UPPSALA UNIVERSITET

Department of Medical Sciences

Annual Report 2015

Fastställd av Lars Rönnblom 2016-05-09

Introduction

The Department of Medical Sciences has continued to grow, both in staff and in revenues. The staff is now over 250 and the Department has more than 300 associated co-workers at the Uppsala University Hospital, working in more than 20 different clinical specialties. The turnover has increased to 310 MSEK, an increase of 50% since 2010, and the external research funding to 212 MSEK which can be attributed to the sustained ability of the researchers at the Department to attract grants from e.g. the Swedish Research council, the Cancer Society, the Swedish Heart & Lung Foundation and from the EU. In this context I also would like to mention the excellent services provided by the platforms hosted by the Department; the SNP&SEQ Technology platform and the Array and Analysis facility, and the two new platforms, Clinical Biomarkers, and In Vitro and Systems Pharmacology.

The performance of the Department's research groups is also shown by the more than 600 peer reviewed publications during 2015, and by the 21theses produced during 2014. The theses presented represent all six research programs at the Department, namely Cardiology and Respiratory Medicine, Endocrinology, Infection, Inflammation, Laboratory Medicine, and Oncology & Haematology. The excellence of the Department's staff is also shown by the many prizes awarded to our researchers. To mention just a few, Tove Fall was awarded the prestigious "Oscarspriset" from Uppsala University, Hans Törmä the Ivar Janson prize from the Swedish Medical Society, and Per-Ola Carlson the Knud Lundbeck Award by the Scandinavian Society for the Study of diabetes. Major research findings achieved during 2015 by researchers at the Department will be presented on the following pages.

Teachers at our department are very active in many of the undergraduate programs at the Faculty of Medicine. Some 2000 students pass courses for which we are responsible every year. The department aims to provide a good environment for learning combined with education given at a high academic level. During 2015 a few persons retired after long and very successful careers. On behalf of the Department I would like to thank assoc.professors Ulla Lindqvist, Ola Rollman and Ewa Billing for their many important contributions. At the same time I would like to welcome all new colleagues who have joined us during the year. I´m also glad that we have three new professors at the Department, namely Magnus Svartengren, Stefan James, and Johan Sundström.

Finally, I would like to conclude by thanking all personnel at the Department for their dedicated work during 2015.

Lars Rönnblom
Head of department

Contents

Organization of the Department of Medical Sciences

Chair, head of department

Lars Rönnblom

Deputy head of department

Johan Sundström

Assistant heads of department

Jan Sjölin, responsible for graduate studies

Christer Janson, responsible for undergraduate studies

Department board

Lars Rönnblom	chair
Lars Lind	teacher
Håkan Melhus	teacher
Johan Sundström	teacher
Eva Lindberg	teacher
Birgitta Sembrant	technical staff
Clara Atterby	PhD student
Vacant	student representative
Vacant	student representative

Deputies

Tove Fall	teacher
Martin Wohlin	teacher
Jan Eriksson	teacher
Per Hellström	teacher
Karin Eriksson	technical staff
Abdul Halim	PhD student
Vacant	student representative
Vacant	student representative

Employees 2015

Adolfsson Sofia
Alexsson Andrei
Alfredsson Jenny
Ali Ahmed Abeir
Alimohammadi Mohammad
Almlöf Jonas
Alvring Saga
Amcoff Karin
Andersson Claes
Axelsson Tomas
Backlin Carin
Baecklund Eva
Bandaru Kumar Manoj
Berglund Eva
Berglund Malin
Björklund My
Björnerfeldt Susanne
Blomström Lundqvist Carin
Bryon Kristin
Brännvall Mathias
Bäckman Ulrika
Bäckström Lars
Cai Guihong
Campos Costa Joao
Carlson Marie
Carlsson Axel
Carlsson Elin
Carlsson Ingmarie
Carlsson Lena
Cars Otto
Cars Thomas
Castegren Markus
Castillejo-Lopez Casimiro
Christersson Christina
Colliander Mia
Collin Sofie
Conrad Lisa
Dahlberg Johan
Dalin Frida
Den Hoed Marcel
Devine Ellenor
di Lorenzo Sebastian
Diaz Hetzel
Dubois Louise
Dunder Linda
Edén Desirée
Ekberg Sara
Ellström Patrik
Eloranta Maija-Leena
Emami Khoonsari Payam
Emmanouilidou Anastasia
Englund Edvard
Engvall Karin
Enström Camilla
Eriksson Barbro
Eriksson Jan
Eriksson Karin
Eriksson Oskar
Eriksson Per
Estvall Ann-Sofie
Fall Tove
Flachskampf Frank
Floderus Gustaf
Forsberg Susanne
Foyer Anna
Freyhult Eva
Fryknäs Mårten
Fuxler Lisbeth
Fällmar Helena
Gasparini Alessandro
Giandomenico Valeria
Granström Therese
Grönberg Malin
Gustafson Ann-Marie
Gustafsson Mats
Gustafsson Stefan
Hagberg Margaretha
Hagberg Niklas
Hagforsen Eva Christina
Haglund Caroline
Halim Muhammad Abdul
Halin Lejonklou Margareta
Hallböök Helene
Hartman Anna
Haukkala Anna
Hedman Åsa
Helgesson Magnus
Hellström Per
Henriksson Catrin
Henriksson Karin
Herman Stephanie
Hermansson Johan
Hjärner Veronica

Hoffman Tove
Holloway Bronwen
Holm Therese
Hägglund Maria
Högman Marieann
Ilbäck Nils-Gunnar
Imgenberg-Kreuz Juliana
Ingelsson Erik
Jacobson Rasmusson Annica
Jakobsson Charlotta
James Stefan
Janson Christer
Jarvius Malin
Jasovsky Dusan
Johansson Cecilia
Jonasson Katarina
Jonholt Paulina
Jumaa Sitaf
Kamble Prasad
Kask Lena
Klingström Tiffany
Kriegholm Cecilia
Kultima Kim
Lagensjö Johanna
Lagerbäck Pernilla
Lampinen Maria
Landegren Nils
Larsson Anders
Larsson Gunnel
Larsson Kristina
Larsson Pontus
Larsson Rolf
Lau Joey
Laxman Navya
Leek Christina
Lehmann Sören
Lenhammar Lena
Liljedahl Ulrika
Liljegren Andersson Ulrik
Lind Lars
Lindahl Bertil
Lindberg Eva
Linde Torbjörn
Lindell Magnus
Linder Stig
Lindersson Marie
Lindgren Komp Patricia
Lindqvist Mårten
Lindström Elisabeth
Lingman Karin
Littmann Jasper
Ljunggren Östen
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Lundmark Anders
Lundmark Per
Manninen Johanna
Marincevic-Zuniga Yanara
Marklund Elisabeth
Martin Thomas
Marzouka Nour Al-Dain
Mcloughlin Anette
Melhus Håkan
Melhus Åsa
Moberg Lena
Mogensen Ida
Mohrs Simone
Mokhtari Dariush
Monazzam Azita
Mourkas Evangelos
Mubanga Mwenya
Muntlin Athlin Åsa
Najafi Nasrin
Nilsson Anna
Nordlinder Lovisa
Nordlund Jessica
Nordstedt Michael
Nowak Christoph
Nyberg Frida
Nykvist Marie
Nystedt Sara
Oldgren Jonas
Olofsson Caroline
Olsen Björn
Omar Shumi
Parrow Vendela
Pereira Maria
Pränting Maria
Quarfordt Pernilla
Raine Amanda
Ramqvist Ulrica
Ramsell Jon
Rask-Andersen Anna
Rautelin Hilpi Iiris
Ronisz Dan Zbigniew
Ronquist Göran
Rönnblom Lars
Rönnerblad Michelle
Sandin Marianne

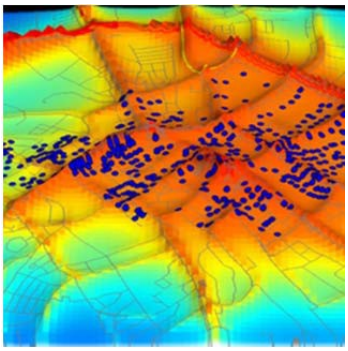
Sandling Johanna
Sembrant Birgitta
Senkowski Wojciech
Sidibeh Cherno
Siegbahn Agneta
Sjölin Jan
Sjöström Rigmor
Skarp Astrid
Skogseid Britt
Smedje Greta
Smeds Patrik
Sollander Karin
Stenemo Markus
Strese Sara
Sturlaugsson Steinar
Stålberg Kjell
Sundelin Johan
Sundström Johan
Svartengren Magnus
Svensson Johanna
Svensson Maria
Sütterlin Susanne
Syvänen Ann-Christine
Tandre Karolina
Tegnér Katarina
Theorell-Haglöw Jenny
Thulin Åsa
Tiensuu Janson Eva
Trombley Susanne
Tängdén Thomas
Törmä Hans
Ungphakorn Wanchana
Wadelius Mia
Wadell Olof
Wahlberg Per
Wallentin Lars
Wallmenius Katarina
Wang Juan
Webb Dominic-Luc
Vega Enrique
Westholm Susanne
Weström Simone
Widell Mikael
Wijethunge Prabash
Viklund Björn
Wille Michelle
Wiman Ann-Christin
Wohlin Martin
von Der Heyde Benedikt
von Kartaschew Anna
Vretman Helena
Yuen Pikkei
Zhang Hanqian
Zorzet Anna
Åberg Mikael
Åkerman Anita
Ånnhagen Eva
Åslin Matilda
Åström Paulsson Sofia
Ärnlöv Johan
Örn Thorsteinsson Ingvar
Öst Torbjörn
Övernäs Elin

Funding 2015

GRANTS	
SWEDISH RESEARCH COUNCIL	38 MSEK
SIDA	21 MSEK
THE SWEDISH RESEARCH COUNCIL FORMAS	11 MSEK
THE SWEDISH HEART-LUNG FOUNDATION	6 MSEK
EU	2,7 MSEK
ERC	3,2 MSEK
WALLENBERG FOUNDATIONS	13 MSEK
VINNOVA	1,6 MSEK
SWEDISH FOUNDATION FOR STRATEGIC RESEARCH	6,7 MSEK
THE SWEDISH CANCER FOUNDATION	4,8 MSEK
GOVERNMENT FOR CLINICAL RESEARCH (ALF) - FUNDING	48,6 MSEK
OTHER FUNDINGS	56 MSEK
SUBTOTAL	**212,6 MSEK**
CONTRACT RESEARCH	
VARIOUS COMMISSIONING AGENTS	3,4 MSEK
TOTAL	**216 MSEK**

Scientific Reports

Circulation and Respiration



The research within this broad area is directed towards cardiovascular and respiratory diseases, but sleep disorders and the importance of environmental factors for health are also studied. A large number of studies are carried out through national or international cooperations. Epidemiological studies are used to identify genetic and environmental risk factors aiming to understand the pathophysiology of atherosclerosis mediated cardiovascular diseases and chronic respiratory diseases. Risk factor analysis is also employed by the environmental medicine group to assess the impact of occupational and environmental exposures. Clinical trials and register studies are used to evaluate both new and old therapies.

Cardiology, ischemic heart disease and heart failure

Bertil Lindahl

The research group has three main lines of research: ischemic heart disease and especially acute coronary syndromes; atrial fibrillation and stroke prevention and heart failure, including pulmonary hypertension. In each of these three areas we are working on different levels in order to be able to ultimately improve the treatment and management of the individual patient. The research group participates in several national and international research collaborations and has leading positions in several of those. Below are some examples of publications from the research group in 2015.

Understanding the disease(-s) and the unmet needs

We published in Heart the so far largest study of type 2 myocardial infarctions. Among 20.138 hospitalizations of acute myocardial infarction in Sweden, 7.1% of the infarctions were classified as type 2 AMI. Patients with type 2 AMI had higher crude mortality compared with type 1 patients with MI. However, after adjustment, the 1-year mortality was similar.

We have shown for the first time that unrecognized myocardial infarctions assessed by cardiovascular magnetic resonance are common in patients with stable CAD and are associated with the severity of the stenosis in the supplying coronary artery in a study (J Cardiovasc Magn Reson).

In a study published in Eur J Prev Cardiol. the relation between paradontitis and heart disease was studied showing that tooth loss is independently associated with poor outcomes in stable coronary heart. Another area of interest of the research group is pulmonary hypertension, the vasodilator response to vardenafil and clinical outcome was described in two articles (Eur J Clin Pharmacol; Vascul Pharmacol).

In the field of genetic studies several studies were published: NLRC4 Inflammasome is an important regulator of Interleukin-18 levels (Circ Cardiovasc Genet); .effect of genetic variations on ticagrelor plasma levels and clinical outcomes (Eur Heart J); Genetically determined height and CAD (N Engl J Med); New genetic loci link adipose and insulin biology to body fat distribution (Nature).

Importance of biomarkers and risk factors for diagnosis and prognosis

High-sensitivity troponins measurement improves risk assessment for cardiovascular events in many clinical settings, but the research group was first to show the added value in atrial fibrillation patients. In new studies we have shown that cTnT and cTnI provide largely similar prognostic information; and that Interleukin-6 and C-reactive protein, and NT-proBNP provide prognostic information in patients with atrial fibrillation. (Clin Chem, Am Heart J and J Am College of Cardiol).

The importance of exercise capacity and muscle strength for risk of vascular disease and arrhythmia were studied in 1.1 million young Swedish men (BMJ). The effect of physical activity, obesity on risk of cardiovascular disease have been demonstrated (Eur J Prev Cardiol).

Our research group has also been pioneering the clinical research on the new biomarker GDF-15 in community dwellers as well in patients with coronary artery disease. During 2015 we were able to show that the GDF -15level also predicts major bleeding and cardiovascular events in patients with ACS.(Eur Heart J). We have also been among the first to use the new proximity extension assay-technique for measuring 92 proteins simultaneously; studies have been published in Atherosclerosis and Stroke.

The implications of introducing High-Sensitivity Cardiac Troponin T into clinical practice in a whole country were studied in the SWEDEHEART Registry and published in J Am Coll Cardiol.

Evaluation of treatments and other interventions in RCTs and Registry studies

The research group is world leading in studies evaluating new antithrombotic and antiplatlet agents in ACS and atrial fibrillation. During 2015 a number of substudies of large RCTs (PLATO, APRAISE-2, TRACER, RELY, RISTOTLE) have been published (Circulation ; J Am Coll Cardiol; Eur Heart J; Am J Cardiol; Heart, JAHA; Am Heart J; Int J Cardiol; Thromb Haemost etc.).

A new approach using therapeutic hypothermia for the treatment of AMI was evaluated in the CHILL-MI trial (Ther Hypothermia Temp Manag.).

The group has published a large number of observational studies based on the Swedeheart registry and other registries describing the effects of gender, age, comorbidities, different treatments on short and long-term but also comparing different treatments; e.g. importance of gender in AMI-patients without obstructive CAD (Am J Cardiol); diabetes (Circ Cardiovasc Interv); time trends and gender differences in prevention guideline adherence and outcome after AMI (J Prev Cardiol); fondaparinux vs low-molecular-weight heparin and clinical outcomes in NSTEMI.(JAMA); comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom (BMJ) .

