UPPSALA UNIVERSITET

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Department of Medical Sciences

Annual Report 2016

Fastställd av Lars Rönnblom 2017-05-29

Introduction

The department of Medical Sciences is the result of an earlier fusion of 11 medical departments. Six major research areas have been defined in the department. These are: Cardiology and Respiratory Medicine, Endocrinology, Infection, Inflammation, Laboratory Medicine, and Oncology & Haematology. During 2016 the Department of Medical Sciences has continued to grow, both in staff and in revenues. The staff is now over 250 employees 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 323 MSEK, an increase of more than 50 % since 2010, and the external research funding to about 200 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 Horizon 2020. 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, Clinical Biomarkers, and In Vitro and Systems Pharmacology.

The performance of the Department's research groups is also shown by the more than 650 peer reviewed publications during 2016, by the 10 Doctoral theses published and by the two Licenciate degrees awarded during 2016. The excellence of the Department’s staff is also illustrated by the many prizes awarded to our researchers. To mention just a few, Tove Fall was awarded the prestigious Göran Gustafsson Prize for young researchers, UU/KTH, the Great Prize in medicine. Niklas Hagberg was awarded the stipend in memory of Andrzej Tarkowski – awarded by “Svensk Reumatologisk Förening”. Hans Törmä was awarded “The Ellis and Ivar Janzon’s prize” from the The Swedish Society of Medicine. Eva Lindberg was elected to the Fellowship of the European Respiratory Society, Abdul Halim won The Ulf von Euler prize in physiology for studies on the nitrergic regulation of the migrating motor complex in humans and Christer Janson and Eva Baecklund were awarded the Uppsala County Research prize. Major research findings achieved during 2016 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 2016 a few persons retired after long and very successful careers. On behalf of the Department I would like to thank Professor Jan Sjölin for his many important contributions. At the same time I would like to welcome all new colleagues who have joined us during the year.

Finally, I would like to conclude by thanking all personnel at the Department for their dedicated work during 2016.

Lars Rönnblom
Head of department

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Head of department

Lars Rönnblom

Deputy head of department

Johan Sundström

Assistant heads of department

Bertil Lindahl, 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/administrative staff
Petros Katsogiannos	PhD student
Samuel Backman	student representative
Vacant	student representative

Deputies

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

Employees 2016

Adolfsson Sofia
Alexsson Andrei
Alfredsson Jenny
Ali Ahmed Abeir
Alimohammadi Mohammad
Almlöf Jonas
Alvring Saga
Amcoff Karin
Andersson Claes
Atterby Clara
Axelsson Tomas
Backlin Carin
Baecklund Eva
Bandaru Manoj
Berglund Eva
Berglund Malin
Björklund My
Björnerfeldt Susanne
Blomström Lundqvist Carin
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Castegren Markus
Castillejo-Lopez Casimiro
Colliander Mia
Collin Sofie
Conrad Lisa
Dahlberg Johan
Dalin Frida
Den Hoed Marcel
Devine Ellenor
di Lorenzo Sebastian
Diaz Hetzel
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
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
Hartman Anna
Haukkala Anna
Hedman Åsa
Helgesson Magnus
Hellström Per
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Linde Torbjörn
Lindell Magnus
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Lingman Karin
Littmann Jasper
Ljunggren Östen
Ljungmark Michelle
Loftsdottir Heidur
Lundgren Johanna
Lundmark Anders
Lundmark Per
Lundström Jenny
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
Nilsson Kenneth
Norbäck Dan
Nordlinder Lovisa
Nordlund Jessica
Nordstedt Michael
Nowak Christoph
Nowrouzi Shamim
Nyberg Frida
Nykvist Marie
Nystedt Sara
Oldgren Jonas
Olofsson Caroline
Olsen Björn
Omar Shumi
Panagiotou Grigorios
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
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
Stålberg Kjell
Sundelin Johan
Sundström Johan
Svartengren Magnus
Svensson Johanna
Svensson Maria
Syvänen Ann-Christine
Tandre Karolina
Tano Eva
Tegnér Katarina
Theorell-Haglöw Jenny
Thulin Åsa
Tiensuu Janson Eva
Trombley Susanne
Tängdén Thomas
Törmä Hans
Ungphakorn Wanchana
Wadelius Mia
Wadell Olof
Wahlberg Per
Wallmenius Katarina
Wang Juan
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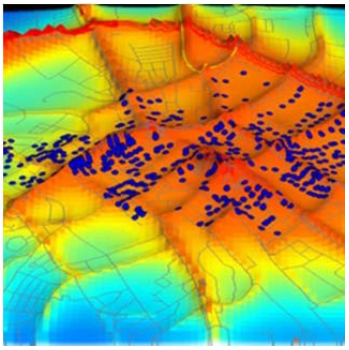
Vega Enrique
Westholm Susanne
Weström Simone
Widell Mikael
Wijethunge Prabash
Viklund Björn
Wille Michelle
Wiman Ann-Christin
Wohlin Martin
von Der Heyde Benedikt
von Kartaschew Anna
Vretman Helena
Yuen Pikkei
Zhang Hanqian
Zorzet Anna
Åberg Mikael
Åkerman Anita
Ånnhagen Eva
Åslin Matilda
Åström Paulsson Sofia
Ärnlöv Johan
Örn Thorsteinsson Ingvar
Öst Torbjörn
Övernäs Elin

Scientific Reports

Research area 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.

Occupational and environmental medicine

Research Group Leader: 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 anlayzed so far. The first manuscript focus on system to promote quality in spirometric testing performed by non-specialists. We also perform human exposure studies regarding the effect from disease such as COPD and pulmomary fibrosis on transition (uptake) of inhaled test nanoparticles.

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 is 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.

- Characterisation, exposure levels and health effects of particles in dwellings.
- Does developmental exposure to bisphenol A contribute to the onset of obesity and osteoporosis?
- Does exposure to perfluorinated substances affect the risk of developing cardiometabolic diseases?
- Epihealth cohort sleep pulmonay function and health
- Estimation of radiation dose to hunters and their families in Gävleborg, Västernorrland and Uppsala counties after the Chernobyl accident - a pilot study
- Hand-intensive work: A methodology for risk assessment, medical examinations and evaluation.
- Health and productivity in health care workers in Uppsala county
- Horse stable environment, health effects on stable workers and horses and the impact of horse on community planning.
- Incidence of cancer 25 years after the Chernobyl accident
- Life Gene Spirometry
- Network for research and development in the field of occupational health service
- Risk factors for asthma, rhinitis and respiratory infections among adults in the home environment
- Schools in Europe and Asia - Associations between the school environment and asthma symptoms, rhinitis, respiratory infections and sick building syndrome (SBS)
- Self-rated health (SRH) and respiratory symptoms among commercial pilots - occupational and non-occupational risk factors
- Stamina Structure and Time efficient Approaches using Methods for INclusion at workplaces
- The Healthy Migrant Effect in the Swedish Context
- Upper arm postures measured with accelerometers and neck shoulder pain among blue collar workers
- Work environment and health in immigrants - a systematic literature review
- Workability Demand functioning present work co-assessment supervisor-employee with focus on work environment
- Working conditions and health among immigrant populations – a systematic review.

Funding

Magnus Svartengren

AFA	2.6 MSEK

Dan Norbäck

Astma och allergiförb.	220 kSEK

VR	245 kSEK

Teresia Nyman

Arbetsmiljöverket	3 MSEK

Members of the group during 2016

Magnus Svartengren, Professor, MD
Eva Vingård, Professor emeritus, MD
Anna Rask Andersen, Professor, MD
Peter Westerholm, Professor emeritus, MD
Dan Norbäck, Professor
Gunilla Wieslander, Assoc professor, MD
Robert Wålinder, Assoc professor, MD
Monica Lind, Assoc professor
Lena Elfman, Assoc professor
Malin Josephson, Assoc professor
Greta Smedje, Assoc professor
Torsten Lindgren, PhD
Roma Runeson Broberg, Assoc professor
Margareta Torgén, PhD, MD,
Xi Fu, PhD
Guihong, Cai, PhD
Mai Leander, PhD
Margareta Halin Lejonklou, Postdoc
Bo Johansson, Researcher, PhD
Pia Rehfisch, Researcher, MD
Martin Toldel, Researcher, PhD, MD
Åsa Stöllman, Psychologist
Hassan Alinaghizadeh, Statistician, PhD-student
Kaj Elgstrand, Adminsitrator
Tomas Eriksson, Investigator
Magnus Helgesson, Med.lic, MD
Lenita Öqvist, inform. assistant
Camilla Zetterberg, PhD-student
Peter Palm, PhD-student
Susanne Victor, PhD-student
Juan Wang, PhD-student
Sofia Åström Paulsson, PhD-student, MD
Teresia Nyman Ergonomist, PhD
Renata Bogo PhD-student
Martin Anderson MD, PhD
Mikaela Qvarfordt, PhD student
Eva Bergsten PhD-student
Linda Dunder, PhD student
Jennie Jackson, PhD student

Publications 2014-2016

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Dissertations 2016

Camilla Zetterberg: The impact of visually demanding near work on neck/shoulder discomfort and trapezius muscle activity: Laboratory studies.

Cardiology, ischemic heart disease and heart failure

Research Group leader: 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 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 research group published in 2016.

Understanding the disease(-s) and the unmet needs

During the year, we continued our new research line, type 2 myocardial infarctions and myocardial infarction with non-obstructive coronary arteries (MINOCA), with showing the importance of atherosclerotic stenosis (285). We also showed that the prognosis of unrecognized myocardial infarctions (UMI) assessed by cardiovascular magnetic resonance is independently associated with the degree of coronary artery disease but not the occurrence of UMI (272).

Stroke prevention in atrial fibrillation is another important area of research and several new findings were published (281, 190, 200, 215).

In a large and rigorously controlled study we were able to show that periodontitis increases the risk of a myocardial Infarction (286).

In the field of genetic studies several papers were published (188, 199, 206, 209, 222, 231, 232, 233).

Importance of biomarkers and risk factors for diagnosis and prognosis

The research group has a long-standing interest in biomarkers. High-sensitivity troponins measurement improves risk assessment for cardiovascular events in many clinical settings; during the year, we published several large and novel studies regarding rapid rule-in and rule-out of myocardial infarction (223, 224, 244, 247, 267, 282).

The research group has been pioneering the study of biomarkers in atrial fibrillation and published several novel and widely acclaimed findings (211, 213, 253, 266, 280).

We have also been among the first to use the new proximity extension assay -technique for measuring 92 proteins simultaneously (196, 207).

Evaluation of treatments and other interventions in RCTs and Registry studies

The research group is world leading in RCTs evaluating new drugs in ACS, IHD and atrial fibrillation. A large number of sub studies of these trials have been published during the year. Likewise, the group has published a large number of observational studies, based on the Swedeheart registry and/or other registries (see publication list).

Miscellaneous

Members of the group have participated in the development of national and international clinical guidelines and published a large number of educational articles and reviews (see below).

Members of the group during 2015

Bertil Lindahl, Professor
Stefan James, Professor
Johan Sundström. Professor
Lars Wallentin, Professor emeritus
Jonas Oldgren, Associate professor
Claes Held, Associate professor
Kai Eggers, Associate professor
Emil Hagström, Associate professor
Nina Johnston, Associate professor
Christina Christersson, Associate professor
Bo Lagerqvist, Ph.D.
Erik Björklund, 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
Marcus Hjort, MD, Ph.D student
Anton Gard, MD, Ph.D student

Funding

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

Publications 2014-2016

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Dissertations 2014-16

Kasper Andersen: Physical activity and cardiovascular disease

Kristina Hambraeus: From stenting to preventing invasive. Invasive and long-term treatment for coronary artery disease in Sweden.

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

Ulf Hållmarker: Epidemiological studies on long distance cross-county skiers participating in the Vasaloppet 1955-2010.

Cardiology – Arrhythmia

Research Group Leader: Carina Blomström-Lundqvist

Research projects

The research group has two main research areas of interest, atrial fibrillation (AF) and inherited cardiac diseases associated with an 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 drugs have poor long term effects for rhythm control and may contribute to the observed higher death rate in AF populations. Our focus is to study the various mechanisms of AF, identify risk modification strategies including predictors for stroke and AF recurrences, and develop new more effective therapeutic alternatives including surgical and catheter based ablation techniques for the elimination of AF.

Non-ischemic ventricular arrhythmias, the diagnosis and prognosis of which, especially arrhythmogenic right ventricular cardiomyopathy (ARVC), is difficult to assess related to a variables phenotype and need for multiple complex investigations. Our focus is on identifying novel diagnostic and genetic and clinical risk markers with regards to disease progression and sudden cardiac death, in patients with ARVC and relatives who are gene carriers.

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), comparing 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. Secondary end-points are AF burden, a composite of morbidity end-points, symptoms, atrial and ventricular function, physical capacity, cardiovascular hospitalisation, health economy and complications evaluated at 12, 24, 26, and 48 months of follow up. The study is unique in that it has a QoL as primary endpoint and that long term treatment effects are evaluated by continuous rhythm monitoring using an implantable device. 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 until January 2018.

The **CryoLPAF** study is an exploratory study assessing whether pulmonary vein isolation (PVI) using a new cryoballoon can effectively reduce AF episodes and improve symptoms in patients with longstanding persistent AF at one year follow up. The primary objective is clinical success of catheter ablation, using a combination of freedom from AF related symptoms irrespective of the presence of asymptomatic AF on Holter, provided AF is absent or only paroxysmal in nature. 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. 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. Patients 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.

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 re-ablations will be compared at 6 and 12 months, and in those requiring a redo ablation procedure the status of PV re-conduction will be assessed.

The study "Targeting the substrate by aggressive life style and risk factor management in patients with atrial fibrillation (AF) – The **Nordic PrevAF**P **study** aims to test in a prospective randomized trial the hypothesis that early life style modification and comprehensive risk factor management will prevent AF progression and reduce AF burden by at least 20% as measured by number of hospitalization visits and cardioversions at 1 year. Obese patients with symptomatic persistent AF, previous electrical cardioversions and at most one tested antiarrhythmic drug will be included and randomized into a conventional treatment (controls) or a risk factor management group subject to dedicated nurses with weight loss-, training-, dietary-, alcohol- and smoking instructions, control of hypertension, diabetes, sleep apnea and lipids with frequent regular check-ups on long-term. Secondary endpoints are quality of life, AF comorbidities, AF biomarkers, echocardiographic atrial contractility and size, and health economy. A total of 280 patients will be included from 3 centers in Denmark and Sweden and one in Norway. The inclusion period is 14 months from Sept. 2017 with 3 years follow up and a study period of 4 years until Dec. 31st 2021. The reverse AF substrate sub study aims to assess the mechanism by which risk factor management exerts its effects by analyzing atrial voltage and conduction as indirect markers of atrial fibrosis using optical mapping. The importance is the possibility of demonstrating efficacy related to reversal of remodelling and fibrosis, since treatment with drugs or other interventions are deficient on long-term.

