal hypertension using transjugular intrahepatic portosystemic shunt (TIPSS)

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Marie Carlson

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Fredrik Rorsman

ALF	166 kSEK

Anders Rönnblom and Marie Törn

ALF	272 kSEK

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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 research. Since its start the group has worked towards this goal by creating close collaborations with clinical scientists at Uppsala 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.

Epigenetics and genomics of acute leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer in the Western world. Although there has recently been great progress in treatment protocols for ALL, 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 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 hematopoetic cells into leukemic cells, and how DNA-methylation affects treatment responses in acute leukemia. In the 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 Academic Children's Hospital in Uppsala. The project is funded by the Swedish Foundation for Strategic Research (SSF), the Swedish Cancer Foundation and 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 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. As partner of the EU FP7 “Geuvadis” consortium, the Molecular Medicine group and the SNP&SEQ Technology Platform worked together with 11 major sequencing and genotyping centers across Europe to define best laboratory practices for second generation

transcriptome and exome sequencing. This work resulted in high impact publications in Nature and Nature Biotechnology, respectively. The Molecular Medicine group is part of the EU FP7 “European Sequencing and Genotyping Infrastructure (ESGI)” to which it contributes by laboratory protocols for epigenetic analyses and bioinformatics tools for allele-specific gene expression, while the SNP&SEQ Platform offers transnational access to SNP genotyping and "next generation" DNA sequencing to European scientist. The Molecular Medicine group and the SNP&SEQ Platform also contribute to the EU FP7 project Prediction ADR, by "next generation" sequencing to detect genetic variants that cause adverse drug reactions (ADR). In addition to the European Commission, 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 2013

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

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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 Vassilis

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 Spirolactone may have a positive effect on cardiovascular morbidity and mortality in haemodialysis patients. Other trials involve e.g. studies in patients with early IgA nephropathy using a corticosteroid compound acting primarily in the gut (budesonide

Based on our substantial track record on both clinical and experimental studies in chronic allograft nephropathy (CAN), we are presently investigating early markers of CAN in biopsies, based upon findings from Tissue Micro Array investigations in lost grafts. Presently we are participating in three different treatment protocols which include switching of immunosuppressive regimen from calcineurine-based treatment to mycophenolate (TRANCEPT) or mTOR inhibitors (CONVERT and ASCERTAIN).

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.

Members of the group during 2013

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Inga Soveri, M.D., PhD
Natalia Ferraz, PhD, Postdoc
Per-Anton Westerberg, MD; PhD-student
Ulf Nisbeth, M.D, PhD-student
Eva Carlsson, MD, tentative PhD student
Liina Vassilis, MD, tentative PhD student
Hilde Kloster, PhD
Magnus Lindberg, RN, PhD-student
Åsa Lidman, Research nurse
Yvonne Lundholm, Research nurse

Funding 2013

ALF	700 kSEK
Swedish Research Council	600 kSEK
Industrial grants	700 kSEK
Uppsala-Örebro region Fou	100 kSEK

Publication 2011-2013

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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 research group and with the contribution of the Swedish SLE network. During 2013 we published together with our collaborator Prof. Pellegrini at Pasteur Institute that a risk polymorphism in signalling molecule TYK2, one our first identified SLE risk genes, causes impaired catalytic activity of Tyk2 protein (J Immunol 2013). We also discovered that an important transcription factor acting within the type I IFN system, IRF8, was associated with increased risk for coronary heart disease in SLE patients (Leonard, Circ Cardiovasc Genet 2013). During 2013 we have continued together with Prof. Tomi Pastinen at McGill University, Montreal, Canada to collect samples and analyse temporal epigenetic changes in regulatory DNA domains in purified B, T cells and monocytes from healthy individuals included in our Bioresource.

. 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 ($p<5x10-8$). Associations between primary Sjögren's syndrome and candidate susceptibility genes in the NK cell receptor gene NCR3 as well as in genes in the NF-kB signalling pathway have been published in collaboration with investigators from France and the UK. We have identified genetic variations associated with germinal centre-like formations in the labial salivary glands, which are important risk factors for lymphoma development.

Regulation of the type I interferon response by immune cells

During 2013 we published a study, in collaboration with Dr. Balboni at Stanford University, showing that the type I IFN signature in juvenile dermatomyositis is associated with the presence of autoantibodies to Ro/La and Sm/RNP complexes (Balboni, Arthritis and Rheum 2013). We have also discovered and characterized autoantibodies to NKG2A in patients with SLE, and investigated the prevalence of these autoantibodies in large SLE and pSS cohorts. The anti-NKG2A autoantibodies impaired the NKG2A-mediated inhibition of NK cell activation, and their presence was associated with high SLE disease activity and increased serum IFN-α levels in SLE patients (Hagberg, Rheumatology, 2013).. During 2013 we published another study on NK cell function in SLE. We showed in this study an altered expression of SLAM receptors CD319 and CD229 in SLE patients, which was mediated by SLE immune complexes (Hagberg, J Immunol, 2013). 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

We have during the year completed the genotyping of the 2000 healthy blood donors in our Bioresource with the ImmunoChip, containing 186 000 SNPs in genes earlier found to be associated with autoimmune diseases. The Bioresource offers an unique opportunity to perform cellular and genetic studies with selected genotyped samples collected repeatedly. Several collaborations based on material from our Bioresource have been established with national and international research groups during 2013.