We have also pioneered the field of Registry based RTCs, e.g. by the TASTE trial and several ongoing large R-RCTs. Several articles on the design of these ongoing studies (e.g. Validate) and substudies of TASTE have been published.

Miscellaneous

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

Members of the group during 2015

Bertil Lindahl, Professor

Stefan James, Professor

Lars Wallentin, Professor emeritus

Jonas Oldgren, Associate professor

Claes Held, Associate professor

Gerhard Wikström, Associate professor

Kai Eggers, Associate professor

Bo Lagerqvist, Ph.D.

Erik Björklund, Ph.D.

Christina Christersson, Ph.D.

Emil Hagström, Ph.D.

Nina Johnston, Ph.D.

Gunnar Frostfeldt, Ph.D.

Christoph Varenhorst, Ph.D.

Axel Åkerblom, Ph.D.

Ziad Hijazi, Ph.D.

Ola Vedin, Ph.D

Kasper Andersen, Ph.D.

Thomasz Baron, Ph.D.

Daniel Lindholm, Ph.D

Cathrin Henriksson, Ph.D. R.N.

Birgitta Jönelid, Ph.D student

Gorav Batra, Ph.D student

Gabriel Arefalk,, Ph.D student

Julia Aulin, MD, Ph.D student

Funding

Members of the research group have funding from the Swedish Heart-Lung foundation, Swedish Foundation for Strategic Research; Selanders foundation, Swedish Society of Medicine, “1.6 milj klubben” and ALF.

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

Publications 2013-2015

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Reviews, guide-lines etc. 2013-2015

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Dissertations

Ola Vedin: Prevalence and prognostic impact of periodontal disease and conventional risk factors in patients with stable coronary heart disease

Daniel Lindholm: Platelet Inhibition, Revascularization, and Risk Prediction in Non-ST-elevation Acute Coronary Syndromes

Cardiology-Arrhythmia

Carina Blomström-Lundqvist

The research group focuses on two different areas, atrial fibrillation (AF) and inherited heart diseases associated with increased risk of sudden cardiac death (SCD). Atrial fibrillation is associated with decreased quality of life, increased risk for stroke and increased mortality. Anti-arrhythmic agents have poor long term effects for AF control, and may contribute to the observed higher death rate in AF populations. Our aim is to study the various mechanisms of AF and develop more effective therapeutic strategies including novel surgical and catheter based ablation techniques for the elimination of AF. We further aim to identify predictors for stroke and AF recurrences.

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

There are 4 ongoing projects evaluating non-pharmacological treatment strategies for AF:

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

The CryoLPAF study is an exploratory study assessing whether pulmonary vein isolation (PVI) can effectively be achieved by a new cryoballoon which thereby can reduce AF episodes and improve symptoms in patients with longstanding persistent AF at one year follow up. Longstanding persistent AF is difficult to treat with ablation, resulting in efficacy rates of 20%. The primary objective is the clinical success of catheter ablation, defined as either freedom from AF related symptoms irrespective of the presence of asymptomatic AF on Holter, provided AF is absent or only paroxysmal in nature, or presence of AF related symptoms but significant symptomatic improvement. Secondary objectives are AF burden, Quality of Life, symptoms, atrial size and function, biomarkers of myocardial damage and inflammation, extent of atrial scar tissue, safety, cardiovascular hospitalization, and health economics at 12 months. Prediction of freedom from AF by analysing various risk factors will be performed. It is hypothesized that PVI achieved by the new cryoballoon will be associated with a clinically successful outcome in at least 50% of patients with longstanding persistent AF at one year follow up after 1-2 procedures. A total of 40 patients will be treated and all will be restudied at 12 months irrespective of symptoms, to assess if PV re-conduction is the cause of AF recurrence in the majority of patients, using a circular mapping catheter. Arrhythmia monitoring will be performed by a 7 day Holter monitoring every third month at 6, 9 and 12 months follow up, and a 12 lead ECG. An echocardiography will be repeated at 12 months follow up to assess LA volume and contractility.

In the “Single versus Double Cryoballoon ablation for PVI in patients with Atrial Fibrillation” (SD-Cryo-AF) study, the use of only one cryoballoon application, that can significantly shorten the procedure, is compared with the conventional 2 application technique. Patients will be randomized to a single

cryoballoon application guided by a multipolar recording catheter or to a conventional technique with 2 cryoballoon applications. The primary hypothesis is that the one shot application strategy is as effective in achieving PVI as standard 2 applications. The primary end-point is frequency of acute PVI after cryoballoon ablation of all pulmonary veins. PV conduction block will be assessed by a circular mapping catheter. Acute procedural success is defined as complete electrical isolation of a pulmonary vein assessed by entrance and exit block, including 20 minutes waiting time. Complications and duration of the procedure will be assessed. Patients will be followed at 3, 6 and 12 months after the ablation procedure. A 12 lead ECG, a 7 day Holter monitoring, quality of life (EQ5D) and EHRA score, biomarkers will be analysed. Predictive variables for successful outcome/AF recurrence will be analysed. The frequency of symptomatic recurrence of AF and number of reablations will be compared at 6 and 12 months, and in those requiring a redo ablation procedure the status of PV reconduction will be assessed.

The aim of the ECAF star trial, a multicentre study, is to assess the effects of electrical cardioversion in patients with recent onset AF with regard to new silent cerebral thromboembolic lesions and cognitive function. The hypothesis is that acute electrical cardioversion will result in a 20 % increase in incidence of new asymptomatic cerebral ischemic lesions as detected by nuclear magnetic resonance imaging (MRI) of the brain directly after and at 7 – 10 days after cardioversion. The presence of new silent embolism after electrical cardioversion of recent onset AF will be assessed by MR scan before, immediately after and 7 – 10 days after cardioversion, in patients with recent onset AF (< 48 hours duration). A total of 40 patients will be included. The secondary endpoints plasma markers for thrombin activity and measures of coagulation activity, left and right atrial volumes, neurohormonal, inflammatory, specific cardiac biomarkers, and a vasoactive peptide will be analysed directly after cardioversion, at day 7 and 30 and compared with baseline. A mini-mental test will be performed as well. Global left atrial ejection fraction and P wave duration / amplitude, as measures of atrial electrical remodelling parameters, will be used to assess timing and degree of reverse remodelling; and left ventricular ejection fraction and diastolic function (transmitral velocities, E/E' index) will also be analysed. The study is conducted at the department of Cardiology in Uppsala, SÖS-Karolinska and in Gävle hospital. The project is in collaboration with the department of Neuroradiology in Uppsala with Professor Elna Marie Larsson. In a 2nd study electrical cardioversion will be compared with pharmacological cardioversion (PhCV) by randomizing patients between the 2 treatments. The Primary end-point is new silent cerebral ischemic events detected on MRI after electrical cardioversion and secondary end-points are electrical and functional/structural remodelling parameters as stated above and including time to AF recurrence, and AF burden. Health economic comparisons will be conducted for electrical cardioversion and PhCV. We will also assess whether cardioversion with vernakalant leads to less AF recurrences as compared with electrical cardioversion during a 12 months follow up period.

Predictors of sudden cardiac death and RVC progression ARVC

The diagnosis of arrhythmogenic right ventricular cardiomyopathy (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. We have in collaboration with the clinical genetics and department of pathology collected potential genetic and clinical risk markers with regards to disease progression and sudden cardiac death, in patients with ARVC and relatives who are gene carriers. Patients and relatives are studied with phenotype characterisation using echocardiography, 12 lead ECG, signal averaged ECG, 40 h Holter, and cardiac MRI, genetic testing, by a systematic long term follow-up of patients. The study population is at present 300 patients followed for at least 10years

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Funding 2015

Swedish research council	1 800 k SEK
Swedish Heart-Lung foundation	300 k SEK
ALF	500 k SEK
External funding	1 200 k SEK

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Cardiovascular epidemiology

Lars Lind

Sweden is a country with unique opportunities for epidemiological research, and has long been one of the world leaders in this field. The prospective cohort study – where a defined, prospectively examined group of people is followed over time based on personal ID number for register linkages – is the most valuable observational study design. Sweden has a large number of carefully collected population-based cohorts that have been followed for decades. We have ongoing recruitment into several world-leading cohorts. We have a variety of high quality national socio-demographic and medical registries, covering the whole population since many decades. We also have a large number of world-leading epidemiological researchers in the country, of which the combined knowledge spans most current research fields.

In addition, we have two strategic research areas in epidemiology funded by the Swedish government via the Swedish Research Council; our research group is leading one of them. A common theme in the research group is the ambition to unravel the pathophysiology behind atherosclerotic disorders such as myocardial infarction and stroke, for improved risk classification in the population and improved treatment strategies.

Besides our ongoing studies on established cohorts, we have initiated new, major cohort initiatives during the last years. The first project, led by Johan Sundström, The Swedish Cohort Consortium, is a novel national infrastructure of existing cohorts in Sweden designed for individual participant data meta-analyses of uncommon diseases, for which very large samples are needed (see below). The second project, led by Lars Lind, is a new cohort study, the EpiHealth cohort, which has been established during the last five years, and has been opened up for research in 2015. During 2015, Johan and Lars have also launched the Uppsala part of the SCAPIS study, a nation-wide cohort study engaging 6 universities in Sweden with the aim to collect detailed data in 30,000 individuals on heart and lung function, including CT coronary angiography, ultrasound of the carotid arteries, a lung function test and CT of lungs.

The Swedish Cohort Consortium (COHORTS.SE)

Johan Sundström, PI

Swedish cohort research is poorly coordinated. Many research projects are underpowered by using only one cohort at a time, leading to uncertain results with little benefit to patients and the public. Furthermore, rare diseases and exposures are impossible to study in individual cohorts due to lack of statistical power and are therefore discriminated.

We propose a coordination of all Swedish cohorts in a common national infrastructure. This will allow us to increase the level of data security, quality and accessibility to our valuable cohorts. It will facilitate greater use of Swedish cohorts for world-leading research. It will also enable collaborations between cohorts. Combining multiple cohorts permits better-powered solutions for any ordinary cohort research question, with higher benefit to patients and the public. Combining multiple cohorts also permits adequately powered research on rare diseases and exposures, as well as analyses of time trends in exposures and diseases, both of which are impossible in single cohorts today. Sweden is one of the very few countries where this is possible, due to our prominent tradition of prospective cohort research and very long history of uniform registry reporting.

We are currently undertaking a pilot study of the infrastructure – *Risk factors for subarachnoid haemorrhage*; a devastating disease associated with a mortality rate of ca 45%, and significant disability among survivors. In this pilot project, the main applicant and co-applicants have a joint experience of successful collaboration, obtaining individual participant data from 21 cohorts including 1,027,999 participants with circa 20,000,000 person-years of follow-up, a successful ethics review board application, successful linking of five of the cohorts to national registries (which had not previously been linked), successful harmonization of data, and successful statistical analysis. The pilot study proves the feasibility of the suggested approach, and our common experience with it. To date, the pilot project has taken 5 years and costed approx. 3 million SEK. The rationale for launching a permanent national infrastructure for cohort collaboration is to be able to decrease the costs and resources needed for such projects, thereby accelerating

world-leading research. Development of statistical methods and drafting of a first manuscript of the main results are currently underway.

For perspective, it would take the UK Biobank (>500,000 screened subjects) more than 40 years to acquire the same amount of person-years as in this pilot study. This means that the Swedish Cohort Consortium will allow world-leading research that is currently impossible to achieve elsewhere. The Swedish Cohort Consortium thus has the potential to significantly increase the knowledge of pathophysiological pathways, target preventive efforts, and ultimately change prognosis for patients and populations.

The Epidemiology for Health (EpiHealth) study

Lars Lind, PI

In the EpiHealth study, 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, and arthrosis. Data on life-style exposures are collected using a web-based questionnaire and serum/plasma/DNA is biobanked at a visit to a test centre where also physiological measures, such as blood pressure, lung function, cognitive function, anthropometry and ECG are recorded. A test centre in Uppsala was started up in April 2011 and in Malmö in Jan 2012. The Uppsala site was closed in 2015. By the end of 2015, abound 23,000 individuals had been enrolled in the study. The cohort is now open for research.

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

Lars Lind, PI

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

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

The Uppsala Longitudinal Study of Adult Men (ULSAM)

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

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

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

Lars Lind, PI

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, PI

Stroke is the most common clinical manifestation of vascular disease in the brain. The onset of symptoms is sudden and the consequences long-lasting. HaemorrhageBleeding (15%) or ischemia (85%) infarction in the brain parenchyma (85%) causes stroke. In Sweden about 30 00025 000 are hospitalised due to an acutepeople suffer strokes every year and approximately 10 000 face a transient ischemic attack (TIA) every year. We performed a cohort study of 105 034>200 000 stroke patients, registered in Riks-Sstroke (the Swedish Stroke Register National Quality Register for Stroke Care) during 2001 through 2009, and a separate cohort study also including TIA-patients for the years 2011 through 20145. Cross-linking with the National Patientto the Hospital Discharge Register, the Prescribed Drug Register and Cause of Death Registers has been done to achieve data on previous hospitalisations, drug therapy, death dates, and causes of death. The objectives were to assess co-morbidity, functionality and drug treatment in stroke patients before and after the stroke/TIA. Of particular interest is the use of anti-thrombotic treatment before and after the stroke/TIA.

In collaboration with Uppsala Clinical Research Center, with founding from the Swedish Research Council, we are planning the world's first randomised clinical trial within a national stroke register (R-RCT). This R-RCT will compare early vs. delayed start of oral anticoagulation in patients with acute ischemic stroke and atrial fibrillation. at onset of acute stroke and at discharge from hospital. Risk and risk factors for fatal and non-fatal recurrent stroke are analysed.

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Hjärt-Lungfonden	3.0 MSEK		
EpiHealth	3.0 MSEK	**Andreas Terént /Signild Åsberg**	
ALF	2.0 MSEK	ALF	0.3 MSEK
EU-FP7	1.3 MSEK	AstraZeneca Nordic-Baltic	0.5MSEK

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Clinical physiology

Hans Hedenström

New techniques for ventilatory support

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

Ventilator-induced lung injury

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

Asthma disease phenotyping and natural history of asthma disease

An asthma cohort of 411 subjects (schoolchildren and young adults) was formed between 2010 and 2012 within the frame of a VINNOVA-funded for research on Minimally Invasive Diagnostics in Allergies and hypersensitivities (MIDAS). Information on respiratory symptoms, disease control, measurements of exhaled nitric oxide (NO), nasal NO, exhaled carbon monoxide, lung function and methacholine reactivity were done along with sampling of blood for measurements of inflammation and allergic sensitization markers. The overall aim was to map asthma disease with emphasis on inflammation and allergic sensitisation pattern as a basis for future therapeutic interventions. A total of six PhD students are working with results from the MIDAS study and five manuscripts have been published on the material and several are being prepared. A follow-up of the MIDAS study has been performed during 2013-2015 and we are currently analysing natural history of the disease, with focus on stability of different asthma phenotypes as well as the predictive value of some of the baseline characteristics for disease deterioration.

