National Molecular Medicine Fellows Program
Stockholm

March 14-15 2018

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Cover image
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Welcome Words

We are delighted to have SciLifeLab Fellows and WCMM Fellows and Associated group leaders taking part in this very first joint meeting within the National Molecular Medicine Fellows Program (NMMP). You are an exclusive group of future leaders in science, selected in an effort to strengthen Swedish Life Science. We really hope that these two days will be valuable and inspiring for you.

The NMMP is a joint venture between SciLifeLab and the four WCMM Centers with the aim to improve scientific networks and collaborations across Sweden. This program will provide you with an arena to get to know and network with colleagues from eight Swedish Universities. The program will also provide you with an opportunity to meet and interact with invited researchers in the field and to get deeper insight into the service and expertise offered by the SciLifeLab research infrastructure.

To spur the networking and leadership coaching activities during the first day, we have engaged certified coaches, Katarina Billing and Birgitta Sahlén, with many years of running leadership and mentor programs in academia. Billing is also the author of the book "Step Towards Trust" on how leaders can create trust and maintain it long-term. Trust is extremely important in research, easy to recognize but difficult to define. Trust may take years to build. As part of the NMMP, you now have a unique opportunity to start building these networks of trust with researchers of the same age and in the same situation as you. This will hopefully facilitate your future activities in academia, especially if you decide to stay in Sweden.

Make your research and voice heard, get inspired by keynote speakers and NMMP peers and together help us shape the life science of tomorrow!

Most welcome!

Olli Kallioniemi & Siv Andersson
SciLifeLab Director & Co-Director
with the support of all WCMM Directors

National Molecular Medicine Fellows Program

Science for Life Laboratory (SciLifeLab) and the Wallenberg Centers for Molecular Medicine (WCMM) in Gothenburg, Linköping, Lund and Umeå have started a collaborative network during 2017 to bring together the future leaders of life science and molecular medicine in Sweden. The collaboration is co-funded by a 9 million SEK grant from the Knut and Alice Wallenberg Foundation. The aim is to promote scientific interactions and technological networking among the more than 100 SciLifeLab and WCMM group leaders that are being recruited to the centers in the coming years. These group leaders have been trained in many of the best universities and laboratories in the world, and represent a major addition of cutting-edge expertise and talent to the Swedish life science sector.

This first NMMP meeting is organized by SciLifeLab and marks the beginning of annual ambulating meetings, giving the opportunity to create a unique and close network across the five sites, with the national life science infrastructures, as well as with the health care regions across the country. A recurring theme will be to highlight the SciLifeLab research infrastructure so that participating group leaders may learn more about the service and expertise that is being offered. The effort also includes co-funding to be distributed equally between the five NMMP members, with the aim to increase interaction and collaboration between WCMM and SciLifeLab.

More than 100 young group leaders are being recruited to Sweden in the next few years to work at the SciLifeLab host universities or at the WCMM Centers. The SciLifeLab fellows program started in 2014 and currently includes 22 group leaders at Karolinska Institutet, KTH Royal Institute of Technology, Stockholm University, Uppsala University, Chalmers University of Technology and Swedish University of Agricultural Sciences and additional fellows are being recruited. The WCMM Centers at the Universities in Gothenburg, Linköping, Lund, and Umeå were initiated during 2015 and have presently recruited some 40 new group leaders all together, and aim to recruit approximately 30 more.

Joint National Effort

SciLifeLab

SciLifeLab (Science for Life Laboratory) is a national center for molecular biosciences. The mission of SciLifeLab is to develop, use and provide cutting-edge technologies and expertise for applications in health and environmental research to all researchers in Sweden. The center is jointly run by four host universities: KTH Royal Institute of Technology, Karolinska Institutet, Stockholm University and Uppsala University; with national facilities present also in Linköping, Lund, Gothenburg and Umeå.

SciLifeLab provides access to frontline life science technologies for the Swedish research ecosystem. The center coordinates an interdisciplinary research community as well as a unique infrastructure of facilities and interacts broadly with health-care, authorities and industry. The ultimate goal is to translate fundamental biological insights into lasting societal benefits. The research community also includes the SciLifeLab Fellows program, a career program aiming at strengthening Swedish research in molecular biosciences and on a long-term perspective lead to societal impact for Sweden. The SciLifeLab Fellows are recruited by one of the host universities; Karolinska Institutet (KI), Royal Institute of Technology (KTH), Stockholm University (SU), Uppsala University (UU).

WCMM

The Wallenberg Centers for Molecular Medicine represents a ten-year and more than 800 million SEK investment from KAW encompassing young scientists from the fields of molecular and translational medicine. This recruitment of fellows and associated clinical fellows, specialists in clinical medicine, builds on the KAW national effort to reposition Sweden as a world-leading science nation. The four WCMMs are located at University of Gothenburg, Linköping University, Lund University and Umeå University. Each center is co-funded by the universities, county councils and industry organizations.

KAW

The Knut and Alice Wallenberg Foundation supports long-term, free basic research beneficial to Sweden, mainly in medicine, technology, and the natural sciences. This is achieved through long-term grants to excellent researchers and to projects. The foundation also initiates grants to strategic projects and scholarship programs.

Programme
14 March

08:15 **Registration, welcome mingle and coffee, Set up of posters.**

09.00 **Welcome and introduction of NMMP**
Siv Andersson, Co-Director SciLifeLab
Göran Sandberg, Executive Director Knut and Alice Wallenberg Foundation

09.15 **NMMP network and centers**
Olli Kallioniemi, Director SciLifeLab
Tommy Olsson, Director WCMM Umeå
Mikael Sigvardsson, Director WCMM Linköping
Göran Landberg, Director WCMTM Göteborg
Freddy Ståhlberg, Director WCMM Lund

09.30 **Perspectives on young group leaders in Sweden**
Karin Dahlman Wright, Pro-Vice-Chancellor Karolinska Institutet

09.40 **Introduction of leadership program and facilitators**
Katarina Billing & Birgitta Sahlén, MiL Institute

09.55 **Fellows in Focus** (**exercise**)
Fellow presentation & interaction – Leadership in academia. Incl. coffee and sandwich

10.25 **Fellows' snapshot**
Mini-lecture on trust – why it matters to researchers and leaders in academia.

10.40 **Short break**

10.55 **Getting to know the SciLifeLab infrastructure**

Introduction to the SciLifeLab infrastructure
Annika Jenmalm Jensen, Infrastructure Director

Drug Discovery platform
Per Arvidsson, Platform Director

Chemical Proteomics & Proteogenomics
Maria Pernemalm, Head of Facility

National Genomics Infrastructure
Ellen Sherwood, Head of Facility

National Bioinformatics Infrastructure
Pär Engström, Head of Facility

Genomic Medicine Sweden & Diagnostics Development platform
Richard Rosenquist Brandell, Platform Director

12.00 **How to be a killer networker** (**exercise**)

12.30 **Lunch mingle & Poster session**

14.20 **The Fellow´s leadership challenges** (**exercise**)
Group discussions on leadership challenges fellows are facing, addressing research leadership. Incl. coffee break.

16.30 **Short break**

16.45 **Do's and Don'ts as a research leader**
My journey by Tuuli Lappalainen, New York Genome Center & Columbia University and Leroy Hood, Institute of Systems Biology

17.30 **Collaborative exercise**

18.00 **Wrap up of the day**

18.15 **Mingle & Poster session**
Incl. refreshments

19.00 **Dinner**

15 March

08.15 **Registration and Coffee**
09.00 **Welcome and introduction**
Olli Kallioniemi, Director SciLifeLab
09.15 **Functional Variation in the Human Genome: Lessons from the Transcriptome**
Tuuli Lappalainen, New York Genome Center & Columbia University
10.15 **Coffee break**
10.45 **Presentations from the WCMTM Gothenburg Fellows/Associated group leaders**
From bioinformatics to clinical translations on type 2 diabetes
Anders Rosengren, WCMTM Gothenburg
Neural circuitry regulating appetite and body weight: mind the sex gap
Karolina Skibicka, WCMTM Gothenburg
11.15 **Presentations from the WCMM Lund Fellows/Associated group leaders**
DCD Lung transplantation – the final solution to organ shortage
Sandra Lindstedt Ingemansson, WCMM Lund
Bioengineering new lungs for transplantation: mission impossible or a whole new world?
Darcy Wagner, WCMM Lund
11.45 **Presentations from the WCMM Umeå Fellows/Associated group leaders**
From material science to virology: Unraveling the molecular mechanisms of virus-membrane interactions using biomimetic systems
Marta Bally, WCMM Umeå
Targeting tumor-stromal interactions in pancreatic cancer
Daniel Öhlund, WCMM Umeå
12.15 **Lunch & Poster session**
13.45 **Presentations from the WCMM Linköping Fellows/Associated group leaders**
Cell signaling in inflammatory bowel diseases
Stefan Koch, WCMM Linköping
Harnessing nuclease biology for the development of diagnostic approaches
Frank Hernandez, WCMM Linköping
14.15 **Presentations from the SciLifeLab Fellows**
The use of Systems Biology in Gastroenterology and Hepatology
Adil Mardinoglu, KTH/SciLifeLab
Genomic and epigenomic studies in the Estonian Biobank
Lili Milani, Uppsala University/SciLifeLab
14.45 **Coffee break**
15.15 **21st Century Medicine Will Transform Healthcare**
Leroy Hood, Institute of Systems Biology
16.15 **Closing words**
Olli Kallioniemi, Director SciLifeLab
16.20 **Mingle**
17.00 **End**

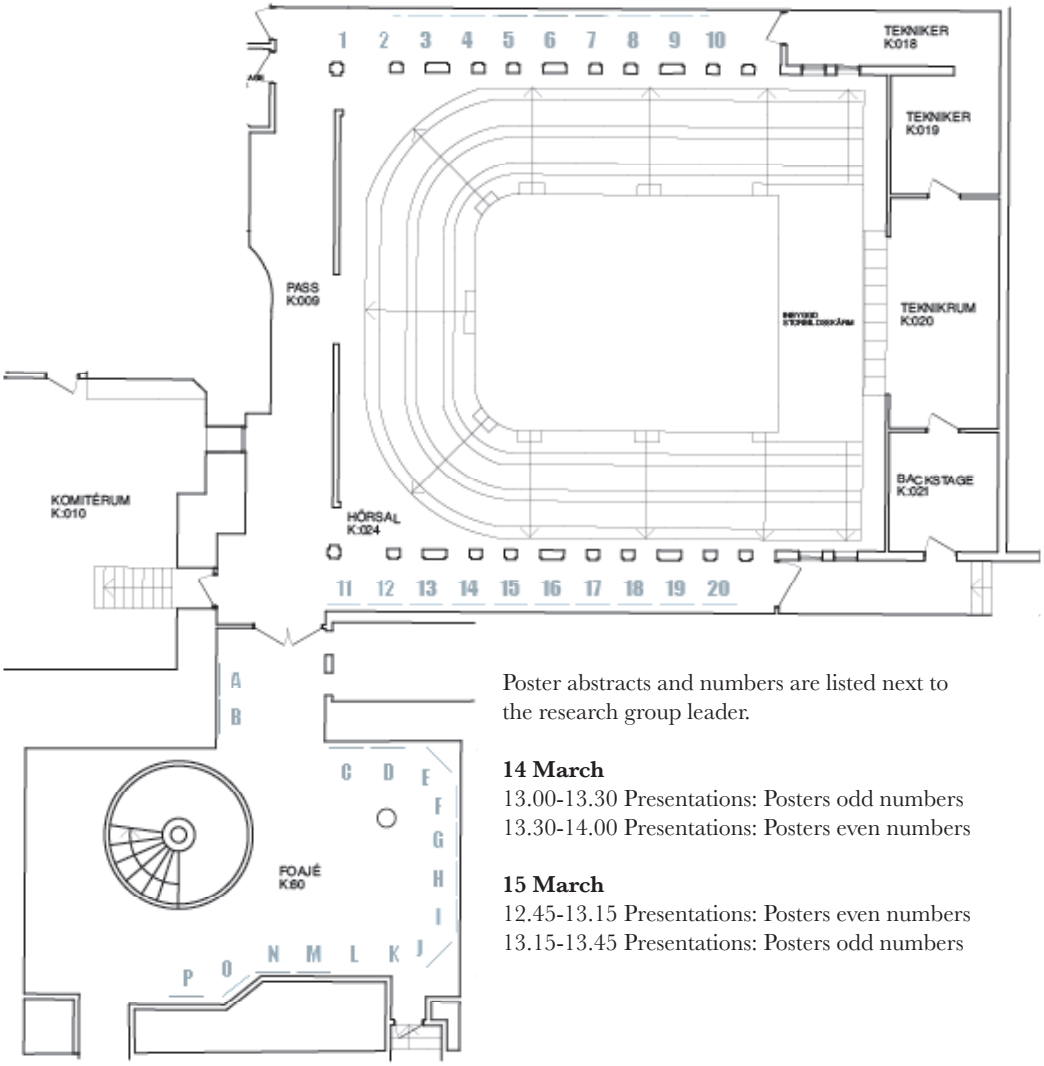
Keynote speakers

Leroy Hood, pioneer of systems biology and the president and co-funder of Institute of Systems Biology in Seattle

Tuuli Lappalainen, Assistant Professor in the Department of Systems Biology at Columbia University and a Junior Investigator and Core Member at the New York Genome Center

Poster Exhibition

Wallenberg Hall, Floor -1



Poster abstracts and numbers are listed next to the research group leader.