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 2013 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 2013

Lars Rönnblom, MD, PhD, Professor

Gunnar Alm, Professor em

Ulla Lindqvist, MD, PhD, associate professor

Eva Baecklund, MD, PhD, associate professor

Maija-Leena Eloranta, PhD, associate professor.

Gunnel Nordmark, MD, PhD

Ann Knight, MD, PhD

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Andrei Alexsson, Research engineer

Carin Backlin, PhD, Project coordinator

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Anne Trönnberg, BMA

Charlottta, Jakobsson, BMA

Lisbeth Fuxler, BMA

Olle Berggren, PhD student

Niklas Hagberg, PhD

Dag Leonard, MD, PhD student

Karin Bolin, MD, PhD student

Peter Matt, MD, PhD-student

Lilian Vasaitis, MD, PhD student

Funding

Lars Rönnblom

Swedish research council	1200 kSEK
King Gustav V 80 year foundation	300 kSEK
Swedish Rheumatism Society	300 kSEK
ALF grant	913 kSEK
Combine	620 kSEK
Söderbergs foundation	1000 kSEK
Wallenberg Foundation	2000 kSEK

Gunnel Nordmark

King Gustav V 80 year foundation	100 kSEK
The Swedish Society of Medicine	117 kSEK
ALF grant	127 kSEK
Swedish Rheumatism Society	150 kSEK

Maija-Leena Eloranta

King Gustav V 80 year foundation	100 kSEK
Swedish Rheumatism Society	125 kSEK
Brunnbergs foundation, UU	122 kSEK

Eva Baecklund/Ann Knight

ALF grant	310 kSEK

Eva Baecklund

Swedish Cancer Society	500 kSEK
King Gustav V 80 year foundation	100 kSEK
Lions Cancer Foundation	150 kSEK

Ulla Lindqvist

ALF grant	100 kSEK
Swedish Rheumatism Society	100 kSEK
Swedish Psoriatic Association	150 kSEK

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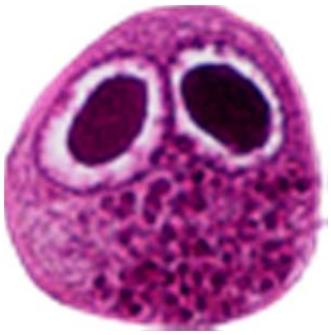
Clinical Microbiology and Infection Medicine



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 and Infectious diseases

Björn Olsen, Jan Sjölin, Otto Cars, Hilpi Rautelin, Jonas Blomberg

Influenza

Josef Järhult, Neus Latorre-Margalef, Goran Orozovic, Conny Tolf, Anna Gillman, Jonas Waldenström, 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.

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 2014. Since we are a One Health journal we are encouraging scientific reports from low income countries.

Campylobacter and other gastrointestinal pathogens

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

Epidemiologically speaking the 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. 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.

Campylobacter infections and intestinal microbiota

Christian Kampmann, David Lennebratt, Anna Nilsson, Anders Lannergård, Erik Torell, Patrik Ellström, Lars Engstrand, Hilpi Rautelin

Campylobacter is the most common cause of bacterial gastroenteritis in the western world, estimated to cause several million infections annually in the EU. Only little is known about the pathogenicity mechanisms used by Campylobacter but the severity of infection varies. Our aim is to increase knowledge at a molecular level, on how Campylobacter cause disease in humans and what determines the different outcomes of disease. Our research strategy is based on three approaches, 1) Bacterial characteristics: A genetic approach to search for novel putative Campylobacter virulence factors and a phenotypic approach to study bacterial virulence properties. 2) Human characteristics with special emphasis on the role of the human intestinal microbiota in colonization resistance for and outcome of Campylobacter infection is studied, as well as other human host response parameters. 3) In our in vitro infection model we study how some of the bacterial and host characteristics studied in approaches 1 and 2 are interconnected on a molecular level. We work with Campylobacter isolates from patients with well-characterized disease. In this way we can connect bacterial virulence to human disease and ascertain the clinical relevance of our findings.