We are also involved in analysis of the Swedish Global Asthma and Allergy Excellence Network (GA2LEN) - study where we have analysed determinants of exhaled nitric oxide in patients with asthma along extensive mapping of different inflammatory markers in the blood (eosinophil activation markers along with other type 2 inflammation markers). Finally, we are investigating the value of combining markers of inflammation in the airways (exhaled nitric oxide) with markers of eosinophil inflammation in the blood (blood eosinophils or serum eosinophil cationic protein) in MIDAS, GA2LEN and National Health, Nutritrion and Examination Survey (NHANES). We could report that simultaneously elevated levels of both this type of markers relate to disease exacerbation and poor control.

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 FEV_1 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. We assess the value of extensive lung function characterization (including DLCO, gas washout, exhaled NO and forced oscillation technique measurements) along with exercise ability, inflammation markers for predicting exacerbations in COPD patients in an ongoing, multicentre study – Tools for Identifying Exacerbations (TIE) study. We have included approximately 500 patients during 2014-2015 that will be followed-up with yearly clinical visits for two ears. Five PhD students are involved at the present moment in the TIE-study. In an EU-funded project, Clinical tRials for elderly patients with MultiplE Disease (CHROMED), we are investigating the value of telemonitoring lung function by forced oscillation technique in elderly subjects with COPD and comorbidities. Data from the CHROMED project are analysed at the present moment.

Evaluation of forced oscillation technique to investigate lung function

Forced oscillation technique (FOT) and impulse oscillometry (IOS) are two lung function methods that can be performed in all subjects as they require only tidal breathing and therefore can be used in small children and elderly persons that are not able to participate in conventional lung function tests. We are investigating the value of this method to be used as screening method for obstructive airway disease in patients referred for lung function testing. Furthermore in the follow-up of our asthma cohort of children and young adults with asthma, MIDAS, we are investigating the value of FOT to detect early changes in lung function and the value of FOT measurements in relation to disease control and airways inflammation.

Within the frame of the Swedish CArdioPulmonary bioImage Study (SCAPIS) we have included the measurements of lung function by IOS in order to investigate the value of lung function changes identifyied by IOS in relation to current symptoms, atheriosclerosis and future morbidity.

These methods are also included in the follow-up of patients with cystic fibrosis and esophagus atresia in order to early identify obstruction of peripheral airways and to predict which patients are at higher risk of developing disease worsening or respiratory symptoms, respectively.

Evaluation of new information in cardiac imaging

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

The following main projects were pursued in Cardiac Imaging during 2015:

- A Hjärtlungfonden-funded study of left ventricular function in asymptomatic severe chronic degenerative mitral regurgitation. This study includes echocardiography including stress echo, VO2 uptake by cardiopulmonary exercise test, magnetic resonance, and positron emission tomography, apart from biomarkers. This study is done together with radiology and the PET center.

- An assessment of test-retest reliability of echocardiographic speckle-tracking strain measurements of the left ventricle in patients with a wide range of ejection fractions. The aim is to assess diagnostic reliability of these parameters when separately acquired by different operators.
- Echocardiographic assessment of patients with biopsy-proven cardiac amyloidosis, in parallel with evaluation of new positron emission tomography markers of amyloidosis (together with the PET center). This includes an industry-sponsored study.
- A retrospective study of the past experience at Akademiska with heart valve replacememt for carcinoid disease. These patients typically have right-sided valvular heart disease, necessitating tricuspid and/or pulmonary valve replacement. We are analyzing survival curves and durability of prosthetic valves in this scenario.
- An industry-sponsored, echocardiographic substudy of left ventricular function in the evaluation of new antidiabetic drugs (FIDELIO/FIGARO).
- A study of the value of pulmonary acceleration time as an echocardiographic parameter to assess pulmonary pressures if tricuspid regurgitant velocity cannot be measured. Echocardiography is compared to direct (right-heart catheterization) pressure measurements.
- A study of longitudinal strain in moderate or severe aortic stenosis, in particular "paradoxic" low-flow, low-gradient aortic stenosis with preserved ejection fraction.

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Dissertations

Antonios Patelis *:* IgE sensitization against food allergens: Natural history, relation to airway inflammation and asthma. 2015.

Respiratory, allergy and sleep research

Christer Janson

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

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

Christer Jansson

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

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

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

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

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

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

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

Sleep and Health

Eva Lindberg

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

major aims are to understand the consequences of sleep-disordered breathing (SDB) to health and to understand the underlying pathophysiology. Our research is mainly epidemiological in design and we follow two unique population-based cohorts (one male and one female) prospectively who were investigated for sleep disorders at baseline and followed for health outcomes. Subsamples have been clinically investigated including polysomnography, blood sampling and oral glucose tolerance test. During 2013-16 we have been working on the SHE study, a unique 10-year follow-up of a community-based cohort of women including repeated full-night polysomnography. In recent years we have focused also on the impact of sleep architecture on metabolism and health. We are about to start a inclusion of matched men for comparison of sleep architecture and consequences of sleep apnea between gender. In addition, in a randomised, controlled trial we study the effect of physical training on sleep-disordered breathing. In the same clinical cohort we analyse the effect on metabolism and systemic inflammation when the sleep-disordered breathing is effectively treated. Since 2013 we are running a clinical trial in obese patients with and without sleep-disordered breathing, the ELVIS study. The main purpose is to analyse effects on glucose metabolism and lung function by treatment of sleep-disordered breathing and by rapid weight loss by surgery. Ongoing clinical trials also include a study to evaluate the role of measuring nose resistance to predict treatment compliance and also to validate questionnaires used to select patients at high risk of sleep apnea syndrome. We do also participate in other large cohort studies performed in Uppsala such as Epi-Health, SCAPIS and the POEM study were we focus on the impact of sleep disorders on health and the interaction with other diseases.

Physical training and physical activity

Margareta Emtner

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

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

In 2012 we started a Nordic multicenter study, the AMBOX study (Ambulatory oxygen), aiming at investigating the benefits of supplemental oxygen to patients with COPD, who do not have long-term oxygen therapy, but desaturate during exercise. Ten sites are now including patients and a total number of 66 out of 144 patients have been included and followed for a year. The study is ongoing.

In 2013 we started collaboration with the Departments of Women's and Children's Health and Surgical Sciences investigating the prevalence of exercise-induced breathing problems in adolescents in Uppsala and reasons for exercise-induced breathing problems. A population based survey (3838) has been performed. In addition, 150 exercise provocation tests, to investigate bronchial and laryngeal obstruction, have been undertaken. Physical activity during seven days has been measured with an accelerometer and analyses are ongoing. Also analyses of blood samples is ongoing. In 2016, a follow-up questionnaire will be sent to the

subjects who participated in the exercise provocation tests (150 subjects) to investigate the development of exercise-induced breathing problems over time.

The TRIAD study including 100 COPD patients from the lung clinics in Uppsala and Gothenburg aiming at identifying physical capacity, physical activity, nutrition status and inflammatory markers is completed and analyses is ongoing. Also the 4-year follow-up of all patients has been completed.

Members of the group during 2015

Christer Janson, MD, PhD, professor
Eva Lindberg, MD, PhD, professor
Margareta Emtner, PT, PhD, professor
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
Antonis Patelis MD, PhD student
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,
Mirjam Lunggren MD, PhD student
Carina Hagman PT, PhD student
Fredrik Sundbom, MD, PhD student
Sören Spörndly-Nees, PT, PhD student
Andreas Palm, MD, PhD student
Caroline Bengtsson, PhD student
Helena Igelström, PT, PhD
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Katarina Nisser, RN
Ulrike Spetz-Nyström, RN
Gunilla Hägg, NA
Shumi Omar RN
Gun-Marie Bodman Lund, project coordinatorS
Shadi Amid-Hägg, MD, PhD

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Christer Jansson

Heart and Lung Foundation	700 kSEK

Eva Lindberg

Heart and Lung Foundation	600 kSEK

Margareta Emtner

Uppsala university	400 kSEK
Astma- and Allergy Foundation	250 kSEK

Publications 2013-2015

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Dissertations

Patelis A. IgE sensitization against food allergens: Natural history, relation to airway inflammation and asthma

Sandelin M. Prognosis, Prediction and Risk Assessment in the Prevention and Treatment of Non-Small Cell Lung Cancer.

Johansson H. Exercise induced breathing problems in adolescents

Occupational and environmental medicine

Magnus Svartengren

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 obstructive lung disease, asthma, ocular and respiratory symptoms, rhinitis and allergic symptoms. We are responsible for lung function testing in the "Life Gene" study with < 5000 spirometries anlyzed so far. Inhaled nanoparticles differences in uptake through the lung due to disease. The indoor studies have covered schools, day care centers, hospitals, dwelling, stables and the cabins in aircraft. Another focus is health and work environment in health care and education. Studies investigating health, work environment, life style and socioeconomic factors are conducted. Some multi-disciplinary studies investigating how building construction and property management together with energy use are associated and affects indoor environment, health and well-being are conducted. Organizational factors for the good work environment are studied as well as musculoskeletal and psychiatric disorders in relation to work. Return to work, rehabilitation causes for and consequences of sick listing are other focus of research for the group as is development of evidence based methods for occupational health services and systematic work environment management. 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. We also continue our research on genetic and environmental influence on hearing function using investigations on twins.

The research group are using epidemiological studies as well as experimental laboratory studies in a translational way. To study and develop methods for occupational health services are another research group within OEM.

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

The overall aims of the research group are to;

discover, explore, assess, analyze and report health and risk factors for occupational and environmental exposures.

develop new methods for research in occupational and environmental medicine

develop and evaluate prevention strategies at work and in the general environment.

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

- Development of evidence based methods for occupational health services
- The Swedish part of the international epi study on hardmetal workers - cancer mortality
- "Life Gene" pulmonary function- effect of feedback on data quality
- Inhaled nanoparticles differences in uptake through the lung due to disease

- 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

Magnus Svartengren

FAS	2.6 MSEK
AFA	2.4 MSEK

Eva Vingård

FAS	1.0 MSEK

Dan Norbäck

Astma och allergiförb.	240 kSEK
VR	350 kSEK

Karin Engvall/Greta Smedje

FORMAS	850 kSEK

Monica Lind

FORMAS	2.5MSEK

Margareta Torgén

FAS	400 kSEK

Members of the group during 2015

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Peter Westerholm, Professor emeritus, MD
Dan Norbäck, Assoc professor
Gunilla Wieslander, Assoc professor, MD
Robert Wålinder, Assoc professor, MD
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Susanne Victor, PhD-student
Juan Wang, PhD-student
Sofia Åström Paulsson, PhD-student, MD
Teresia Nyman MD Ergonomist
Renata Bogo PhD-student
Katarina Aili MD ergonomist
Martin Anderson MD, PhD
Mikaela Qvarfordt research student
Eva Bergsten PhD-student

Publications 2013-2015

1. Lind Y S, Lind L, Salihovic S, van Bavel B, Lind P M. Persistent organic pollutants and abnormal geometry of the left ventricle in the elderly. Journal of Hypertension. 2013;31(8):1547-1553.
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Dissertations 2015

Magnus Helgesson: Unemployment and sick leave at a young age and associations with future health and work

Erik Lampa Mixture Effects of Environmental Contaminants

Katarina Aili (at Karolinska Institute**)** Markers of Stress as Predictors of Wellbeing and Workability

Molecular epidemiology

Erik Ingelsson, Tove Fall, Marcel den Hoed

Summary of ongoing projects

Our research area is cardiovascular medicine with a special focus on metabolic disturbances, such as obesity and insulin resistance and their role in the development of subclinical and clinical cardiovascular disease. The methods used are primarily from the molecular epidemiology field where we use -omics methods and their impact on cardiovascular disease. We are also conducting large-scale data analysis based on cohort studies and register data using traditional epidemiology methods. Further, 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.

Genomics

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

Over the past 4-5 years, we have also been working with Mendelian randomization (MR) as a method to address causality - a key concept in clinical medicine and epidemiology. Several of these projects that we have led have now been published in high-impact journals, and we have several additional projects using this methodology in the pipeline.

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

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

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

Other -omics

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

We have a range of ongoing projects using transcriptomics, epigenomics, proteomics, metabolomics, microbiomics - all aiming at increase the biological knowledge of cardiovascular diseases and to identify new biomarkers and drug targets. In proteomics, we are working with the proximity extension assay and have published several papers during 2015, one of them selected as one of the scientific highlights for SciLifeLab 2015. In metabolomics, we are using liquid chromatography (LC)- and gas chromatography (GC-) tandem mass spectrometry (MS/MS) methods, and we have run analyses in about 5,500 samples from several longitudinal cohort studies. Regarding microbiomics, we are currently setting up methods and analysing 400 pilot samples in our own lab to assess key microbiome characteristics and in the future link these to important phenotypes. Over the next few years, we plan to continue to analyse new samples using these methods, combine data across studies and data types, and to use -omics to improve knowledge about cardiometabolic diseases.

Large-scale epidemiology

During the year, we have published several articles using traditional epidemiology including two papers reaching high public attention. One of these led by Prof. Ingelsson investigated novel predictors of mortality (Altmetric 535, top 5% of all research scored) and the other one led by Dr Fall investigated the association of animal exposure on childhood asthma risk (Altmetric 430, top 5% of all research scored). We continue to work on these two unique resources, the UK Biobank (502,000 participants) and the Swedish national registers with other important public health questions.

Significance and novelty

Our research program combines comprehensive characterization in humans using both -omics methods and detailed phenotyping, with experiments in both *in vitro* and *in vivo* model systems in an integrative fashion providing a translation-back translation framework. We have access to unique study materials, state-of-the art methods, and a strong track record of successful projects in this field. Our work is anticipated to lead to new important insights into the pathophysiology of obesity, lipid metabolism, type 2 diabetes and cardiovascular diseases, and to new approaches to prevention and treatment that could have a huge impact on public health.

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

Members of the group

Erik Ingelsson, professor
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Funding

Erik Ingelsson

Swedish Research Council	6.1 MSEK
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Knut och Alice Wallenberg Foundation	1.5 MSEK
Swedish Heart-Lung Foundation	0.6 MSEK
Swedish Diabetes Foundation	0.3 MSEK

Marcel den Hoed

Swedish Heart-Lung Foundation	0.6 MSEK

Tove Fall

Swedish Research Council (co-PI)	4.0 MSEK
FORMAS	0.9 MSEK
Borgströms stiftelse	0.25 MSEK
Swedish Diabetes Foundation	0.15 MSEK
AGRIA	0.15 MSEK

Publications 2013-2015

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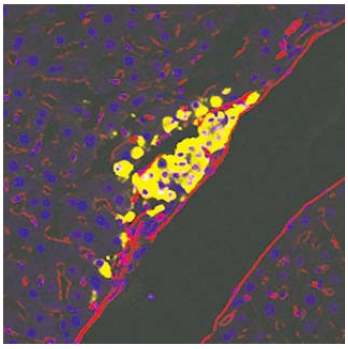
Endocrinology

Research in the field of endocrinology is performed by three research groups focused on strategies for treatment of diabetes, obesity and metabolic bone diseases. Why is adiposity of importance for insulin resistance? Can stem cells be used to treat type-1 diabetes? and what causes metabolic bone diseases? are examples of questions that are addressed. A large number of different methods are used in studies mostly with human subjects, including clinical trials.