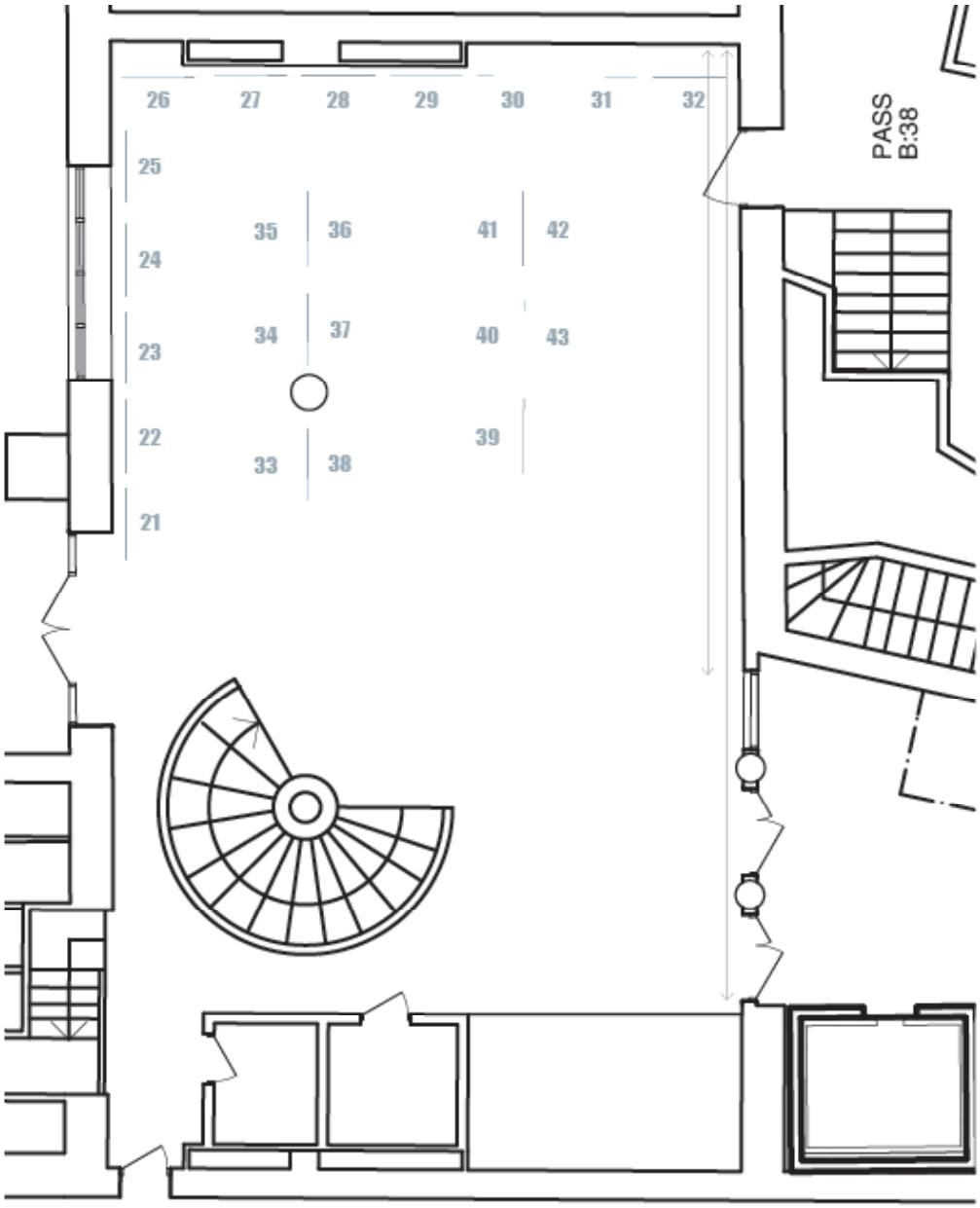
14 March
13.00-13.30 Presentations: Posters odd numbers
13.30-14.00 Presentations: Posters even numbers

15 March
12.45-13.15 Presentations: Posters even numbers
13.15-13.45 Presentations: Posters odd numbers

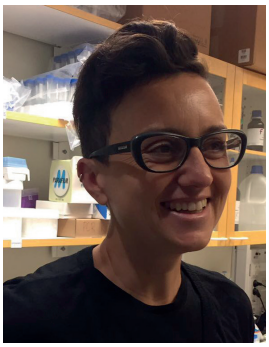
Facilities

A	DDD platform
B	Human Antibody Therapeutics
C	Chemical Proteomics & Proteogenomics
D	Chemical Biology Consortium Sweden
E	Advanced Light Microscopy
F	PLA Proteomics
G	BioImage Informatics
H	High Throughput Genome Engineering
I	Single Cell Proteomics and Microbial Single Cell Genomics
J	Swedish NMR Centre, Umeå
K	Swedish NMR Centre, Gothenburg
L	National Mass Cytometry Facility, Stockholm
M	National Mass Cytometry Facility, Linköping
M	Cell Profiling
N	National Genomics Infrastructure (NGI)
O	Clincial Biomarkers
P	Bioinformatics (NBIS)

Foyer, Ground Floor



Fellow Presentations



Francesca Aguilo

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Area of interest

RNA-based gene regulation of cell fate and breast cancer

Our main interest is to decipher novel epigenetic and epitranscriptomic mechanisms affecting global gene expression and their implication in cell fate and cancer initiation and progression with a focus on breast cancer.

Following the completion of two postdoctoral trainings in epigenetics and stem cell biology at Icahn School of Medicine at Mount Sinai (New York), I joined the WCMM at Umeå University with the aim to elucidate the function of RNA modification, specifically adenosine methylation, and their crosstalk with other epigenetic marks, using stem cells and breast cancer cells, as physiological and pathological models.

RNA is not only an essential intermediate in the flux of genetic information from DNA to proteins, but rather a molecule that plays crucial roles in the regulation of fundamental cellular processes. Importantly, the dysregulation of certain RNAs has been shown to be implicated in numerous pathological processes, including cancer. The transcriptome is reversibly and dynamically regulated by chemical modifications, adding a new layer of complexity and functionality to the emerging roles of RNAs in health and disease. The impact of these modifications has recently begun to be explored within a new field of study: 'Epitranscriptomics'. Providing a new level of knowledge on the interplay between epigenetic and RNA modifications is a requisite for the development of novel promising therapeutic compounds for use in breast cancer patients.

I have extensive collaborators both at international and national level. Moreover, the Aguilo's lab is part of EpiCoN (Epigenetic Cooperation Norrland), an initiative which carries out internationally competitive epigenetics research and aims to promote the public awareness of epigenetics in Northern Sweden. We also participate in the RNA Society of Sweden in order to increase the communication and collaboration between scientist and students in the field of RNA biology in Sweden.

Strengths in lab

We combine classical biochemical methods with state-of-the-art genome-wide sequencing and proteomic techniques to interrogate the role of RNAs modifications and the interplay with other epigenetic marks in stem and cancer cells. 2D and 3D cell culture models, patient samples, as well as mouse orthotropic transplantation are also used to study the central RNA-based regulatory circuitry in breast tumorigenesis.

LSD1: Role in mouse embryonic stem cell pluripotency or differentiation

Sandhya Malla[1,2] & Francesca Aguilo[1,2]
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[2]Department of Medical Biosciences, Umeå University, Umeå, Sweden

Abstract
Investigating the role of histone modifications and histone modifier enzymes in embryonic stem cells (ESCs) and during differentiation is crucial to understand the basis of pluripotency and development. Lysine-specific demethylase 1 (LSD1, also known as KDM1, AOF2) is a demethylase that specifically removes mono and di -methyl group from H3K4 and H3K9. LSD1 is a component of several complexes, including CoREST, and the histone deacetylase enzymes HDAC1 and HDAC2. Genetic studies in multiple model systems have shown that LSD1 is an important player in developmental processes. However, contradictory roles for LSD1 in ESCs have been reported: some studies highlighted the importance of LSD1 in the maintenance of pluripotency whereas others in normal differentiation. Therefore, to understand the role of the LSD1 in ESC we have generated LSD1 KO ESCs by using CRISPR/Cas9 technology. Loss of LSD1 is associated with decreased in cellular proliferation, increased apoptosis and loss of alkaline phosphatase staining, suggesting that LSD1 plays a central role in the maintenance of pluripotency. Furthermore, LSD1 KO ESCs fail to maintain the global levels of DNA methylation as previously suggested by others. We are currently performing RNA sequencing, DNA and RNA methylation analysis in order to elucidate the central molecular mechanism by which LSD1 controls ESC maintenance.

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Area of interest

Electron cryo-microscopy visualisation of macromolecules

Our research group investigates the fundamental question of how proteins are synthesized, folded and assembled into functional multicomponent membrane complexes that drive the cellular energy production. Living cells ultimately depend on the conversion of energy derived from foodstuff and light into the chemical form of energy. This crucial bioenergetic step is performed in the specialized membrane systems of mitochondria and chloroplasts. Each one of these organelle types developed dedicated ribosomes that have diverged from the cytoplasmic counterparts. While mitoribosomes synthesize proteins involved in oxidative phosphorylation, chlororibosomes produce components driving the pohotosynthetic reactions through pigment-protein units. To dissect the mechanism and dynamics of translation, membrane insertion and bioenergetics in organelles, we use cryo-EM.

Strengths in lab

Our group determined cryo-EM structures of the human mitoribosome with mRNA, tRNAs and translation activators in 8 different functional states, as well as its assembly intermediates. It revealed unique mechanisms of mRNA binding, tRNA translocation and assembly regulation. We also determined structures of the chlororibosome with translation factors that revealed divarication of the exit tunnel and experimental evidence for convergent evolution of ribosomes from chloroplasts and mitochondria. This work showed that the translation mechanisms have adopted intricate compositions and unique tasks in organelles, which adds incredible complexity to the records. The understanding of the architecture of these specialized ribosomes provides now a framework to study the mechanisms and evolution of the synthesis of macromolecular complexes in the critical bioenergetic membranes.

Marta Bally

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Area of interest

Virus-membrane interactions

Marta Bally's interdisciplinary approach bridges medical sciences, engineering, and physics to study the mechanisms governing the interactions between cell surfaces and biological nanoparticles (e.g., viruses, drug delivery vehicles, and extracellular vesicles).