The **ECAF star trial** a multicentre study, aims 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 ($\leq$48 hours duration). 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.

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. Left ventricular ejection fraction and diastolic function (transmitral velocities, E/E' index) and mini-mental test will be performed as well. 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 frequently relies on findings from several types of investigations. The prognosis is also difficult to evaluate. 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. A new body surface mapping system will be sued to detect preclinical signs of ARVC in gene carriers. The study population is at present 300 patients followed for at least 10 years.

List of publications 2014-16

1. Potpara TS, Lip GY, Dagres N, Estner HL, Larsen TB, Blomström-Lundqvist C; Conducted by the Scientific Initiatives Committee, European Heart Rhythm Association. Management of acute coronary syndrome in patients with non-valvular atrial fibrillation: results of the European Heart Rhythm Association Survey. Europace. 2014 Feb;16(2):293-8.

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Research Grants 2016

Swedish research council (VR)	4 205 k SEK
Swedish Heart-Lung foundation	800 k SEK
ALF	700 k SEK
External funding	2 214 k SEK

Dissertations during the year 2016:

None

Members of the group during 2016

Carina Blomström-Lundqvist, MD prof
Stefan Lönnerholm, M.D, Ph.D
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Cardiovascular epidemiology

Research Group leader 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 Riksstroke

Signild Åsberg, 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. Haemorrhage (15%) or ischemia (85%) in the brain parenchyma (85%) causes stroke. In Sweden, about 25 000 are hospitalised due to an acute stroke every year and approximately 10 000 faces a transient ischemic attack (TIA) every year. We performed a cohort study of >200 000 stroke patients, registered in Riksstroke (the Swedish Stroke Register) during 2001 through 2009, and a separate cohort study also including TIA-patients for the years 2011 through 2014. Cross-linking with the National Patient 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. A particular focus has been use of anti-thrombotic treatment before and after stroke/TIA and epilepsia.

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. In sub study, cardiovascular biomarkers from 1500 acute stroke patients (50% of the entire cohort) will be analysed.

Members of the group during 2015

Lars Lind, MD, professor
Andreas Terént, MD, professor
Johan Sundström, MD, professor
Johan Ärnlöv, Assoc Professor
Anders Holmlund, PhD
Signild Åsberg, MD, PhD
Jessika Andersson, MD, PhD-student
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Said Mashia, MD, PhD-student
Kasper Andersen, MD, Ph.D

Funding

Lars Lind

Hjärt-Lungfonden	3.0 MSEK
EpiHealth	3.0 MSEK
ALF	2.0 MSEK
EU-FP7	1.3 MSEK
FORMAS	1.2 MSEK

Andreas Terént /Signild Åsberg

ALF	0.3 MSEK
AstraZeneca Nordic-Baltic	1.15MSEK

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Clinical physiology

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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 forced expiratory volume in 1 second (FEV_1) is only to a less degree explaining the exercise capacity limitation and has limited value even in disease prognosis. In both cross-sectional studies and longitudinal studies, we have demonstrated that diffusing capacity for carbon monoxide (DLCO) relates with exercise capacity and exercise capacity decline 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) along with exercise ability, inflammation markers for predicting exacerbations in COPD patients in a multicentre study – Tools for Identifying Exacerbations (TIE). We included 571 patients during 2014-2016 that will be followed-up with yearly clinical visits for two years. 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. The first manuscript based on this material is under preparation.

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. The cohort is called Minimally Invasive Diagnostics in Allergies and hypersensitivities (MIDAS) cohort. Subjects were broadly characterized with regard to local and systemic inflammation, allergic sensitization, lung function and bronchial hyper responsiveness. 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. A follow-up of the MIDAS study was performed during 2013-2015 and we are currently analysing natural history of the disease, with focus on stability of asthma phenotypes and predictive value of baseline characteristics for disease deterioration.

We have recently published determinants of exhaled nitric oxide (FeNO) in patients with asthma along with the clinical value of mapping FeNO and different inflammatory markers in the blood (eosinophil activation markers along with other type 2 inflammation markers) in the Swedish Global Asthma and Allergy Excellence Network (GA^2LEN). We have reported the value of having simultaneously elevated markers of inflammation in the airways (FeNO) and eosinophil inflammation in the blood (blood eosinophils or serum eosinophil cationic protein) in relation with different asthma outcomes, such as symptoms, exacerbations, in MIDAS, GA^2LEN and National Health, Nutrition and Examination Survey (NHANES).

In a collaborative study with the group of Professor Michils in Brussels we are investigating the value of measurements of exhaled NO before and after bronchodilation as a marker of small airways involvement in asthma. This measurement is feasible and of potential broad interest to identify a phenotype with small airways involvement that might be suitable for treatment with ultrafine particles inhaled corticosteroids.

Clinical value of forced oscillation technique to investigate lung function

Forced oscillation technique (FOT) and impulse oscillometry (IOS) are two lung function methods that are effort-independent, requiring 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 have studied 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. Our results suggest that FOT has as good discriminative value behind asthma and healthy controls and spirometry and measures of small airways involvement, assessed by FOT, relate with poorer disease control.

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 identified by IOS in relation to respiratory symptoms, systemic inflammation, atherosclerosis and future morbidity.

These methods, together with nitrogen washout, 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.

Clinical value of cardiopulmonary exercise testing

In a series of studies we are investigating the value of cardiopulmonary exercise testing in the follow-up of patients with COPD, cystic fibrosis, esophagus atresia and leukemia patients, after bone marrow transplantation. Two PhD students are involved in these projects and a first manuscript is currently drafted.

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). An important observation is that the diaphragm is active during expiration, preventing lung collapse.

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.

Research 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 analyze echocardiographic patterns in these patients.

- Studies of patients with aortic or mitral regurgitation (LV-regurge) are ongoing 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.

The following main projects were pursued in Cardiac Imaging during 2016:

- A Swedish Heart and Lung Foundation-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 patients with heart valve replacement 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 sub study 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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PhD thesis 2016

Charlotte Heijkenskjöld Rentzhog

Publications 2016

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Respiratory, allergy and sleep research

Research Group leader: 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, pulmonary fibrosis and tuberculosis.

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

Christer Janson

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. We are now planning for a 10-year follow-up which will be started in 2018.

In 2010 we followed 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. In 2016 we started the RHINESSA study were we contacted children from the RHINE cohort through a web based survey. A subsample of this population is examined with different lung function methods, allergy testing and sampling of biomarkers.

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 was 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.

We're also engaged in several projects where we work with data extracted from electronic medical records and merged with national registry data. These studies involve both COPD, asthma and idiopathic pulmonary fibrosis.

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 criteria. 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.
During 2016 the MUSTACHE (Men in Uppsala; a Study of sleep, Apnea and Cardiometabolic Health) study was started. This is a new cohort study were we perform clinical investigation, polysomnography and high-frequency ultrasound of the common carotid artery in a community-based sample 400 men. The participants are carefully matched with women who have already been investigated in a similar manner for comparison of sleep architecture and consequences of sleep apnea between genders. 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 also use national registers to analyse outcome of patients treated with long-term home mechanical ventilation and continuous positive airway pressure. In addition to clinical studies performed within the research group, we 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.

Beside sleep-disordered breathing there are clinical studies going on to evaluate the effect of Auricular Acupuncture and Cognitive Behavioural Therapy for Insomnia in a randomized controlled trial as well as studies on delayed sleep phase disorder.

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 and increased morbidity and mortality in subjects with lung 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, identify functional tests to measure physical capacity, evaluate measures of physical activity both objectively and subjectively measured and evaluate 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. Seventy 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 84 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 and reported. In addition, 150 exercise provocation tests, to investigate bronchial and laryngeal obstruction, have been undertaken and reported. Physical activity during seven days has been measured with an accelerometer and analyses are ongoing. Also an analysis of blood samples is ongoing. In 2016, a follow-up questionnaire was 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.

Exhaled nitric oxide in health and disease

Marieann Högman

In respiratory medicine, we have developed non-invasive methods to seek more knowledge about the lung physiology in both health and disease. To use non-invasive methods to diagnose respiratory diseases and to monitor the treatment is an advantage for both patients and health care professionals. Exhaled nitric oxide (F_ENO) has been used extensively since its discovery in human breath, especially in asthma where clinical practice guidelines have been published. During 2014-2016 a task force of the European Respiratory Society was formed to set the technical standard for exhaled biomarkers in lung disease, where I was the group leader of exhaled nitric oxide. This document will be published during 2017 and holds the recommendations for pulmonary nitric oxide dynamics models of the respiratory system. The Högman & Meriläinen Algorithm (HMA) is such a model and was first published in 2000. Since there are no large studies on reference values our group has started to collect values on healthy subject in Europe. In The Netherlands we have applied HMA in asthmatic children to evaluate treatment with inhaled corticosteroids. Since the hypothesis that rheumatoid arthritis starts in the lung we have applied the HMA in a group of patients at the rheumatology clinic at Gävle. These two studies are included in PhD studies by Alexandra Thornadtsson.

Exhaled NO is said to be an inflammatory marker but it could also be said to be a marker of pathophysiological response. Increased alveolar NO values have been observed in several pulmonary diseases with gas exchange deficiencies. Therefore we found it interesting to study this in a group of patients with, airway inflammation and gas exchange impairment, chronic obstructive pulmonary disease. This group of patients cost the Swedish society around 13 billion per year. If we can find tools to identify exacerbations before they occur it would be an advantage both for the patient quality of life and health care economics. A prospective multidisciplinary study was formed in the region of Dalarna, Gävleborg and Uppsala together with Uppsala University. It was given the name TIE-study (Tools Identifying Exacerbation in COPD). The 2-year follow up period will be finished in the fall 2018 and we are analysing the inclusion data (nearly 600 patients) and some results have already been presented at international congresses. The TIE-study includes material for 5 PhD-students.

In addition to the medical science our group has performed studies in the field of caring sciences; such as interventional studies of pressure ulcer prevention, patients' safety during anaesthesia induction with endotracheal intubation and an observational study before and after introduction of an oncology centre for ambulatory patients driven by nurses.

Members of the group during 2016

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Christer Jansson

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Eva Lindberg

Heart and Lung Foundation	780 kSEK

Margareta Emtner

Uppsala university	400 kSEK
Astma- and Allergy Foundation	250 kSEK

Marieann Högman

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Region Gävleborg	300 kSEK
Region Uppsala (NO analysator)	500 kSEK

Publications 2014-2016

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Dissertations

Hagman C. Dysfunctional breathing clinical characteristics and treatment
Emilsson Ö. Nocturnal Gastroesophageal Reflux: Respiratory Symptoms and Obstructive Sleep Apnea Prognosis, Prediction and Risk Assessment in the Prevention and Treatment of Non-Small Cell Lung Cancer (Islands universitet).
Danielsson K. Delayed sleep phase disorder. Prevalence, diagnostic aspects, associated factors and treatment concepts.

Awards

Lindberg E. Elected to the Fellowship of the European Respiraotry Society

Janson C.-Uppsala County Research prize, Elected to the position as Chair Elect of the Epidemiology and Occupation Assembly of the European Respiratory Society

Högman M. Elected to the position as Chair Elect of the International Association of Breath Research. (2015-2017)

Molecular epidemiology

Research Group leader (acting); Tove Fall
Erik Ingelsson, 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 5-6 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 bio samples 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 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.

During 2016 we have published three papers combining metabolomics or proteomics data with genetics data for causal inference and have highlighted the causal effect of insulin resistance on tissue plasminogen activator and monounsaturated fatty acids and well as a genetic link between bile acids, LDL-cholesterol and type 2 diabetes.

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.

Courses

Marcel den Hoed and Tove Fall organized a 2-weeks course in Molecular Epidemiology for PhD students in Nov 2016, which was very much appreciated by the participants.

Awards and Prizes

Tove Fall received the following prizes:

1. Göran Gustafsson award in Medicine (UU/KTH)
2. Science Slam winner, SciFest, UU
3. 3rd prize in SciLifeLab's Scientific Highlight

Read more at our home page: www.ingelsson.org and tovefall.se

Members of the group

Erik Ingelsson, professor
Tove Fall, associate professor
Marcel den Hoed, associate professor
Casimiro Castillejo-Lopez, associate professor
Stefan Gustafsson, bioinformatician
Ulrika Bäckman, coordinator

Dan Ronisz, research administrator
Naomi Cook, postdoc
Åsa Hedman, postdoc
Samira Salihovic, postdoc
Susanne Trombley, postdoc
Manoj Bandaru, PhD student
Benedikt von der Heyde, PhD student
Mikael Janiec, PhD student
Mwenya Mubanga, PhD student
Christoph Nowak, PhD student
Sari Peura, postdoc
Markus Stenemo, PhD student
Mona-Lisa Wernroth, PhD student
Anastasia Emmanouilidou, research engineer
Lisa Conrad, research assistant
João Costa, research assistant
Sitaf Jumaa, research assistant
Tiffany Klingström, research assistant
Anna Pirona, research assistant
Lingjie Tao, research assistant
Silvia Vicenzi, guest student

Funding

Tove Fall

Swedish Research Council (co-PI)	4.0 MSEK
Swedish Research Council (PI)	1.2 MSEK
FORMAS	0.9 MSEK
Swedish Heart-Lung Foundation	0.3 MSEK
Göran Gustafssons Stiftelse	1.0 MSEK

Erik Ingelsson

Swedish Research Council	6.1 MSEK
ERC – starting grant	2.8 MSEK
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
Swedish Research Council (PI)	1.5 MSEK

Samira Salihovic

FORMAS	1,1 MSEK

Publications 2014-2016

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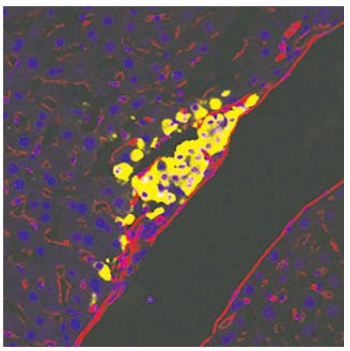
Research area Endocrinology

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 type 2 diabetes? How do we improve diabetes patients' self-management? Can stem cells be used to treat type-1 diabetes? What causes metabolic bone diseases? These are examples of research questions that are addressed. A large number of different methods are used in studies mostly with human subjects, including exploratory clinical trials.



Clinical diabetology and endocrinology

Research Group leader: 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 components of the metabolic syndrome. This can in turn promote the development of diabetes and its complications. Thus, type 2 diabetes is strongly associated with abdominal obesity. The factors of interest include biomolecules that are produced by the adipose tissue, such as hormones and cytokines. We also explore cell and tissue morphology, nervous and nutritional regulation of adipose tissue. 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.

Key results during 2016

- Clinical proof-of-concept for obesity treatment with a combination of two diabetes medicines, a GLP1 receptor agonist and an SGLT2 inhibitor.
- Reports on benefits with novel diabetes medicines compared to traditional treatment with sulphonylurea and insulin. Less risk of cardiovascular events and premature death according to large-scale observational registry-based studies.
- Discovery of an attenuated neuroendocrine response to hypoglycaemia following obesity surgery. Such adaptive mechanisms may explain much of the beneficial metabolic effects seen after such surgery.
- Discovery of new adipose tissue mechanisms in insulin resistance, FKBP5, cannabinoid receptors and lipocalin 2.
- All those findings can lead to optimisation or new discovery of pharmacological principles for prevention and treatment of type 2 diabetes and its complications.