Clinical diabetology and metabolism

Jan Eriksson

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

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

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

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

Most patients with type 2 diabetes are obese, and the global epidemic of obesity largely explains the dramatic increase in the incidence and prevalence of type 2 diabetes over the past 20 years. Excess weight, particularly excess weight in the abdomen region, is an established risk factor for type 2 diabetes, yet most obese individuals do not develop type 2 diabetes. Diferent studies have identified associations between obesity and type 2 diabetes involving proinflammatory cytokines, deranged fatty acid metabolism, and cellular processes such as mitochondrial dysfunction. However, these interactions are complex, and isn´t well established how these mechanisms cause diabetes.

The project focuses on metabolic dysregulation in human adipose tissue and its importance for insulin resistance, type 2 diabetes and their complications. The primary objective is to increase understanding of mechanisms in human adipose tissue that play a role in the development of insulin resistance and type 2 diabetes. An important long-term aim is to identify new therapeutic principles for prevention and treatment of type 2 diabetes.

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

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

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

The project is run in collaboration with the Dept of Surgery, and it focuses on the profound changes seen in glucose and lipid metabolism following bariatric surgery. Obese patients undergoing gastric by-pass (GBP)

markedly improve their insulin sensitivity and glucose tolerance. According to most available data, these effects are much greater that what the weight loss itself can explain. Thus, it is believed that there are important factors induced by the rearrangement of intestinal anatomy that influence metabolism in various organs.

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

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

Insulin resistance caused by immunosuppressive drugs.

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

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

In addition to common risk factors and clinical characteristics between NODAT and type 2 diabetes, there may be also common mechanisms. This project aims to identify novel mechanisms for insulin resistance in insulin sensitive cells, including human adipocytes, by exploring pharmacologic manipulation with immunosuppressive agents, in vitro, leading to insulin resistance.

Our recent results indicate that the immunosuppressive agents cyclosporin A and tacrolimus impair glucose uptake in peripheral tissues, without affecting the insulin signalling cascade, and by removing the major glucose transporter GLUT4 from the cell surface. The project will evaluate in detail the effects of the calcineurin inhibitors on the cellular trafficking of the GLUT4. Effects of the IAs on expression of specific proteins involved in GLUT4 trafficking, will be evaluated. Furthermore, our work has identified FKBP5, cannabinoid receptor type 1 and lipocalin-2 as genes in adipose tissue that are highly regulated by glucocorticoids and that are associated with clinical measures of insulin resistance. However, the mechanisms by which they affect insulin resistance are not characterized. Therefore, we will perform mechanistic and clinical characterization to address the molecular pathways and causal relationships. We explore the cellular pathways, including regulation of key genes and proteins that lead to metabolic dysregulation.

This may point to novel pharmacological concepts that can mitigate the adverse effects caused by glucocorticoids and IAs. Importantly, such findings can also be of relevance for the development of future treatments for other forms of diabetes including type 2.

Metabolic and hormonal effects of SGLT2 inhibition.

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

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

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

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

We have since almost 30 years prospectively followed a group of type 1 diabetic patients and have been able to identify important factors for the management of diabetes. As part of this larger study we have recently examined the long-term effects of glycaemic control and treatment satisfaction in people with Type1 diabetes mellitus who changed from multiple daily insulin injections to insulin pump therapy. The aim of the study was through deep interviews describe experiences of the impact of insulin pump therapy in adults with Type1 diabetes mellitus after >5years' use of an insulin pump. The performed analysis revealed that insulin pump therapy was experienced as both a shackle and a lifeline. Sub-themes emerged that could be used by physicians and diabetes specialist nurses to support self-management among people with insulin pump treatment.

Evaluate the patient perspective on diabetes care

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

Damage to the eye is the most feared complications of diabetes and one of the most common causes of vision loss is diabetic macular edema (DME). In January 2011 a new treatment for DME, called anti-VEGF treatment was approved. This study is focused on patients experience in relation to need for information in connection with the named treatment. The treatment involves an injection into the vitreous of the eye and begins with three injections every four weeks for the first 12 weeks. The treatment places increasing demands on the patient with more visits and a stressful treatment. The aim is to evaluate the new treatment, anti-VEGF, using both qualitative and quantitative evaluation, by describing the patients experience and measuring their health-related quality of life as well as medical endpoint. This work was conducted in a real-world setting and has shown that approximately 50 % of patients that receive anti-VEGF treatment for DME have an improvement in their visual acuity and a reduction in retinal thickness. However, the results also show that nearly half of the participants do not improve their visual acuity. More research is required to determine what factors affect the treatment outcome. It is also important to determine the patients' experience of the treatment and their visual impairment due to DME.

Members of the group during 2015

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AstraZeneca	4 100 kSEK
Diabetesförbundet	180 kSEK
Diabetesförbundet	200 kSEK
Vårdvetenskap, UU	700 kSEK

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Endocrinology and mineral metabolism

Östen Ljunggren

The main projects within the research group are based on clinical samples from a specialized 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 four main areas. Male osteoporosis, osteogenesis imperfect, micro RNA in bone cells, and phosphate homeostasis. In the research group there is also a separate clinical project concerning pituitary diseases.

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.

Micro RNA

In collaboration with the department of orthopedic surgery studies on isolated human osteoblasts are performed. During 2015 especially the existence and regulation of micro RNA in human bone cells has been the focus of interest.

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.

Pituitary diseases

In collaboration with Dr Engström the research group is also involved in studies concerning pituitary diseases. These projects are focused around patient registers, and treatment studies.

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Dissertations

Navya Laxman: miRNA and Asymmetric siRNA : Small RNAs with Large Effects on Bone Metabolism

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, stromal or their progenitor cells for beta-cell regeneration and function, and to investigate the concept of islet heterogeneity. Other studies investigate the adaptation of pancreatic islets to the implantation organ, i.e. the so called engraftment process, following transplantation, and develop bioengineering strategies (coating of islets with supporting stem cells, oxygen carriers and growth factors, as well as with use of scaffolds) to improve results of pancreatic islet transplantation by enhancement of engraftment e.g. by improved revascularization. Human islets are tested in these experimental systems with a focus to produce clinically applicable protocols. We also perform research to develop safe and effective means to generate new human beta-cells by stimulating adult beta-cell proliferation, e.g. by stem cell stimulation, or by stem cell differentiation in vivo. Clinical studies are performed to prevent development of type 1 diabetes in patients, e.g. by autologous mesenchymal stem cell transplantation, and to develop means for beta-cell imaging by positron emission tomography. We also conduct studies to improve the results of clinical islet transplantation, e.g. by encapsulation in order to avoid immune suppression of the patients.

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, more prone to cellular death when stressed by hypoxia or cytokines and are the first affected by disease at development of type 1 diabetes.

Communication between endothelial or neural cells and beta-cells

Liza Grapensparr, Joey Lau, Carl Johan Drott, Monica Sandberg, Per-Ola Carlsson

We have observed an importance for endothelial-beta-cell communication to maintain beta-cell proliferation, differentiation and function. In other experiments, the possibility for endothelial progenitor cells, neural crest stem cells and Schwann cells to stimulate human beta-cell proliferation and function have been investigated. We have established techniques to bioengineer islet surfaces with neural crest stem cells and endothelial progenitor cells and to in this manner improve human islet vascularization, beta-cell survival and proliferation after transplantation. Parenterally administered mesenchymal stem cells and neural crest stem cells home to damaged endogenous islets in mice, repair (mesenchymal stem cells) and induce regeneration (neural crest stem cells) in the damaged pancreatic tissue with substantial regrowth of insulin-producing cells.

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

Daniel Espes, José Caballero, Louise Magnusson, 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 in investigator-initiated studies. In a first phase 1/2a trial, we observed no adverse events of the procedure and preserved residual insulin production for at least a year. These individuals are now followed up to five years after diagnosis to investigate if the effect is sustained and the immunological changes to a Th2 phenotype persistent. We have also initiated a larger

(national), blinded, phase 2 efficacy trial with the same concept. 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 human islets is tested in an ongoing investigator-initiated phase 1/2a trial in type 1 diabetes patients. The macrodevice protects the islets from immune rejection, whereas oxygen is supplied daily into a refillable oxygen tank. A follow up study is also planned with instead transplantation of human embryonic stem cells derived to insulin producing cells within the same device.

Members of the group 2015

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Funding for 2015

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

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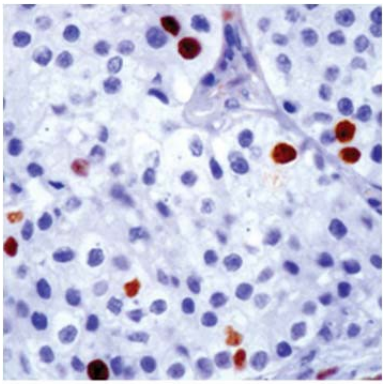
Oncology and Haematology

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 two groups working in the area of neuroendocrine tumours, studying carcinogenesis, development of biomarkers, exploring new treatment concepts and conducting clinical trials. Research on haematological malignancies is focused on development and testing of new drugs and development of registers for malignant haematological disorders. The cancer pharmacology and computational medicine research program acts at the intersection of clinical pharmacology, oncology and medical bioinformatics. Key issues are related to drug resistance and improved multi-compound therapies.



Endocrine Oncology

Eva Tiensuu Janson and Kjell Öberg

The research group with Eva Tiensuu Janson as principal investigator focuses on research concerning neuroendocrine tumors (NETs) with a special emphasis on small intestinal NETs and the highly malignant neuroendocrine carcinomas (NECs). The research group of Kjell Öberg has two main objectives; the first is to develop new potential biomarkers for small intestinal and lung neuroendocrine tumors, and the second is to develop new NET-therapies.

Genetics in familial and sporadic neuroendocrine tumors

Eva Tiensuu Janson, Malin Grönberg, Abir Ali and Staffan Welin

Small intestinal NETs (SI-NETs) have generally been considered a sporadic disease. We have now identified 20 Swedish families with an inherited variant of SI-NETs. We have performed exome and whole genome sequencing of familial and sporadic patients' tumors and blood in order to define the specific genetic events which lead to tumor development. This work is performed in collaboration with researchers at the department of immunology, genetics and pathology at Uppsala University (Professor Jan Dumanski). We have recently identified mutations in a group of genes which are potentially interesting as possible disease causing and we are now working to confirm this in a large cohort of 150 SI-NET patients. We are also expanding our material with families from Norway and Denmark.

Studies of neuroendocrine carcinomas (NEC)

Staffan Welin, Abir Ali, Malin Grönberg and Eva Tiensuu Janson

The Nordic NEC study has become highly recognized worldwide. The Nordic Neuroendocrine Tumor Group, led by Tiensuu Janson continues to perform research on this tumor group. In 2015 a group of international pathologists visited Uppsala to go through the tumor samples collected from patients in the Nordic NEC registry with the aim to develop a new classification. A clinical trial with a new combination of drugs (temozolomide and everolimus) for the subgroup of patients with a lower Ki67 has started and is recruiting patients from the Nordic countries. Further studies on this patient group are ongoing to evaluate the expression of tumor biomarkers in tissue and to evaluate the impact of surgery on survival for NEC patients.

Expression of neuroendocrine markers in tumors

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

An area of interest is the expression of neuroendocrine biomarkers in cancer. Ghrelin expression was significantly correlated to better recurrence-free survival and breast cancer-specific survival. In related

projects we have studied the expression of somatostatin receptors on neuroblastomas, and found frequent expression of these receptors, suggesting that treatment with somatostatin analogs should be further explored in neuroblastomas. Further studies of neuroendocrine markers in neuroblastomas are ongoing.

MicroRNAs during early tumourigenesis and tumour progression

Valeria Giandomenico, Su-Chen Li, Kjell Öberg

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.

Oncolytic virus, basic and clinical studies.

Kjell Öberg

Patients with liver dominant NET will receive intra hepatic infusions of an engineered oncolytic adenovirus.Phase 1 is a dose finding study, whereas Phase IIa is an efficacy study .Totally 35 patients will be included. Immunology parameters as well as a new biomarker test will be applied (NET-test).Ga68PET/MRI as well as FDGPET/MRI will be applied for tumor biology studies.

Members of the group 2015

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Funding

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

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Books

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Dissertations

Xia Chu : Aspects of MEN1 Tumorigenesis in Endocrine Pancreas and Adrenal Glands.

Endocrine tumor biology

Britt Skogseid

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

Tumors of the endocrine pancreas and the adrenal

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

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

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

MEN1 tumorogenesis and haploinsufficiency

Our hypothesis is that the MEN1 gene is a haploinsufficient suppressor resulting in growth advantage in endocrine cells of carriers of the MEN1 trait (heterozygous), but also alterations of the phenotype of the non-tumorous surrounding tissue. In a recent study supporting our hypothesis we used five-week-old conventional MEN1 knock-out mice to show that Ki67 proliferation index in heterozygous islets of Langerhans was indeed twice as high compared to that found in islets of wild type littermates. Furthermore, numerous genes were differentially expressed in these islets, e.g. up-regulated genes ontogenetically belonged to growth factor families, mitochondrial membrane transport, apoptosis inhibition and transcriptional regulation, and down-regulated genes involved cell structure and chromatin modification. In order to further understand the very onset of transformation, i.e. the effect of MEN1 heterozygosity per se, we have preceded by performing proteomics as well as microRNA array on heterozygous MEN1 mouse adrenals compared to that of wild type littermates. Interestingly, several proteins involved in lipid metabolism are obviously differentially regulated. We currently run cell line experiments to evaluate if inhibition of some of these proteins might compromise cell growth, and thus may be candidate targets for future drug development. Preliminary data in adrenocortical cancer cell lines are promising.

Angiogenesis and pre-clinical PET

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

autoradiography as well as micro-PET/CT of our MEN1 mouse model. Furthermore, micro-PET-MR is now available in house, and we are currently planning a project applying this new technique in our MEN1 mouse model.

The PI3K/Akt/mTOR pathway in MEN1 tissue

Inhibitors of the PI3K/Akt/mTOR pathway have entered the oncological arsenal of targeted therapies. Data on tumorigenesis and signal transduction in neuroendocrine tumor are however limited, so we aim at recognizing how menin interacts with the PI3K pathway and how mTOR and PI3K inhibitors function in the complete absence of menin as well as in MEN1 heterozygous cells. In these ongoing studies we use various drugs inhibiting this pathway as well as our MEN1 mouse model treated with these inhibitors. Preliminary data indicate that menin is essential for maximal effect of mTOR inhibition (rapamycin, everolimus) in neuroendocrine cell lines.

Adrenocortical carcinoma

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

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

Serous ovarian cancer

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

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

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

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

Members of the group 2015

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Funding

The Swedish Cancer foundation	1000 kSEK
ALF	650 kSEK

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Haematology

Sören Lehmann

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

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

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

Molecular studies and preclinical drug development in acute myeloid leukaemia (AML)

Anna Eriksson, Martin Höglund

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

Sören Lehmann, Anna Eriksson, My Björklund, Albin Österros

From November 2015 the new professor Sören Lehmann started to set up his lab group at the Rudbeck Laboratory focused on epigenetics and novel drug development in AML. The Lehmann group is a translational research group with research projects spanning from basic molecular characterization of AML through developing novel drugs to clinical trials and epidemiologic studies of AML. The moleckular studies are focues on epigenetic aberrations in AML. The group currently consists of 11 persons with activity both in Uppsala and in Karolinska with successively increasing activity at Uppsala University.