With a background in engineering and a fascination for fundamental biology, I strive to take advantage of my expertise in the development of bioanalytical assays as well as enthusiasm for translational research to investigate the mechanisms by which biological nanoparticles interact with the cell surface. To address such questions, my group adopts a multidisciplinary approach based on the use of in vitro cell-surface mimics of various complexities and on live-cell microscopy. By combining platforms which span the spectrum, in terms of control and complexity, our aim is to elucidate interaction mechanisms occurring at the cell membrane that have failed to be understood previously.
My current main research focus is centered on elucidating the interactions between viruses and the cell surface; in particular, I study the mechanisms modulating binding and release of Herpes Simplex Viruses from cell-surface carbohydrates. Other activities include the design of new liposome-based vaccine vectors, the development of bioanalytical assays to detect, sort, and characterize biological nanoparticles, as well as the development of platforms for testing anti-viral drugs.

Strengths in lab

As a complement to traditional cell studies used in the field of virology, our group develops surface-based assays in combination with advanced microscopy techniques. We work with minimal models of the cell membrane (cell-membrane mimics), to study processes occurring at the cell surface in a highly controlled manner. Cell-surface mimics are model systems whose composition can be fine-tuned to study specific interactions occurring at the cell surface with great precision and accessibility by many surface-sensitive analytical techniques. Using total internal reflection fluorescence (TIRF) microscopy, we analyze the binding kinetics and diffusion behavior of virus particles at the single particle level.
As a complement to cell-membrane mimics, we plan to add single particle tracking in live-cell microscopy experiments to our assay portfolio. Live-cell microscopy allows for interactions to be investigated within the complex milieu of natural components and provide physiological feedback on interactions taking place at the cell surface.
We also have a track-record in studying biomolecular interactions with surface-based analytical methods such as the Quartz Crystal Microbalance and Surface Plasmon Resonance.
Finally, we develop and implement methods to characterize biological nanoparticles at the single particle level in order to study heterogeneities in virus or extracellular vesicle populations. In this context, we have recently developed a microfluidic tool working as a nano- flow cytometer which allows for the fluorescence based detection, quantification, and characterization of biological nanoparticles.

Biophysical studies of the mechanisms modulating the interaction between Herpes Simplex Viruses and cell-surface carbohydrates

Many enveloped viruses, including HSV, attach to susceptible host cells via interaction between their glycoproteins and cell-surface glycosaminoglycans (GAGs). This initial recognition is crucial in the viruses' life cycle as it leads to infection. Of equal importance, is also the capability of the virus to overcome these interactions upon egress to ensure its propagation.

In our work, we study the molecular and physical mechanisms modulating HSV binding and release from the cell surface. Our approach is primarily based on the use of cell-membrane mimics of various complexities: A minimal model of the cell's carbohydrate coat based on the end-on immobilization of GAG chains makes it possible to study the details of virus-GAG interactions; a molecularly complete model constructed from plasma membrane material allows for a more comprehensive study, taking into account all biomolecules involved. Analysis of the binding behavior of individual virions with TIRF microscopy makes it possible to characterize affinities and diffusion coefficients of surface-bound viruses on a single virion level. With our in vitro assays, we gain insight into the modulatory function of protein glycosylation and interrogate the role of GAG sulfation in the process: We show that mucin-like regions found on the glycoproteins of HSV play an important role in modulating the interaction, an observation further supported by cell experiments. We further show that the diffusion of virions on the surface depends on the type of GAGs and their degree of sulfation.

Our research contributes to a better understanding of the mechanisms governing virus-cell interactions, thereby facilitating the design of more efficient antiviral drugs.

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Photo: Stefan Zimmerman

Magda Bienko

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Area of interest

Genome organization and its interplay with gene expression

My lab combines microscopy with sequencing to cast new light on how is the human genome arranged in the space of the nucleus, and in turn how does this 3D architecture affect gene expression.

It is well established that, inside the human cell nucleus, chromatin is spatially organized in a non-random manner that is believed to have profound consequences on how genetic information is read. In the case of human DNA, a two-meter long molecule is compressed into a volume whose linear size is five orders of magnitude smaller. How is this extreme compaction repeatedly enforced in different cell types? What is the degree of structural variability from cell to cell? What are the functional implications of this complex architecture?

These questions are the main focus of my Lab for Quantitative Biology of the Nucleus. The lab builds upon powerful methods for in situ quantification of DNA and RNA molecules, and integrates them with newly developed genomic assays to measure chromosome positioning, epigenetic states, and gene expression in a high-throughput fashion. We are combining technology development and experimental work with mathematical modeling and quantitative analyses to cast light on the fascinating question of how is human genome arranged in 3D. The projects in the lab range from quantitative assessment of chromosomal sketches and chromosomal intermingling, studying the relationship between local DNA topology and gene expression bursting, developing new method to probe structures of enhancer-promoter loops, to mapping radial positioning of DNA loci genome-wide.

I have been awarded the Swedish Research Council grant in 2015, Career Development Award by HFSP in 2016, the ERC Starting Grant in 2016, and was appointed a Ragnar Söderberg Fellow in Medicine 2016.

Strengths in lab

Our lab relies on single-cell resolution provided by microscopy and high-throughput power given by next-generation technologies. We are using FISH to visualize single RNA molecules as well as DNA loci at a sub-diffraction limit. We are building a large repertoire of pipelines in order to increase the throughput of the FISH technique by generating new databases of probes, creating streamlined protocols for fast production of probes, as well as building analysis suites. These efforts are there to visualize hundreds of DNA loci simultaneously in an unambiguous manner. In parallel, we are developing novel sequencing approaches, which can be used for a broad range of applications.

Charting chromosome architecture at high resolution in single cells

Eleni Gelali, Gabriele Girelli, Joaquin Custodio, Erik Wernersson, Ana Mota, Xinge Li, Silvano Garnerone, Nicola Crosetto, Magda Bienko,
Science for Life Laboratory, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

In interphase human nuclei, 46 chromosomes of different length are tightly packed in discrete domains known as chromosome territories. Understanding how this spatial organization is achieved and how much it is deterministic or stochastic are key questions.

Here, we describe high-throughput, high-resolution DNA FISH (highFISH) to accurately map the three-dimensional position and topology of chromosome territories in hundreds of single cells. We generated >300 highFISH probes covering all human autosomes and the X chromosome. Using these probes, we are detecting individual chromosomes either by targeting multiple loci simultaneously or by visualizing selected landmark loci. We observe very high cell-to-cell variability both in the radial position of the tested loci as well in the 3D arrangement of loci belonging to the same chromosome. We are investigating how different cellular features (e.g., nuclear volume, cell cycle phase, ploidy) contribute to the observed cell-to-cell variability. highFISH is a powerful method to study genome architecture in single cells.

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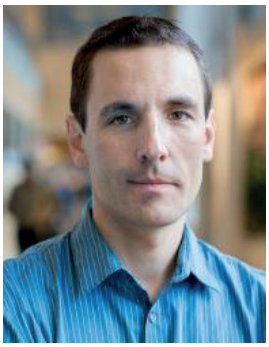

Jeremie Boucher

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Area of interest

Type 2 diabetes and Obesity

Jeremie Boucher, PhD, is a group leader of bench-to-bedside projects focused on finding new targets for the treatment of metabolic diseases

He is a Principal Scientist at AstraZeneca, coordinating and driving early drug discovery programs for the treatment of type 2 diabetes. He also leads a research group at Gothenburg University, focusing on adipose tissue biology, and characterizing the molecular pathways controlling the development, differentiation and function of white, beige and brown adipose cells. In particular, he is investigating white-to-brown adipocyte phenotypic conversion and the role that the transcription factor PPARγ plays in that process, through canonical and non-canonical mechanisms.

Jeremie Boucher has extensive international collaborations with researchers from Harvard Medical School, University of Pennsylvania, University of Virginia, University of Campinas, INSERM, the Novo Nordisk Foundation Center for Basic Metabolic Research, and the Integrated Cardio Metabolic Centre/Karolinska Institute.

Strengths in lab

The Boucher lab has both in vitro and in vivo capabilities: the lab has developed expertise in mouse, non human primate and human preadipocyte and adipocyte culture methods. It employs a combination of molecular biology techniques and functional assays such as lipolysis, glucose uptake, and glucose and fatty acid oxidation. In vivo, obese, insulin resistant, diabetic and NASH mouse and rat models are routinely used. Metabolic status of animals is analyzed by GTT, ITT, CLAMS, clamp and metabolic tracer studies.

Identification of small molecules converting human white into brown adipocytes

Converting white into brown-like adipocytes that express high levels of UCP1 with increased oxidative and energy wasting capacity is a promising therapeutic strategy to treat insulin resistance and type 2 diabetes. We developed a phenotypic screen using human preadipocytes isolated from subcutaneous fat to identify small molecules that increase UCP1 expression and function, and induce the "browning" of white adipocytes. Preadipocytes were differentiated for up to 15 days in the presence or absence of compounds and UCP1 mRNA levels were measured. From the ~3000 small molecules tested, covering more than a thousand targets, the strongest UCP1 inducers were found to be PPARγ modulators. They robustly induced UCP1 mRNA and protein, which co-localized with mitochondria. UCP1 was functional, as β-adrenergic/free fatty acid or retinoic acid treatment increased stimulated uncoupled respiration in compound-treated cells, which correlated with UCP1 content. The small-molecule UCP1 inducers also induced other brown/beige fat markers such as Dio2, PGC1α, PRDM16 and TMEM26, indicating a conversion of white adipocytes to a brown-like phenotype. Classical PPARγ agonists such as rosiglitazone, currently among the most robust UCP1 inducers in cultured primary adipocytes, induced UCP1 levels to a much lower extent than our current best compounds. UCP1 levels in compound treated human adipocytes reached levels close to UCP1 levels in mouse or non-human primate brown fat. Thus, the identification of compounds able to induce a robust white to brown adipocyte phenotypic switch in human cells opens up the possibility to develop new pharmacological treatments for type 2 diabetes and obesity.

Paul Bourgine

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Area of interest

Human skeletal and hematopoietic regeneration

Bone is a complex organ offering structural and mechanical support of our body, but also consisting in our principal hematopoietic center. During development and repair, bones pre-dominantly form through the endochondral ossification route. This involves the condensation of mesenchymal cells, forming a cartilage tissue progressively vascularized and remodeled into a mature Bone Organ, hosting functional hematopoiesis.

The timely cellular and molecular mechanisms occurring throughout Bone Organ formation remain elusive. These include the distinct and successive stages of cartilage, vasculature, bone and hematopoiesis establishment. Compiling human-specific knowledge on these processes may have tremendous applications in regenerative medicine, toward the development of innovative therapies for skeletal and hematopoiesis tissues repair.

My lab will aim at deciphering the mechanisms driving human bone and bone marrow formation to establish repair strategies. Toward this objective, we developed robust 3D in vitro and in vivo systems capable of recapitulating the tissue stages of human Bone Organ formation. These biotechnological platforms were primarily designed for skeletal repair but can also be exploited for the study/regeneration of the hematopoietic tissue. Together with the manipulation of dedicated human mesenchymal lines, these models will allow gaining considerable fundamental knowledge on human bone and bone marrow biology, for translational applications. Ultimately, we target the design of cell-free biological matrices molecularly customized in composition, as grafts capable to instruct tissue regeneration.

Keywords: cartilage, bone, human hematopoiesis, 3D culture systems, mesenchymal cells, biomaterial, tissue engineering, extracellular matrices.