Pharmacology of human adipose tissue in metabolic disease

Researchers: Maria Joao Pereira, Cherno Sidibeh, Prasad Kamble, Gretha Boersma, Petros Katsogiannos, Per Lundkvist, Xesus Abalo, Jan Eriksson

Many therapeutic agents affect glucose tolerance and can predispose to diabetes, especially when pre-existing factors are present. These drugs may act by increasing insulin resistance, by affecting insulin secretion or both. Examples include glucocorticoids, immunosuppressive agents and antipsychotic drugs. Our group aims to identify novel mechanisms for insulin resistance induced by these drugs in insulin sensitive cells, in particular human adipocytes, by exploring pharmacologic manipulation, in vitro and in vivo, leading to insulin resistance.

Glucocorticoids and immunosuppressive agents

Glucocorticoids and immunosuppressive agents are used to prevent graft rejection after organ transplantation and to treat autoimmune and inflammatory diseases. In addition to suppression of the immune system, these drugs can increase the risk for dyslipidemia, diabetes, central adiposity and cardiovascular disease. Our previous work indicate that the immunosuppressive calcineurin inhibitors cyclosporin A and tacrolimus impair cellular glucose uptake in peripheral tissues by removing the major glucose transporter, GLUT4, from the cell surface, but without affecting the insulin signalling cascade. The project evaluates effects of calcineurin inhibitors on the expression of specific proteins involved in GLUT4 trafficking and glucose transport. Furthermore, our work has identified genes in adipose tissue that are highly regulated by glucocorticoids and that are associated with insulin resistance, and they include FKBP5, cannabinoid receptor type 1 and lipocalin-2. We perform mechanistic studies, using for example specific antagonists or agonists or gene editing (CRISPR/Cas9) to address their molecular pathways and causal role in metabolic disorders.

Antipsychotic agents.

The underlying mechanisms by which antipsychotic drugs contribute to the development of insulin resistance, weight gain, dyslipidemia and type 2 diabetes are not clear. We will address the effects of antipsychotic drugs on whole-body and adipose tissue metabolism as well as on adipose tissue hormones, inflammatory markers and nerve activity that may be of importance for the development of type 2 diabetes and obesity.

These studies can provide novel mechanisms and biomarkers for drug-induced metabolic dysfunction of the adipose tissue. They can be used to identify therapeutic strategies to minimize or reverse such adverse effects. Importantly, these mechanisms can be of relevance for the development of future treatments for other forms of insulin resistance, including prediabetes and manifest type 2 diabetes.

Effects of gastric bypass surgery on glucose and lipid metabolism

Niclas Abrahamsson, Anders Karlsson, Petros Katsogiannos, Gretha Boersma, Kristina Almby, Maria Joao Pereira, Jan Eriksson

The project is run in collaboration with the Dept. of Surgery (Prof Magnus Sundbom), and it focuses on the profound changes seen in glucose and lipid metabolism following bariatric surgery. Obese patients undergoing gastric bypass (GBP) markedly improve their insulin sensitivity and glucose tolerance. According to most available data, these effects are much greater than 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, glucose challenge 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. Such findings could potentially also lead to discovery of non-surgical treatment concepts, involving pharmaceuticals or life-style, to prevent or treat diabetes and obesity. In the long-term perspective, the results could also support bariatric/metabolic surgery as a treatment of choice for many type 2-diabetes patients.

Studies of clinical and metabolic effects of novel medicines

Researchers: Per Lundkvist, Maria Joao Pereira, Jan Eriksson, Maria Eriksson-Svensson

We currently perform several studies exploring possible novel indications for the antidiabetic drug class of SGLT2 inhibitors. They include exploratory clinical trials for proof-of-concept as well as mechanistic human studies. They focus on energy balance and obesity, effects on fatty liver disease and endocrine effects relating to gut and pancreatic islets in particular. We plan to use PET/MRI investigations to performed detailed measurements of energy metabolism in specific organs. We are also involved in registry-based epidemiological studies addressing the clinical outcomes of such drugs in comparison to other diabetes treatments. Effects on cardiovascular and other organ complications and mortality as well as health economy are evaluated.

There are also collaborative studies on outcomes following treatment with new medicines, in particular biologicals, in dyslipidemia, osteoporosis and renal failure.

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

Janeth Leksell, Anna Lindholm Olinder, Violeta Armijo del Valle, Therese Granström, Maria Svedbo Engström, Rebecka Husdal, Anna-Lena Brorsson.

Our research programs relate to diabetes nursing throughout the life cycle and include three main parts:

- Studies designed to evaluate the patient's perspective and perception of diabetes care.
- Studies that evaluate models and educational programs to prepare the patient the opportunity to take care control of their self-management and health.
- Studies which highlight the development of diabetes in primary care, and the factors contributing to equitable diabetes care.

In longitudinal studies we evaluate factors of importance to evaluate both patient’s perspective and perception of provided in inpatient care and primary care. It is of importance to evaluate evidence-based nursing care in order to assess whether they are effective or not. Another part of our research includes the development and testing of the measurements that give the care givers information about the patient’s health and impact of the diabetes on the daily life and health.

Members of the group during 2016

Jan Eriksson, Professor
Anders Karlsson, Professor emeritus
Christian Berne, Professor emeritus
Karin Wikblad, Professor emerita
Janeth Leksell, Assoc Prof
Anna Lindholm Olinder, PhD
Maria João Pereira, Researcher, PhD
Gretha Boersma, Researcher, PhD
Niclas Abrahamsson, Physician, PhD
Petros Katsogiannis, Physician, PhD student
Per Lundkvist, Physician, PhD student
Violeta Armijo del Valle, specialist nurse
Jan Hall, BMA
Prasad Kamble, PhD-student
Selwan Khamisi, PhD-student
Cherno Sidibeh, PhD-student
Therese Granström PhD student
Maria Svedbo Engström PhD student
Rebecka Husdal, PhD student

Funding

AstraZeneca	5.000 kSEK
Heart-Lung foundation	450 kSEK
Exodiab	250 kSEK
Diabetesförbundet	200 kSEK
Vårdvetenskap, UU	700 kSEK

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Endocrinology and mineral metabolism

Research Group leader: 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.

Members of the group during 2015

Östen Ljunggren, Professor

Andreas Kindmark, Associate professor

Britt Eden Engström, Associate professor

Katarina Lindahl, MD, PhD

Anne Björk, MD, Phd student

Selwan Khamisi, MD, PhD student

Magnus Isaksson, MD, PhD

Elin Carlsson, Research engineer

Funding

ALF 700.000SEK
Gustav V and Queen Victoria foundation: 200.000SEK
Amgen research grant: 150 000:-

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Transplantation and regenerative medicine

Research Group leader: Per-Ola Carlsson

The overall aim of the research group on beta-cells: transplantation and 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 from embryonic or induced pluripotent stem cells, as well as by stimulating adult beta-cell proliferation, e.g. by stem cell stimulation. Clinical studies are performed to prevent development of type 1 diabetes in patients, e.g. by autologous 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.

Translational studies of insulin-secreting cells derived from pluripotent stem cells

Joey Lau, Daniel Espes, Per-Ola Carlsson

Insulin-secreting cells derived from human embryonic stem cells or induced pluripotent stem cells have shown potency to cure diabetic mice and these cells are of the highest interest for translation into type 1 diabetic patients. We evaluate the best implantation sites of these cells for clinical translation, and also by bioengineering techniques create composite grafts with auxiliary stem cells. In this manner

safety, cellular survival, differentiation and function can be optimized and a product established for GMP production and clinical translation.

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. A larger (national), blinded, phase 2 efficacy trial with the same concept awaits regulatory approval. 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 macro device 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 2016

Per-Ola Carlsson, M.D., Ph.D., Professor
Arne Andersson, MD, Professor emeritus
Joey Lau, Associate Professor
Monica Sandberg, Associate Professor
Sara Bohman, post-doc
José Caballero, MD., post-doc
Xuan Wang, post-doc
Daniel Espes, M.D., post-doc
Carl Johan Drott, M.D., PhD student
Liza Grapensparr, PhD student
Sara Ullsten, PhD student
Hanna Liljebäck. MD., PhD student
Louise Magnusson, PhD student
My Quach, laboratory engineer
Lisbeth Sagulin, laboratory engineer
Zhanchun Li, laboratory engineer
Petra Franzén, laboratory engineer
Karin Kjellström, research nurse
Rebecca Hilmius, research nurse

Funding for 2016

Swedish Research Council -Clinical Treatment Research grant	8.4 MSEK
Juvenile Diabetes Research Foundation USA	2.0 MSEK
Novo Nordisk Foundation DK	1.2 MSEK
Swedish Research Council -Regular grant	1.7 MSEK
Torsten Söderbergs Stiftelse	2.0 MSEK
Swedish Diabetes Association	0.4 MSEK
The Swedish Juvenile Diabetes Foundation	1.0 MSEK

Strategic funding, Exodiab	1.0 MSEK
Strategic funding, StemTherapy	1.0 MSEK
Diabetes Wellness	0.4 MSEK
Regional Research Council	1.1 MSEK
Olle Engkvist Byggmästare	1.0 MSEK

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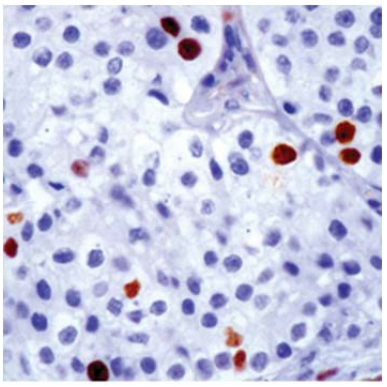
Research area Haematology and oncology

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

Research Group leader: Eva Tiensuu Janson

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). We have a close collaboration within the Nordic Neuroendocrine Tumor Group (NNTG) for which ETJ is chairman and the NEC projects are carried out within this collaboration.

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 and also included families from Norway and Denmark in our study. 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 blood from hereditary SI-NET patients in a group of genes which are potentially interesting as possible disease causing. We have also checked to presence of these mutations in a cohort of 218 sporadic SI-NETs and found mutations in some of these patients. These findings have recently been submitted for publication.

Studies of neuroendocrine carcinomas (NEC)

Staffan Welin, Abir Ali, Malin Grönberg and Eva Tiensuu Janson together with NNTG members

The Nordic NEC study published in 2013 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.

During 2016 the Nordic group published a paper on the possible benefit of surgery for patients with pancreatic primaries and a manuscript describing the outcome for NEC patients undergoing surgery for

liver metastases has been submitted. We have also submitted a paper describing the possible usefulness of immunohistochemical staining for p53 for prediction of treatment response and survival in patients with gastroenteropancreatic NECs.

Expression of neuroendocrine markers in tumors

Malin Grönberg, Clary Georgantzi, Abir Ali, Ieva Lase, 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. This work has been extended and a manuscript describing the findings has recently been submitted. We have also studied the impact of ghrelin in male breast cancer and this will soon also be submitted for publication.

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.

In the thesis of Ieva Lase, biochemical markers related to Cushing's disease will be studied.

Members of the group 2016

Eva Tiensuu Janson, Professor of Medicine

Staffan Welin, MD, PhD

Malin Grönberg, PhD

Abir Ali, PhD student

Clary Georgantzi MD, PhD-student

Ieva Lase MD, PhD-student

Funding

Swedish Cancer foundation	600 kSEK,
Söderbergs foundation	125 kSEK
Selanders foundation	110 kSEK
ALF	450 kSEK
Lions foundation for Cancer research	75 kSEK

Publications 2014-2016

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Endocrine tumour biology

Research Group leader: Britt Skogseid

Researchers in our translational group represent various disciplines, *e.g.* endocrinology, oncology, 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.** Group members are also tightly connected with the Endocrine oncology clinic, 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 but the majority are silent. 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 tumorigenesis

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). 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. 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 as well as microRNAs involved in lipid metabolism are obviously differentially regulated. We have run experiments in human adrenocortical carcinoma cell lines using compounds known to inhibit two of these proteins and found a clear dose-dependent effect on cell growth and fatty acid synthesis (by lipidomics). Thus preliminary data in summary indicates that inhibition of these proteins of relevance for de novo fatty acid synthesis may be a new way to inhibit adrenocortical proliferation. For one of these proteins there exists a compound currently in clinical trials for breast cancer. We are now in the process of establishing collaboration with the biotech company producing this compound. We plan for xenograft experiments followed by a Phase II trial in patients with advanced chemo-resistant adrenocortical carcinoma.

Metformin treatment and PET of the endocrine pancreas

The biguanide metformin is well established as an oral diabetes type II drug. Recently, anti-tumoral effects have been attributed to the drug. Activation of AMP activated protein kinase (AMPK) leading to inhibition mTOR has been suggested. Retrospective studies have indeed suggested that metformin might have anti-proliferative effects also in and P-NETs (16). A majority of MEN1 patients undergo pancreatic resection for macroscopically detectable P-NETs, but significant part of the pancreas (1/3) will be left in place. After first resection a number of patients (around 20%) have impaired glucose tolerance or diabetes, and diabetes

treatment is often indicated. Within a decade many of the operated P-NET patients will need reoperations due to recurrences in the pancreatic remnant. *Hypothesis:* 1) metformin treatment of heterozygous MEN1 mouse islets inhibits mTOR pathway activation and proliferation into neoplasms, 2) metformin treatment of MEN1 patients after pancreatic surgery inhibits tumorigenesis in heterozygous islets of the pancreatic remnant, which may postpone second surgery for many years. Work plan: We will analyze the dose-response effect of metformin in human endocrine pancreatic tumor cell lines BON1 and QGP1. ***Preliminary data*** suggest significant growth inhibition already at therapeutic doses (<0.5 mM) after 8 days. The AMPK and mTOR-Akt activation in treated and untreated cells will be analyzed, but to really decide the role of levels of MEN1 gene expression *per se* in relation to metformin effects we need access to an endocrine pancreatic cell line with permanently disrupted endogenous MEN1 gene expression. We have therefore ordered MEN1 knock-out BON1 cells, produced by CRIPR/Cas9 editing provided by Thermo Fisher Scientific, USA. The MEN1 disrupted BON1 cells as well as wild type cells will be used for subcutaneous xenografting to nude mice. They will be exposed to metformin in drinking water, 1.5 mg /ml (*i.e.* 12 mg/day/mouse, equivalent to 2000 mg/d in humans). Tumor size and signaling pathways will be assessed. We have started assessing the EdU activity in harvested mouse islets as read-out of proliferation. Metformin effects in heterozygous and wild type islets, both *in vitro* and *in vivo* in MEN1 mice, will be assessed by EdU activity and by western of AMPK and mTOR-Akt pathway activity, as well as FLT- and Exendin-PET/CT scanning. We use the special unit for preclinical PET, equipped with micro-PET/CT and micro-PET/MR, for use in small animals and cell culture. PhD and PET specialist Monazzam has recently finalized an explorative study of the potential usefulness of the GLP-1R antagonist Exendin-4 as a tracer for detection of increased proliferation in MEN1 mouse islets and microadenomas. This project will now continue by comparing the efficacy of Exendin-4 in tumor recognition and metformin treatment monitoring in mice and endocrine cell lines with the efficacy of other tracers, such as 5-HTP, and FLT. Prof B Eriksson will start an Exendin-4 trial in P-NET patients (ethical- and drug agency approvals pending).