Epidemiology and development of molecular methods for analysis of bacteria with special reference to Chlamydia infections

Jenny Isaksson, Isam Saleh, Johan Lagmo, Björn Olsen, Guma Abdeldaim, Per Hagblom, Björn Herrmann

Chlamydia is the most commonly reported sexually transmitted bacterium in Sweden. We have developed the first high resolution typing system for Chlamydia trachomatis The system contributes to our understanding of sexual networks and sources of outbreaks; this is of importance in order to reduce the incidence of the infection. Other applications have been analysis of reinfections and transmission and treatment of blinding trachoma. This has generated several international collaboration projects and a database for global analysis of Chlamydia genotypes. A second branch of chlamydia research is investigation of Chlamydia like organisms in birds and other hosts. We are currently investigating the role of such organisms as zoonotic pathogens. The field is new and we have access to exclusive specimen collections from birds world wide. A third research branch is development of diagnostic methods for respiratory tract infections. To improve diagnosis of pneumococci and Haemophilus influenzae real-time PCR methods have been developed and evaluated on clinical materials. Multiplex detection, quantification of bacteria and the ability to detect bacterial infections after antibiotic treatment is installed have been shown to improve the quality of diagnosis.

Tick borne infections

Erik Salaneck, Christian Ehrenborg, Göran Günther, Mats Lindeborg, 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.

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

Mia Furebring, Miklos Lipcsey, Markus Castegren, Anders Lignell, Eva Söderberg, Paul Skorup, Magnus von Seth, Jesper Sperber. Axel Nyberg, Anna Hedberg, 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 neurosurgical infections. Translational projects involving clinical studies, in vitro experiments and animal models with a focus mainly on clinical issues that cannot be solved by randomized clinical trials.

During 2013 the importance of bactericidal antibiotic effect for the treatment of septic shock has been studied in our intensive care porcine model in order to relate the pharmacodynamic antimicrobial effects to clinical outcome parameters such as hypoperfusion and organ dysfunction. With this model the effect of the addition of an aminoglycoside to a β-lactam antibiotic was studied and the clearance of susceptible bacteria was significantly improved in healthy pigs. 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, the effect of which on this model was published during the year. The effect of endotoxin tolerance on clinical symptoms has not previously been well studied but we have shown that organ dysfunction induced by the systemic inflammatory response is attenuated in all organs with the exception of the lungs, where a worse outcome is seen at a rechallenge. 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 ventilalator-associated pneumonia. These different types of large animal intensive care models with different inflammatory and anti-inflammatory responses have not been used previously and during 2013 we have investigated the effect of volume rescucitation with albumin, effects of different ventilatory modes on bacterial count and organ dysfunction.
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 presented 2013.
In another section of the group the effect of neurosurgical trauma and the innate immune response on the specific immunity is being studied by vaccination of patients with T-cell dependent and T-cell independent vaccines. The study has been completed and the results have been analyzed demonstrating an impaired T cell response during the first 10 posttraumtic days. Because it is of importance to achieve a quick protection against pneumococcal infection in patients with leakage of the cerebrospinal fluid, it might be an advantage to use a T-cell independent pneumococcal vaccine.

Pharmacodynamic in vitro studies on antifungals has during the year continued with the development of a new biofilm in vitro model that will be used in future projects.

Development of treatment strategies for bacterial infections in order to increase dosage efficacy and reduce resistance development.

Otto Cars, Elisabeth Löwdin, Thomas Tängdén, Matti Karvanen, Patricia Komp Lindgren, Pernilla Lagerbäck, Juliana Larsson, Christer Malmberg, Rachel Hickman, Petter Bertilsson-Forsberg, Lisa Albrecht

Infections with multi drug resistant (MDR) Gram negative bacteria are a rapidly increasing concern world-wide and new antibiotic groups with Gram negative effect are not expected within the next 10 years. This is a major threat to modern medicine which is dependent on effective antibiotics after surgery, immunosuppressive therapies etc. In the absence of new antibiotics, we aim to optimize the use, dosage regimens and combinations of existing antibiotics with respect to bactericidal effect as well as minimizing the risk for emergence of resistant strains. Our studies include the carbapenems, colistin and tigecycline which are often the last effective treatment for infections with MDR Gram negative bacteria.

By looking at the pharmacodynamics and pharmacokinetics of different drugs, alone and in combination at both static concentrations and in our *in vitro* kinetic system which mimics human pharmacokinetics, we can improve the knowledge on how to design dosage regimens for optimal antibacterial efficacy and optimal resistance prevention. In collaboration with the pharmacometrics group at Uppsala University *in silico* models are also created to better predict the efficacy of different dosing regimens.

For example, we have screened several antibiotic combinations by time-kill experiments *in vitro* against e.g. Escherichia coli, Klebsiella pneumoniae and Acinetobacter baumannii, where we have some interesting, previously unreported indications of increased antibacterial effect with the chosen combinations (two to three drugs) compared to the drugs alone. The effect of ertapenem at different dosage against E.coli with and without an ESBL plasmid has also been investigated as well as the magnitude of the inconvenient artefact caused by unspecific binding of colistin to glass and plastic in commonly used laboratory material. MDR development and resistance prevention in Acinetobacter baumannii is also under investigation, including molecular mechanisms, mutator phenotypes and fitness costs of mutants, with specific aim at colistin and tigecyclin. All of this work is important to discover suitable candidates for combination therapies in clinical use.

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 was seen in 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 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.