Strengths in lab

- 3D culture systems
- Death-inducible cell lines
- Engineering of biological extracellular matrices
- Cartilage and bone tissue generation
- In vitro and In vivo engineering of human hematopoietic niches

Bone as an Organ system
Study of processes involved in Bone formation for design of regenerative therapies
In vitro model
Perfusion bioreactor
Cord blood
scaffolds
hMSC
Generation of human bone grafts and hematopoietic models in 3D perfusion-based bioreactor
mesenchyma cells
HSC
blood cells
bone
In vivo model
Cord blood
Hypertrophic Cartilage
NSG
hMSC in vitro
Humanized Ossicle
Lamin Venus DAPI
400µm
Engineering of humanized ossicles, as developmental model of bone and bone marrow formation.
Design of regenerative therapies
5

Fabien Burki

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Area of interest

Deep evolution of eukaryotes

Dr. Fabien Burki pioneers the approach of phylogenomics to integrate in global evolutionary models the poorly studied protists. These microbial eukaryotes, often single-celled, have dominated the Earth since the origin of complex life, but very few species are in culture and so have mostly remained enigmatic. Using a combination of novel culture-independent genomic methods, Dr. Burki explores the microbial dark matter to bridge evolutionary gaps in our understanding of the deep eukaryote evolution.

In my group, we are primarily interested in fitting the origin and evolutionary history of eukaryotes into a global phylogenomic framework. To do so, we reconstruct the deep nodes in the tree of eukaryotes and map onto this tree some of the most transformative lifestyle transitions in the evolution of complex cells, such as the origin and spread of plastids or transition to parasitism.

All of these lifestyle transitions have occurred repeatedly across the tree, but because we are missing key evolutionary lineages our understanding is patchy. Thus, we combine traditional protistology to novel culture-free transcriptomics, genomics, and bioinformatics to identify unknown or orphan groups that represent missing evolutionary links. We then use the genome information of these cells to reconstruct the history of life and the ancestral characteristics of the major eukaryotic groups.

We focus on the timing of plastid acquisitions, which have turned heterotrophic behaviors into autotrophs, and the transition to parasitism and associated reductive evolution of mitochondria in an enigmatic group of protist pathogens of marine invertebrates.

Strengths in lab

We are a computational and experimental lab. We develop phylogenomic pipelines that combine genome data and phylogenetic principles. We have strong expertise in single-cell genomics and transcriptomics. We are also developing methods to better assess the diversity using long-read high-throughput sequencing. Lately, we have acquired a micromanipulator to precisely isolate from environmental samples minute eukaryotic cells (<5µm).

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Area of interest

Structural Biology of Protein Quality Control and Transcription-associated Processes

Dr. Björn Burmann, Associate Senior Lecturer (Assistant Professor) in Chemistry oriented towards life science, investigates macromolecular protein machines by high-resolution Nuclear Magnetic Resonance (NMR) underlying essential cellular functions, e.g. protein quality control and DNA-repair processes.

I aim to elucidate their respective function at the atomic level in order to understand their dysfunction underlying several neurodegenerative diseases and cancer-types. My group studies these large molecular protein complexes (~500–800 kDa) by sophisticated NMR-methods, to be able to derive structural and dynamical adaptions of these complexes at the atomic level in solution. These NMR-studies are complemented and combined with additional information from other structural biology and biophysical methods.

These integrated structural biology approaches are used to understand the possible allosteric mechanism of these proteins and their respective complexes underlying their functionality. This knowledge will be used to understand the effect of disease-related mutations and for the subsequent design of either antibiotics or drugs.

I have the privilege of extensive international collaborations, which currently include researchers from Columbia University, New York University, University of Orléans, ETH Zurich, and Technical University Munich, in addition to multiple active local collaborative projects.

I was appointed a Wallenberg Academy Fellow in 2017. In addition, I have also been awarded the Anatole Abragam Price for a Young Investigator in 2017 for his pioneering contributions to the determination of structure and dynamics of chaperone-client complexes at atomic resolution by solution NMR.

Strengths in lab

My lab has extensive experience in expressing, specific isotope-labeling, and purification of a wide range of different proteins and nucleic acids, which we subsequently study by a wide range of biophysical methods. Besides our main technique, high-resolution advanced NMR-spectroscopy, we also study our complexes with biophysical methods like SEC-MALLS, Bio-Layer Interferometry and CD-Spectroscopy, which we also combine with bioinformatics methods.

The functional basis for α-Synuclein regulation by molecular chaperones in mammalian cells

Neurodegeneration in Parkinson's disease is correlated with the occurrence of Lewy bodies, intracellular aggregates containing the intrinsically disordered protein α-Synuclein. Thereby, the aggregation propensity of α-Synuclein is significantly modulated by specific cellular factors including oxidative stress and posttranslational modifications. Interactions with cellular proteins that regulate the molecular conformations of α-Synuclein can thus control outbreak and progress of the disease. In particular, some molecular chaperones have been shown to modulate α-Synuclein aggregation in vitro, but the underlying mechanisms are unclear. Here, we characterize the interaction mechanism of molecular chaperones on α-Synuclein at the atomic level. We find that six different molecular chaperones with substantially differing architectures commonly recognize a canonical motif consisting of the α-Synuclein amino-terminus together with a segment around Tyr39, hindering its aggregation. In-cell NMR-experiments show unambiguously that this chaperone-specific interaction pattern is preserved inside living mammalian cells and is not due to transient membrane interactions as described recently. Furthermore, specific inhibition of the chaperone interaction by targeted knockdown of the chaperones Hsc70 and Hsp90 triggers localization of α-Synuclein to membranes and concomitant aggregate formation. Methionine oxidation and phosphorylation of α-Synuclein directly impair the interaction with chaperones, thus providing a mechanistic rationale for these risk factors of Parkinson's disease and a functional explanation for the role of Abelson kinase in Parkinson's disease progression. Our results establish molecular chaperones as a master regulator of α-Synuclein in healthy mammalian cells in line with a plethora of experimental observations. This regulatory role extends the functional repertoire of molecular chaperones and opens new mechanistic perspectives for therapeutic approaches to Parkinson's disease.

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Area of interest

Therapeutic potential of immunomodulation in cardiometabolic pathophysiology

My lab is a translational research team, investigating the underlying disease mechanisms of obesity and cardiometabolic disease, with a special interest in inflammatory resolution. We investigate the therapeutic potential of immunomodulation in obesity-related cardiometabolic pathophysiology, aiming to identify the underlying cause of metabolic disease and a more effective treatment targeting the inflammation that underlies pathophysiology.

Inflammation is a key driver of obesity-induced cardiometabolic pathophysiology and consists of two phases: an initial acute phase followed by a resolving phase. The latter is actively regulated by specialized pro-resolving lipid mediators (SPMs). Lipoxins are one group of SPMs that act through defined receptors to promote the resolution of inflammation.

The overall aim of our research is to investigate and harness the therapeutic potential of lipoxins. Our previous studies suggest that treatment with lipoxins attenuates obesity-induced adipose inflammation and subsequent development of systemic disease (Börgeson et al, Cell Metabolism, 2015). The lab is currently investigating the underlying molecular mechanisms that mediate this protection, and whether the results from preclinical models can be translated to human pathophysiology. We are also attempting to identify novel inflammatory and cardiometabolic fingerprints and biomarkers that characterize metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) patient phenotypes.

Strengths in lab

My research team combines experimental studies with clinical basic research to address hypothesis in a translational manner. We primarily utilize ex vivo cultures of patient tissue biopsies (e.g. adipose and intestine explants), which provides valuable "proof-of-principle" models which allows us to correlate experimental data with human physiology. As experimental "readouts" we use standard molecular biology techniques (digital droplet PCR, western blot, immunohistochemistry, immunofluorescence, ELISA etc.) and extensive flow cytometry characterization of leukocyte phenotype and number.

Comprehensive lipidome and proteome analyses to identify the inflammatory and cardiometabolic fingerprints of metabolically "healthy" versus "unhealthy" obese subjects

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Study Objective

Obesity-related co-morbidities pose a serious health care system burden. However, 30% of obese subjects do not present with cardiometabolic complications. Here we perform comprehensive lipidome and proteome analyses to identify inflammatory and cardiometabolic fingerprints that characterize metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) phenotypes.

Methods

Obese patients (BMI 35-50) donated plasma before undergoing bariatric surgery (clinicaltrial.gov NCT02322073). Patients were classified as MHO (n=5) versus MUO (n=9) according to International Diabetes Federation criteria. Metabolically healthy lean (MHL, n=14) subjects were age- and sex-matched to the obese cohort. Plasma samples were analyzed for 480 protein biomarkers related to inflammation and cardiometabolic processes in a multiplexed array. Samples were also subjected to untargeted lipidomics and targeted oxylipin lipidomics analyses.

Results

Gene-ontology term analysis of the 15 proteins that were significantly decreased/elevated in MHO vs. MUO patients revealed differences in inflammation, metabolism, apoptosis and fibrosis signaling pathways. Furthermore, lipidomics show distinct differences in the lipid profile of MHO and MUO groups. The MUO group displayed increased levels of ceramides, which are implicated in development of insulin resistance and cardiovascular diseases. In contrast, the MHO group exhibited increased levels of anandamide and dihomo-gamma-linolenoyl ethanolamide, which are lipids associated with anti-inflammatory effects. The MUO group also exhibited elevated levels of the cardiometabolic risk factor plasminogen activator inhibitor 1 (PAI-1). Interestingly, MHO patients presented with increased levels of myeloblastin, which is a serine protease that degrades the PAI-1–stabilizing protein vitronectin.

Conclusion

In conclusion, we have performed a comprehensive lipidomic and proteomic fingerprinting of MHO and MUO subjects. Our analyses reveal clear stratification of the groups and identify lipid mediators that may be of possible therapeutic use as novel interventions for obesity-associated pathophysiologies. Work is ongoing to explore the molecular mechanism by which the identified proteins and lipid mediators affect cardiometabolic health in obese patients.

Acknowledgements

The Börgeson laboratory is supported by the Knut & Alice Wallenberg Foundation, Wallenberg Centre for Molecular and Translational Medicine, the Swedish Research Council, (no. 2016/82), the Swedish Society for Medical Research (no. S150086), Åke Wiberg's Foundation (no. M15-0058) and Konrad and Helfrid Johansson's foundation. The lipidomics analysis were supported by a National Institute of Health Pilot award (Lange & Börgeson, #DK097154) at the Westcoast Metabolomics Center, UC Davis, USA.

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Area of interest

Gene Regulation Downstream of Signaling Pathways

My main ambition is to understand how genes are regulated, spatially and over time, to ensure animal development. Gene regulation is the first and primary agent determining cell, tissue and organ identity.

Our current knowledge comprises a mechanistic understanding of many factors involved in this process; however, several fundamental questions remain to be answered. How, for example, can the relatively small number of known signaling cascades impose the countless amount of cell types existing in a human body? Why most of the known Transcription Factors, the final effectors of signaling cascades, are still "orphans" for the signal that initiates their activity? What events determine the combinatorial activity of Transcription Factors that can explain cell differentiation in one direction or the other? What is the ensemble of biochemical consequences on the chromatin structure the follows the activity of Transcription Factors, and precedes gene activation or repression?

My research will try to contribute in understanding these phenomena. To do so, I will use the mouse as model organism, and focus on the activity, during embryonic development, of the combined action of signaling pathways and their effectors, Transcription Factors.

Because cell identity is of central importance for the correct functioning of tissue and organs (e.g. in the balance between proliferation and differentiation), a precise understanding of how gene regulation is achieved will shed light on our comprehension of human disease, including cancer and developmental malformations. A central theme of the work plan is, in fact, to directly connect the acquired knowledge to human pathologies in which gene regulation mechanisms are perturbed.

Strengths in lab

The main expertise of the lab includes mouse genetics, in vivo and in vitro genome engineering, gene expression profiling, protein-protein interaction studies, chromatin analyses, and genome-wide protein-DNA interaction studies (Chromatin ImmunoPrecipitation followed by deep sequencing). In addition, we employ histological analyses, tissue and cell staining techniques, and standard molecular and cell biology methods.