Oncolytic virus, basic and clinical studies.

Professor Kjell Öberg together with Professor Magnus Essand is currently running a phase I trial using an engineered oncolytic adenovirus directed against neuroendocrine tumor cells. Patients with liver dominant disease receive intra hepatic infusions in a tolerability study, whereas the approved Phase IIa will be an efficacy study. So far four of totally 35 patients have been be included. Immunology parameters, new biomarker test (NET-test) and Ga68PET/MRI as well as FDGPET/MRI is performed.

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:

a) We will participate in the second round of studies of treatment together with the network, comparing efficacy of new treatments to the FIRM-ACT bench-mark. A protocol for Lipoplatin treatment has been submitted as Horizon 2020 project.

b) Coordination of the international trial Adiuvo I (PI M Terzolo, Turin) on adjuvant therapy, randomizing mitotane vs expectancy in adrenocortical carcinoma with low Ki67 index. Adiuvo II, randomization of mitotane vs cisplatin in radically operated and Ki67 >10, is pending.

c) Continue our participation in an EU-financed study of different PET tracers for diagnosis of adrenocortical carcinoma: the FAMIAN study. PI Wurtzburg, Germany.

d) Start a new phase II trial for treatment of advanced disease that failed on standard therapy using the FASN inhibitor TBV2640. We are writing the protocol and contacting the BioTech-company producing and testing this compound (ClinicalTrials.gov:NCT02223247).

Members of the group 2016

Britt Skogseid, MD, professor

Barbro Eriksson, MD, professor

Kjell Öberg, M.D. professor

Joakim Crona, MD, PhD

Mikael Björk, research nurse and system developer

Valeria Giandomenico, PhD, researcher

Katarzyna Fröss-Baron, physician

Azita Monazzam, PhD, researcher

Duska Bajic, MD

Su Chen Li, PhD

Monica Hurtig, research nurse

Masoud Razmara, PhD, technician

Pantelis Antonodimitrakis, MD

Lillebil Andersson, secret

Funding

The Swedish Cancer foundation	1000 kSEK
ALF	650 kSEK
Lions cancer fund	200k SEK

Publications 2014-2016

Original papers

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2. Velikyan I, et al. Quantitative and qualitative comparison of 68Ga-DOTATOC and 68Ga-DOTATATE in clinical imaging of neuroendocrine tumors: net uptake for accurate quantification. J Nuclear Med 2014;55:204-210

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6. Li SC, et al. Roles of miR-196a on gene regulation of neuroendocrine tumor cells. Mol Cell Endocrinol. 2015; 412:131-139

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15. Barbu A, et al. Progranulin stimulates proliferation of mouse pancreatic islet cells and is overexpressed in the endocrine pancreatic tissue of a Men 1 mouse model. Pancreas 2016; 45: 533-540

16. Antonodimitrakis P, et al. Streptozotocin and 5-FU for the treatment of pancreatic neuroendocrine tumors: efficacy, toxicity and prognostic factors. Neuroendocinology 2016; 103: 345-353

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25. Backman S, et al. Detection of somatic mutations in gastroenteropancreatic neuroendocrine tumors using targeted deep sequencing. Anticancer Research 2017;37(2):705-712

26. Carlbom L, et al. Whole-body diffusion weighted MRI compared to 5-HTP-PET in the detection of neuroendocrine tumors. Upsala J Medical Sci 2017;122:43-50

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29. Backman S, et al. Global DNA Methylation Analysis Identifies Two Discrete clusters of Pheochromocytoma with Distinct Genomic and Genetic Alterations. Epub March 24 2017, *Scientific Reports*.

30. Johansson T, et al. Lack of nuclear HES1 expression coincides with transformation of endocrine pancreatic cells in *Men1* knock-out mice. Manuscript

31. Chu X, et al. Quantitative protein profiling of adrenal glands of a MEN1 mouse model. Manuscript

32. Monazzam A, et al. Increased Expression of GLP-1R in Proliferating Islets of Men1 Mice is Detectable by [^{68}Ga]Ga-DO3A-VS-Cys^{40}-Exendin-4 /PET. Manuscript

33. Monazzam A, et al. MicroRNA expression profiling in adrenals of multiple endocrine neoplasia type 1 mice. Manuscript

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Peer-reviewed international consensus papers

1. Sundin A, et al, et al. ENETS Consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine and hybrid imaging. Neuroendocrinology 2017 Mar 30. doi: 10.1159/000471879 (Epub ahead of print)

2. Falconi M, et al. Consensus guidelines update for the management of functional p-NETs and non-functional p-NETs. Neuroendocrinology 2016;103:153-171

3. Pavel M, et al. ENETS consensus guidelines for the standard of care in NETs: Systemic therapy in patients with neuroendocrine neoplasms. Neuroendocrinology. 2017 Mars 29. doi: 10. 1159/000471880

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Reviews/chapters

I. Skogseid B, Wängberg B. Endokrina tumörer i gastrointestinalkanalen och pankreas. *In* ”Endokrinologi”by Liber. Ed Werner S. 2014 Chapter 8, 215-231

II. Skogseid B, Wängberg B. Binjurebarkscancer. *In* ”Endokrinologi”by Liber. *Ed* Werner S. 2014 Chapter 6, 187-191

III. Akerstrom G, Stalberg P, Skogseid B. Multiple Endocrine Neoplasia type 2. Eds Balch, Mortia *In:* Textbook of Complex Surgical Oncology. McGraw-Hill 2014.

IV. Ekeblad S, Skogseid B. Pancreatic endocrine tumors. *In* Hematology oncology Therapy. *Eds* Boyiadzis M, Lebowitz P, Frame J, Kohler D, FojoT. McGraw-Hill 2014 Chapter 28: 579-602

V. Crona J, Skogseid B. GEP-NETS Update: Genetics of Neuroendocrine tumors. *Invited review* Eur J Endocrinol 2016; 17: 275-290

VI. Eriksson B. Chemotherapy. *In* Neuroendocrine Tumors: Diagnosis and Management. 2015:535-550 Eds Yalcin S, Öberg K. Springer

VII. Åkerström G, et al. A review on management discussions of small intestinal neuroendocrine tumors ‘midgut carcinoids’. Epub May 9 2015. *International Journal of Endocrine Oncology*.

VIII. Björklund P, Pacak K, Crona J. Precision medicine in Pheochromocytoma and Paraganglioma: Current and future concepts. Epub May 10 2016. *Journal of Internal Medicine*.

IX. Öberg K. Universal everolimus for malignant neuroendocrine tumours? The Lancet, 2016; 387(10022): 924-926

X. Öberg K, Lamberts S. Somatostatin analogues in acromegaly and gastroenteropancreatic neuroendocrine tumours: past, present and future. Endocrine Related Cancer, 2016; 23(12): R551-R566

XI. Kidd M, Modlin I, Öberg K. Towards a new classification of gastroenteropancreatic neuroendocrine neoplasms. Nature Reviews Clinical Oncology, 2016; 13(11): 691-705

XII. Öberg K, Sundin A. Imaging of Neuroendocrine Tumors. Frontiers of Hormone Research, 2016; 45: 142-51

Haematology

Research Group leader: 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 leukemia
- 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 centers of clinical excellence. We participate actively in the U-CAN project (structured biobanking at diagnosis, follow-up and relapse). In January 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 acute 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 field (“repositioning”) e.g. the anti-malarial drug quinacrin 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. Utilizing samples from U-CAN we also try to identify new prognostic protein markers in plasma using the unique the proximity extension assay (Proseek Multiplex Oncology II and Proseek Multiplex CVD III.).

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 molecular studies are focus 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 and Helene Hallböök

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 predictive biomarkers, clonal evolution and

resistance in patients with advanced disease treated with the BCR inhibitors ibrutinib or idealisib. In another projects, we aim to clinically and genetically characterize subsets of CLL with very good prognosis. In collaboration with Prof Anders Larsson, we are studying inflammatory markers in newly diagnosed CLL.

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

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

The Swedish population based registries in patients with haematological malignancies are internationally unique. Presently, more than 1000 patients with CML and more than 6000 patients with acute leukaemia are included. In a recent publication, 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, Bengt Simonsson, Sören Lehmann and Lind Arngården

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. We have investigated for the presence of immune escape mechanisms such as myeloid-derived suppressor cells and T regulatory cells. We are also developing a proximity ligation assay (PLA) for detecting the bcr-abl fusion protein with flow cytometry. 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 center 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 are conducting several clinical and laboratory studies aiming to improve the diagnosis and management of complications in patients receiving treatment for haematological cancers. These studies includes the assessment of the impact of IgG subgroup deficiency in patients with Chronic Lymphocytic Leukaemia (CLL), the role of conjugated pneumococcal vaccination in patients with CLL, exploring 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 anemia we are involved in several clinical trials including a large European multicenter 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 to 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.

Members of the group during 2015

Sören Lehmann, MD, professor
Gunnar Birgegård, MD, prof. emeritus
Kristina Carlson, MD, assoc. prof
Honar Cherif, MD, assoc. prof
Elisabeth Ejerblad, MD, PhD
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Blodcancerförbundet	300

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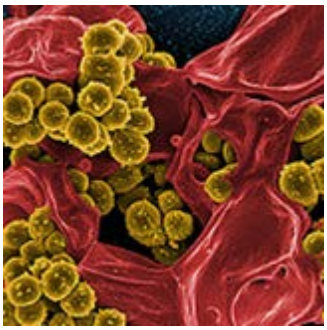
Research area Infection

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

Research Group leader: 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, 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 pathogenesis 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 next generation sequencing 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 pathogenesis of *Campylobacter* at a molecular level and helps to direct preventive measures. We recently showed, in pioneering studies, that the composition of the human faecal microbiota was connected to the susceptibility of *Campylobacter* infection. We also showed that e.g. some previously established virulence factors were disrupted in invasive *Campylobacter* isolates and that processes beyond the DNA level, such as epigenetic regulatory mechanisms, could actually play a prominent role in the invasiveness. 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, Muhammad Rizwan, Bengt Rönnberg, Hongyan Xia

The research during 2016 took place along three lines. 1. **Development of microbiological multiplex diagnostic techniques and corresponding bioinformatics:** The ConSort Primer and probe design program was further developed. We also further developed the VOCMA system for multiplex and broadly targeted PCRs, using internal quenchers. It is being tested for development of virus family-specific PCRs

together with prof. Modra Murovska in Riga. Together with Finnish researchers we developed a multiplex serology for viruses and parasites which can give intrauterine infections. Together with Uppsala researchers we studied herpes family antibodies in Alzheimer patients. The multiplex suspension microarray serology is also utilized for the study of Myalgic Encephalomyelitis (ME), in collaboration with clinicians and researchers in Gothenburg, Uppsala, Umeå, Linköping and Stockholm. The ME study is now a major part of our effort. 2. **Diagnosis of zoonotic virus infections**: We developed a novel technique for mimicking proteins from zoonotic viruses (hanta- and filoviruses; patent application) using exceptionally long synthetic peptides. We also developed a computer program for interpretation of multiplex serology for flavi-and hantaviruses (patent application). Diagnosis of zoonotic virus infections has been a major part of our effort. The collaboration with Finnish and German researchers is a valuable asset. 3: **Study of Human Endogenous Retroviruses**: We have published the most comprehensive account of HERVs so far, and on HERV expression in human autoimmune diseases and neuroblastoma cells. Together with Sardinian collaborators we made a special effort on HERVW. Together with researchers in Uppsala, California, Boston, Glasgow, London, Homburg and Paris we work on improving HERV nomenclature. Furthermore, broadly detecting RT-PCR system was developed for gastroenteric viruses like Sapovirus, Adenovirus F40/41 and Rotavirus and multiplex analyses of gastroenteric pathogens were performed in healthy Swedish children in day care centers.

Chlamydial infections in humans and birds

Björn Herrmann, Jenny Isaksson, 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 and its role as zoonotic disease is investigated. An additional research topic in our group is the detection and identification of bacteria causing respiratory tract infections.

Antiviral drug discovery, treatment and resistance

Johan Lennerstrand, Midori Kjellin, Dario Akaberi, Vesna Radić, Anders Lannergård, Tore Gutteberg (Tromsö), Navaneethan Palanisamy (Heidelberg), Jarl Wikberg, Åke Lundkvist

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 drug candidates, with in silico and in vitro methods, against Zika virus and other flaviviruses such as TBE and Dengue - in collaboration with Zoonosis Science Center, Uppsala. 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 and health-care associated infections, infection prevention and control interventions. In several projects, local and international collaborators and networks are involved.

Members of the groups during 2016

Guma Abdeldaim, scientist

Dario Akaberi, 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
Muhammad Rizwan, MSc
Bengt Rönnberg, scientist
Astrid Skarp, scientist
Hongyan Xia, scientist
Christina Öhrmalm, scientist

Funding 2016

FORMAS	1.4 MSEK
ALF	1.4 MSEK
Uppsala-Örebro Regional Research Council:	0.3 MSEK
Selander Foundation:	0.1 MSEK
EUROSTARS/Vinnova	0,8 MSEK

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1. Lytsy, B, Andersen, LP, Popp, W. Health Care Facility Design, Construction, and Renovation" in Basic Concepts of Infection Control, 3rd edition, revised 2015 The IFIC (International Federation of Infection Control

Patent applications

1. Dec 18, 2015: J. Blomberg: Large Synthetic Antigens Useful for Diagnosis of Infections and Infection-Induced Autoimmunity. US provisional, serial no. 62/264,737

2. Dec 20, 2016: J. Blomberg: Multiplex Immunoassay with Enhanced Specificity for Improved Serodiagnosis of infection with Cross-reactive Microbes. US provisional, serial no. 62/432,726

Infectious Diseases

Research Group leader: Britt-Marie Eriksson

Mia Furebring, Thomas Tängdén, Britt-Marie Eriksson, Karlis Pauksens

The principal research fields of the group are the host response to infection and antibiotic treatment, resistant bacteria, infections in the immunocompromised host and infections affecting the central nervous system.

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 2016 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 that might change current recommendations. In 2016 the effect of immunomodulation by corticosteroids given before antibiotic treatment has been assessed in a registry comprising 1500 patients with meningitis. This is up to now the largest study on corticosteroids and meningitis and for the first time it was demonstrated that a beneficial effect was seen regardless of presumed etiology and that the effect was dependent on mental status on admission. During 2016 the effects of following Swedish, European and American guidelines have been evaluated.