The studies have been carried out in collaboration with members of the Departments of Medical Sciences, Immunology, Genetic and Pathology, Public Health and Caring Services, Women´s and Children´s Health and Surgical Sciences..

New biomarkers for diagnostics of bacterial and viral infections.

Karlis Pauksens, Daniel Garwitz, Per Venge, Lena Douhan-Håkansson

In this project patients with acute infections are studied with new biomarkers to detect early a bacterial infection from other causes of fever or infections as predominantly virus infections. The development of different rapid tests to be used at point of care also investigated. Patients who visit primary health care or the emergency Department of infectious diseases with an acute infection are included in the study. Hitherto

approximately 700 subjects have been included. Several biomarkers are studied as human neutrophil lipocain (HNL) and also different rapid tests to be used at point of care have been developed and evaluated.

Study of the innate and adaptive immune defence in elderly and patients with cancer, post allogeneic stem cell transplantation and solid organ transplantation

Karlis Pauksens, Amelie Kinch, Gunilla Enblad, Eva Bäcklund, Daniel Molin, Åke Berglund, Helene Hallböök, Honar Cherif

Special interests are focused on the role of Ebstein-Barr virus (EBV) and then 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 infiltratingregulatory 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 gatheredfrom Sweden and Denmark. The material has previously been analyzed regarding presence of EBV in lymphoma tissue and blood.

The responses after immunization in elderly, patients with cancer, hematological diseases and after stemcell transplantation are studied with different kind of vaccines against influenza, pneumococcal infections and herpes zoster. The responses with adjuvanted protein vaccines, non-adjuvanted protein vaccines, conjugated pneumococcal vaccine, pneumococcal polysaccharide vaccine and pan-pneumococcal vaccine are studied. Different formulations of zoster vaccine are studied and also long-term follow-up is on-going.

Antibiotic Resistance

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

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 still limited and we need to find methods 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.

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, devolop new diagnostics, and are also engaged in the safety issues during blood transfusions and transplantation. Endogenous retroviruses (ERVs) are present in all vertebrates. Their pathogenic potential is largely unknown. Especially active ERVs occur in mice, cats and pigs. They are potental zoonotic sources of contagion. We have a unique database of retroviruses, as well as unique bioinformatics tools, so we are well positioned to develop diagnostic test for these viruses. We investigate if some of them are associated with the chronic fatigues syndrome. With respect to diagnosis, we have continued to work with our, now patented, multiplex nucleic acid based assay Variation tolerant Capture Multiplex Assay; VOCMA. Using this technique we have developed several diagnostic microbiological panels. A new type of multiplex serological test for IgG and IgM antibodies has also been developed, and used on sera from blood donors and patients suffering from the Chronic fatigue syndrome.

Antiviral resistance

Johan Lennerstrand, Kåre Bondeson, Anders Lannergård, Dennis Leenheer, Nader Kameli, Adam Ameur

We are focusing on antiviral resistance to Hepatitis C virus (HCV) and HIV. Current treatment of HCV with interferon and ribavirin is only partially effective, but new directly acting drugs, e.g. protease NS3 inhibitors and NS5A inhibitors, will be used more effectively in interferon-free regimes. As such directly acting drugs render resistance mutations during treatment failure; we have developed molecular diagnostic methods that allow us to detect resistant mutations in a broad spectrum of HCV genotypes. The methods will used to monitor resistance to protease inhibitors and study baseline resistance to NS5A inhibitors in clinical studies in the Uppsala region and Tromsö, Norway. We are currently developing a new method for NS5B non-nucleoside resistance, and a deep-sequencing method in collaboration with SciLife for studying minor baseline polymorphism in the NS5A gene.

Johan Lennerstrand, Per Stålhandske, Rolf Larsson, Martin Höglund

We have developed novel methods for clinical use in disease progression and monitoring of recidive during antimetabolite cancer therapy. The patented method platform enables measuring several DNA building block enzyme activities simultaneously, in real-time and in solution. We plan to study, in collaboration with Dept. of Haematology, dCK as a new resistance marker in treatment of AML.

Virus-induced immune suppression – novel therapeutic targets in hepatitis C and other chronic virus infections

Anders Bergqvist, Kåre Bondeson, Bo Albinsson, Bengt Kallin, Sara Sundström, Juan Wang

Hepatitis C virus (HCV) constitutes a global health problem since it often causes persistent infections with chronic hepatitis that may result in liver cirrhosis and liver cancer. No robust protection against challenge has yet been accomplished and antiviral chemotherapy is hampered by considerable side-effects and limited efficiency. To combat the disease, a better understanding of the intrinsic features of the virus and the specific immune response that decides disease progression is therefore essential. Previous studies have shown HCV chronicity is associated with a dysfunctional T cells response. We have shown that expression of the HCV core protein triggers calcium oscillations that activates the nuclear factor of activated T cell (NFAT) pathway. Prolonged expression of core resulted in anergy-like, hyporesponsive state characterized by decreased inducibility of IL-2 – a cytokine required for sustained CTL responses. We are further deciphering the mechanisms whereby HCV counteracts the development of an efficient immune response and pathology. The results of our study will give a better understanding of the disease and may provide a novel rational for treatment of HCV infections.