Redefining Signaling Pathways

Signaling pathways orchestrate the development of multicellular organisms, instructing cells in committing to specific differentiation programs. Most pathways' components have been historically discovered by their epistatic effects. Therefore, it is widely accepted that signaling pathways are conserved linear series of molecular events, irrespective of the cell-type in which they are triggered. However, a growing body of evidence indicates that this might be a simplistic view. Among the signaling cascades, the Wnt pathway is fundamental in virtually all aspects of embryonic development, and its deregulation causes human malformations and cancer. It came as a great surprise from our studies that, even in the so-called canonical Wnt signaling, supposedly constitutive components are required in a tissue-specific fashion, and the way in which this pathway is transduced in a transcriptional output depends on the context. This supports the notion that different cells possess alternative molecular machineries to respond to extracellular signals. I hypothesize that, scaffolded by some key preserved features, signaling pathways are complex tissue- or cell-specific entities, and how a cell responds to extracellular signals depends on the specific nature of that cell. I am therefore determined to investigate the possibility that mechanistically different responses to extracellular ligands could drive the wide range of differentiation fates necessary to develop complex tissues and organs. To do so, I will exploit mutant mouse strains bearing specific domain deletions in *Ctnnb1* (the gene encoding for β-catenin), and in genes encoding for the β-catenin cofactors Bcl9 and Pygo. These will allow me to perform sophisticated in vivo genetic experiments, which will be complemented by high-throughput biochemical approaches and ex vivo culture systems. This project will contribute in responding to long-standing questions in the field, such as how can the Wnt signaling drive a variety of tissue-specific, often apparently contradicting, responses in different contexts, and how human diseases take over when such mechanisms are perturbed.

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Area of interest

Structure and mechanism of RNA virus replication

Positive-sense RNA viruses are a vast group of viruses that causes human diseases ranging from common cold to hepatitis C to Chikungunya, Dengue and Zika fevers. While these viruses differ from one another in many respects, they all share the same modus operandi of hijacking host-cell membranes, reshaping them to so-called replication complexes (RCs - also known as spherules, replication vesicles, etc). These virus-induced organelles contain the entire machinery needed to copy the viral RNA genome, and may serve the additional function of hiding the viral RNA from detection by the innate immune system. As the intracellular manifestation of the virus, the RCs have been much less tractable to detailed structural and mechanistic studies than the cell-free virus particles. Our goal is to use innovative methods to advance our understanding or RCs, ultimately aiding the design of new antiviral treatments.

Strengths in lab

Two orthogonal methods form the basis of our experimental work on replication complexes:

1. Cryo-electron tomography of cells. This method is uniquely capable of visualising the macromolecular architecture of the interior of cells at (sub)nanometre resolution, thus enabling in situ structural biology. These studies are conducted at the world-class instruments of the Umeå Core Facility Electron Microscopy (UCEM), affilited with SciLifeLab.
2. In vitro reconstitution of membrane-localised biological processes. This is a synthetic biology approach aimed at recreating a biological process from its individual components, thus identifying and characterising the minimal machinery required to perform a certain task. For in vitro reconstitution experiments we are highly depending on our biochemistry skills to isolate functional forms of the macromolecules involved in the process. In a typical experiment we label individual components with fluorescent dyes, assemble them on synthetic membranes such as GUVs (giant unilamellar vesicles) and SLBs (supported lipid bilayers), and analyse their interactions by quantitative fluorescence microscopy at the Biochemical Imaging Centre Umeå (BiCU), part of National Microscopy Initiative (NMI).

Abstract

HIV-1 Gag selects and packages a dimeric, unspliced viral RNA in the context of a large excess of cytosolic human RNAs. As Gag assembles on the plasma membrane, the HIV-1 genome is enriched relative to cellular RNAs by an unknown mechanism. On this poster, I will describe how we used a minimal system consisting of purified RNAs, recombinant HIV-1 Gag and giant unilamellar vesicles to recapitulate the selective packaging of the 5' untranslated region of the HIV-1 genome. Mutations in the CA-CTD domain of Gag which subtly affect the self-assembly of Gag abrogated RNA selectivity. We further found that tRNA suppresses Gag membrane binding less when Gag has bound viral RNA. The ability of HIV-1 Gag to selectively package its RNA genome and its self-assembly on membranes are thus interdependent on one another.

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Area of interest

Strategies for structure-based drug discovery

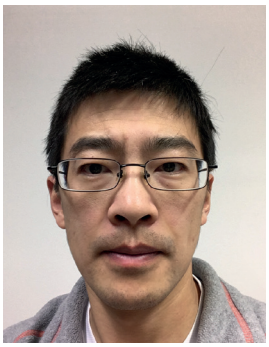
The goal of my research is to improve atomic level understanding of protein-ligand interactions with the vision to develop new strategies for early phase drug discovery and identify novel mechanisms for target modulation. We have mainly focused our efforts on G protein-coupled receptors (GPCRs), which constitute the largest family of cell surface proteins and are involved in numerous physiological processes. GPCRs have received considerable attention from the pharmaceutical industry and close to 30% of all marketed drugs interact with these targets.

By taking advantage of the revolution in structural biology for GPCRs, we hope to contribute to development of novel drugs with improved efficacy and fewer side effects. Computational and experimental approaches are combined to study GPCR-ligand complexes at atomic resolution. We gain molecular level understanding of how receptor-receptor and receptor-ligand interactions can modulate physiological processes from atomistic simulations. By combining computational prediction of receptor binding sites with in silico screening of millions of compounds from virtual databases, we can predict lead candidates to therapeutic targets of unknown structure. Lead compounds are synthesized in our laboratory and evaluated experimentally to test the accuracy of the computational models.

Our research projects are carried out in close collaboration with experimental groups in academia and industry. The Carlsson group currently has 12 members and is mainly funded by grants from the Science for Life Laboratory, the Swedish Research Council, and the European Research Council.

Strengths in lab

We use a combination of several computational approaches in our work: molecular docking, compound library design, virtual screening, molecular dynamics simulations, free energy calculations, and protein structure prediction. We also carry out part of the experimental work in the areas of medicinal chemistry and pharmacology.



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Area of interest

Oxygen (O_2) levels vary enormously in the environment, which induces dramatic behavioral and physiological changes to resident animals. Adaptations to O_2 variations can be either acute or sustained. How animals detect and respond to the changes of O_2 availability remains elusive at the molecular level. In particular, what is the precise mechanism of acute O_2 sensing, and why do neurons of various species exhibit completely different sensitivity to hypoxic challenges? My lab aims to address these intriguing questions in nematode *C. elegans*, which offers unique advantages to systematically dissect O_2 sensing at both genetic and neural circuit levels. *C. elegans* responds dramatically to acute O_2 variations by altering its locomotory speed. We will make use of this robust behavioral response to O_2 stimulation for high-throughput genetic screens, aiming to identify a collection of molecules critical for acute O_2 sensing. These molecules will be subsequently characterized in the context of a well-described nervous system of *C. elegans*. Our findings will offer the opportunity to shed light on conserved principles of acute O_2 sensing that are operating in the O_2 sensing systems in humans such as carotid body. In addition to its robust responses to O_2 variation, *C. elegans* exhibits remarkable tolerance to a complete lack of O_2, anoxic exposure. My team will thoroughly investigate anoxia tolerance of *C. elegans* by performing a screen for anoxia-sensitive mutants that has previously been challenging. The discoveries will allow us to delineate the molecular underpinning of anoxia tolerance in *C. elegans*, and to inspire other researchers to develop better strategies to cope with hypoxic challenges caused by certain diseases such as stroke and ischemia.

Strengths in lab

Behavioral genetics, high-throughput screen, next generation sequencing, calcium imaging, optogenetic manipulation, CRISPR/Cas9 in *C. elegans*

Systematic dissection of acute O_2 sensing and O_2 tolerance

Nematode *C. elegans* prefers 7% O_2, and aggregates to form clumps when exposed to 21% O_2. This escape attempt to avoid 21% O_2 exposure is driven by a well-defined O_2 sensing circuit in C. elegans. In a high throughput behavioral screen for aggregation-defective mutants, we establish an interleukin-17 (IL-17) signaling pathway that acts directly on neurons to alter their response properties and contribution to behavior. IL-17 is a major pro-inflammatory cytokine, playing critical roles in host defense against pathogens as well as in the development of inflammatory diseases. Knowledge about IL-17 in the other cellular processes is very limited. We delineate that IL-17 signaling pathway acts cell-autonomously in a pair of interneurons to increase their responsiveness to input from pre-synaptic O_2-sensors. This pair of interneurons integrates information from multiple sensory receptors to drive persistent escape from 21% O_2 and control *C. elegans* aggregation. In IL-17 signaling mutants, reduced RMG responsiveness to O_2 input renders escape from 21% O_2transitory. Conversely, over-activating IL-17 receptors by ligand overexpression abnormally heightens the responsiveness of the interneurons and whole animals to 21% O_2, and can confer aggregation behavior on non-aggregating strains. Heat-shock induced expression of IL-17 in adult animals can rescue mutant defects within 6 hours. Global IL-17 deficiency can be bypassed by selective optogenetic stimulation of this pair of interneurons, confirming its essential site of action. These findings reveal a non-immunologic role of IL-17 signaling modulating neural circuit function and behavior.

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Area of interest

Biological Psychiatry

With the help of state-of-the-art techniques, we aim to make advances in understanding the biological substrates of psychiatric disorders, such as addiction and premenstrual dysphoric disorder.

For instance, together with Prof. Sundström-Poromaa, we are conducting a constellation of studies in healthy subjects as well as psychiatric patients to investigate interactive effects of sex hormones and drugs (e.g., nicotine and antidepressants) on brain and behaviour. The psychoneuroendocrine underpinnings of sex differences and gonadal hormone effects on mental health indeed remain largely unknown, thus impeding the development of sex-specific treatments. Ongoing studies of the group aim to make a major headway in understanding the psychobiology of women's behavior and mental health. By employing genetic, endocrine, pharmacological, neurophysiological and neuroimaging measures, we aim to characterize diagnosis- and treatment-related biomarkers of sex-specific disorders.

In collaboration with Prof. Nylander and Prof. Nilsson, for example, we research on the effects of exposure to early-life stress and addictive drugs (e.g., alcohol and nicotine) on brain and behaviour. Stressors during critical periods of brain development, such as childhood maltreatment, have the potential to leave signatures on hormonal and neural systems, thus malprogramming emotional and cognitive functioning. Focusing on adolescence, (epi)gene-environment interactions are investigated in rodents as well as human population-based samples to identify biomarkers of vulnerability to addiction.

Strengths in lab

We aim to contribute to a nosology of psychiatric disorders informed by disease neurobiology, therefore we make use of national facilities available at Uppsala University, such as the Uppsala Genome Center as well as the MR and PET centers. We use validated psychological assessment tools, gold standard preclinical and clinical procedures, and perform ad hoc genotyping and gene expression analyses.

Abstract

Sex differences in psychiatry have been abundantly reported, as well as effects of gonadal hormones on brain and behaviour. Biological signatures of gender identity disorder (GID), a psychiatric disorder characterized by distress driven by incongruence between one´s sex and gender, and treated with cross-sex hormones, have only begun to be unveiled. Gene expression profiling at the transcriptional level can contribute identifying markers not only of the disorder but also of the physiological response to its pharmacological treatment. The present study investigated the transcriptomic profile in blood of patients with GID compared to healthy controls, as well as during cross-sex hormone treatment. Transcriptome-wide high-throughput sequencing analyses were performed in Female-to-Male (FtM) and Male-to-Female (MtF) GID patients, as well as healthy females and males, recruited at the Medical University of Vienna. Patients were also assessed after approximately four-week and four-month cross-sex hormone therapy. Ongoing analyses aim to identify transcriptome-wide gene expression markers of GID before and during cross-sex hormonal treatment.
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Area of interest

My group studies how the molecular structures and dynamics of protein machines together enable their function and regulation. One major focus are nucleic-acid interacting proteins and protein complexes whose aberrant function or dysregulation is often associated with severe diseases such as cancer. We aim to identify the mechanisms by which nucleic-acid interacting proteins can convert chemical energy into conformational changes to move along DNA. We are also interested in understanding how many nucleic-acid interacting proteins can rapidly identify a cognate binding site. In order to address these fundamental questions, we apply and develop novel single-molecule fluorescence imaging strategies and combine them with structural and biochemical approaches.