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

Emma Bergfelt, Helene Hallböök and Bengt Smedmyr

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

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

Mattias Mattsson, Karin Larson and Martin Höglund

In close collaboration with professor Richard Rosenquist (Dept of Immunology, Genetics and Pathology), we are presently performing studies in CLL on prognostic and prediciive biomarkers, clonal evolution and resistance in patients with advanced disease treated with the BCR inhibitors ibrutinib or idealisib. In

another project, we aim to clinically and genetically characterise subsets of CLL with very good prognosis.

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

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

The Swedish population based registries in patients with haematological malignancies are internationally unique. Presently, more than 1000 patients with CMLand more than 6000 patients with acute leukaemia are included. In a recent publication (Hoglund ta al, Blood 2013, 122, p 1284), we have shown that the estimated 5 yrs. survival for patients with CML is 80% and in certain diagnostic subgroups 95%. At present, our studies focus on the outcome of patients with secondary leukaemia, relapsed AML, patient related outcome measures (PROM) and the association of CML with other types of cancer.. Using the Nordic Registry for Hematopoietic Stem Cell Donors (NRHSD) and linking it other national registries, we are studying short-term and possible long-term complications following donation of hematopoietic stem cells.

Chronic myelogenous leukaemia (CML)

Stina Söderlund, Ulla Olsson-Strömberg, and Bengt Simonsson

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

Plasma cell disorders

Sara Rosengren, Torbjörn Karlsson and Kristina Carlson

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

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

Tobias Svensson, Honar Cherif

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

Myeloproliferative neoplasms (MPN), cancer anaemia and supportive care

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

In MPN and cancer anaemia we are involved in several clinical trials including a large European multicentre study for long term follow-up of platelet-reducing therapy in essential thrombocythemia (ET), a 7-year prospective follow-up of ET patients treated with anagrelide, and a randomised phase II trial investigating the effect of IV iron alone in cancer patients with functional iron deficiency. As regards

supportive care, we have previously shown that cryotherapy significantly reduces mucositis after high dose chemotherapy, and in two recently performed studies investigated the physiological mucosal effects on oral mucosa and the protective effect of a new saturated calcium-phosphate solution in addition to cryotherapy during chemotherapy.

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Swedish Cancer foundation:	100 kSEK,
Regional research council	250 kSEK
Nordic CML Study group	100 kSEK
Swedish Research Council (Lehmann)	1000 kSEK
Cancer Foudation (Lehmann)	700 kSEK
The Wallenberg Fundation (Lehmann)	1400 kSEK
Uppsala County Council	2000 kSEK

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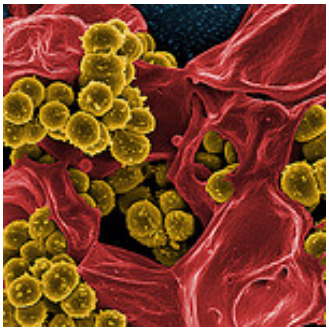
Infection



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

Clinical Microbiology

Hilpi Rautelin

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

Campylobacter infections and intestinal microbiota

Hilpi Rautelin, Cecilia Johansson, René Kaden, Christian Kampmann , Anna Nilsson, Astrid Skarp, Erik Torell, Lars Engstrand (KI),

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

Multiplex virus diagnostics, and bioinformatics-led definition of variation tolerant nucleic acid detection and endogenous retroviral sequences

Jonas Blomberg, Christina Öhrmalm, Bengt Rönnberg, Hongyan Xia

We develop nucleic acid and antibody based diagnostic tests which address many viruses at the same time, i.e. multiplex tests. We use these methods for studying zoonotic infections and myalgic encephalomyelitis, the chronic fatigue syndrome. We have unique bioinformatic tools for creation of these tests. Our bioinformatical effort also led to the identification and classification of human endogenous retroviruses.

Chlamydial infections in humans and birds

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

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

Antiviral treatment and resistance

Johan Lennerstrand, Assar Bergfors, Midori Kjellin, Dario Akaberi, Adam Ameur, Anders Lannergård, Tore Gutteberg

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

1. Study of resistance in Hepatitis C virus prior to treatment with new directly acting antivirals. A Nordic Multicenter Study.2. Ultra deep-sequencing of Hepatitis C virus resistance - in collaboration with SciLifeLab Uppsala. 3. Studying nucleoside analogs candidates against Flaviviruses such as Dengue and TBE. 4. Biochemical mechanism of HIV RT resistance to nucleoside analogs.

Infection Prevention and Control

Birgitta Lytsy, Anna Hambraeus, Ulrika Ransjö

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

Members of the groups during 2015

Guma Abdeldaim, scientist
Assar Bergfors, scientist
Jonas Blomberg, prof. emer.
Lars Engstrand, professor (KI)
Anna Hambreus, Senior advisor
Björn Herrmann, assoc. prof.
Jenny Isaksson, research engineer
Cecilia Johansson, scientist
René Kaden, scientist
Midori Kjellin, PhD-student
Christian Kampmann, PhD-student
Johan Lennerstrand, assoc. prof
Birgitta Lytsy, scientist
Anna Nilsson, PhD-student
Ulrika Ransjö, senior advisor
Hilpi Rautelin, professor
Bengt Rönnberg, scientist
Astrid Skarp, scientist
Hongyan Xia, scientist
Christina Öhrmalm, scientist

Funding 2015

FORMAS	2.0 MSEK
ALF	1.9 MSEK
Uppsala-Örebro Regional Research Council:	0.4 MSEK
Selander Foundation:	0.1 MSEK
SSAC Svenska Läkaresällskapet:	0.1 MSEK

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Books and book chapters

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Infectious diseases

Jan Sjölin, Britt-Marie Eriksson, Thomas Tängdén

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

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

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

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

In previous sepsis models we have demonstrated that the inflammatory response and bacterial killing in the blood may be reduced in secondary sepsis, in which inflammatory and anti-inflammatory activities have been activated by preceding infection or trauma. This was also seen in a clinical pilot study published in 2015. In a new study bacterial killing of the phagocytic cells in the liver and the spleen was investigated after a 24-h infusion of endotoxin in our intensive care large animal (porcine) model and compared to that in healthy animals. Surprisingly, an increased bacterial killing was noticed and thus the concern that bacterial killing is negatively affected if bacteria enter the bloodstream once the inflammatory systems have been activated seems not valid. In another study on ventilator associated pneumonia there was, in contrast, a reduced bacterial killing in the lung using the same model indicating different systemic and local capacities to kill bacteria. During 2015 we have continued our efforts to develop a tertiary sepsis model, in which the inflammatory response is blunted by an endotoxin-induced anti-inflammatory response in combination with high-dose steroid treatment. This model will primarily be used to test in vivo killing of bacteria and Candida. We have almost solved the problems with this model and, if so, it will be the first large animal model of candidemia. With these varying models established, the antibacterial activity of different treatments with antibiotics and immunomodulatory drugs will be the primary focus. The present models will increase our knowledge and ability to conduct future clinical trials.

The effect of neurosurgical trauma and the innate immune response on the specific immunity by vaccination of patients with a T-cell dependent vaccine was published in 2015. A reduced response was seen if vaccinated during the 10 first days after trauma. We have now extended that analysis to the response to a T-cell independent pneumococcal vaccine that is not affected and thus preferably should be used for an early protection against pneumococcal meningitis. In 2015 two registry studies evaluating the effect on antibiotic treatment and outcome by early recognition of the inflammatory response in the treatment of community-acquired meningitis and the effect of the qualification of the first line physician have been published. The effect of immunomodulation by corticosteroids given before antibiotic treatment is now being assessed in the registry comprising 1500 patients with meningitis. This is up to now the largest study on corticosteroids and meningitis.

Clinical studies evaluating the effect of the systemic inflammatory response on pharmacokinetics of antibiotics and antifungals change have continued during the year. Furthermore, the work with an ex vivo antifungal model has been initiated determining the antifungal activity of patient blood.

Improved antibiotic therapy for multidrug-resistant bacteria and studies on the impact of antibiotics on the intestinal microbiota

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

Ongoing *in vitro* studies include experiments aiming to find antibiotic combinations effective against multidrug-resistant Gram-negative bacteria and the evaluation of rapid antibiotic susceptibility tests. During 2015, we have completed a study on carbapenem-resistant Enterobacteriacae, demonstrating bactericidal effects with combinations of colistin and rifampicin (manuscript under review). Automated methods have been evaluated for potential use in a high-throughput screening for combinations against multidrug-resistant strains. The oCelloScope, which is based on automated microscopy and image analysis, has been considered feasible (manuscript under review) and will be used for this purpose in a 3-year project funded within the framework of JPIAMR. A microfluidic assay using a linear antibiotic gradient to determine antibiotic susceptibility with high accuracy, CellDirector 3D, has been evaluated in collaboration with Gradientech AB within a 2-year project funded by VINNOVA, with promising results (manuscript under review) and will be further improved.

Clinical studies include a multicenter clinical study on optimal antibiotic therapy for urinary tract infections caused by ESBL-producing bacteria. During 2015, approximately 50% of the targeted 250 patients were included, and the project will be completed during 2016. A study addressing impact of antibiotics on the intestinal microbiota in hematological patients was initiated in late 2014 and approximately half of the planned 100 subjects have now been included. Further, a study on patients treated at the intensive care unit for burn injuries has been initiated and will address not only the impact of antibiotic therapy on the intestinal microbiota bur also the feasibility to restore the diversity with fecal transplantation.

Cytomegalovirus- and other herpesvirus 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 (AD).

In our latest studies on AD, which also involve antibody responses towards different viruses in the Herpes group, CMV specific and general T-cell immunity was studied in patients with AD and in age-matched controls. Our hypothesis was that persons with AD have an aged immune system with an immune profile corresponding to that seen in the very old with an inversed CD4:CD8 ratio and a shift from naive T-cells to memory T-cells. Unexpectedly a decreased proportion of Cytomegalovirus specific CD8 T-Cells but no signs of general immunosenescence were seen in AD. Cytokine analysis showed a pro-inflammatory pattern in AD

In a collaborative study, enteric biopsies as well as plasma and faeces were collected from patients with newly diagnosed inflammatory bowel disease (IBD). Patients with irritable bowel syndrome served as controls. CMV was found in a higher proportion of IBD patients but this did not affect outcome during follow-up unless immuno-suppressive therapy was given.

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.

The results of a multi-national placebo-controlled RCT of valacyclovir for 3 months after initial iv acyclovir therapy of Herpes simplex encephalitis was published (Gnann et al, NEJM 2015). No beneficial effect on neuro-cognitive outcome was seen in the treatment group.

Members of the group

Otto Cars, Professor
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AFA	1 700 kSEK
Vinnova	600 kSEK
SSF	760 kSEK
Folkhälsomyndigheten	500 kSEK
Svenska Läkaresällskapet	100 kSEK

Publications 2013-2015

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Dissertations

Gabriel Westman: Herpesvirus Infection and Immunity in Neurocognitive Disorders

Infection medicine

Björn Olsen

Professor Björn Olsen, Professor Åke Lundkvist, MD, PhD Erik Salaneck and MD, PhD Josef Järhult have been instrumental in building up "The Zoonosis Science Center" at BMC, IMBIM. This joint venture has created an arena for theoretical and practical research in all aspects of zoonotic infections. Therefore, we have associated researchers from a plethora of disciplines such as human and veterinary medicine, ecology, and molecular biology and virology. From the first initiative taken in early spring 2014 we are now an established part of the high diversity of research within the medical faculty in particular and Uppsala University in general. By generous support partly by the medical faculty we are increasing our strength with a high security laboratory (BSL 3) that will be working from the summer 2016. There we will be able to conduct high quality research on pathogens as haemorrhagic fever virus, influenza virus of higher pathogenicity and particular hazardous bacteria.

We have also created an online forum www.onehealth.se and an open access journal (www.InfectionEcologyandEpidemiology.net), under the same name, to publish papers, share ideas and raise awareness of its work among politicians, industry and to the wider public. The journal is open access and publication has been free of charge for the first three years. We are searchable via pubmed and will probably receive the impact factor of 2015. The preliminary and unofficial impact as this is written is 2.34.

Influenza

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

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

Campylobacter and other gastrointestinal pathogens

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

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

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

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

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

Tick borne infections

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

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

Antibiotic Resistance

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

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

Members of the groups during 2015

Anders Lannergård, MD, PhD
David Lennebratt MD PhD student
Björn Olsen, MD PhD, Professor
Åsa Melhus, PhD, MD, Assoc. Professor
Anders Bergqvist, PhD
Kåre Bondeson, MD PhD
Marie Edvinsson MD, PhD
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Josef Järhult, MD, PhD
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Anders Lannergård, MD, PhD
Heidi Lindbäck, PhD-student
Mats Lindeborg, MD, PhD student
Carl-Johan Neiderud, MD,
Kenneth Nilsson, MD, PhD, Assoc. Professor
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Susanne Sütterlin, MD, PhD
Erik Torell, MD, PhD
Katharina Wallménius, PhD

Funding 2015

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

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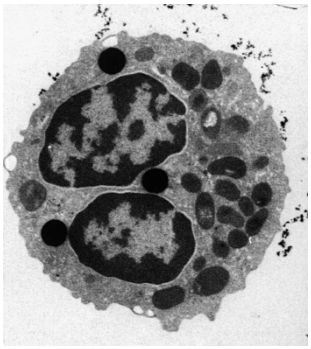
Dissertations

Susanne Sütterlin: Aspects of Bacterial Resistance to Silver

Eva Tano: Survival of infectious agents and detection of their resistance and virulence factors.

Jenny Olofsson: Amoebae as Hosts and Vectors for Spread of *Campylobacter jejuni.*

Inflammation



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.

Coagulation and Inflammation Science

Agneta Siegbahn

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

TF expression and procoagulant activity

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

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

Microparticles; methods and biological functions

Upon activation platelets, leukocytes and endothelial cells form MPs. Circulating platelet MPs have been found in inflammatory diseases and are related to the severity of disease. We have during the year developed a new flow cytometry method to calculate the amount of MPs with different cellular origin in whole blood. The new method is superior to earlier used methods, and is now implemented in a number of

new clinical studies in patients with CAD and pulmonary arterial hypertension. Characterization of the biological effects induced by purified platelet MPs upon interaction with a number of human cells and whether new antiplatelet/antithrombotic drugs can interfere with this interaction are a subject of our ongoing experimental studies.

TF non-coagulant, signalling and biological funcions

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

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

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

MicroRNA: TF regulation and arrays for clinical studies

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

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

Identification of biomarkers in atherothromboembolic diseases

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

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

We have been actively involved in the design of the substudy programs of biomarkers, genome wide association studies and the analyses of the plasma samples and to translate candidate genes and proteins into functional studies. During the last year we have in close collaboration with the Cardiology research group at IMV been very actively involved in establishing new clinical tools for improving the identification of risk of stroke, MI and bleeding during anticoagulant treatment. These tools are based on age, biomarkers

and previous cardiovascular events, and therefore called ABC-risk scores. The first version of three different scores, based on biomarker results analysed in our large trials in ACS and AF, have recently been presented.