Clinical studies evaluating the effect of the systemic inflammatory response on pharmacokinetics of antibiotics and antifungals 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, Hanna Montelin, Wanchana Ungphakorn, Kari-Pekka Skarp, Ayda Shams, Pikkel Yuen, Christer Malmberg

Ongoing *in vitro* studies include experiments aiming to find antibiotic combinations effective against multidrug-resistant bacteria and the evaluation of rapid antibiotic susceptibility tests. During 2016, we have completed an evaluation on automated methods for potential use in high-throughput screening for combinations against multidrug-resistant strains. The oCelloScope, which is based on automated microscopy and image analysis, has been considered feasible -and is being used for this purpose in a 3-year European collaboration project (CO-ACTION) funded by the Swedish research council 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 and will be further improved for use with positive blood cultures.

Clinical studies include a multicenter study on optimal antibiotic therapy for urinary tract infections caused by ESBL-producing bacteria and a study addressing the impact of antibiotics on the intestinal microbiota in hematological patients. The inclusion of patients in these studies will be completed in Q1 2017. A study on patients treated at the intensive care unit for burn injuries is ongoing and will address not only the impact of antibiotic therapy on the intestinal microbiota bur also the feasibility to restore the microbial diversity with fecal transplantation.

Infections in solid organ transplantation and infections of the brain

Britt-Marie Eriksson, Camilla Lorant, Gabriel Westman, Jakob Sparby, Fredrik Sund

The numbers of solid organ transplant recipients increases continuously, demanding more knowledge about opportunistic infections. Main focus has been research on cytomegalovirus infections after renal transplantation but also in congenital infection, inflammatory bowel disease and in patients with Alzheimer´s disease. In collaboration with Department of Clinical Immunology, different aspects of T-cell immunity were studied. Ongoing is a project of BK-virus infection in renal transplant recipients, an infection with potential to destroy graft function.

Another part of research is concerning infections of the brain. During a ten-year period we have been part of an international multi-center study of additional valaciclovir therapy to patients with herpes simplex encephalitis (HSE). In a follow-up study of the Swedish patients we have been able to show that one fourth develop synaptic antibodies (NMDAR) which seems to affect the recovery of neuro-cognitive function. These are new data that probably will change treatment policies of a sub-group of patients with HSE. In another study we have mapped the incidence and the handling of ventricle-drainage related infections after neurosurgery. The findings of that study show the need for better diagnostics and we are now planning new studies for the evaluation of more rapid diagnostic methods. The purpose is to substantially reduce the need of empirical antibiotic treatment.

Infections in and vaccination of immunocompromised patients

Karlis Pauksens, Amelie Kinch

Data on safety, immunogenicity, and efficacy of vaccines for immunocompromised populations are limited. We have studied response to vaccination in different immunocompromised individuals such as elderly patients, patients with rheumatoid arthritis, and patients with cancer. Furthermore, we study opportunistic

infections with special focus on Epstein-Barr virus (EBV) and post-transplant lymphoproliferative disorder (PTLD) after allogenic stem cell transplantation and solid organ transplantation.

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Dissertations

Jesper Sperber May 28th 2016. Protective mechanical ventilation in inflammatory and ventilator-associated pneumonia

Eva Söderberg Oct 28th 2016. Experimental septic shock – effects of endotoxemia with special reference to pathophysiological responses in the pig

Infection Medicine

Research Group leader: Björn Olsen

Projects

Björn Olsen

Professor Björn Olsen, Professor Åke Lundkvist, MD, PhD Erik Salaneck and MD, PhD Patrik Ellström and 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 is working from 2016. There we can 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 in 2017. The preliminary and unofficial impact as this is written is 2.34.

Influenza

Josef Järhult, Anna Gillman, Jonas Waldenström, Erik Skog, Per Eriksson Patrik Ellström 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 re-assortment 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 OC resistance in IAV and retention of resistance mutations in repeated replications and transmission without drug pressure. Furthermore, we have demonstrated resistance development to ZA and the newer neuraminidase inhibitor peramivir. To assess the risk for transmission of resistance towards humans, we have studied transmission of resistant IAVs to chickens and re-assortment. We have also performed several observational and experimental studies to better understand IAV transmission and epidemiology in its natural host. Our results will be of value for organizations and authorities working with strategic pandemic preparedness planning, like WHO. In another project, we study attachment of IAV to target tissues from humans, pigs and wild birds by virus histochemistry. By combining this with virus attachment studies to glycan arrays with defined glycan structures, we have detected novel attachment patterns for viruses from humans and birds. This technology is currently developed within the group as a tool to screen for avian IAV strains with potential to transmit to poultry, pigs and humans. By the end of the year we received a new grant from VR for 2017-2020 that will allow us to study interspecies transmission of IAV in more detail.

Campylobacter and other gastrointestinal pathogens

Patrik Ellström, Evangelos Mourkas, Clara Atterby, Petra Griekspoor, Jenny Olofsson, Jonas Waldenström, Björn Olsen

Campylobacter is our most common zoonotic infection and most human cases can be attributed to the broiler industry. Despite years of research efforts, we still know very little about how Campylobacter reach the food industry, how they survive in the environment or how they transmit between species and cause disease in humans. In our group, we study barriers for transmission of Campylobacter between species. This year, we have completed an infection experiment in a wild bird (mallard) model, suggesting that barriers for transmission of Campylobacter between wild bird species are maintained because of strong adaptation of Campylobacter strains to certain host resulting in reduced colonization ability of these strains in other hosts. Further, by collaboration with British researchers we have conducted whole genome sequencing (WGS) of C. jejuni to get information of the genetic thresholds behind the different infectivity of certain genotypes in different vertebrate species. We are also in the process of completing a large population genetic characterization of campylobacters from humans, farm animals, wild birds and water using WGS analysis on a unique collection of strains. As part of this study, we particularly assess the role of the outer membrane lipooligosaccharide for bacterial fitness in these environments. In 1995 we discovered that Campylobacter can survive and replicate in free living amoebae and currently we focus on understanding the process of Campylobacter infection of protozoans using proteomic analysis. During a number of expeditions, we have isolated Campylobacter from penguins and other birds in Antarctica. Currently, we study the ecology of Campylobacter in these remote areas as well as their relation to the host intestinal microbiota. Finally, we have received a new FORMAS grant for 2017 an onwards that will allow us to study Campylobacter in organic chicken production.

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 Hoffman, 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 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.

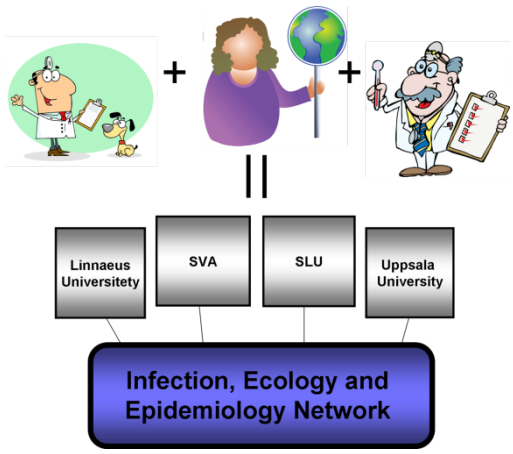
Antibiotic Resistance

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

The main force behind emergence of antibiotic resistance is the use of antimicrobial agents in human and veterinary medicine and domestic animal husbandry, providing a strong selection pressure for bacteria to acquire resistance. However, there is also evidence that epidemic spread of drug-resistant bacteria and horizontal transfer of resistance genes are contributing factors to resistance emergence. It is important to realize that there are no closed systems – the bacteria we select for in environments close to humans will, back and forth, find their way to bacterial communities in nature and vice versa. In recent studies, we have shown the presence of antibiotic resistant bacteria in areas lacking antibiotic usage. This strongly indicates that the resistance emergence in countries like Sweden, are not only governed by national concerns but also by what happens in a larger context. The knowledge of antibiotic resistance in the environment is 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 harbor valuable sets of bacterial collections from different reservoirs that are a good foundation for comparative studies.

One World – One Health

Combating emerging infections requires an approach where researchers take in account the “one health” concept. I started The Infection Ecology and Epidemiology, IEE network to stimulate interdisciplinary collaborations with potential to increase knowledge of the emergence, spread and effects of infectious disease in humans, domestic animals and wildlife. The main objective for IEE is to provide a platform where researchers from multiple medical and ecological disciplines can interact and create synergies through collaboration, annual meetings and workshops. The research group Infection Medicine is located at Uppsala University where we have during the last ten years, built up a research laboratory working primarily with ecology, clinical picture and host parasite interaction of various microorganisms.
The IEE network will be vital in strengthening the scientific output as well as providing an economic synergistic effect of present and further funding. This network has and will continue to lead to increasing collaborations between research groups and universities, as well as providing strong international research links. The principle aim of the IEE network is to provide a stable platform for cross-disciplinary collaboration, sharing of material and equipment and exchange of ideas. The research teams included in this network represent the width of zoonotic infection research, from wildlife ecology to advanced virology and bacteriology.



The projects within the IEE network range from antibiotic and antiviral resistance, to the genetics of vector-borne pathogens, zoonotic viruses and gastrointestinal pathogens. The rationale is not to build up new laboratory facilities, but to use and collaborate within already established research structures. Within the network we have access to thousands of samples of viruses, bacteria and protozoa of animal, human and environmental origin for collaborative projects for detection and characterization of microorganisms. The collective strength of this network is synergisms – we believe that the cross-disciplinary nature of the projects, which have been the result of the initial work with establishing IEE will be a new standpoint for research on zoonotic emerging or re-emerging infections. We have gathered top-researchers from the fields of human and veterinary medicine together with

epidemiologists, virologists, bacteriologists, ecologists and wildlife disease specialists.

Members of the group 2016

Björn Olsen, MD PhD, Professor
Åsa Melhus, PhD, MD, Assoc. Professor
Anders Bergqvist, PhD
Kåre Bondeson, MD PhD
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Katarina Engdahl, PhD-student
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Funding 2016

VR	2.3 MSEK
FORMAS	2.8 MSEK
ALF	1.5 MSEK
Karin Korsner Foundation	0.15 MSEK
VINNOVA	0.85 MSEK

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Dissertations 2014-16

Jorge Hernandez 2014 Human pathogens and Antibiotic Resistant Bacteria in the Polar Regions.

Susanne Sütterlin 2015Aspects of Bacterial Resistance to Silver.

Eva Tano 2015 Survival of infectious agents and detection of their resistance and virulence factors.

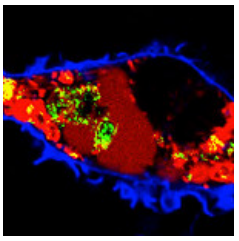
Jenny Olofsson 2015Amoebae as Hosts and Vectors for Spread of Campylobacter jejuni.

Anna Gillman graduated 2016 Tamiflu® in the Water: Resistance Dynamics of Influenza A Virus in Mallards Exposed to Oseltamivir.

Anders Lindblom 2016 Spotted fever Rickettsiosis in Sweden; aspects of epidemiology, clinical manifestations and co-infections.

Katarina Wallménius 2016 Studies of Spotted Fever Rickettsia-distribution, detection, diagnosis and clinical context: with a focus on vectors and patients in Sweden.

Research area 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.

Dermatology and Venerology

Research Group leader: 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 mast cell-mediated inflammation. Clinical characteristics and serologic markers are also studied in autoimmune disorders of the skin.

During 2016 we have focused on the following projects;

Etiologies and new therapies for monogenetic epidermal diseases

Hans Törmä, Marie Virtanen, 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.

Members of the group during 2016

Hans Törmä, PhD, Professor
Anders Vahlquist, MD, PhD, Professor emeritus
Berit Berne, MD, PhD, Professor
Ola Rollman, MD, PhD, Associate professor
Eva Hagforsen, PhD, Lecturer
Marie Virtanen, MD, PhD
Mohammad Alimohammadi, MD, PhD, Associate professor
Håkan Hedstrand, MD, PhD
Simone Weström, PhD, Research engineer
Maja Ericsson, Technician
Hanqian Zhang, MSc, PhD-student
Peter Norén, MD, PhD-student
Anna V. Bergström, BSc, MD
Mats Berg, MD, PhD
Carl Swartling, MD, PhD

Funding

Dermatology fund/Hudfonden (total) HT/MV/EH/MA/OR	1200 kSEK
ALF (Projekt: Virtanen and Alimohammadi)	1014 kSEK

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Gastroenterology and hepatology

Research Group leader: Per M. Hellström

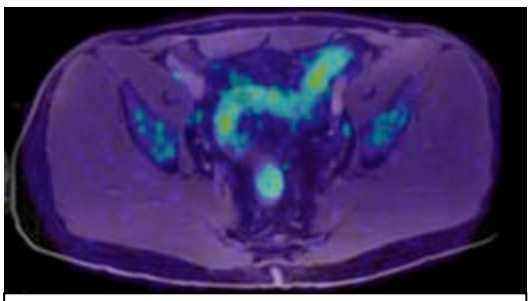
Research in gastroenterology and hepatology is focused on inflammatory reactions in the gastrointestinal tract and liver. From a patient registry (SWIBREG), special attention is given to inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis) and microscopic colitides (collagenous colitis, lymphocytic colitis) as well as primary sclerosing cholangitis (PSC) as complication of IBD. Furthermore, the ongoing epidemiological project ICURE (IBD Cohort Uppsala Region) covering approximately 790 individuals with ulcerative colitis and Crohn's disease has reported on the five-year clinical result regarding mortality, medical treatment, need for surgery and mortality. Compared to the most recent previous Swedish results, a considerably improved outcome was demonstrated.

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. A novel finding of intestinal fatty acid binding protein (I-FABP) has shown to be related to the clinical response and plasma level of tumour necrosis factor in infliximab treatment of IBD. A distinct parallel relationship speaks in favour of I-FABP as a reliable biomarker of disease.

Special attention is also given to diagnostic procedures in inflammatory liver diseases for prediction of malignant development in PSC. Patients with PSC display a different T-cell profile with less expression of CD 25 on CD4+ cells in the colon. In addition, CD 8+T-cells express CXCR3 which is in line with cell migration to the liver and phenotypic eosinophilic diversity as a link to the pathogenesis of liver disease. Mechanisms between IBD and PSC in terms of coagulation and malignancy as regards tissue factor (TF) are studied. A flow sight method has been developed to visualize where TF is binding on the cellular surface with activation of M1-macrophages as studied with FACS analysis. Gut permeability using Ussing chamber technique has been employed for IBD-PSC against micro RNAs as markers of disease in IBD-PSC. To this end, the prognostic value of fecal biomarkers of IBD is studied longitudinally along with colonoscopic controls in IBD. Calprotectin, myeloperoxidase, eosinophilic cationic protein, eosinophilic protein X and chromogranins are studied. Furthermore, plasma, serum and fecal samples are continuously being collected in biobanks.

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.