One major focus of my research is on ATP-dependent chromatin remodelers. These translocases can alter the the packaging state of chromatin, thereby regulating a wide range of vital processes that depend on direct access to the genetic information. The dysregulation or functional impairment of chromatin remodelers has been linked to various cancers and multisystem developmental disorders. A deeper mechanistic understanding of chromatin remodeling is therefore expected to reveal links between remodeler dysfunction and diseases.

My group benefits from strong collaborators both in Sweden (Uppsala University; Stockholm University; and Karolinska Institute) and elsewhere (The Crick Institute, London, UK; LMB-MRC, Cambridge, UK; Johns Hopkins, Baltimore, USA etc). Our research activities are supported by SciLifeLab, the Wallenberg Academy Fellows Program, the Swedish Research Council, and an ERC starting grant.

Strengths in lab

My laboratory develops and applies advanced *in vitro* single-molecule fluorescence microscopy techniques (e.g., single-molecule FRET) in order to unravel the complex dynamics of protein machines. We combine these imaging methodologies with an integrative strutural approach (SAXS, cryo-EM, structural biology) and biochemistry (characterization of activity and binding etc.).

Abstract

Published in Molecular Cell, December 2017

Human ALC1 is an oncogene-encoded chromatin-remodeling enzyme required for DNA repair that possesses a poly(ADP-ribose) (PAR)-binding macro domain. Its engagement with PARylated PARP1 activates ALC1 at sites of DNA damage, but the underlying mechanism remains unclear. Here, we establish a dual role for the macro domain in auto-inhibition of ALC1 ATPase activity and coupling to nucleosome mobilization. In the absence of DNA damage, an inactive conformation of the ATPase is maintained by juxtaposition of the macro domain against predominantly the C-terminal ATPase lobe through conserved electrostatic interactions. Mutations within this interface displace the macro domain, constitutively activate the ALC1 ATPase independent of PARylated PARP1, and alter the dynamics of ALC1 recruitment at DNA damage sites. Upon DNA damage, binding of PARylated PARP1 by the macro domain induces a conformational change that relieves auto-inhibitory interactions with the ATPase motor, which selectively activates ALC1 remodeling upon recruitment to sites of DNA damage.

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Area of interest

Computational Biophysics

Lucie Delemotte, PhD, Assistant Professor at KTH and SciLifeLab fellow, uses computational methods to understand biological phenomenal occurring at the cellular membrane. An understanding of the basic biophysical phenomena opens new avenues of the design of modulators with an original mode of action.

I focus on understanding the biophysical properties of complex membrane systems, and in particular of the membrane proteins whose role is to enable the cell to communicate with the outside world. To do this, I use an arsenal of computational techniques (molecular dynamics simulations, enhanced sampling techniques, QM/MM simulations, clustering, machine learning, sequence analysis, Markov state modeling, etc.) that allow a multiscale insight. My PhD and postdoc work has focused on gaining a molecular insight on the activation mechanism of voltage gated ion channels, the membrane proteins that propagate electrical signals along cells.

Nowadays, I am developing methodologies to tackle the fundamental problem of broadening the scope of applicability of molecular simulations. In particular, I aim at enabling to tackle extremely complex problems involving multiple time and length scales. Thus, the focus of my research has shifted towards the development of data-driven approaches to analyze and conduct simulations in a way that is less biased by the user. We have thus developed an unsupervised method to infer probability densities and free energy landscapes from molecular dynamics simulations data and optimized a clustering protocol to characterize conformational states automatically. We are now working on using machine-learning to optimize the protocols that allow to sample complex conformational changes.

This allows to tackle several applications of biomedical and pharmacological relevance including activation of G-protein coupled receptors, activation and gating of different families of ion channels and modulation of membrane proteins by small molecule drugs such as insecticides or anti-epileptic and anti-arrhythmia drugs.

Strengths in lab

- Molecular dynamics simulations
- Data analysis (of time series, specifically)
- Molecular modeling, docking

Effect of Ca^{2+} binding on the promiscuous target-protein binding mechanism of calmodulin

Annie Westerlund and Lucie Delemotte

Calmodulin (CaM) is a promiscuous calcium sensing protein that plays part in many physiologically crucial pathways. Through binding Ca^{2+}, hydrophobic residues are exposed which enables binding to and regulating more than 300 different target peptides. Here, we identify states that may be compatible with binding Ca^{2+} through a conformational selection mechanism and explore the CaM selective promiscuity for target proteins using molecular dynamics with enhanced sampling of Ca^{2+}-CaM (holo) and Ca^{2+}-free CaM (apo).

Spectral clustering of the N-term domain (N-CaM) and C-term domain (C-CaM) conformational space provided states with insights into Ca^{2+} and protein binding. We observed holo-like states in the apo N-CaM and C-CaM conformations which may increase the likelihood of Ca^{2+}-binding and a compact state in apo C-CaM with the 4th Ca^{2+}-loop participating in a beta sheet, inhibiting any sort of binding.

The importance of the different states for target-protein binding was studied using a set of CaM-complex structures. Solvent exposed residues in the different states were mapped to contact residues in the complexes. This mapping was used to characterize binding classes; shallow, intermediate and deep. Deep binding, with a hydrophobic pocket, is observed in holo C-CaM, while intermediate binding class is seen in apo C-CaM structures. Apo N-CaM showed shallow binding with more polar and charged residues. The long-ranged electrostatic interactions of the N-CaM charged residues may initiate binding, while the hydrophobic pocket in C-CaM may account for selectivity. Binding Ca^{2+} modifies the pockets which allows for deeper binding. We observed three binding classes in holo C-CaM while the N-CaM only shows two (shallow and deep). Interestingly, an extra C-CaM open state seems to facilitate deep binding to target proteins. We hypothesize that the C-CaM is selective with binding directly favored by distinct states, while N-CaM protein-binding happens through a more flexible mechanism.

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Area of interest

Impact of diabetes on the brain

Diabetes mellitus has a major impact on brain function. Diabetic encephalopathy can derive from cellular damage caused by both glucose neurotoxicity upon hyperglycemia and defective insulin signaling due to either insulin deficiency or receptor desensitization. Insulin signaling has a role in modulating brain function, namely through control of metabolism and synaptic plasticity, and its deterioration occurs in neurodegenerative disorders, such as Alzheimer's disease, and in diabetes. Our lab is particularly interested on the coupling between brain metabolism and function, and its deregulation in diabetes, as well as contributing to identify strategies for rescuing brain metabolic regulation in diabetes. This research is focused on the hippocampus and cortex, which are brain regions involved in cognition, and on the hypothalamus, which has a major role in whole-body energy balance. Notably, since metabolic alterations are likely early events in the process of neurodegeneration, this line of research may provide early encephalopathy biomarkers before severe structural damage and irreversible loss of brain functions in diabetes patients.

Strengths in lab

Magnetic resonance methods to investigate brain metabolism, structure and function.

Deterioration of neuronal and glial intermediary metabolism, neurochemical profiles and brain morphology in insulin-resistant Goto-Kakizaki rats: a multimodal magnetic resonance study in vivo

Type 2 diabetes (T2D) deteriorates brain structure and function leading to cognitive deficits. While the T2D-induced neurodegeneration process has been studied, early metabolic modifications associated to such events remain to be elucidated. We performed a multimodal magnetic resonance imaging and spectroscopy (MRS) study in insulin-resistant Goto-Kakizaki (GK) and Wistar rats at 2, 4 and 6 months of age to evaluate brain morphology and metabolic profiles. At all ages, GK rats displayed smaller hippocampi and cortex, but larger ventricular volume, compared to controls. Hippocampal and cortical metabolic profiles were affected by insulin resistance: out of 20 metabolites, GK rats displayed reduced glutamine and choline in both regions; higher taurine and ascorbate, and reduced alanine in the hippocampus; lower cortical aspartate. Spatial memory performance evaluated as the spontaneous alternation in a Y-maze was lower in GK than Wistar rats, and interestingly correlated to hippocampal concentrations of ascorbate, glutamine and taurine. 13C MRS was then employed to detect isotopomers of glutamate, glutamine and aspartate during [1,6-^{13}C]glucose infusion. Mathematical modelling of ^{13}C time courses in vivo revealed that insulin resistance caused mitochondrial oxidation rate to be reduced in neurons but increased in astrocytes. Additionally, both glutamatergic neurotransmission and glutamine synthesis were reduced in the brain of GK rats compared to controls. In conclusion, the brain of insulin-resistant GK rats had impaired mitochondrial metabolism and abnormal metabolic interactions between neurons and astrocytes. This led to neurochemical alterations that were associated with the degree of brain dysfunction, namely impaired memory performance.

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Area of interest

Chemical and Synthetic Systems Biology

My laboratory is combining new synthetic and chemical biology methods with 'omics readouts to study dynamic processes in the cell at the systems level. We are developing tools to engineer proteins in living cells based on genetic code expansion and unnatural amino acid mutagenesis.

Unnatural amino acids with a variety of chemical functionalities can be inserted site-specifically into a target protein within a living cells using so-called amber suppression or unnatural amino acid mutagenesis. Novel functionalities include site-specific photo-crosslinkers, biorthogonal reactive handles, fluorescent tags, photocages, post-translational modifications. Expanding the genetic code in mammalian cells holds great potential for engineering proteins in vivo, but its applicability to basic biology and human disease research has been hampered by the limited scope of existing technology. We have developed an optimized system that allows highly efficient amber suppression in a wide range of mammalian cells. Using this system, we aim to do biochemistry in a living cell, controlling and observing proteins 'at work' in their in vivo environment.

Our main interest is gene expression regulation at the transcriptional and translational level. We are, for example, controlling and probing chromatin proteins using light-activated and bioorthogonal chemistries. These methods, combined with quantitative, high-throughput, proteomic and genomic read-outs, will allow us to dissect the complex mechanisms governing chromatin dynamics, histone modifications and epigenetic inheritance.

Further, we study non-canonical regulation of translation including stop codon read-through and generation of functional peptides from short open reading frames.

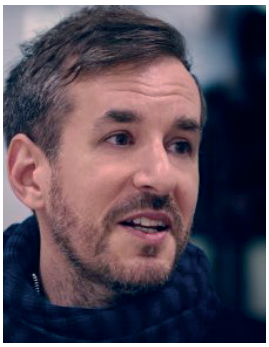
Strengths in lab

For protein engineering applications, we have created a comprehensive toolbox for incorporating unnatural amino acids in recombinant proteins in mammalian cells, that can easily implemented into existing protein production methods.

Our chemical and synthetic systems biology portfolio includes methods for dynamic labeling of target proteins and chemical capture methods for downstream mass spec analysis. We employ unnatural amino acids for live cell imaging and superresolution microscopy. For quantitative epigenomic profiling, we have developed a multiplexed, barcoded ChIP-Seq methodology. We also apply other state-of-the art 'omics methods such as transient-transcriptomics (TT-Seq).

Dynamic features of pluripotent chromatin

To unravel the molecular circuits that underlie epigenetic gene regulation and inheritance, my laboratory combines chemical and synthetic biology manipulation of living cells with systems-level (genomic and proteomic) readouts. We are particularly interested in the chromatin regulation in pluripotency and cell fate decisions. To facilitate high-throughput quantitative profiling of chromatin features, we have developed a chromatin barcoding protocol that allows multiplexing of chromatin profiling assays such as MNase footprinting and ChIP-Seq, and yields a unique molecule-based quantitative readout. I will present several applications of this technology, in particular related to the chromatin dynamics in mouse embryonic stem cells.



Marc Friedländer

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Area of interest

microRNA biogenesis and function at the single-cell level

The Friedländer group applies state-of-the-art computational and genomic methods to address fundamental questions in RNA biology. The focus is on quantitatively describing and functionally characterizing mammalian transcriptomes, and methods include next-generation sequencing of single and pooled cells, as well as development of source code and custom wet-lab protocols.