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Heart and Lung Foundation:	800 kSEK
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Christina Christersson

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Dariush Mokhtari

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Dermatology and Venereology

Hans Törmä

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

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

During 2015 we have focused on the following projects;

Etiologies and new therapies for monogenetic epidermal diseases

Hans Törmä, Marie Virtanen, Berit Berne, Anders Vahlquist

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

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

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

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

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 (Uppsala) indicate that such drugs will indeed reduce the number of dermal mast cells and the expression of pro-inflammatory mediators in cultured biopsies of lesional and non-lesional psoriatic skin. Our results support the idea that cutaneous mast cells contribute to the inflammatory process in psoriasis, and that

lysosomotropic drugs should be evaluated as pro-apoptotic agents in mast cell-mediated dermatoses.

Immunologic mechanisms in idiopathic inflammatory skin diseases

Mohammad Alimohammadi

One of the major challenges in care of patients with skin disorders is to manage disease symptoms in a disease-specific manner. The majority of dermatologic disorders are today considered as idiopathic although in most of them, a role of the immune system can be observed. For example histological examination of most of skin disorders involve lymphocytic infiltration. Although, the underlying molecular reason for this immune action is rarely contemplated in the routine clinical work.

The overall purpose of this project is to elucidate and understand underlying disease mechanisms and determine biomarkers for diseases that may have autoimmune components. This could lead to better diagnosis and better treatment strategies for these patients. We collect tissue samples, including serum, PBMC and skin biopsies from clinically well characterized patients and use the samples. The collected samples are later examined for signs of autoimmune mechanisms using different autoantibody detection methods such as SEREX, candidate autoantigen approach, cytokine profiling, western blotting and T cell activation experiments.

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Publications 2013-2015

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Dissertations

Frida Dalin: Model diseases for studies of autoimmunity

Gastroenterology and hepatology

Per M. Hellström

Research in gastroenterology and hepatology is focused on inflammatory reactions in the gastrointestinal tract and liver. From a patient registry (SWIBREG), special attention is given to inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis) and microscopic colitides (collagenous colitis, lymphocytic colitis) as well as sclerosing cholangitis as complication of IBD. Epidemiologic and etiopathogenic perspectives of disease are covered through studies on the commensal microflora and inflammatory reaction in the gut mucosa. Plasma and fecal biomarkers of inflammation are studied and evaluated as regards their usefulness as predictors of disease progression in IBD and sclerosing cholangitis. Special attention is given to the inflammatory aerocrine biomarkers nitric oxide (NO) in rectal gas, circulating biomarkers as cytokines and chemokines; and fecal biomarkers, all of which known to drive inflammatory process in the gastrointestinal tract. To this end, regulatory gut peptide functions are studied in neuroregulatory disorders of the gut. Special attention is also given to diagnostic procedures in inflammatory liver diseases for prediction of malignant development in sclerosing cholangitis.

A developmental research branch emanating from the IBD concept is *gut permeability* for diagnosis of the "leaky gut syndrome". This is combined with imaging techniques using combined positron emission tomography in combination with magnetic resonance imaging (PET-MRI) for visualization of gut inflammatory conditions and simultaneously the leakage of specific molecules over the gut mucosa. The autoinflammatory concept of IBD is also extended over to neurodegenerative diseases commonly expressed as enteral dysmotility and pseudoobstruction as defined using the SmartPill diagnostic system.

Metabolic interactions with inflammation are studied focusing on gastroparesis and enteric dysmotility as primary steps in the endocrine dysregulation after food intake. In broad collaborations, work has been carried out to study the importance of gastric emptying in obesity, bariatric surgery and diabetes, as well as diabetic complications such as gastroparesis and enteropathy. A generalized concept has been worked out using ghrelin and glucagon-like peptide-1 as biochemical markers of typical motility patterns during fasting and fed conditions. The pattern recognition of specific motility patterns along with specific gut peptides is presented as a general concept for "the healthy gut", to which metabolic and motility diseases can be related.

The composite work includes epidemiological, experimental, and clinical studies aiming at delineating events at the imaging, molecular and subcellular level leading to relevant clinical diagnostic and monitoring biomarkers of gastrointestinal and liver disease.

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

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

Select projects

- Epidemiology of IBD and microscopic colitides and complications of disease
- Nitric oxide, nitrite and nitrate in the inflammatory IBD response
- Eosinophilic granulocyte activation in IBD.
- The leaky gut syndrome in celiac disease, IBD and IBS involving imaging techniques for visualization of inflammation
- Diagnostic and predictive markers of malignant progression in IBD with sclerosing cholangitis

- Regulatory gut peptide hormones in metabolic and autoinflammatory gastrointestinal disorders against the "healthy gut" concept.
- Fecal eosinophil inflammatory markers in IBD and sclerosing cholangitis
- Fecal microbiota transplantation in IBD and IBS
- Treatment of liver disease with portal hypertension using transjugular intrahepatic portosystemic shunt (TIPSS)
- Detection, treatment and prognostic markers of biliary cancer in sclerosing cholangitis.

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ALF	150 kSEK

Anders Rönnblom and Mari Thörn

ALF	200 kSEK

Publications 2013-2015

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Renal Medicine

Bengt Fellström

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

Cardio Vascular Complications in Chronic Kidney Disease and Renal Transplantation

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

Cardiovascular disease (CVD) is extremely common in patients with renal insufficiency, which includes dialysis and renal transplant patients. Our efforts are targeting the importance of e.g. endothelial dysfunction, oxidative stress, and inflammation as contributing factors to the high rate of CVD. An important part of our efforts is treatment studies, often initiated from our own unit. Such studies include the ALERT trial in renal transplant patients, the AURORA trial in haemodialysis patients, and the SHARP trial in preuremic and dialysis patients. In a new study we are investigating if a low-dose aldosterone blockade by Spironolactone may have a positive effect on cardiovascular morbidity and mortality in haemodialysis patients. We have also initiated a CV study in renal transplant patients studying CV biomarkers while switching from CNI based immunosuppression to a belatacept based regimen. Other trials involve e.g. studies in patients with IgA nephropathy using a corticosteroid compound acting primarily in the gut (budesonide) and results from a phase 2b trial demonstrated reduction in proteinuria and stabilisation of renal function (GFR). In diabetic nephropathy, the benefit (and safety) of mineralocorticoid receptor antagonist is being investigated focusing on renal as well as cardiovascular endpoints (FIDELIO/FIGARO). Another study is focusing on effects on proteinuria and outcome in DM2 by use of of an endothelin receptor antagonist atrasentan (SONAR).

A new line of research in CVD in renal failure includes studies of complement activation, formation of microparticles and screening of inflammatory markers using the multiplex PLA technology. In addition we are also collecting samples such as plasma and vascular tissue for proteomics analysis in collaboration with Prof. J Bergqvist at SciLifeLab. Preliminary results are emerging and pointing at new potentially important pathways. In parallel vascular tissue from patients with ESRD and healthy controls(donors) are also captured for proteomics studies along the same lines. The dynamics of anti-PC levels in the course of dialysis is being studied as well as complement and contact systems to detect possible new players responsible for sustained inflammation in these patients.

In addition, the accuracy of GFR measurement has been looked into and the study on physiological variability of urinary biomarkers is ongoing.

Superb biobanks have been collected from 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.. A regional biobank with follow-up in SNR (Swedish Renal Registry) is in a start-up phase and will be an important infrastructure in future biomarker research.

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.

Polycystic kidney disease (PKD)

Jan Melin, Hans Furuland, Inga Soveri, Bengt Fellström

A novel research path includes studies of biomarkers for progression of PKD , as well as initiation of a treatment study using Tolvaptan, which was just recently started. Patient recruitement has been going on and three aptients in Uppsala have entered the study

Members of the group during 2015

Bengt Fellström, Professor, M.D, PhD
Torbjörn Linde, Assoc. professor, M.D, PhD
Hans Furuland, M.D, PhD
Thomas Nilsson, MD, PhD
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Liina Vassil, MD , researcher
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Fjölnir Elvarsson, PhD student
Jenny Stenberg, PhD student
Danielle Lundqvist, Research nurse
Yvonne Lundholm, Research nurse

Funding

ALF	950 kSEK
Industrial grants	1500 kSEK
Uppsala-Örebro region Fund	300 kSEK

Publication 2013-2015

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Reviews

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Rheumatology

Lars Rönnblom

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

Project group Systemic Autoimmunity

Lars Rönnblom, Maija-Leena Eloranta, Gunnel Nordmark.

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

We have continued to identify new risk loci for SLE and primary Sjögren's syndrome. The work on susceptibility genes has been done in collaboration with Prof. Syvänen's and Prof. Lindblad-Toh's research groups together with our international partners and with the contribution of the different networks. Several new risk genes have been identified and results published.

In March 2014 we launched a collaborative project, for which Lars Rönnblom is the PI, between AstraZeneca and SciLifeLab. The project is entitled "Dissecting disease mechanisms in three systemic inflammatory autoimmune diseases with an interferon signature –DISSECT". The overall aim of the study is to identify molecular pathways in sub phenotypes of three systemic inflammatory autoimmune diseases which share the type I interferon signature in blood and target organs. In DISSECT we aim to perform targeted sequencing of 1900 genes in 1000 patients each for the diseases SLE, Sjögren's syndrome and myositis, as well as 1000 common control individuals. During 2015 most of the individuals have been sequenced, clinical information has been collected and a database has been established. Our epigenetic studies have continued and also expanded with several collaborative projects.

Johanna Sandling was awarded prize for best poster at the international SLE congress in Vienna for an abstract on epigenetic changes in lupus patients.

Regulation of the type I interferon response by immune cells

We have continued to characterize autoantibodies to NKG2A and NKG2C in patients with SLE, and results have been published. The presence of anti-NKG2A autoantibodies was associated with high SLE disease activity and damage index, and thus a more severe disease phenotype. Several other projects describing the interaction between innate and adaptive immune cells have been finalized and among these are our study of the role of T cells in the type I interferon response. We are also in the DISSECT project investigating potentially new drugs in vitro for their capacity to modulate immune activation and interferon production.

Niklas Hagberg was awarded the stipend to Andrzej Tarkowskis memory for his novel line of research in clarifying disease mechanisms in rheumatic diseases

Karin Hjorton was awarded prize for best poster at the Swedish Society for Rheumatology annual meeting.

Bioresource of healthy blood donor samples

Uppsala Bioresource (UBR) is a permanent resource of genotyped (200K Immunochip, Illumina) healthy blood donors visiting the Uppsala Blood Transfusion Center, Uppsala University Hospital. UBR keeps a sample collection within Uppsala Biobank and currently the UBR sample collection contains cellular material, DNA and serum from 2000 donors. Hitherto a total of 16,300 samples have been collected in UBR and over 11,300 samples have been withdrawn for analysis in-house, locally, nationally as well as

internationally by 10 different research groups. UBR has contributed to several large international projects which have been published in highly acknowledged journals such as Nature, Nat Commun and Ann Rheum Disease.

Studies of associations between inflammatory rheumatic diseases and malignant lymphomas

Clinical, immunological and genetic studies of granulomatosis with polyangiitis

Studies of safety of anti-rheumatic treatments

Eva Baecklund, Ann Knight

We have continued the studies of associations between inflammatory diseases and lymphoma development with focus on RA, Sjögren's syndrome, granulomatosis with polyangiitis, and safety follow-ups of new biologic drugs used in rheumatic diseases. The AUTO-LYMPHOMA study continues successfully and now includes more than 150 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. We have also continued the work within the national vasculitis project to study clinical, therapeutical and genetic implications of small-vessel vasculitis, in particular GPA. The studies of safety of anti-rheumatic treatments continue. Apart from studies of lymphoma risk we have soon completed a study of liver complications after methotrexate therapy which includes genetic analyses in cooperation with the SWEDE-GENE study.

Eva Baecklund was awarded the 2015 Uppsala country council research prize for the clinical implications of the research in inflammatory diseases and lymphoma.

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

Ulla Lindqvist

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.. 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, results that have been published.

Members of Rheumatology research group during 2015

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, associate professor
Ann Knight, MD, PhD
Karolina Tandre, PhD, Research engineer
Andrei Alexsson, Research engineer
Carin Backlin, PhD, Project coordinator
Johanna Sandling, PhD, Project coordinator
Karin Hjorton, MD, PhD student
Rezvan Kiani Dehkordi, Research nurse
Charlottta, Jakobsson, BMA
Lisbeth Fuxler, BMA
Olle Berggren, PhD student
Niklas Hagberg, PhD
Dag Leonard, MD, PhD
Karin Bolin, MD, PhD student
Peter Matt, MD, PhD-student
Lilian Vasaitis, MD, PhD student

Funding 2015

Lars Rönnblom

AstraZeneca/SciLife	6100 kSEK
Wallenberg Foundation	2400 kSEK
Swedish research council	1000 kSEK
King Gustav V 80 year foundation	300 kSEK
Swedish Rheumatism Society	300 kSEK
ALF grant	1700 kSEK

Gunnel Nordmark

King Gustav V 80 year foundation	150 kSEK
Swedish Rheumatism Society	150 kSEK

Maija-Leena Eloranta

King Gustav V 80 year foundation	100 kSEK
Swedish Rheumatism Society	100 kSEK

Eva Baecklund/Ann Knight

ALF grant	310 kSEK

Eva Baecklund

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

Ulla Lindqvist

SIDA	560 kSEK
ALF grant	100 kSEK

Publications 2013-2015

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Reviews

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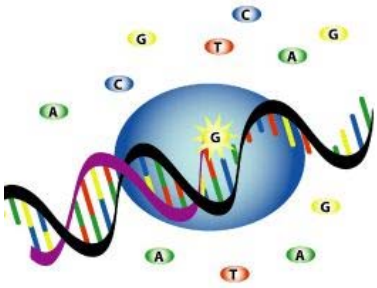
Dissertations 2015

Olof Berggren: Regulation of Type I Interferon Production in Plasmacytoid Dendritic Cells : Effect of Genetic Factors and Interactions with NK Cells and B Cells

Laboratory Medicine

Within this area there are several independent research groups working to identify risk factors for, and causes to, several common diseases such as cancer, and osteoporosis. State of the are genomics, epigenetics and computational modeling methods are employed together with *in vitro* experiments, utilizing biological materials in the form of DNA, protein or metabolites. High throughput experimental techniques are also used to discover novel, and improve existing, therapies for cancer and other complex diseases.



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

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

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

The hormonal responses elicited by stress and pain are an area of interest. In animals there are no solid methods to monitor pain and stress responses. We have shown that Chromogranins and Secretogranins can be measured in dogs and cats. We have also shown that these markers can be used as biochemical markers for stress and pain in humans. This project focuses on improvement and development of biochemical markers to monitor stress and pain responses in animals.

Members of the group during 2015

Mats Stridsberg, MD, PhD, Assoc. Prof.

Torbjörn Åkerfeldt, MD, PhD student

Funding

ALF

Publications 2013-2015

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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.

The researchers in the research group have more than 100 publications with 100 citations or more. Anders Larsson was the most read author at Department of Medical Sciences during 2016 according to Researchgate.