The gut microbiome has been studied by the use of an anaerobic cultured human intestinal microflora (ACHIM) in *Clostridium difficile-infection* and diarrhea-dominant irritable bowel syndrome (IBS-D). Treatment with ACHIM has shown to be effective in 92% of *C diff*-infected and in 78% of IBS-D, in 5% with complete healing of IBS. Follow-up studies on gut permeability and 16S-rRNA is now being pursued in order to disentangle the relationship between IBS and the gut microbiota.



NK1-receptor expression in ulcerative colitis, magnetic resosonance combined with radioactive labeling.

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. Metabolomics are applied to disentangle food sensitivity in IBS and celiac disease. This concept is now applied both to an adult and to a pediatric population with dominant gastrointestinal symptoms are being evaluated using gastric emptying test, small bowel manometry and colonic scintigraphy for motility disorders.

In terms of hepatology a registry of patients with liver decompensation and portal hypertension has been established. The unit has become the main center in Sweden for treatment by means of interventional radiology for transjugular intrahepatic portosystemic shunt (TIPS) placement. This intervention aims to relieve portal hypertension, improve bowel circulation and reduce the risk of variceal hemorrhage, thereby bridging the patient to a liver transplant. In line with this, liver decompensation with ascites and hepatic encephalopathy is extensively studied. The TIPS technique has evolved into a safe treatment of circulatory hepatic diseases such as symptomatic Budd-Chiari syndrome with improvement in transplantation-free survival compared with conservatory medical treatment. The impact of a specialist nurse out-patient clinic for prognosis, quality of life and health care quality in cirrhosis is studied in a randomized clinical trial. Imaging and serological biomarkers for development of liver fibrosis in non-alcoholic fatty liver disease are investigated.

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 as academic and industry-sponsored clinical trials
- Interventional therapy in gastroenterology and hepatology
- Gastroenterology lab unit with basic chemistry and physiology for clinical and investigational studies of pathophysiology in gastrointestinal and liver disease

Dissertations

- Md. Abdul Halim, Gut peptides in gastrointestinal motility and mucosal permeability, 2016-06-14.

Awards

- Md. Abdul Halim, PhD, was awarded the *Ulf von Euler prize in physiology* for studies on the nitrergic regulation of the migrating motor complex in humans, 2016.
  Publication: Nitric oxide regulation of migrating motor complex: randomized trial of N(G)-monomethyl-L-arginine effects in relation to muscarinic and serotonergic receptor blockade. Acta Physiol (Oxf). 2015;215:105-18

Select projects

- Epidemiology of IBD and microscopic colitides and complications of disease
- Nitric oxide, nitrite and nitrate in the inflammatory IBD response
- Prognostic value of fecal leukocyte and esosinophilic biomarkers in IBD.
- The leaky gut syndrome in and microbiome 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 employing metabolomics for diagnostic purposes.

- Fecal microbiota transplantation in IBD and IBS
- Detection, treatment and prognostic markers of biliary cancer in primary sclerosing cholangitis.
- Treatment of liver disease with portal hypertension using transjugular intrahepatic portosystemic shunt (TIPSS)

Members of the group during 2016

Per M. Hellström, MD, PhD, professor
Marie Carlson, MD, PhD, professor
Fredrik Rorsman, MD, PhD, associate prof
Anders Rönnblom, MD, PhD, associate prof
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Per M. Hellström

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Marie Carlson

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Fredrik Rorsman

ALF	102 kSEK
Center for clinical research	125 KSEK

Anders Rönnblom and Mari Thörn

ALF	124 kSEK

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Renal Medicine

Research Group leader (acting) Torbjörn Linde
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 in chronic kidney disease and haemodialysis treatment, as well as studies on new biomarkers for renal failure. 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. 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.

Cardiovascular Complications in Chronic Kidney Disease and Renal Transplantation

Inga Soveri , Hans Furuland, Eva Carlsson, Philip de Laval , Bengt Fellström

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 pre-uremic 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. (See below)

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 (see below). In addition we are also collecting samples such as plasma and vascular tissue for proteomics analysis in collaboration with Prof. J Bergqvist at SciLifeLab. No results are available as yet, but awaiting a substantial amount of data emerging during 2017.

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

Proteomics on vascular tissue from CKD vs. healthy subject

Inga Soveri, Philip de Laval, Bengt Fellström, Jonas Bergqvist

In collaboration with SciLife Labs proteomics lab, we study protein expression and modifications in uraemic arteries. Biopsies during kidney transplantations are compared to arteries from deceased kidney donors. Also, uraemic plasma from dialysis patients is used, although proteins have high dynamic in plasma. In this manner, we can study the target organ protein composition and identify possible mechanisms leading to cardiovascular disease in uraemia. Biomaterial has been sampled in collaboration with transplant surgery and awaits analysis. Also, in collaboration with Karolinska Institutet and the Univeristy of Glasgow, markers of biological ageing will be investigated in the arteries.

Renal transplantation

Bengt Fellström, Inga Soveri, Jan Melin, Hans Furuland

We have initiated a CV and renal function study in renal transplant patients focusing on CV biomarkers while switching from CNI based immunosuppression to a belatacept (a fusion protein acting by blocking co-stimulatory pathways of T-cell activation) based regimen. Altogether 102 (out of 110 planned) patients have been enrolled in four northern European countries. Patients will be followed during 12 months for sampling of biomarkers and follow up on clinical events. The study will reach LPLV in Q2 2018 and report in Q3 2018. A CV risk calculator for renal transplantation has been established and will now be made easier available for professionals and maybe for patients as well.

IgA Nephropathy

Bengt Fellström, Inga Soveri, Jan Melin, Hans Furuland, Hild Kloster Smerud

There has been a special interest in IgA nephropathy in our unit, with one PhD thesis in 2012 (Smerud). Based upon the connection between formation of aberrantly glycosylated IgA 1 in patients with IgAN, a phase 2a study was completed in 2012, showing quite promising results on proteinuria and GFR in 16 IgAN patients. The NEFIGAN trial was the corresponding phase 2b trial, which was recently finalized and published in The Lancet in March 2017. In the NEFIGAN study it was clearly demonstrated that treatment with NEFECON, acting primarily on mucosal immune cells in distal ileum, caused a 27% reduction of proteinuria on top of full RAS blockade and also led to a complete stabilization of renal dysfunction in actively treated patients compared with subjects on placebo. Intriguing results are now emerging from posthoc analyses of biobanked material from the trial, pointing in detail on the mechanism of action of this novel approach. New studies are in pipeline along the same lines, one of which is a global phase 3 trial in IgAN and a small scale trial in patients with recurrence of IgAN in a renal transplant.

Anti-GBM disease (Goodpasture syndrome)

Inga Soveri, Bengt Fellström

2016 the first ever antiGBM disease patient, refractory to plasma exchange/immunoadsorption, was treated with IdeS in Uppsala. The antibodies that couldn´t be removed with 16 plasma exchanges were cleared 2h after the infusion. A clinical trial will start 2017 (collaboration with Linköping University)

Complement activation during dialysis treatment

Inga Soveri, Philip de Laval, Hans Furuland, Bengt Fellström, Kristina Ekdahl-Nilsson, Bo Nilsson

A new line of studies emerging from the renal unit in close collaboration with Nilssons at IGP, relates to complement and contact activation during dialysis treatment. This also includes formation of microparticles, when blood gets in contact with biomaterials such as the ones used in dialysers (Summarized in our recent article in Nature Rev Nephrol, 2017). This contributes to a state of thromboinflammation, activation of inflammatory pathways and depletion of essential contact proteins. These pathways may be important for the systemic inflammation seen in dialysis patients, which is strongly related with the appearance of cardiovascular complications as well. It may also be responsible for the high risk of thromboembolic complications and vascular remodelling, which occurs in dialysis patients. We have already identified a number of activation steps and generation of subclasses of microparticles of endothelial, platelet and monocytic origin during a hemodialysis session. P de Laval will report on these findings shortly. In parallel we are also analyzing a set of contact proteins, ficolins and complement activations derivatives in patient materials with outcome data available, in order to find out to what extent these activation steps are related to actual clinical outcome. These are largely ongoing studies, which we anticipate to be published within the next year.

B-type natriuretic peptide (BNP) as marker of overhydration in hemodialysis patients

Jenny Stenberg, Hans Furuland, Magnus Lindberg, Jan Melin

Hydration status is related to clinical outcome in long-term dialysis patients, and chronic over hydration, has been identified as an independent predictor of mortality. For assessment of volume status, utilization of multiple complimentary methods such as data regarding fluid balance (body weight changes), BP, bioimpedance, blood volume measurement and biomarkers is recommended.

As part of a PhD-project we plan to investigate the potential of B-type natriuretic peptide (BNP) as a marker of over hydration in hemodialysis patients. In the first step, we aim to investigate how BNP is distributed in a cohort of approximately 100 hemodialysis patients and to analyse how it correlates to inflammatory markers and hydration status (defined by bioimpedance). Additionally we will follow the patients for five years to evaluate the relationship between plasma BNP levels and mortality risk. In the second step we aim to investigate if BNP, when elevated, correlates to the degree of volume overload, to inflammation and to heart rate variability. Thus, is BNP reproducible; does the same level of BNP correlate with the same degree of over hydration in the same patient?

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

Torbjörn Linde, PerAnton Westerberg

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

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

Biomarkers of renal injury

Inga Soveri, Jan Melin, Per Venge, Anders Larsson, Bengt Fellström and scientists at OLINK.

Acute kidney injury is an increasing problem, and there are many conditions and procedures that put the kidneys at risk. Current markers of renal injury, such as creatine, are unspecific, but new biomarkers that show the actual degree of renal injury are now emerging; e.g. Human Neutrophil Lipocalin/Neutrophil gelatinase-associated lipocalin (HNL/NGAL), Kidney injury molecule (KIM-1), and Cystatin. We are currently evaluating several of these new biomarkers of renal injury in different clinical settings. The ability to identify parenchymal renal injury at a much earlier time than today would be beneficial for the patient, and would allow the physicians to customize the treatment. In addition a close collaboration has been initiated with OLINK, Uppsala, for development of renal platforms using the OLINK based PEA technology. The strategy is to identify relevant markers of disease progression in plasma and urine by analysing existing biobank material from existing largescale clinical trials in nephrology. That will include studies in diabetic nephropathy, polycystic kidney disease, hypertensive nephrosclerosis, glomerulonephritis and also transplantation cohorts / biobanks.

Renal Biobank Project

Inga Soveri, Bengt Fellström et al

We will also start a healthcare-coordinated biobank linked to the Swedish Renal Registry kidney biopsy sub registry. The ethics approval is in place and biobanking in Uppsala, Gävle, Västerås, Linköping and Örebro is ready to start. Danderyd will also join. The sampled biomaterial will be analysed regarding diagnostics, prognostics and treatment response. The sample size is crucial as several of the diagnoses of interest are rare and first output from the project cannot be expected before 3-4 years.

Commissioned research

We are currently involved in conducting three phase 3 trials in diabetes nephropathy: SONAR (Fellström), FIGARO and FIDELIO (Soveri). Also, we recruit patients for a NIH-funded study ISCHAEMIA-CKD (Soveri) comparing optimal medical treatment with invasive treatment in CKD patients with stable angina pectoris. 2017 we will start recruiting patients with ANCA-associated vasculitis for ADVOCATE study (phase 3; Soveri).

A novel research path includes studies of biomarkers for progression of polycystic kidney disease (ADPKD), as well as initiation of a treatment study using tolvaptan (Melin). We have participated in a randomized double blinded clinical trial with treating ADPKD-patients with tolvaptan that ended in March. An open label follow-up study with tolvaptan has just started.

Members of the renal medicine research group

Bengt Fellström, MD, PhD, Professor emerit.

Torbjörn Linde, MD, PhD, Assoc. professor,

Inga Soveri, M.D., PhD , Assoc. Professor.

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Danielle Lundqvist, RN, Research nurse

Yvonne Lundholm, RN, Research nurse

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Peer reviewed Original Publications 2014-2016

1. Rosanna Coppo,,Stéphan Troyanov , Shubha Bellur, Daniel Cattran , H Terence Cook, John Feehally , Ian SD Roberts, Fellström B, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments**. Kidney Intl 2014** :86: 828-836
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Book chapters 2014-2016

Hallvard Holdaas MD[1], Jon A Kobishigawa MD[2], Bengt Fellstrøm MD[3], Alan Jardine MD. Dyslipidemia in Transplant recipients. In: **Clinical Lipidology: A Companion to Braunwald's Heart Disease,** ed. C. Ballantyne, Elsevier , **2014 ,** chapter 40 : 469-481

Alan G Jardine, Patrick B Mark , Rajan K Patel , Hallvard Holdaas, Bengt Fellstrom . Dyslipidemia in Chronic Kidney Disease . In: **Clinical Lipidology : A Companion to Braunwald's Heart Disease,** ed. C.Ballantyne, Elsevier, **2014,** chapter 41: 482-489

Bengt von zur-Muhlen, Bengt Fellström. Njurtransplantation ur ett njurmedicinskt perspektiv, **Studentlitteratur , 2015**

Lars Rönnblom

Research Group leader: Lars Rönnblom

Chronic inflammatory diseases affect more than 5% of the population and the most common among these are the rheumatic diseases, which are associated with loss of function, increased mortality among the patients and high costs for the society. Major improvements in the development of new treatments have been accomplished for rheumatoid arthritis, but for the relatively large group of patients with systemic inflammatory autoimmune diseases efficient drugs without severe adverse effects are still missing. 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 the different disease focussed networks in Sweden and our international partners. Several new risk genes and epigenetic changes 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 subphenotypes 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 healthy individuals. During 2016 most of the samples 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.

Regulation of the type I interferon response by immune cells

We have continued to characterize the interaction between plasmacytoid dendritic cells and adaptive immune cells, and results describing the role of T cells in the type I interferon response have been published. We are also in the DISSECT project investigating potentially new drugs in vitro for their capacity to modulate immune activation and interferon production.

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 large number of samples have been collected in UBR and over 11,300 samples have been withdrawn for analysis in-house, nationally as well as internationally by 10 different research groups. The results have been published in highly acknowledged journals such as Nature, Nat Commun and Ann Rheum Disease, see publication list.

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 (GPA), 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 and aspects concerning lymphoma and other malignancy risks. 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.

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. Dr Peter Matt defended his thesis in the fall, see below.