Of particular interest to us are microRNAs: 22 nucleotide RNAs that can regulate the expression of protein-coding genes. Since they confer regulation on the majority of human genes, it is not surprising that microRNAs are involved in numerous biological processes, including cardiovascular, immunological, neurodegenerative, and psychiatric diseases and cancer. Even though miRNAs have been systematically studied for more than ten years, fundamental questions regarding their biogenesis and function remain unanswered.

We study microRNA function by profiling these regulators and their gene targets in the single cells where the interactions between them occur. From the measurements we infer copy-per-cell numbers for the transcripts, and we develop mathematical models to describe the kinetics of regulation. For this purpose we apply single-cell sequencing methods and single-molecule FISH. To study microRNA biogenesis we have developed a method to measure processing of thousands of RNA structures simultaneously in mammalian cells.

Among our collaborators are Rory Johnson (University of Bern), Rickard Sandberg, Magda Bienko, Nicola Crosetto (KI) and the SciLifeLab Eukaryotic Single Cell Genomics facility. Our research is funded by SFO, by Vetenskapsrådet and an ERC starting grant.

Strengths in lab

The Friedländer group is balanced between researchers with wet-lab and dry-lab expertise. We focus on wet-lab methods that concern (small) RNA biology and mammalian cell culture experiments. We extensively generate standard and custom next-generation sequencing libraries that we sequence on our Illumina NextSeq instrument, which is shared with four other junior groups.

Our dry-lab expertise is focused on sequence analysis, with special focus on next-generation sequencing transcriptome analyses. We apply standard software and also develop our own solutions for custom data. Members of our group have developed miRDeep which is one of the most widely used software tools in the microRNA field.

Unraveling novel microRNA functions through single cell sequencing

MicroRNAs can each target hundreds of mRNAs. Some strongly down-regulate their targets during dynamic processes such as development. However, the functions of microRNAs in non-dynamic conditions are not well understood and many deeply conserved microRNAs only have subtle effects on their target transcripts. We here investigate the hypothesis that microRNAs may buffer variations in gene expression and propose a new microRNA function - the induction of temporal covariances between target genes.

We performed single-cell sequencing on a highly homogeneous non-dynamic population of mouse embryonic stem cells, allowing us to infer both gene variations and gene covariances on the transcriptome level, independent of differentiation and cell-cycle effects.

It has been proposed that microRNA may buffer gene expression variations of their targets. However the main support for the hypothesis stems from artificial reporter constructs, and evidence from more physiological systems is lacking. We present data for >8000 individual genes in over 300 control cells and over 300 Drosha knockout cells to examine noise buffering transcriptome-wide.

Last, when investigating gene expression covariances, we surprisingly detect ~100,000 significantly correlated pairs of genes, at a low false discovery rate (FDR < 0.01). Many of these covarying genes form biologically meaningful networks. Importantly, many microRNA target genes specifically cease to correlate in the Drosha knockout cells, suggesting that microRNAs can induce covariances in their target pool.

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Area of interest

Biomarker discovery for pancreatic cancer through the link to gut microbiota metabolism

The laboratory of Associate Professor Daniel Globisch, PhD combines metabolomics with chemical biology methodologies, chemical synthesis and systems biology for the selective investigation of microbiota metabolism. Our comprehensive and interdisciplinary projects represent an advanced strategy for metabolite biomarker discovery for pancreatic cancer.

I started my independent laboratory in September 2015 as a SciLifeLab Fellow at Uppsala University with the ambition to discover unknown metabolic biomarkers for pancreatic cancer. I have also been awarded a starting grant from Vetenskapsrådet in 2016 to accomplish my research goals. The multidisciplinary nature of my research projects includes chemical synthesis, mass spectrometry, bioassays, biochemical pathway analysis, and systems biology.

Biomarker discovery is a challenging task in any type of human specimen as these are comprised of a complex mixture of biomolecules. The analysis of metabolites is termed metabolomics, the newest 'omics'-research field. One of the most exciting scientific developments in the past decade has been the understanding that gut microbiota profoundly impact human physiology. This complex consortium of trillions of microbes possesses a diverse range of biochemical and metabolic activities and plays a crucial role in multiple physiological processes. This metabolic interspecies communication represents a tremendous and new opportunity for biomarker discovery. However, tools for the selective analysis are lacking. We are developing unique methodologies at the interface of chemistry and biology for analysis of specific metabolite classes with focus on microbiota human-host co-metabolism. These methods will allow for the discovery of unknown metabolites in medical relevant samples to evaluate their potential as biomarkers.

Strengths in lab

My laboratory uses state-of-the-art Chemical Biology techniques and metabolomics software. We perform chemical synthesis and enzymatic assays to achieve an advanced metabolites analysis for analysis using ultra-performance liquid chromatography-coupled with tandem mass spectrometry (UHPLC-MS/MS). We quantitatively and qualitatively analyze metabolites in any human and other mammalian sample type such as urine, plasma, feces, saliva, and tissue. Our strength lies in the analysis of biosynthetic pathways, metabolite structure elucidation and chemical synthesis of isotope labeled internal standards for precise quantification. I have started several strategic important national and international collaborations to enhance the scope of our studies including biomarker discovery projects for colorectal cancer.

Advanced biomarker discovery strategies for pancreatic cancer through analysis of gut microbiota and human host co-metabolism

Pancreatic cancer is one of the most lethal cancer types worldwide with steadily increasing patient numbers. The mortality rate is higher than 95% for pancreatic cancer patients within 5 years after initial diagnosis. A lack of sensitive, reliable and non-invasive diagnostics for an early detection is one of the major reasons for this low survival rate. It can only be detected at a very advanced developmental stage through biopsies, which are highly invasive, lack sensitivity and only allow for an insufficient treatment. The discovery of unknown early-stage biomarkers for both cancer types is urgently required to significantly improve patients' lives. The detailed investigation of small molecule metabolites in human samples including fecal, serum/plasma and urine comprises a high potential for identification of unknown biomarkers. This research field has been termed metabolomics, which still lacks advanced methods compared to other 'omics-based research fields.

We are developing unique metabolite-analyzing methodologies at the interface of Chemistry and Biology to overcome limitations in mass spectrometry-based disease-specific metabolite analysis. Our methodologies represent a new and unique strategy for small molecule biomarker discovery with a focus on the interaction between gut microbiota and the human host as the impact of host-microbiome interactions for the development of pancreatic cancer has recently been identified. However, on a molecular level this interspecies communication is still unknown. Validated specific early-stage biomarkers are the crucial step for the development of new diagnostics and the potential to identify new drug targets for disease prevention, management and personalized medicine.

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Area of interest

Focus on Multiple Myeloma

Markus Hansson combines clinical work as a senior consultant in hematology at Skåne University Hospital with clinical trials and basic science regarding multiple myeloma (MM). He heads the clinical myeloma team and the myeloma research group including three PhD students (MDs), three research nurses, one assistant nurse and two laboratory technicians.

MM is the second most common malignancy of the blood, with an incidence of 600 patients per year in Sweden. The disease is characterized by an uncontrolled growth of an abnormal malignant plasma cell clone in the bone marrow, producing monoclonal antibodies that can be detected as a paraprotein in serum ("M component"). MM arise from a premalignant disease, monoclonal gammopathy of undetermined significance (MGUS), which is a common condition with a prevalence of 1% in the Swedish population35. In contrast to MGUS, which is without symptoms, MM is clinically characterized by bone marrow failure (leading to anemia and compromised immunity), lytic bone destructions (leading to pain, pathological fractures and hypercalcemia) and renal failure. Current therapy includes corticosteroids, chemotherapy, immunomodulators, proteasome inhibitors, and autologous stem cell transplant. Even with ASCT most patients get relapses and MM remains incurable and fatal36, with a survival of 3 to 8 years, depending on age at diagnosis.

Markus Hansson has since 2013 been working in the board of the Nordic Myeloma Study Group (NMSG) that coordinates many clinical trials in the Nordic region. He is also in the board of the Swedish myeloma biobank and in the Swedish myeloma group.

Strengths in lab

The Swedish myeloma biobank (located in Lund) and a Swedish myeloma registry. Locally we have excellent experience in clinical trial design, in advanced multicolor flow cytometry and cell sorting, protein purification, cell culture and immuno-fluorescence microscopy. Furthermore, we share laboratory with Björn Nilssons group creating a strong multi-disciplinary environment with computational, experimental or clinical expertise.

Abstract

Our main goal is to improve outcome for the painful and fatal tumor disease, multiple myeloma (MM). To do this we will pursue three lines of research; i) use investigator initiated clinical trials to test prevention strategies and ii) to test new drug combinations and iii) investigate phagocyte subsets and functions during treatment and progression of MM. If successful, this project will i) show that elimination of common subclinical infections could abrogate the small plasma cell clones and possibly prevent or decrease the risk of progression into MM ii) improve MM treatment and iii) gain knowledge of how phagocytes contribute to progression of MM, this could also lead to completely new treatment strategies targeting the MM supporting bone marrow milieu.

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Area of interest

At Linköping University, Frank is a WCMM fellow in the Department of Physics, Chemistry and Biology (IFM) and the Group Leader of the Nucleic Acids Technologies Lab (NAT-Lab). His lab is exploring the utility of nucleases as biomarkers of disease. The ultimate goal of the NAT-Lab is to develop diagnostic and therapeutic approaches with properties outside the scope of the existing technologies for their use in a broad range of clinical and industrial applications. Frank has created a platform for the identification of activatable probes for targeting human and animal diseases with high incidence and mortality. This technology exploits the tremendous diversity and widespread expression of nucleases for the purpose of identifying specific oligonucleotide substrates. The oligonucleotide substrates selection is carried out using different sequences, structures and chemical modifications. Using this technology several successful oligonucleotide probes have been identified, for targeting several bacteria species and pathological conditions such as cancer. NAT-Lab is also exploring the construction of MRI-activatable probes with the ambition of translating this technology into contrast agents for clinical use.

Strengths of the lab:

NAT-Lab is working on three main research lines:

- Screening of nuclease activity as biomarker for targeting diseases.
- Adaptation of nucleic acid probes to several detection modalities.
- Therapeutics based on nucleic acid probes.

We have extensive expertise in nucleic acids design, synthesis and nucleotide chemical modifications.

Harnessing nuclease biology for the development of diagnostic strategies

Over expression of nucleases has been reported as promising biomarker for infectious diseases, and other human conditions such as cancer and autoimmune diseases. In our studies, we have demonstrated the capability of nucleases for detecting specific bacteria in animal models of disease. With this strategy we developed nucleic acid probes with high sensitivity and specificity that allows in vivo detection of bacteria in 45 min, clearly demonstrating the great potential of this technology for targeting applications where nuclease activity is present. Therefore, any method based on this property (nuclease degradation activity) represents a novel alternative for diagnostic and therapeutic intervention.

As a proof-of-concept, we have previously developed a novel molecular imaging approach that rapidly and specifically detects S. aureus infections via fluorescent probe activation by a specific nuclease (micrococcal nuclease) secreted by S. aureus (Hernandez et. al. Nat Med. 2014, 20, 301-306). To overcome the limitations with the fluorescence-based probes regarding tissue penetration and background signal, we are now pursuing a novel approach based on activatable contrast agents that can be measured with magnetic resonance imaging (MRI).

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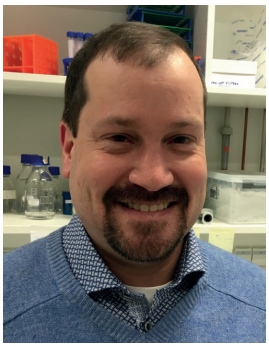

Walker S. Jackson

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Area of interest

Neurodegeneration

Walker Jackson studies neurodegenerative diseases using mouse models, especially during early disease, with the goal of identifying therapies.

My lab is interested in why neurodegenerative diseases tend to target specific brain regions, a feature known as selective vulnerability. For example, why are brain regions involved in memory targeted in Alzheimer's disease whereas brain regions important for motor control are targeted in Huntington's disease? On the other hand, how do other brain regions resist these diseases? If we can learn the secrets from the resistant regions maybe we can transfer those traits to the vulnerable regions and slow disease progression. Since these diseases typically affect people later in life, even a modest deceleration could make a large impact.