Pathogenesis in severe cases of flu and other respiratory infections, and multiplex methods for molecular diagnosis

Kåre Bondeson, Bo Albinsson, Midori Kjellin, Karolina Gullsby, Bengt Kallin, Anders Bergqvist

Influenza and other respiratory diseases constitute a major health problem worldwide. Although most cases resolves spontaneously without major consequences, a significant fraction will display more serious complications that require intensive care and may have fatal outcome, including viral pneumonia and acute respiratory distress syndrome. The aim of the study is to identify the critical factors that are associated with severe disease outcome. Characterization of the disease mechanisms and factors associated with pathology will facilitate future identification of specific risk groups that require more individualized health care. We also develop new sensitive and more specific molecular diagnostics that can identify B. pertussis and other Bordetella spp., as well as several highly multiplexed real-time PCR methods of bacterial and viral targets.

Development of methods for molecular detection of respiratory tract infections and studies of co-infections of bacterial and viral respiratory pathogens

Karolina Gullsby, Björn Olsen, Kåre Bondeson

Respiratory tract infections are caused by a number of different bacteria and viruses and most commonly by; Streptococcus pneumoniae, Haemphilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Bordetella pertussis, Adenovirus, RS-virus and Influenza virus. The incidence of reported agent differs partly depending on how extensive the diagnostics has been. There are probably an underestimation of for example B. pertussis among older children and adults, due to the atypical symptoms. Susceptibility testing is not routinely done in M. pneumoniae since culturing is difficult and tedious. Recently, acquired macrolide resistant M. pneumoniae has been found in patient samples in several European countries including Denmark. It is important to monitor the spread of macrolide resistance especially since it is the major choice of treatment when treating children. Molecular typing of clinical isolates of M. pneumoniae can help in understanding the epidemiology and see the relationship between different outbreaks.

We aim to develop and evaluate improved molecular methods for detection of respiratory infections. The methods will be used to investigate the prevalence of co-infections of bacterial and viral respiratory agents. New methods for molecular typing of M. pneumoniae and detection of mutation related to macrolide resistence will be developed and studies will be made of Swedish clinical samples collected over a number of years.

New virus vaccines

Bror Morein, Kefei Hu, Saideh Berenjian

Based on the now established ISCOM-technology, we have developed a new adjuvant concept for vaccine against several viruses, including influenza, RSV and rabies. We are also developing new anti-cancer drugs: The concept is based on differentation of effect on replication versus apoptosis. Xenograft experiments have shown effects in vivo.

Members of the groups during 2013

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Otto Cars MD, PhD, Professor,
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Publications 2011-2013

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Dissertations 2013

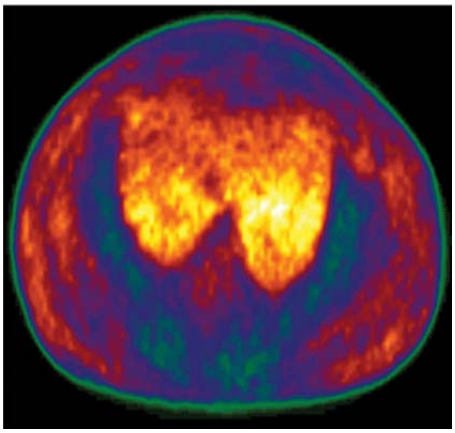
Badrul Hasan: Antimicrobial Resistance and Production of Extended Spectrum Beta-Lactamases in Enterobacteriaceae from Birds in Bangladesh.

Karin Elfving: Epidemiological and Bacteriological Aspects of Spotted Fever Rickettsioses in Humans, Vectors and Mammals in Sweden

Matti Karvanen: Optimization of Colistin Dosage in the Treatment of Multiresistant Gram-negative Infections.

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's main focuses are Acute Coronary Syndromes and to a lesser degree, heart failure. A special focus is aspects of the atherothrombotic process in ACS. In order to be able to improve the treatment and management for the individual patient we have worked in the following area during 2013:

The group has published a large number of epidemiological studies based on quality registers or other epidemiological cohorts. We have also conducted some pathophysiological studies.

The TOTAL-AMI project is running, a collaboration between researchers in Uppsala, KI and Lund supported by SSF.

Diagnosis, risk assessment and tailoring of treatment

During the year the group has continued to elucidate the pathophysiological basis and the usefulness of different biomarkers for diagnosis and prognosis of overt or concealed coronary and/or myocardial disease as well as in development of new assay technologies.

Evaluation of treatments

In order to evaluate both old and new treatments we perform both Industry sponsored randomized clinical trials (RCTs), independent, quality registry associated RCTs as well as Quality registry based evaluation of treatments in clinical routine. During the year the group has led, analysed and worked on the reporting of studies of new oral anticoagulation and new P2Y12 inhibitors.