Studies of the role of prostasome in fertility and prostate cancer

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

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

Participation in international research consortia (Global Burden of Disease Study 2013 Collaborators and Chronic Kidney Disease consortia)

Anders Larsson

We have during 2015 participated in these two large consorties. This has resulted in a number of publications in Lancet, Lancet Diabetes Endocrinol and Lancet Pediatrics.

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

Johan Stålberg, Anders Larsson

Cystic fibrosis (CF) is a hereditary life-shortening disorder with repeated respiratory infections and malnutrition as main clinical manifestations. Chronic lung infections with Pseudomonas aeruginosa (PA) are major causes of morbidity and mortality. We have shown that we can reduce the number of pseudomonas infections in CF patients by oral immunotherapy with anti-pseudomonas IgY. The study includes more than 50.000 daily patient doses and is the world's largest study with IgY. We have received an orphan drug designation from EMEA. We also have initiated development of therapies against candida albicans and ESBL-klebsiella. We are currently performing a Phase III, placebo-controlled randomized

double blind study supported by an EU grant (EUR 5.35 million over a 4 year period) for a clinical study to prevent pseudomonas infections in CF patients. We are now fully recruited and have patientsin nine European countries. The maximum treatment period is 2 years so the study will be ended in june 2017. This is the only ongoing phase III studies in Europe that focus on antibiotics resistance and alternatives to antibiotics.

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

Leif Wide and Karin Eriksson

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

Studies of F-calprotectin and S-calprotectin

Tom Nilsen, Anders Larsson

Calprotectin is found in neutrophil and the protein is released when the neutrophils are activated. Faeces calprotectin is widely used as a marker for inflammatory bowel disorder while S-calprotectin could be used as a marker for neutrophil activation. We are currently, together with Gentian and Buhlmann, developing a turbidimetric calprotectin assay. The project is supported by EU through Eurostar. The aim of the project is to develop calibrators and reagents for F-calprotectin and S-calprotectin and evaluated them with clinical materials. The F-calprotectin reagent was CE labelled and introduced on the European market in 2015.

Urinary biomarkers for tubular kidney damage, cardiovascular disease and mortality

Johanna Helmersson Karlqvist, Mats Flodin, 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 and as a cardiovascular risk marker. We are one of the leading groups in cystatin C research and have been involved in the new international calibrator for cystatin C and the new CAPA equation. We have shown that cystatin C-estimated GFR has a very good correlation with iohexol-estimated GFR both in patients with slight and severe kidney disease. Cystatin C also has a low diurnal variability, which facilitates the use of the marker. Cystatin C is also a promising risk marker for cardiovascular morbidity and mortality and is significantly correlated with HbA1c, diabetes and inflammation in elderly males. A natural step is to expand the research field to other types of kidney damage (glomerular and tubular damage). We have in our laboratory set up new tubular biomarkers for kidney damage urinary neutrophil gelatinase-associated lipocalin (U-NGAL), urinary kidney injury molecule (U-KIM-1) and urinary cystatin C (U-cystatin C). We are currently evaluating them as biomarkers of acute kidney injury in intensive care units. Recently it was shown that mild to moderate increases of these biomarkers may also reflect chronic kidney damage and subsequently cardiovascular risk. Increased concentrations of U-NGAL, U-KIM-1 and U-Cystatin C are independently associated with cardiovascular morbidity and mortality in prospective studies of elderly men. During the last three years we have been involved in a number of publications in JAMA, Lancet and New Engl J Med on mortality and GFR markers.

Members of the group during 2015

Anders Larsson, professor/consultant
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Publications 2013-2015

1. Castegren M, Skorup P, Lipcsey M, Larsson A, Sjölin J. Endotoxin tolerance variation over 24 h during porcine endotoxemia : association to changes in circulation and organ dysfunction. PLoS ONE. 2013;8(1):e53221-.
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Cancer Pharmacology and Computational Medicine

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

I. Drug and multi-compound therapy discovery

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

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. This work has resulted in the first iterative approach reported designed explicitly to optimize a therapeutic index which reflects the difference in effect between normal/reference cells and cancer cells. The method was successfully used to identify a most promising therapy consisting of 3 compounds with ability to kill 6 *in vitro* cancer models of CRC, without affecting normal/reference cells much. In this context we have also developed a computational framework allowing integrated synergy analyses including both the two classical Bliss and Loewe approaches. 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 these kinds of questions while at the same time developing beyond state-of-the-art alternatives. The main issues 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 apoptotic cells. We have also demonstrated how this approach can be greatly enhanced by combining the outputs from several vesicle detectors (corresponding to difference sizes) with the outputs from an apoptosis detector and a confluence estimator (fraction of the well covered by the cell culture) to identify compounds, concentrations and time points where there are large differences (a large therapeutic index) between normal cells and cancer cells.

In mechanistic studies we have found that MBZ interfere with the dual-specificity kinase DYRK1b at very low concentrations (Kd 7 nM). DYRK1B is a serine/threonine kinase that is widely expressed in various cells and mediates cell survival in some solid tumors, e.g. ovarian, pancreatic and colon cancer and is believed to be an oncogene. We have also recently observed that MBZ induces a gene expression, surface marker and cytokine release patterns characteristic of a pro-inflammatory, anticancer M1 phenotype in monocyte and macrophage models. We are now planning for a clinical phase I/II study in CRC to be launched Q4 2016.

Recent results demonstrated that QC appears especially active against AML cells and in silico analysis of large cell line panels confirms myeloid leukemias as the most promising target diagnosis based on quinacrine ability to reverse the disease-specific gene expression signature. Interestingly, enrichment analysis of gene expression after treatment of HL-60 cells with quinacrine indicate that specific inhibition of ribosome biogenesis (nucleolar RNA Polymerase 1, Pol-1) could be a primary molecular target for this drug. Ribosome biogenesis has recently emerged as a promising target for cancer therapy and there is a growing interest in the industry to develop specific Pol-1 inhibitors to attack this target. In a pilot study in a patient derived xenograft (PDX) of AML in vivo at Accelera (Nerviano, Italy) we observed that QC could prolong survival compared to untreated control.

During 2015 we combined a high-throughput gene-expression profiling method (L1000 from Genometry USA – offering mRNA gene expression levels for ≈1000 ”landmark” genes) with a tumor spheroid-based drug-screening assay to identify context dependent treatment responses. We aimed to identify compounds that enhance effects of oxidative phosphorylation (OXPHOS) inhibitors in quiescent cancer cells. We thereby generated over 1000 gene-expression profiles of compound-treated cells grown in three distinct models (monolayer, spheroids cultured in standard conditions and physiologically-relevant quiescent spheroids). The analysis revealed that the mevalonate pathway, readily inhibited by statins, is a vulnerability of quiescent cells during OXPHOS inhibition. OXPHOS inhibitors, including NZA, and statins were synergistically toxic to quiescent spheroids. We will now follow-up with a proof of concept study in vivo using NZA in combination with simvastatin in a xenograft model (HCT116) of CRC at Adlego AB.

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.

During 2015, together with the Academic Laboratory at Uppsala University Hospital and based on research grants provided by Mats Gustafsson and Kim Kultima in our group as well as from the hospital side, we were able to start using CARAMBA (Clinical Analysis & Research Applying Mass spectrometry & Bioinformatics at Akademiska, http://www.medsci.uu.se/caramba/), a mass spectrometry unit consisting of three modern high resolution mass spectrometer instruments (orbitraps). One of the instruments is almost completely devoted to pre-clinical research and development and has been upgraded with a quadropole to enable refined analyses. Under the supervision of Kim Kultima, this instrument has been used to develop protocols for metabolomics and proteomics and some pilot as well as real systems pathology studies have been performed. The main application examples so far hare related to pain research (as part of a collaboration with KI) and neurodegenerative diseases (as part of a PhD project supported by Uppsala Berzelii Technology Center for Neurodiagnostics). Pilot studies have also been performed for in vitro systems pharmacology studies where cell cultures are exposed to different drug compounds and then the cells (the cytoplasm) were analysed after some hours/days with respect to molecular changes relative to untreated controls.

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 as part of an on-going PhD project aimed at high-throughput mass spectrometry data analysis, we started to develop new algorithms aimed for suppression of batch effects and other experimental artefacts..We also started to work on improvements of the iterative search algorithm used to identify promising drug combinations.

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

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Funding 2015

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Oncopeptides	240 kSEK	NordForsk	250 kSEK
Akinion AB	300 kSEK	ENABLE	600 kSEK
ALF	1300 kSEK	Lions	400 kSEK
KAW	1300 kSEK		

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Dissertations:

Christoffer Bäcklin: Machine Learning Based Analysis of DNA Methylation Patterns in Pediatric Acute Leukemia.

Muhammad Kashif: Integrated Computational and Experimental Approaches for Accelerated Drug Combination Discovery and Development : Applications in Cancer Pharmacology

Sara Strese: Anticancer Activity of Melflufen : Preclinical Studies of a Novel Peptidase-Potentiated Alkylator.

Clinical Pharmacogenetics and Osteoporosis

Håkan Melhus, Mia Wadelius, Pär Hallberg and Gabriella Scordo

Genetic,dietary and environmental risk factors for osteoporosis

Thomas Lind, Annica Rasmusson, 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.
In a collaboration project with Assoc. Prof. M Lind financed by Formas we also investigate if developmental low-dose exposure to bisphenol A disturbs the balance between bone and adipose tissue. Our first results were presented at the 8th Copenhagen Workshop on Endocrine Disrupters 2015.

Mechanistic studies on Vitamin A-induced bone toxicity

Thomas Lind, Annica Rasmusson, Håkan Melhus

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

Warfarin pharmacogenetics and pharmacometrics

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

There have been significant advances in the pharmacogenetics of warfarin, but also controversies. In 2015, we further explored reasons for discordant results in randomised clinical trials. We published a tool for pharmacometric modelling and simulation of warfarin dose. We presented a novel gene regulatory variant associated with warfarin dose at the American Society of Human Genetics (ASHG) meeting in October 2015.

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 2300 cases and access to genome-wide data plus diagnoses and withdrawn prescriptions from 5000 Swedish controls. We lead the European Drug-induced Agranulocytosis Consortium, and presented these results at the American Society of Human Genetics (ASHG) meeting in October 2015. We are partners of the EU FP7 funded study PREDICTION-ADR. Genome-wide genotyping or exome sequencing is performed at the Uppsala SciLife SNP&SEQ platform.

Improving the Quality and Safety of Drug Use in Hospitalized Elderly

Anna Alassaad, Håkan Melhus

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

Bisphosphonate-Associated Atypical Fractures and osteoporosis

Pär Hallberg, Mohammad Kharazmi

We aim to increase the knowledge about the adverse effects of bisphosphonates, manifesting as atypical fractures in the skeleton and osteonecrosis of the jaw. Specifically, we have studied the relative risks of atypical fractures associated with different bisphosphonates, whether gender is a risk factor, described the

characteristics of prodromal symptoms, and published case reports of bisphosphonate-related osteonecrosis of the jaw. We are currently investigating whether or not atypical fractures are associated with an increased mortality compared with ordinary low-trauma fractures of the femoral shaft. These studies are partly based on data from SWEDEGENE.

Pharmacogenetics and therapeutic outcome

Gabriella Scordo

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

Clinical consequences of polymorphisms in xenobiotics metabolising enzymes

Gabriella Scordo

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

Members of the group during 2015

Håkan Melhus, Professor
Mia Wadelius, MD Lecturer
Pär Hallberg, MD PhD
Gabriella Scordo, MD PhD
Thomas Lind, Researcher, PhD
Annica Jacobson Rasmusson, Researcher, PhD
Ann-Mari Gustavsson, Biomedical analyst Msc
Anna-Alassaad, Pharmacist, PhD
Anna-Karin Hamberg, Pharmacist ,PhD
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Eva Prado, Research assistant
Ulrica Ramqvist, Research nurse
Elisabet Stjernberg, Research nurse
Charlotta Haglund, Research nurse
Hugo Kohnke, Biomedical analyst MSc
Caroline Johansson, Biotech engineer student
Mohammad Kharazmi, PhD student

Funding 2015

Håkan Melhus:

Swedish Research Council	1000 kSEK
ALF	676 kSEK
Formas	568 kSEK

Mia Wadelius:

Heart-Lung foundation	600 kSEK
Swedish Research Council	1600 kSEK
ALF	465 kSEK
EU FP7 (PREDICTION-ADR)	1400 kSEK
Thuréus' foundation	100 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 and medical research. Since its start the group has worked towards this goal by creating close collaborations with clinical scientists at Uppsala University and University Hospital and by hosting the SNP&SEQ Technology Platform in Uppsala that offers genotyping and "next generation sequencing" services and training to academic researchers. The Molecular Medicine group is interested in methods for large-scale genomic analyses and applies them to human diseases, with a focus on acute pediatric leukemia and autoimmune diseases. A-C Syvänen also heads the SNP&SEQ Technology Platform, which is part of the National Genomics Infrastructure (NGI) at Science for Life Laboratory. In the beginning of 2014 the Molecular Medicine group and the SNP&SEQ Platform moved from the Research Department at the Academic Hospital to excellent laboratory and office facilities at the Uppsala University Biomedical Centre (BMC).

Epigenetics and genomics of acute leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer in the Western world. Although there has been great progress in treatment protocols for ALL during the past decade, 10-20% of the patients do not respond to drug treatment for unknown reasons. In the research project on ALL, the Molecular Medicine group uses genome-wide genotyping and “next generation” sequencing for detection of somatic mutations, analysis of gene expression, DNA methylation and regulatory genomic sequence variation in primary cells from patients with ALL. The aim of the project is to identify genetic and epigenetic signatures that may be used as biomarkers for prognosis of the disease progression and response to treatment in individual patients. The group is also involved in similar research in pediatric acute myeloid leukemia (AML). A second objective of the project is to gain in-sights into mechanisms by which DNA methylation transforms normal hematopoietic cells into leukemic cells, and how DNA-methylation affects treatment responses in acute leukemia. In 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 Children's Hospital in Uppsala. During 2015 the project was funded by the Swedish Foundation for Strategic Research (SSF), the Swedish Cancer Foundation, the and the Pediatric Cancer Foundation.

From genes to function in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is regarded as the prototype for autoimmune diseases because it involves most immune cells and can affect all organs of the human body. SLE has a strong heritable component. There are about 70 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 one third 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 “next generation” DNA sequencing in combination with functional analysis of fractionated human blood cells. The group is also performing epigenetic analysis of DNA methylation and of chemical modifications of histone proteins in immune cells from healthy individuals and patients to elucidate the mechanisms for the regulation of gene expression in SLE and Sjögren’s syndrome. The project involves a close collaboration with the research group in Rheumatology and the Rheumatology Clinic at Uppsala University Hospital. The project is funded by the Knut and Alice Wallenberg Foundation and the Swedish Research Council for Medicine & Health (VR MH).