Members of Rheumatology research group during 2016

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
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Lisbeth Fuxler, BMA
Olle Berggren, PhD
Niklas Hagberg, PhD
Dag Leonard, MD, PhD
Karin Bolin, MD, PhD student
Peter Matt, MD, PhD
Lilian Vasaitis, MD, PhD student
Erik Hellbacher, MD, PhD student
Johanna Dahlqvist, MD, PhD

Funding 2016

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
HarmonicSS (H2020) 2700 kSEK

Gunnel Nordmark
King Gustav V 80 year foundation 150 kSEK
Swedish Rheumatism Society 150 kSEK
Swedish research council
1000 kSEK

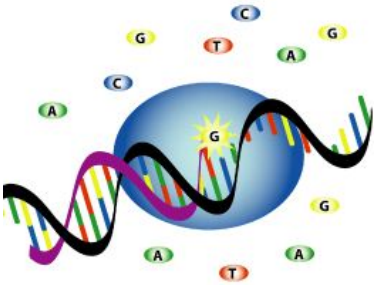
Maija-Leena Eloranta
King Gustav V 80 year foundation 100 kSEK
Swedish Rheumatism Society 100 kSEK

Eva Baecklund/Ann Knight
ALF grant 310 kSEK

Eva Baecklund
Swedish Cancer Society 500 kSEK
Selanders foundation 100 kSEK
Swedish Rheumatism Society 150 kSEK
King Gustav V 80 year Foundation 150 SEK
Lions Cancer Foundation 100 SEK

Ulla Lindqvist
SIDA 560 kSEK
ALF grant 100 kSEK

Research area 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 art genomics, epigenetics and computational modeling methods are employed together with *in vitro* experiments, utilizing biological materials in the form of DNA, protein or metabolites to uncover casual links between environment, heredity and disease. High throughput experimental techniques are also used to discover novel, and improve existing, therapies for cancer and other complex diseases.

Cancer pharmacology and computational medicine

Research Group Leader: Rolf Larsson

Rolf Larsson, Mats Gustafsson, Mårten Fryknäs, Joachim Gullbo and Peter Nygren

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

I. Drug and multi-compound therapy discovery

This activity is aimed at discovering novel drugs and multi-compound treatments for problems associated with drug resistance and toxicity in cancer therapy. In-house compound libraries, information-rich model systems, high-throughput technologies for drug screening, and the most recent methods for systemic molecular and phenotypic profiling (spectroscopy, arrays, sequencing, and microscopy) are available for this purpose together with required theory and algorithms for quantitative bioinformatics systems analysis. Among several novel assays we have established is 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 2017.

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 2016 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.

Many tumors express hydrolytic enzymes to modulate the microenvironment and maintain malignant growth. For example, aminopeptidase N is an ubiquitous enzyme with strong association with the characteristics of malignancy, e.g. angiogenesis, cell motility and aggressive growth. These enzymes may be utilized as targets for therapy. In this project we have synthesized derivatives of cytotoxic compounds to be activated or potentiated by these enzymes in order to develop anti-cancerous therapy with higher therapeutic index. The project has led to the development of one candidate drug, melflufen, currently evaluated in clinical trials in multiple myeloma. Current research will further investigate the spectrum of preclinical activity of melflufen in different tumor types, screening for promising combination partners and explore the effects on the immune system.

III. Systems Pathology

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

IV. Algorithmic biosystems analysis & control

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

Members of the group during 2016

Aftab Obaid, PhD student

Andersson Claes, PhD, researcher

Bäcklin Christofer, PhD student

Berglund Malin, laboratory technician

Emami, Payam, PhD student

Freyhult Eva, PhD, post-doc

Fryknäs Mårten, PhD, assoc professor

Gullbo Joachim, MD, PhD, assoc professor
Gustafsson Mats, TeknD, professor
Haglund Caroline, post-doc
Hammerling Ulf, PhD, assoc professor
Hassan Saadia, PhD, assoc professor
Jarvius Malin, PhD, post-doc
Karlsson Henning, PhD student
Kashif Muhammad, PhD student
Krishnan, Shibu, PhD, post-doc
Kultima Kim, PhD, researcher
Lannergård Anna K, laboratory technician
Larsson Rolf, MD, professor
Leek Christina, laboratory technician
Lenhammar Lena, laboratory technician
Najafi Nasrin, laboratory technician
Nazir Madhia, PhD student
Nygren Peter, MD, professor
Parrow Vendela, PhD
Strese Sara, PhD student
Strömbergsson Helena, PhD, post-doc
Senkowski Wojciech PhD student
Åleskog Anna, MD, PhD

Funding 2015

Swedish Cancer Foundation	1400 kSEK	VR	1000 kSEK
Oncopeptides	240 kSEK	ENABLE	600 kSEK
ALF	1300 kSEK	Lions	300 kSEK
KAW	1300 kSEK		

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7. Hammerling U, Freyhult E, Edberg A, et al. Identifying Food Consumption Patterns among Young Consumers by Unsupervised and Supervised Multivariate Data Analysis. European Journal of Nutrition & Food Safety. 2014;4(4):392-403.

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Clinical Chemistry

Research Group leader: 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 2016 participated in these two large consortia. This has resulted in a number of publications in Lancet.

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 patients in 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.

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 patient 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 is 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 functions

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 gene regulation.

We have also shown that Eph RTKs are novel proteolytic 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 demonstrated that TF/FVIIa phosphorylates serine 897 in the cytoplasmic domain of EphA2. EphA2/ephrinA1 pathway is a novel pro-inflammatory 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 sub study 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, has recently been presented.

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 coronary 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.

Per Venge: Biomarker discovery and development

Infectious disease

Human neutrophil lipocalin (HNL) is a protein discovered many years ago by our research group. HNL was shown to be a superior biomarker in the distinction between acute infections caused by either bacteria or virus. Some studies were performed in serum with excellent results. However, serum production needs strict standardization why user-independent techniques have been developed involving in vitro activation in whole blood of neutrophils to release HNL. This technique showed similar performance as serum measurement and is now exploited further and adapted to the point-of-care (POC) format with response times of 5-10 minutes from blood draw. Ongoing and upcoming studies will investigate the clinical performance of this POC format further. Other programmes involving HNL are studies on sepsis and the use of HNL for sepsis prediction and therapy monitoring

Acute kidney injury

HNL is the same protein as NGAL, which has been investigated intensely as a marker of early injury to the kidney (AKI). Many of these studies, however, failed to show a satisfactory clinical performance of HNL (NGAL) in this regard which likely relates to the fact that current assays measures all different forms of HNL in the urine or blood, both the forms originating from the kidney and the forms originating from neutrophils. We are developing assays that may discriminate between these different HNL (NGAL) forms and expect such assays to have a better clinical performance. In recent years we have also discovered and purified from human sources a couple of new proteins, Human phospholipase B-precursor (HPLB-P) and prolylcarboxypeptidase (PRCP) for which we have made sensitive ELISA. These two proteins are expressed in the kidney glomeruli and tubuli, respectively, and current research has shown highly elevated urine levels in patients admitted to an intensive care unit and the levels were closely associated to kidney functions in these patients. Thus, these two proteins may be novel biomarkers in the search for biomarker predictors of AKI together with HNL (NGAL).

Alzheimer's disease (AD and multiple sclerosis (MS)

The biomarkers, HNL, HPLB-P and PRCP are found in the cerebrospinal fluids of patients with neurodegenerative and inflammatory diseases of the brain. Ongoing research has shown that HNL is raised in AD but also in elderly healthy subjects and seem to be related to ageing. The two enzymes HPLB-P and PRCP are highly raised in MS, but the latter also in AD. HPLB-P is expressed by neurons and PRCP ubiquitously found in most cells of the brain. The production of HNL is induced by astrocytes and considered not to be produced by the healthy brain. The biological functions of the three biomarkers may be involved in key processes of AD and MS and should therefore be of interest to investigate further as indicators of these processes. Whether the three biomarkers can be used for diagnosis or outcome prediction of the diseases will be investigated in future studies.

Cardiovascular disease

The investigation of cardiac biomarkers for the diagnosis or outcome prediction of patients with cardiovascular disease has been ongoing for many years. Recent studies together with the Icelandic heart institute has shown the predictive power of high-sensitive troponin I in a large community-based population and further studies are ongoing defining the utility of this and other cardiac markers. Our strong reputation in the scientific world of cardiovascular disease has led to interactions with many of the largest companies in the world. Per Venge is the chairman of the cardiac advisory board of Philips in Europe and member of the American branch of this activity. He also acts as consultant to bioMerieux, and Radiometer.

Eosinophil research

The research on eosinophils has been going on since our discovery in the70 and 80tieths of the eosinophil granule proteins, ECP (eosinophil cationic protein), EDN (EPX) (eosinophil derived neurotoxin/ eosinophil protein-x) and EPO (eosinophil peroxidase). Currently focus has been on the genetics of ECP in various populations affected by parasites, but also on the measurement of the proteins in large collaborative studies on chronic lung diseases and on IBS (irritable bowel syndrome). The studies further emphasize the potential key role of the eosinophil in many large diseases and should lead to more efficient therapeutics.

Members of the group during 2016

Anders Larsson, Professor/consultant
Lena Carlsson, Post doc
Karin Eriksson, Laboratory engineer
Mats Flodin, Laboratory engineer
Tom Nilsen, PhD student
Peter Ridefelt, Associate professor/consultant
Gunnar Ronquist, Professor em.
Göran Ronquist, Post doc
Louis Dubois, PhD student
Leif Wide, Professor em
Johanna Helmersson-Karlqvist, Postdoc
Per Venge, Professor em.
Mats Stridsberg, MD, PhD, Assoc. Prof.
Torbjörn Åkerfeldt, MD, PhD student
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Jenny Alfredsson, PhD
Christina Christersson, MD, PhD
Desireé Edén, PhD-student
Oskar Eriksson, PhD-student
Lena Kask, PhD
Åsa Thulin, PhD
Mikael Åberg, PhD
Helena Vretman, Research engineer

Funding

Anders Larsson

FP-7	600 kSEK
Eurostar	300 kSEK
ALF	1000 kSEK
Selanders fond	100 kSEK

Agneta Siegbahn

Heart and Lung Foundation:	800 kSEK
Swedish research council:	1.2 MSEK
ALF grant:	600 kSEK
Industrial grants	500 kSEK

Christina Christersson

ALF grant:	100 kSEK

Per Venge

Swedish research council	600 tkr
ALF	250 tkr
Industrial grants	1500 tkr

Publications 2014-2016

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Clinical Pharmacogenetics and Osteoporosis

Research group leader, 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.

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

Pharmacogenetic warfarin dosing algorithms incorporating only CYP2C9*2, *3 and VKORC1 rs9923231 predict dose less well in people of African than European or Asian ancestry. In 2016, we published a novel gene regulatory variant close to VKORC1 that may be important for Africans, and a genome-wide association study (GWAS) of warfarin dose. We are publishing new ancestry-specific warfarin dose recommendations together with the Clinical Pharmacogenetics Implementation Consortium (CPIC) in USA.

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 2400 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 published the first results in Lancet Diabetes & Endocrinology in 2016. 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

Ulrika Gillespie, 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 have investigated 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 2016

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Håkan Melhus:

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Mia Wadelius:

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Swedish Research Council	1100 kSEK

ALF	734 kSEK	Thuréus' foundation	100 kSEK
EU FP7 (PREDICTION-ADR)	1400 kSEK		

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Molecular medicine

Research Group leader: 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. During 2016 human whole genome sequencing was a key approach in the studies performed by the Molecular Medicine group. 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). At BMC the molecular medicine group is located in close physical vicinity with other groups that are affiliated with Science for Life Laboratory.

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 “next generation” sequencing and genome-wide genotyping 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 2016 the project was mainly funded by the Swedish Cancer Foundation and the Pediatric Cancer Foundation.

From genes to function in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is regarded as the prototype for autoimmune diseases because it involves most immune cells and can affect all organs of the human body. SLE has a strong heritable component. There are about 90 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 analyses 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 Swedish Research Council for Medicine & Health (VR MH) and the Knut and Alice Wallenberg Foundation (KAW).

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. During 2016 the Molecular Medicine group and the SNP&SEQ Platform 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 was 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://www.molmed.medsci.uu.se/

Members of the group during 2016

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
Carl Mårten Lindqvist, PhD student
Tom Martin, PhD, research engineer,
Yanara Marincevic-Zuniga, PhD student
Nour-al-dain Marzouka, PhD, post doc
Jessica Nordlund, PhD, research scientist
Sara Nystedt, research engineer
Amanda Raine, PhD, research scientist
Michelle Rönnerblad, PhD, post doc
Per Wahlberg, PhD, post doc

Dissertation during 2016

Carl Mårten Lindqvist. Genomic characterization of pediatric acute lymphoblastic leukemia by deep sequencing.

Funding 2016

Swedish Research Council for Science and Technology (VR NT)	1.0 Mkr
Swedish Research Council for Medicine and Health (VR MH)	1.0 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	1.5 Mkr

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Undergraduate Teaching

Medicine Programme;	**Students**
Clinical Medicine I 23,5 hp	211
Clinical Medicine III 30 hp	208
Occupational and Environmental Medicine 1,5 hp	166
Clinical Practice and the Physician's Role 3hp	80
Physiotherapy Programme:	
Internal Medicine 3 hp	80
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
Biomedical Laboratory Science Programme:	
Medical Microbiology 11 hp	47
Medical Laboratory Data Analysis, 7 hp	50
Projectics 9 hp	44
Clinical Chemistry and Haematology, Toxicology and Pharmacology 13 hp	55
Clinical Physiology, 5 hp	48
Practical Tuition I, 12 hp	49
Practical Tuition II, 8 hp	41
Advanced Course II 8 hp	39
Biomedicine Programme:	
Basic Statistics, 3 hp	39
Applied Biostatistics, 5 hp	30
Diseases – Clinical Survey, 15 hp	26
Specialist Nursing Programme – Diabetes Care:	
Diabetes Care I 7,5hp (3ME076)	16
Single Subject Courses:	
Diabetes Care I 7,5hp	23
Person-Centred Care Related to Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM), 7,5 hp	18
Diabetes Care, Scientific Methodology and Essay 15 hp, Basic Course	1
Diabetes Care, Scientific Methodology and Essay 15 hp, Advanced Course	1
Advanced Course in Cardiac Care, 7,5hp	8
Treatment and Nursing in Ischemic Heart Disease, 7,5hp	43
Clinical Clerkship (Exchange Students)	10
Clinical Drug Development 30 hp	21
Work Environment in the New Working Life 7,5 (Contract Educ)	18
Introduction to Scientific Research, Step 1 3,5 hp (Contract Educ)	38
Introduction to Scientific Research, Step 2 4 hp (Contract Educ)	3
Treatment and Nursing in Asthma, Allergy and Chronic Obstructive Pulmonary Disease (COPD), 7,5 hp (Contract Educ)	33
Treatment and Nursing in Congestive Heart Failure, 7,5 hp (Contract Educ)	20
TOTAL:	2266

Centres and Facilities

Clinical Biomarker Facility

Director: Professor Agneta Siegbhahn

Our main focus

The Clinical Biomarker facility offers services for high-throughput and multiplex analyses of protein biomarker candidates in body fluids and other biological samples using the molecular tool proximity extension assay technology (PEA) with integrated fluidic circuits real-time PCR read-out format to analyse sets of 92 proteins in 90 samples in one run using only one microliter sample. The samples are analysed using ready-made panels developed by Olink Proteomics. Currently there are 12 panels available for analysis.