At the ESC annual scientific congress 2013 the innovative Register based RCT, Taste, was presented and got world wide attention (published N Engl J Med. 2014 Feb 13;370(7):675-6.)

Miscellaneous

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

Members of the group during 2013

During 2013 Associate professor Johan Sundström joined the group.

Bertil Lindahl, Professor
Lars Wallentin, Professor emeritus
Frank Flachskampf, Professor
Stefan James, Associate professor
Johan Sundström, Associate professor
Jonas Oldgren, Associate professor
Claes Held, Associate professor
Gerhard Wikström, Associate professor
Bo Lagerqvist, Post Doc
Erik Björklund, Post Doc
Christina Christersson, Post Doc
Emil Hagström, Post Doc
Nina Johnston, Post Doc
Kai Eggers, Post Doc
Christoph Varenhorst, Post Doc
Mohammamd Kavianipour, Post Doc
Axel Åkerblom, Ph.D student
Ziad Hijazi, Ph.D student
Cathrin Henriksson, Ph.D. R.N.
Birgitta Jönelid, Ph.D student
Daniel Lindholm, Ph.D student
Julia Aulin, MD
Ola Vedin, MD
Daniel Lind, Ph.D student
Kasper Andersen, Ph.D student
Thomasz Baron, Post Doc

Funding

Swedish Heart-Lung foundation, Vetenskapsrådet, SSF, ALF, other funds, industrial grants

Publications 2011-2013

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Dissertations 2013

Ziad Hijazi: New Risk Markers in Atrial Fibrillation.

Axel Åkerblom: Biomarkers of Renal Function in Acute Coronary Syndromes.

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 control of AF, 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 interventions for the elimination of AF and to assess predictors of AF recurrence.

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:

- A Nordic Multicenter and randomised study comparing atrial fibrillation ablation with conventional medical treatment with regard to quality of life as the primary end-point. Secondary end-points are AF burden, a composite of morbidity end-points, symptoms, left atrial and ventricular function, physical capacity, health economy and complications evaluated during a period of 48 months follow-up, with Uppsala as coordinating centre. The study is unique in that it will demonstrate long term treatment effects and the use of continuous monitoring of heart rhythm. It has important implications since previous reports have indicated that a high proportion of patients originally defined as successful after ablation, have relapses of silent atrial fibrillation. The CAPTAF study includes centers from Umeå, Stockholm, Uppsala (co-ordinating center), Gothenburg and Finland. The study is supported by SBU and Swedish Heart and Lung Foundation.
- The second study evaluates the effect of combind epicardial pulmonary vein isolation combined with vagal denervation and extra left atrial linear lesions using total thoracoscopic off-pump technique with regard to AF burden, quality of life and atrial function in patients with persistent atrial fibrillation. This novel technique was introduced in 2008 in Uppsala in collaboration with thoracic surgeons, and will be finalised late autumn 2010. A further study will assess the effects on atrial size and function, and on neuropeptides and myocardial markers.
- The third study will randomize patients with paroxysmal AF scheduled for pulmonary vein isolation to either cryoablation or radiofrequency ablation with a novel circular catheter. Endpoints used include AF burden, quality of life, atrial function and procedure related variables.

The purpose is further to study the role of vagal denervation for elimination of atrial fibrillation which will clarify AF mechanism and development of novel therapies in two studies by

a) assessing the presence of vagal activity by PET prior to and after surgical and catheter ablation procedures. The degree of vagal activity will indirectly be measured by assessing the marker for sympathetic activity. A marker for parasympathetic activity is not commercially available and ganglionic plexus contain both sympathetic and parasympathetic fibres. Patients undergoing catheter based atrial fibrillation, off-pump epicardial pulmonary vein isolation, and Maze-surgery will be studied before and after their respective procedures. The study may clarify whether vagal denervation is more pronounced using the surgical techniques compared with the transvenous techniques. The studies will also clarify the importance of vagal denervation for the initiation of AF.

b. 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.

Projects on bi-ventricular pacing in patients with heart failure relates to new diagnostic techniques for optimal pacemaker programming and reduction of heart rate to ensure biventricular pacing during atrial fibrillation

The new diagnostic techniques include measurements of cardiac impedance and left ventricular contractility using DP/DT for optimizing time intervals for biventricular stimulation. Two studies published and one will be submitted for publication. One study evaluating effect of high frequency atrial pacing on vagal gangle plexa to reduce heart rate during atrial fibrillation will start this year.

Underlying aetiology and predictors of sudden cardiac death and ventricular tachycardia in young patients without coronary artery disease – 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 GenPat section and BMC, recently developed a genetic test for ARVC, that will identify the most common gen, covering about 45% of ARVC affected individuals. We 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 2013

Stefan Lönnerholm, M.D, Ph.D

Per Blomström, Associate professor

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Helena Malmborg, Ph.D-student

Louise Bagge, Ph.D-student

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Joanna Wessbergh, Research Nurse

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Clinical physiology

Hans Hedenström

Cardio-pulmonary aspects in acute and chronic lung disease

This a new research program 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 MV. 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.