Large collaborative projects

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

For more information see http://molmed.medsci.uu.se/Research/

Members of the group during 2015

Ann-Christine Syvänen, PhD, professor
Eva Berglund, PhD, post doc
Mathias Brännvall, PhD, project coordinator
Jonas Carlsson Almlöf, PhD, bioinformatician
Johan Dahlberg, PhD student
Juliana Imgenberg-Kreuz, PhD student
Katarina Jonasson, administrator
Anders Lundmark, research engineer
Mårten Lindqvist, PhD student
Tom Martin, PhD, research engineer,
Erika Manlig, project assistant
Yanara Marincevic-Zuniga, PhD student
Nour-al-dain Marzouka, PhD, post doc
Sara Nilsson, project assistant
Jessica Nordlund, PhD, research scientist
Sara Nystedt, research engineer
Amanda Raine, PhD, research scientist
Michelle Rönnerblad, PhD, post doc
Per Wahlberg, PhD, post doc

Funding 2015

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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Undergraduate Teaching 2015

Medicine Programme;	**Approx. students**
Clinical Medicine I 28,5 hp	211
Clinical Medicine III 30 hp	187
Occupational and Environmental Medicine	153
Physiotherapy Programme:	
Internal Medicine 3 hp	118
Nursing Programme:	
Health and prevention of Ill I parts of (Pharmacology, Clinical Microbiology)	200
Health and prevention of Ill II parts of (Pharmacology, Clinical Microbiology)	200
Ill, Health and prevention of Ill I parts of.	200
Ill, Health and prevention of Ill II parts of.	200
Biomedicial Laboratory Science Programme:	
Medical Microbiology 11 hp	50
Medical Laboratory Data Analysis, 7 hp	38
Projectic 9 hp	38
Clinical Chemistry and Hematology, Toxicology and Pharmacology 13 hp	51
Clinical Physiology, 5 hp	49
Practical Tuition I, 12 hp	43
Practical Tuition II, 8 hp	36
Advanced Course II 8 hp	43
Biomedicine Programme:	
Basic Statistics, 3 hp	42
Applied Biostatistics, 5 hp	24
Diseases – Clinical Survey, 15 hp	11
Specialist Nursing Programme – Diabetes Care:	
Diabetes Care I 15 hp	20
Single Subject Courses:	
Diabetes Care I 15 hp	40
Person-Centred Care Related to Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM), 7,5 hp	30
Diabetes Care, Scientific Methodology and Essay 15 hp, Basic Course	3
Diabetes Care, Scientific Methodology and Essay 15 hp, Advanced Course	2
Treatment and Nursing in Congestive Heart Failure 7,5 hp	30
Treatment and Care of Patients with Arrhythmia 7,5 hp	38
Clinical Clerkship (Exchange Students)	5
Clinical Drug Development 30 hp	29
Work Environment in the New Working Life 7,5 (Contract Education)	21
Introduction to Scientific Research, Step 1 3,5 hp (Contract Education)	35
Introduction to Scientific Research, Step 2 4 hp (Contract Education)	3
TOTAL:	2000

Core Facilities

The SNP&SEQ Technology Platform in Uppsala

Director: Professor Ann-Christine Syvänen

Providing access to genotyping and sequencing on all scales

The vision of the SNP&SEQ Technology Platform is to enable Swedish scientists to perform world class research in human disease genomics and evolutionary studies of all organisms, by providing access to the most modern technologies for genomics. This is today a prerequisite for publication of studies in involving genomics in the best international journals. The SNP&SEQ Platform also strives to introduce modern genomic approaches to new groups of scientists, especially in clinical research. Access to genomics services in Sweden gives the clinical scientists a more prominent role in international studies by avoiding shipping of samples abroad. The SNP&SEQ Technology Platform aims to o make large-scale SNP genotyping and "next generation" DNA sequencing of the highest possible quality available to it users. The SNP&SEQ Platform has a professional staff of ~35 FTEs, including research engineers/laboratory technicians, bioinformatics and systems developers, IT-staff, project coordinators, facility heads, and scientists for research and development. To assure a high quality of all aspects of its activities, the SNP&SEQ Platform works according to the ISO/IEC 17025:2005 quality standard, and the genotyping and sequencing process are accredited by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC). Genome-wide SNP panels facilitate association studies in human complex diseases and traits, determination of copy number alterations and DNA-methylation across the genome. "Next generation" sequencing is applied to sequence large and small genomes, discovery of SNPs in targeted regions of large genomes, functional analyses of gene regulation by analysis of chromatin immunoprecipitated DNA and transcriptome sequencing. The SNP&SEQ Technology Platform constitutes a major part of the National Genomics Infrastructure (NGI) hosted by Science for Life Laboratory. Since 2009, the SNP&SEQ Platform has been supported as a national research infrastructure by the Swedish Council for Research Infrastructures (VR RFI), and is run according to the principles defined for national infrastructures defined by VR. The SNP&SEQ Platform also participates in collaborative EU projects, including the FP7 project European Sequencing and Genotyping Infrastructure (ESGI) that provided transnational access to genotyping and sequencing to scientist in Europe. The SNP&SEQ Technology Platform is well equipped for assisting academic research projects over a broad size range, with four genotyping instrument and 10 sequencing instruments, including 5 HiSeqX instruments for large-scale human whole genome sequencing and computer systems for analysis and storing the large amount of data produced for which the Knut and Alice Wallenberg foundation granted funding in 2014.

Projects

The users of the services of the SNP&SEQ Technology Platform are affiliated with the Faculties for Medicine and Pharmacy and the Faculty for Science and Technology at Uppsala University and with the Academic Hospital in Uppsala. In accordance with the status of the SNP&SEQ Platform as a national infrastructure, 47% of the users of the SNP genotyping services, and 30% of the users of the sequencing services are affiliated with other Swedish universities and research institutes than Uppsala University. During 2015, 60 genotyping projects including a total of 17600 DNA samples and 166 sequencing projects of 15900 DNA or RNA samples were completed. Many projects study human diseases or populations, but genotyping and sequencing in numerous other organisms, like birds, domestic animals, plants, insects, fungi and bacteria were also performed. So far the SNP&SEQ Platform has contributed to several hundred publications in respectable scientific journals, of which 128 appeared in 2015. Of the 128 publications that appeared in 2015, as many as 42 were published in journals with an impact factor > 9, including 25 publications in top journals like New England Journal of Medicine, Science, Nature and Nature Genetics.

The large number of publications in high-impact journal illustrates that the services offered by the SNP&SEQ Platform contribute to research of a high international standard in Sweden.

For a complete list of publications and for more information see

http://molmed.medsci.uu.se/SNP+SEQ+Technology+Platform/

Staff of the SNP&SEQ Technology Platform during 2015

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

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

Director: Associate Professor Anders Isaksson

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

Continued high demand for platform services during 2015

Continued interest in the Axiom platform for flexible genotyping has led to a high total number of analysed samples (2255 in 2015). By providing a diverse set of array-based analyses and bioinformatics support continues to provide services to a large number of projects. The samples mainly come from UU (23%), Akademiska sjukhuset (22%), other Swedish Universities (43%) and other countries (13%). The platform has a staff of 6 full-time positions. The platform has contributed to 28 publications in high ranking international journals during 2012-2014 (see list below).

Array-based analyses for improved health care

Our vision is to continue to develop the platform and offer a wide variety of array-based analyses. Together with Clinical Genetics we have since 2008 offered array-based diagnostics of children with suspected mental retardation of as a routine clinical analysis. The number of clinical samples have increased from 359 in 2014 to 451 in 2015. The pre-natal testing is also increasing.

We have developed a new bioinformatic tool for raw data processing called Rawcopy that provides data with superior signal-to noise ratio. During 2016 will try to implement this tool in clinical applications.

Future

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

Staff of Array and Analysis Facility during 2015

Anders Isaksson, director
Hanna Göransson Kultima Bioinformatician
Malin Olsson, Research engineer
Maria Rydåker, Research engineer
Rigmor Sjöström, Research engineer
Björn Viklund, Bioinformatician

Publications 2013-2015

Uppsala array platform has contributed to 18 published articles during 2013- 2014. Eight of them are published without platform employees as co-authors and 10 with co-authors from the platform.

Publications without platform employees as co-authors.

1. Botling J, Edlund K, Lohr M, Hellwig B, Holmberg L, et al. Biomarker discovery in non-small cell lung cancer: integrating gene expression profiling, meta-analysis, and tissue microarray validation Clin Cancer Res. 2013 Jan 1;19(1):194-204
2. Vikholm P, Schiller P, Johansson J, Hellgren L. A modified Glenn shunt improves haemodynamics in acute right ventricular failure in an experimental model. Eur J Cardiothorac Surg. 2013 Mar;43(3):612-8
3. K, Caglayan D, Caja L, et al. Snail depletes the tumorigenic potential of glioblastoma. Oncogene 32(47): 5409–5420. 2013.

4. Xie Y, Bergström T, Jiang Y, et al. The Human Glioblastoma Cell Culture Resource: Validated Cell Models Representing All Molecular Subtypes. EBioMedicine. 2015 Aug 15;2(10):1351-63
5. Sommer F, Nookaew I, Sommer N, Fogelstrand P, Bäckhed F Site-specific programming of the host epithelial transcriptome by the gut microbiota.. Genome Biol. 2015 Mar 28;16:62.
6. Int J Cosmet Sci. 2015 Oct;37 Suppl 1:9-14. The use of gene arrays and corresponding connectivity mapping (Cmap) to identify novel anti-ageing ingredients. Gillbro JM, Merinville E, Olsson M, Al-Bader T, Klack A, Visdal-Johnsen L, Mavon A.
7. Mansouri L, Sutton LA, Ljungström V, et al. Functional loss of IκBε leads to NF-κB deregulation in aggressive chronic lymphocytic leukemia. J Exp Med. 2015 Jun 1;212(6):833-43.
8. Dahlin JS, Ding Z, Hallgren J. Distinguishing Mast Cell Progenitors from Mature Mast Cells in Mice Stem Cells Dev. 2015 Jul 15;24(14):1703-11.

Publications with platform employees as co-authors

1. Mayrhofer M, DiLorenzo S, Isaksson A Patchwork: allele-specific copy number analysis of whole genome sequenced tumor tissue. Genome Biol. 2013 Mar 25;14(3):R24.
2. Cahill N, Bergh AC, Kanduri M, et al. 450K-array analysis of chronic lymphocytic leukemia cells reveals global DNA methylation to be relatively stable over time and similar in resting and proliferative compartments. Leukemia. 2013 Jan;27(1):150-8.
3. Brunberg E, Jensen P, Isaksson A, Keeling L. Behavioural and Brain Gene Expression Profiling in Pigs During Tail Biting Outbreaks - Evidence of a Tail Biting Resistant Phenotype PLoS ONE. 2013 Jun 18; 8(6):e66513.
4. Sooman L, Ekman S, Andersson C, et al. 2013. Synergistic interactions between camptothecin and EGFR or RAC1 inhibitors and between imatinib and Notch signaling or RAC1 inhibitors in glioblastoma cell lines. Cancer Chemotherapy and Pharmacology Aug;72(2):329-40.
5. Mayrhofer M, Göransson Kultima H, Birgisson H, et al. 1p36 deletion is a marker for tumour dissemination in microsatellite stable stage II-III colon cancer. BMC Cancer 14(1):872. 2014.
6. Eriksson A, Kalushkova A, Jarvius M, et al. AKN-028 induces cell cycle arrest, downregulation of Myc associated genes and dose dependent reduction of tyrosine kinase activity in acute myeloid leukemia. Biochem Pharmacol. 2014 Jan 15;87(2):284-91.
7. Crona J, Backman S, Maharjan R, et al. Spatiotemporal Heterogeneity Characterizes the Genetic Landscape of Pheochromocytoma and Defines Early Events in Tumorigenesis. Clin Cancer Res. 2015 Oct 1;21(19):4451-60.
8. Birgisson H, Edlund K, Wallin U, et al. Microsatellite instability and mutations in BRAF and KRAS are significant predictors of disseminated disease in colon cancer. BMC Cancer. 2015 Mar 14;15:125.
9. Mengelbier LH, Karlsson J, Lindgren D, Valind A, et al. Intratumoral genome diversity parallels progression and predicts outcome in pediatric cancer. Nat Commun. 2015 Jan 27;6:6125.

Drug discovery and development platform, In vitro and systems pharmacology

Directors; Professor Rolf Larsson and professor Mats Gustafsson

Our vision is to be experts in transforming validated biological ideas into drug discovery programs meeting unmet medical needs, and to be the partner of choice for Swedish academic groups interested in drug discovery.

The main focus of the Facility is to contribute to the progression of well-validated cross-functional drug discovery projects from Swedish academia or SME by pharmacological characterisation of novel small molecule or biological leads. This is achieved by offering in vitro pharmacology support investigating mechanism of action, on-target/off-target effects and systemic effects, and toxicity of compounds either as single drugs or in combinations.

Facility vision

Principle types of support available to users and how users get access to the facility

All projects are prioritized by platform steering committee and then projects are staffed by facility manager. In case of free capacity, facility manager with support from DDDP Operational Management Group (OMG), can take in service projects. Examples of services include: project management, mechanism of action studies, assay development, determining potency and toxicity of compounds, testing compounds on cell-line panels using multiple readouts including systemic profiling.

Projects handled at the facility during 2015

The main focus of IVSP during 2015 has been on full project DP_MH_004, aiming at finding a new treatment for neurpathic pain, and a technology development project DP_IVSP_002.

The facility is responsible for project management and pharmacological characterisation, in vitro efficacy and mode of action, of putative lead compounds generated by medicinal chemists on the DDD-platform.

The technology development project DP_IVSP_002 aims at assay development, validation and implementation of novel high throughput transcriptomics, proteomics and metabolomic assays for mechanism of action studies applicable to many different drug discovery projects.
In addition the facility has contributed with mechanism of action studies (based on modern concepts such as CMAP, GSEA and quantitative imaging) for two other full projects on the platform, and to service projects in collaboration with two SMEs and with advice for other full projects.

All projects at our facility are run under confidentiality on the therapeutic target involved. We work in an integrated way with together with the other facilities on the DDD-platform.

The DDD-platform currently operates 11 full drug discovery projects prioritized by the platform steering board; these project utilize resources from most facilities. In addition to these, the platfrom has 20 service projects, 2 which are run at our facility.

Achievements of the facility during 2015.

- Project management, assay development and analysis of compounds for project DP_MH_004, aiming at a novel treatment for neuropathic pain.
- Assay development and analysis of compounds for oncology project DP_MF.
- Assay development and characterisation of novel antibody-drug conjugates for project DP_FL.
- Novel integrative image processing algorithms and screening of compounds for oncology project DP_EA.
- Initiating infrastructure project DP_IVSP_002 aiming at establishing novel high throughput systems pharmacology techniques combining RNA-profiling with protein expression and metabolomics.

In addition the facility continues to offer clinical pharmacology expertise and to all projects at the DDD-platform.

For more information, please see: https://www.scilifelab.se/facilities/in-vitro-systems-pharmacology/

Staff of Array and Analysis Facility during 2015

Vendela Parrow, assoc prof
Malin Jarvius, PhD
Claes Andersson, PhD
Nasrin Najafi, BMA
PhD Jenny Rubin PhD
Kim Kultima, assoc prof

Awards and Appointments 2015

Tove Fall – The Oscar's award. Uppsala University.

Per-Ola Carlsson - The Knud Lundbeck Award by the Scandinavian Society for the Study of diabetes.

Håkan Melhus – "Årets artikel" in Läkartidningen (together with Karl Michaëlsson).