At the platform, a novel method for analysing protein expression on microparticles from platelets and leukocytes using proximity ligation assays (PLA) have been establishment in collaboration with Div. of Molecular Tools, and Research Group of Clinical Coagulation and Inflammation, Dept. Medical Sciences (IMV), UU. The establishment of a platform for microRNA plasma analyses is ongoing.

We have also developed a novel high-throughput method for multiplexing and analyzing up to 96 miRNA simultaneously in a single sample using LNA™-primers from Exiqon on the Biomark HD 96.96 Fluidic arrays. The first analysis of samples from a clinical study using this method is currently ongoing with expected results April2017.

Our vision

The long-term goal for this national facility is to implement PLA/PEA technique for analysis of patterns of proteins, circulating microparticles, and patterns of microRNAs in clinical diagnostics, with special focus on cardiovascular diseases, cancer, inflammatory and neurodegenerative diseases. The goal is to transfer the novel technique and offer clinical validated panels of biomarkers for clinical routine use. We will continue to offer service to academic researchers, national and international, with larger biomarker panels for research purposes in clinical studies.

Projects

During 2016 we completed 42 projects totaling almost 40 000 samples. The project ranges in size from 90-16000 samples. Our users are scientists from all the Swedish universities and local counties (landsting) such as Lund-, Uppsala-, Linköping-, Göteborg-, Umeå and Örebro universities, KI, Skåne and Västmanland regions. We have also customers from Oslo University, Norway and from the Swedish industry, AstraZeneca, and from Institut Produits Synthèse (IPSEN) AB.

The projects concerns: cardiovascular diseases, different types of cancer, diabetes, neurological conditions, inflammatory disease, and population based screening studies (i.e. the EpiHealth study) for finding biomarkers for primary prevention.

We apply ”first demand-first served” principle, however, larger projects are prioritized upon the scientific level and importance and financing, for instance grants from EU, the Swedish Research Council, Heart and Lung Foundation, the Swedish Cancer Foundation. For these larger projects the queue time is about 2-3

months. For smaller projects, 90-360 samples (1-4 chips), the queue time varies between one and three weeks depending on work load. These smaller studies are analysed in parallel with larger ones.

Staff

Jenny Alfredsson, PhD, Head of Facility

Cecilia Kriegholm (Research Engineer/Project Coordinator)

Johanna Svensson (Research Engineer)

Helena Vretman (Research Engineer)

Prabash Wijethunga (Research Engineer, until 161231)

Drug discovery and development platform, In vitro and systems pharmacology (IVSP) Facility

Facility Directors

Professor Rolf Larsson.

Professor Mats Gustafsson

Head of Facility

PhD Vendela Parrow

Personnel of the facility

PhD Malin Jarvius.

PhD Claes Andersson.

BMA Nasrin Najafi.

PhD Jenny Rubin (Q1-Q2 2016).

Drug Discovery and Development Platform vision.

In vitro and systems pharmacology is one of the facilities of the cross-functional SciLifeLab Drug Discovery and Development platform, for more information on the platform and the different facilities see homepage https://www.scilifelab.se/platforms/ddd/. The different facilities work together with an overall aim to help academic projects with validated biological ideas to be able to transform their projects into drug discovery programs, aiming at meeting unmet medical needs

In vitro and systems pharmacology facility focus.

IVSP offers in vitro and systems pharmacology support to drug discovery projects, at all stages of preclinical research. This includes in vitro systemic profiling using multiple readouts, mechanism of action studies, on-target/off-target effects and in vitro therapeutic window of compounds or biologics either as single drugs or in combinations. In addition, the facility offer advice, project management and assay development.

The facility perform studies either in collaboration with Swedish academic groups, in so called full projects after prioritisation by the platform steering committee, or in case of free capacity, as small service projects on a fee for service basis.

Projects at the facility during 2016

The main focus of IVSP during 2016 has been on full project DP_MH_004, aiming at finding a new treatment for neuropathic pain, DP_SL_033 aiming at finding a novel treatment for melanoma, and the technology development project DP_IVSP_002, aiming at developing miniaturised protocols for transcriptomics, proteomics and metabolomics.

The assays have been implemented on several different drug discovery projects.

All projects at our facility are run under confidentiality agreement.

Table 1, full reports delivered by IVSP to projects 2016.

DP_IVSP_002_01	Technology development of experimental-computational methodsfor transcriptomics, proteomics and metabolomics applied to in vitro analysis of drug induced systemic changes
DP_IVSP_002_02	Technology Development of Experimental Protocols For Exploratory Proteomics in 96 well format
DP_IVSP_002_03	L1000 transcriptomics
DP_IVSP_002_04	Technology development of mass spectrometry based in vitro analysis of drug induced changes of the metabolome
DP_EA_057_IVSP_1	Summary of Auranofin mRNA profile from LINCS database.
DP_EA_057_IVSP_2	Systems Pharmacology Analysis of TRi-1, TRi-2 and TRi-3 in MCF7 breast cancer cells
DP_JF_051_IVSP_1	Systems Pharmacology Analysis of Selvita and Senexin B in MCF7 breast cancer cells
DP_UB_068_IVSP_1	Systems Pharmacology Analysis B_A3_11 and B_Q1_56 in MCF7 cells
DP_MF_029_IVSP_01	MB1mRNA profile analyzed using the LINCS database
DP_MF_029_IVSP_02	Systems Pharmacology Analysis of MB1 activity in THP-1 cells
DP_SL_033_IVSP_02	Combination study of DHODH inhibitors and uridine uptake inhibitors, synergistic effects and therapeutic index using melanoma cells and hepatocarcinoma cells
DP_SL_033_IVSP_01	3x3 Combination study of DHODH inhibitors and uridine uptake inhibitors, synergistic effects and therapeutic index using melanoma cells and hepatocarcinoma cells.
DP_SL_033_IVSP_03	Systems Pharmacology proteomics analysis of A77-1726 and UU_BK4304001 in MCF7 breast cancer cells
DP_SL_033_IVSP_04	Systems Pharmacology Analysis A77-1726, UU_BK4304001 and UU_BK4304002 in MCF7 breast cancer cells
DP_MH_004_IVSP_04	Detection of Angiotensin II induced Calcium signalling in cultured rodent cells and transfected CHO-cells

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/

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 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 analysis across the genome. "Next generation" sequencing is applied to 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. In addition to Science for Life Laboratory and VR RFI, the SNP&SEQ Platform is financially supported by the Knut and Alice Wallenberg foundation. The SNP&SEQ Platform also participates in collaborative EU projects, in the FP7 and Horizon 2020 framework programs. As partner in the European Sequencing and Genotyping Infrastructure (ESGI) the SNP&SEQ Technology Platform 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 instruments and 10 sequencing instruments, including 5 HiSeqX instruments for large-scale whole genome sequencing and computer systems for managing and analysis of the large amount of data produced. New technologies implemented during 2016 at the SNP&SEQ Platform are a new SNP genotyping and DNA methylation analysis system (Agena MassArray) for small to medium scale projects, whole-genome bisulfite sequencing for DNA methylation analysis on HiSeqX (Illumina) and single-cell 3'-trancriptome sequencing using the Chromium system (10xGenomics).

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, 45% of the users of the genotyping and sequencing services are affiliated with other Swedish universities and research institutes than Uppsala University. During 2016, 53 genotyping projects including a total of 12,300 DNA samples and 228 sequencing projects of 17,300 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. A remarkable achievement in 2016 was that 2900 whole human genomes were sequenced and the data was delivered to users of the SNP&SEQ Platform. During 2016, in total 509 terabases of sequence data was produced and delivered to the users of the SNP&SEQ Platform. So far the SNP&SEQ Platform has contributed to several hundred publications in respectable scientific journals, of which 178 appeared in 2016. Of the 178 publications that appeared in 2016, as many as 53 were published in journals with an impact factor > 9, including 18 publications in top journals like Science, Nature and Nature Genetics. The large number of publications in high-impact journal illustrates that the services offered by the SNP&SEQ Platform contribute to research of a high international standards in Sweden.

For a complete list of publications and for more information see http://snpseq.medsci.uu.se/

Staff of the SNP&SEQ Technology Platform during 2016

Tomas Axelsson, PhD, head of SNP unit
Ulrika Liljedahl, PhD, head of SEQ unit
Pontus Larsson, PhD, head of bioinformatics unit
Jessica Nordlund, head of R&D
Lars Bäckström, computer systems manager
Sofia Adolfsson, engineer
Susanne Björnerfeldt, PhD, research engineer
Monica Brandt, bioinformatician
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 Hermansson, systems developer
Maria Hägglund, PhD, research engineer
Katarina Jonasson, administrator
Johanna Lagensjö, project coordinator
Kristina Larsson, quality system manager research engineer
Ulrika Liljegren, research engineer
Magnus Lindell, PhD, research engineer
Marie Lindersson, senior research engineer
Heidur Loftsdottir, research engineer
Stephan Lohse, systems administrator
Per Lundmark, PhD, bioinformatician
Johanna Manninen, research engineer
Amanda Raine, PhD, senior research engineer
Jon Ramsell, PhD, laboratory coordinator
Alisa Rizvanovic, research engineer
Karin Sollander, research engineer
Steinar Sturlaugsson, systems developer
Kjell Stålberg, PhD, research engineer
Katarina Tegnér, research engineer
Ann-Christin Wiman, senior research engineer
Ingvar Örn Thorsteinsson, research engineer
Matilda Åslin, bioinformatician
Torbjörn Öst, research engineer
Elin Övernäs, PhD, senior 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 bioinformatics support and develop algorithms for problems that many user face. For more information see the platform home page: http://www.medsci.uu.se/array-och-analysfaciliteteten/

Continued high demand for platform services during 2016

Continued interest in the Axiom platform for flexible genotyping has led to a high total number of analysed samples (2288 in 2016). 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 (20%), Akademiska sjukhuset (29%), other Swedish Universities (53%) and other countries (9%). The platform has a staff of 6 full-time positions. The platform has contributed to 19 publications in high ranking international journals during 2014-2016 (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. We have developed a new bioinformatics tool for raw data processing called Rawcopy that provides data with superior signal-to noise ratio that was published during the year. It can improve DNA copy number analysis both for research and in the clinic.

Future

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

Staff of Array and Analysis Facility during 2016

Hanna Göransson Kultima, Bioinformatician

Malin Rosth, Research engineer

Angleiki Pournara, Research engineer

Rigmor Sjöström, Research engineer

Björn Viklund, Bioinformatic

Publications 2014-2016

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. 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
2. 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.
3. Gillbro JM, Merinville E, Olsson M, Al-Bader T, Klack A, Visdal-Johnsen L, Mavon A. 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.
4. 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.
5. 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.
6. François L, Jäderkvist Fegraeus K, Eriksson S, Andersson LS, Tesfayonas YG, Viluma A, Imsland F, Buys N, Mikko S, Lindgren G, Velie BD. Conformation Traits and Gaits in the Icelandic Horse are Associated with Genetic Variants in Myostatin (MSTN). J Hered. 2016 Sep;107(5):431-7. doi: 10.1093/jhered/esw031. Epub 2016 May 13.
7. Velie BD, Shrestha M, François L, Schurink A, Tesfayonas YG, Stinckens A, Blott S, Ducro BJ, Mikko S, Thomas R, Swinburne JE, Sundqvist M, Eriksson S, Buys N, Lindgren G. Using an Inbred Horse Breed in a High Density Genome-Wide Scan for Genetic Risk Factors of Insect Bite Hypersensitivity (IBH). PLoS One. 2016 Apr 12;11(4):e0152966.
8. Jiang Y, Marinescu VD, Xie Y, Jarvius M, Maturi NP, Haglund C, Olofsson S, Lindberg N, Olofsson T, Leijonmarck C, Hesselager G, Alafuzoff I, Fryknäs M, Larsson R, Nelander S, Uhrbom L. Glioblastoma Cell Malignancy and Drug Sensitivity Are Affected by the Cell of Origin. Cell Rep. 2017 Jan 24;18(4):977-990.

Publications with platform employees as co-authors

1. 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.
2. Hakelius M, Saiepour D, Göransson H, Rubin K, Gerdin B, Nowinski D. Differential Gene Regulation in Fibroblasts in Co-culture with Keratinocytes and Head and Neck SCC Cells. Anticancer Res. 2015 Jun;35(6):3253-65.
3. 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.
4. 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.
5. 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.

6. 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.

7. Watkins J, Weekes D, Shah V, Gazinska P, Joshi S, Sidhu B, Gillett C, Pinder S, Vanoli F, Jasin M, Mayrhofer M, Isaksson A, Cheang MC, Mirza H, Frankum J, Lord CJ, Ashworth A, Vinayak S, Ford JM, Telli ML, Grigoriadis A, Tutt AN. Genomic Complexity Profiling Reveals That HORMAD1 Overexpression Contributes to Homologous Recombination Deficiency in Triple-Negative Breast Cancers. Cancer Discov. 2015 May;5(5):488-505

8. Charles Walther, Markus Mayrhofer, Jenny Nilsson, Jakob Hofvander, Tord Jonson, Nils Mandahl, Ingrid Øra, David Gisselsson and Fredrik Mertens. Genetic heterogeneity in rhabdomyosarcoma revealed by SNP array analysis. Genes, Chromosomes and Cancer, Volume 55, Issue 1, pages 3–15, January 2016.

9. Mayrhofer M, Viklund B, Isaksson A. Rawcopy: Improved copy number analysis with Affymetrix arrays. Sci Rep. 2016 Oct 31;6:36158.

10. Mathot L, Kundu S, Ljungström V, Svedlund J, Moens L, Adlerteg T, Falk-Sörqvist E, Rendo V, Bellomo C, Mayrhofer M, Cortina C, Sundström M, Micke P, Botling J, Isaksson A, Moustakas A, Batlle E, Birgisson H, Glimelius B, Nilsson M, Sjöblom T. Somatic Ephrin Receptor Mutations Are Associated with Metastasis in Primary Colorectal Cancer. Cancer Res. 2017 Jan 20

11. Kalikstad B, Kultima HG, Andersstuen TK, Klungland A, Isaksson A. Gene expression profiles in preterm infants on continuous long-term oxygen therapy suggest reduced oxidative stress-dependent signaling during hypoxia. Mol Med Rep. 2017 Apr;15(4):1513-1526.

Awards and Appointments 2016

Namn på utmärkelse och mottagare, numrerad lista.

1. Göran Gustafsson award in Medicine (UU/KTH) **Tove Fall**
2. Science Slam winner, SciFest, UU **Tove Fall**
3. 3rd prize in SciLifeLab's Scientific Highlight **Tove Fall**
4. The *Ulf von Euler prize in physiology* for studies on the nitrergic regulation of the migrating motor complex in humans, 2016. **Abdul Halim**
5. Elected to the Fellowship of the European Respiratory Society **Eva Lindberg**
6. Uppsala County Research prize, Elected to the position as Chair Elect of the Epidemiology and Occupation Assembly of the European Respiratory Society **Christer Janson**
7. Elected to the position as Chair Elect of the International Association of Breath Research. (2015-2017) **Marianne Högman**
8. Uppsala County Research prize, **Eva Baecklund**