Steroid resistance

A highly challenging research area is steroid resistance. Previous studies have shown that NO might have augmented the response to steroids. We will now studdy the combination of steroids and NO inhalation in a porcine endotoxin sepsis model. Endotoxin down-regulated the glucocorticoid receptor (GR) and subsequent steroid treatment had no effect. NO up-regulated the GR and steroids given after the up-regulation resulted in a strong anti-inflammatory response to the treatment. A positive effect on respiratory mechanics in a mouse asthma model by combining NO and steroid was also seen in a recent paper from us. These observations create the basis for the third track in our research program where the effect of sepsis, a common underlying mechanism of acute respiratory failure, on the GR will be studied

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 herapeutic 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.

Detection of small airways disease

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 in order to early identify obstruction of peripheral airways and to predict which patients are at higher risk. The methods are going to be used also in the follow-up of MIDAS-study and the methods will be compared to each other, as well as to alveolar NO, a non-invasive method to estimate inflammation in small airways. Furthermore, the methods will be used in two new started COPD studies, 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 in the Uppsala-Örebro region, 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. Forced oscillation technique is a technique that allows a more sensitive assessment of airways obstruction as well as expiratory flow limitation. Daily measurements of FOT will be tested in a EU-financed, multicentre, telemedicine studyin order to analyse if exacerbations can be prevented by this system, allowing daily quantification of symptoms, lung function, blood pressure and saturation.

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.

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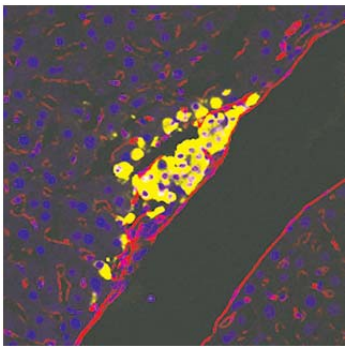
Diabetes and Metabolic diseases

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 of measures 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, Cherno Sidibeh, Petros Katsogiannos, Niclas Abrahamsson, 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, Britt Edén-Engström, 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.

Cherno Sidibeh, Maria Joao Pereira, 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.

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

Karin Wikblad, Janeth Leksell, Ewa Billing, Anna Lindholm Olinder

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 have described the protocol and plans for study enrolment in a 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 have plans for study an intervention, 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. However, the questionnaire needs to be further scrutinized and assessed before it can be adopted as a systematic measure within the NDR. In addition, persons living with diabetes need to be consulted and involved in its development process, so that the items are understandable, considered relevant and easy to answer. 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. The development of the measurement will take place in four phases.

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.

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

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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.

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Publications 2011-2013

1. Ohlsson C, Wallaschofski H, Lunetta K, et al. Genetic Determinants of Serum Testosterone Concentrations in Men. PLoS Genetics. 2011;7(10):e1002313-.
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Dissertations

Per-Anton Westerberg: Aspects of Fibroblast Growth Factor 23 in Mild to Moderate Renal Dysfunction

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 strategies 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. 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, Per-Ola Carlsson

In recent studies 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 in recombinant human islet amyloid overexpressing (rhIAPP) mice, likely due to their increased IAPP gene expression.

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 is 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. Ongoing research projects compare outcome to another promising site, the omentum, and develop means to improve also early survival of the islet grafts by e.g. 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 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.

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 islets will be

tested in a pilot trial. This macrodevice will protect the islets from immune rejection, whereas oxygen is supplied daily into a refillable oxygen tank. Regulatory approval has been obtained during 2013, and a pilot trial will start spring 2014.

Members of the group 2013

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
Daniel Espes, M.D., PhD student
Liza Grapensparr, PhD student
Carl Johan Drott, M.D., PhD student
Sara Ullsten, PhD student
Zhanchun Li, laboratory engineer
Astrid Nordin, laboratory engineer
Ing-Britt Hallgren, laboratory engineer
Hanna Liljebäck. MD/PhD student
Svitlana Vasylovska, post-doc
My Quach, laboratory engineer
Lisbeth Sagulin, laboratory engineer
Eva Törnelius, laboratory technician
Violeta Armijo Del Valle, research nurse

Funding

European Foundation for the Study of Diabetes/JDRF/Novo	1.0 MSEK
Novo Nordisk Foundation DK 2012	0.5 MSEK
Swedish Research Council	1.7 MSEK
Swedish Diabetes Association	0.3 MSEK
AFA	1.0 MSEK
Thuring Foundation	0.1 MSEK
Strategic funding, Exodiab	0.6 MSEK
Diabetes Wellness	0.6 MSEK

Publications 2011-2013

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Undergraduate Teaching 2013

Medicine Programme;	**Approx. students**
Clinical Medicine I 28,5 hp	189
Clinical Medicine III 30 hp	178
Clinical Medicine IV 19,5 hp	156
Occupational and Environmental Medicine	152
Physiotherapy Programme:	
Internal Medicine 3 hp	76
Physiology 9 hp	46
Nursing Programme:	
Pharmacology 6 hp	213
Clinical Microbiology 4,5 hp	213
Pharmacology and microbiology 10,5 hp	4
Nursing and Medical Sciences within Medical Care 15 hp	220
Biomedicial Laboratory Science Programme:	
Medical Microbiology 10,5 hp	47
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	39
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
Experimental Dermatology and Skin Biology 15 hp	1
Clinical Drug Development 30 hp	29
Methodology in Clinical Trials 3 hp	18
Treatment and Nursing in Congestic Heart Failure 7,5 hp	32
Treatment and Care of Patients with Arrythmia 7,5 hp	37
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

The objective of SNP&SEQ Technology Platform in Uppsala is to make large-scale SNP genotyping and "second 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, including 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 have been 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 Research Council for 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.

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, 48% of the users of the SNP genotyping services, and 28% of the users of the sequencing services are affiliated with other universities than Uppsala University. During 2013, 69 genotyping projects including a total of 29.900 DNA samples and 114 sequencing projects of 5670 DNA or RNA samples were performed. Most of the projects study human diseases or populations, but genotyping and sequencing in many other organisms, like birds, domestic animals, plants, insects, fungi and bacteria were also performed. So far the SNP&SEQ Platform has contributed to ~283 publications in well respected scientific journals, of which 62 appeared in 2013. Of the publications that appeared in 2013 as many as 19 were published in journals with an impact factor > 9, which illustrates that the SNP&SEQ platform enables research of a high international standard.

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 2013

Tomas Axelsson, PhD, SNP genotyping manger

Ulrika Liljedahl, PhD, DNA sequencing manager

Lars Bäckström, computer systems manager

Olof Karlberg, PhD, bioinformatics manager

Johan Dahlberg, bioinformatician

Camilla Enström, research engineer

Edvard Englund, PhD, database systems developer

Helena Fällmar, PhD, research engineer
Michael Nordstedt, computer system administrator
Johanna Lagensjö, research engineer
Kristina Larsson, senior research engineer, quality system manger
Ulrika Liljegren, research engineer
Marie Lindersson, senior research engineer
Per Lundmark, PhD, bioinformatician
Karin Sollander, research engineer
Magnus Lindell, PhD, research engineer
Hanna Edlund, PhD, research engineer
Jon Ramsell, PhD, research engineer
Ann-Christine Wiman, research engineer
Ingvar Örn Thorsteinsson, research engineer
Anna Haukkala, research engineer
Kjell Stålberg, PhD, research engineer
Pia Uusitalo, research engineer
Torbjörn Öst, research engineer
Katarina Jonasson, administrator
Mathias Brännvall, PhD, project coordinator

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

Director: Associate Professor Anders Isaksson

During the year the platform has changed names to Array and Analysis Facility and has moved to the Biomedical Center. 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 GeneTitan 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/

High demand for platform services

By providing a diverse set of array-based analyses and bioinformatics support continues to provide services to a large number of projects. The facility acquired an instrument for automated array analysis (Gene Titan) in May that allowed an 26% increase in the number of array analyses from 1024 to 1294. The analyses mainly come from UU (59%), Akademiska sjukhuset (24%), other Swedish Universities (17%) and companies (1%). The platform has a staff of 8 full-time positions. The platform has contributed to 36 publications in high ranking international journals during 2011-2013 (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 analyzed about 300 patients during 2013. In December of 2013 these analyses were extended also to pre-natal testing

Our focus is on developing clinically useful diagnostic and predictive tests based on array analyses. One example is a pilot project run together with clinical genetics where we evaluated whether array-based methods can replace conventional FISH analysis for diagnosis of ALL.

We also published a bioinformatic tool called Patchwork. It uses whole genome sequencing data from cancer samples to determine allele-specific copy numbers in the tumor cells. Information that may be used for clinical diagnostic purposes.

Future

Array and Analysis facility is planning to further develop our support for array analyses and bioinformatic support at BMC. We plan have our clinical analyses accredited by SWEDAC during 2014.

Staff of Uppsala Array Platform during 2013

Hanna Göransson Kultima Bioinformatician
Malin Olsson, Research engineer
Anders Isaksson, director
Markus Mayrhofer, Bioinformatician
Maria Rydåker, Research engineer
Belinda Fridman, Bioinformatician
Björn Viklund, Bioinformatician
Sebastian DiLorenzo, Bioinformatician

Publications 2011-2013

Uppsala array platform has contributed to 36 published articles during 2011- 2013. Fifteen of them are published without platform employees as co-authors and 21 with co-authors from the platform.

Publications without platform employees as co-authors

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Publications with platform employees as co-authors

16. BMC Genomics. 2011 Dec 13;12:602. Muscle wasting and the temporal gene expression pattern in a novel rat intensive care unit model. Llano-Diez M, Gustafson AM, Olsson C, Goransson H, Larsson L.

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Awards and Appointments 2013

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

2. **Åsa Hedman** – Winner of Linnéus Foundation for Medical Research