We study several neurodegenerative diseases in genetically modified mice. Although mice and humans have obvious differences, in good mouse models the brain regions affected in humans are also affected in mice, with the same types of neuropathological lesions. Rather than using scalpels, we use molecular approaches to dissect the brain into component parts. We also study the models in vivo with a variety of techniques including automated video based behavioral analyses, magnetic resonance imaging and telemetric electroencephalography.

Once a human is clinically affected by a neurodegenerative disease the brain is drastically altered, causing current treatments to generally be insufficient. Therefore, we study models before there are clinical or neuropathological changes to identify very early disease mechanisms and therapeutic targets.

Strengths in lab

Our key technology is based on a tool we created to study, specifically in any cell type of interest, gene regulation at 4 levels:

1. Epigenetics/chromatin regulation,
2. Translating mRNAs,
3. Argonaute 2 bound miRNAs, and
4. Pulse labeled RNA (useful to label mitochondrial RNA and lncRNAs, among others).

We also have extensive experience with genome manipulation, especially for knock-in mouse lines, using conventional and CRISPR/Cas9 based methods

Abstract

Neurodegenerative diseases progressively transform healthy adult brains into dysfunctional states, generally leading to premature death. Since initial stages of any given neurodegenerative disease targets only a small subset of cells, the large abundance of resistant cells masks affected cells, hampering progress in understanding the earliest changes. To reduce this complexity we have employed the RiboTag technique to capture and study mRNAs from specific cell types to study how they respond to neurodegenerative disease at a very early stage. Surprisingly, although GABAergic neurons are unfazed, glutamatergic neurons have an expression profile indicative of reshaping of neuronal architecture. Moreover, astrocytes are very sick early in the disease process. These results are the exact opposite of what was predicted from existing literature, emphasizing the usefulness of this approach.

Inspired by these results we developed a new mouse line to obtain even more information about changes in gene regulation. This new mouse line simultaneously expresses four separate protein components in a specific cell type to enable the capture of multiple types of nucleic acids. The nucleic acids captured include 1) the nucleus for epigenetics and RNA splicing 2) translating mRNAs, 3) miRNAs attached to Argonaute2 and 4) total RNAs (especially useful for lncRNAs and mitochondrial transcription). Although single cell transcriptomic techniques are gaining in popularity, the advantages of a "population" approach is that the detected transcripts are not limited to those that are highly expressed and fewer samples need to be collected, sequenced and analyzed to identify the most vulnerable cell types and their pathogenic processes. Moreover, this model can be used for marking specific cell types for single cell experiments, providing a nice bridge between the two methods.

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Area of interest

Pathophysiology of Glaucoma

Gauti Jóhannesson, Consultant in Ophthalmology and Associate Senior Lecturer (Assistant Professor) incorporates clinical investigations and neuroimaging techniques to improve the understanding of the pathophysiology of glaucoma.

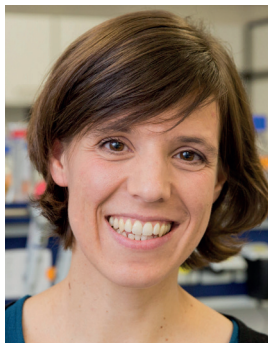
The main thread of my research has been glaucoma. Through my career I have studied glaucoma with respect to its prevalence, follow-up and enhanced drug delivery with nanoparticles. Taking the next step in glaucoma research, I have gotten increasingly more interested in the pathophysiology of glaucoma. After my postdoctoral experience abroad, I am leading a project focused on intracranial blood flow measurements with advanced magnetic resonance imaging in glaucoma patients. This project studies the interaction between the intraocular pressure and the blood flow of intracranial arteries, specifically the ophthalmic artery, in different types of glaucoma and healthy controls.

As a natural continuation of the blood flow project, I am PI for a project that takes advantage of the unique possibilities of simultaneous positron emission tomography – magnetic resonance imaging (PET-MRI). In this interdisciplinary and translational project, we aim to get a deeper understanding of the pathophysiology of glaucoma by studying the metabolism and blood flow of the visual pathways in the brain. We will mainly focus on the activity of astrocytes, a potentially important player in glaucoma pathophysiology, glucose metabolism and blood flow. When a cross-sectional comparison of glaucoma patients and healthy controls is finished, I further aim to determine if we can identify physiological biomarkers tied to rate of progression of the visual field deterioration by following the patients longitudinally.

I have national and international collaborations and have received several external grants for my research as main applicant. In particular the 4-year grant from the Swedish Society of Medical Research (SSMF) has enabled me to focus on my glaucoma pathophysiology research.

Strengths in lab

The methods we use include the newly installed combined PET-MRI in Umeå, one of the first PET-MRI in Sweden. It enables molecular imaging by means of PET combined with magnetic resonance imaging which offers simultaneous functional, metabolic, physiologic and anatomic information about the brain. We also have access to a 3 Tesla MRI for intracranial blood flow measurement. For ocular imaging we use swept-source ocular coherence tomography, perimetry to determine visual field damage as well as tonometry for measurement of intraocular pressure.



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Area of interest

My group investigates the molecular mechanisms by which bacteria control their own growth and reproduction. In particular, we want to understand how bacteria dynamically adjust their growth rate and mode of proliferation in response to fluctuating external conditions, for example changes in nutrient availability or at the onset of environmental stress, to ensure their survival. To this end, we study the regulatory circuits governing bacterial cell cycle progression and how these circuits cross-talk with stress response pathways to allow the integration of environmental information into the cell cycle. For our studies, we use a multi-disciplinary approach combining classical genetics, cell biology and biochemistry with modern live-cell imaging and high-throughput techniques. As our primary model organism we utilize the fresh water bacterium *Caulobacter crescentus*, which divides asymmetrically and has well-defined cell cycle phases. In addition, we do some of our work in *Escherichia coli* and *Salmonella enterica* to study how the *C. crescentus* cell cycle circuit relates to the one of other bacteria, and to investigate how precise regulation of cell cycle decisions contributes to bacterial persistence and pathogenesis.

Strengths in lab

Bacterial genetics, genetic screens, time-lapse fluorescence microscopy, protein biochemistry, molecular biology, quantitative proteomics

How bacteria make decisions

Whether to divide or not is an important decision that most cells have to make. In particular unicellular bacteria that are exposed to drastic environmental changes must constantly adjust their growth rate and cell division cycle in response to external inputs. Here, I will present some of our recent progress in elucidating the molecular mechanisms transducing environmental information into the bacterial cell cycle. My group's previous work revealed new mechanisms by which different stress conditions modulate the synthesis, activity and stability of key cell cycle factors and in this way delay the processes of DNA replication and cell division until after conditions improve (1-3). Our ongoing studies demonstrate that under certain stress conditions the regulation of essential cell cycle processes is accompanied by drastic alterations in bacterial cell size and morphology and that this phenotypic response is highly heterogeneous on the population level. We are currently studying the mechanisms underlying this morphological plasticity and how it helps bacteria to survive in the environment.

(1) Leslie et al. (2015). PLoS Genet. 11: e1005342
(2) Jonas et al. (2013). Cell. 154: 623-636
(3) Heinrich et al. (2016). PLoS Genet. 12: e1006522

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Area of interest

Cell signaling controls all aspects of life, from early development to tissue maintenance and regeneration. A highly interconnected network of conserved signal transduction cascades controls the fate of each individual cell. This complexity allows an organism to respond dynamically to changes in its surroundings, such as injury or infection. However, it is also an Achilles' heel, since loss of control of cell signaling can do considerable damage. In allergies and autoimmune diseases, for example, the immune system reacts incorrectly to harmless stimuli, and turns against its own host with sometimes life-threatening consequences.

My group studies cell signaling in intestinal inflammation. Chronic inflammatory bowel diseases, including Crohn's disease, ulcerative colitis, and microscopic colitis, pose a considerable global health burden, particularly also in Scandinavia. The etiology of these disorders remains enigmatic, but involves erroneous communication between the immune system, the gut microbiota, and the intestinal epithelium that lines the tissue.

We are particularly interested in understanding what signaling events control the injury and repair of the epithelial barrier, which is the first line of defense against pathogens in the gut. We have observed previously that inflammatory and homeostatic signaling pathways converge on shared molecular targets to regulate the life and death of the epithelium during inflammation. Going forward we intend to build on these findings, and manipulate signaling pathways to promote wound repair in the gut.

Projects in our lab span the entire breadth of basic biomedical research, from molecular cloning and protein analysis in cell lines, to preclinical animal models of colitis. We are collaborating with scientific, technical, and clinical partners at LiU and beyond, and we are always happy to share our own expertise.

Strengths in lab

Our main strength lies in molecular cell biology and cell signaling. We are particularly skilled in the analysis of protein post-translational modifications by immunoblotting and immunofluorescence microscopy. We apply these techniques in vitro in normal and gene edited model cell lines, as well as in preclinical animal model of colitis, in particular the dextran sulfate sodium model of intestinal injury and repair.

Protein kinase GSK3 is a regulator of FOX family transcription factors

The promiscuous serine/threonine kinase GSK3 is a central mediator of several homeostatic signaling pathways, in particular Wnt/beta-catenin and AKT signaling. Recent in silico and proteomics studies suggested that the GSK3 target pool might considerably larger than expected. In particular, we observed that transcription (co-)factors are significantly over-represented among putative GSK3 targets. Here we identify multiple forkhead box (FOX) family transcription factors as novel GSK3 substrates. FOX proteins are ubiquitous regulators of gene transcription, and their dysregulation is commonly observed in human diseases, notably cancer. We find that as with other target proteins, GSK3 destabilizes specific FOX transcription factors presumably by phosphorylation-dependent ubiquitination and proteasomal degradation. Moreover, by mutation screening of predicted GSK3 sites, we exemplarily identify regulatory phosphorylation sites in a FOX family tumor suppressor. Upstream of GSK3, AKT but not Wnt receptor activation partially rescues select FOX protein levels, suggesting that stress response/cytokine signaling might control gene transcription through AKT-dependent GSK3 inhibition. The results outline a prominent role of GSK3 in the regulation of protein stability, which may have important implications for transcription regulation particularly in inflammation and cancer.

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Area of interest

Over 200 specialized cells with diverse morphologies and functions exist in the human body, yet virtually every cell in the body contains the same genetic information. To exert cell-specific functions high fidelity mechanisms evolved to restrict the synthesis and processing of distinct regulatory RNAs. By using state-of-the-art deep sequencing technology and comparative genomics, our group investigates the transcriptional and epigenetic control of gene expression in mammalian cells. We have identified that transcription of coding and noncoding RNAs is entwined to ensure proper cellular function. This process is dynamic and tightly controlled when a cell is undergoing normal differentiation during development but gets unhinged upon transformation into cancer cells. Moreover, our recent findings show that transcripts are subject to further processing into metabolically stable RNA fragments that influence and alter global gene expression and protein translation.

With a particular focus on the processes that regulate gene expression and processing of RNA molecules, we are working towards understanding how they drive liver cancer. We aim to achieve this goal by:

- Performing extensive transcriptomic analysis in liver cancer cells to identify cancer-driving abnormalities.
- Study RNA signatures that are altered in cancer cells compared to normal cells to discover molecular differences.
- Understand the impact of these molecular differences in normal cell development.

Strengths in lab

- Genome-wide analysis of gene expression, transcriptomics, epigenomics, Illumina next generation sequencing
- Cell-based assays, mouse genetics
- CRISPR genome engineering

Sandra Lindstedt

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Area of interest

Lungtransplantation, Donation after circulatory arrest, Ex Vivo Lung Perfusion, Analyzing biomarkers in exhaled air

Sandra has a long-standing interest in lung transplantation (LTx) and her research focus has been on two main challenges in LTx, organ shortage and organ rejection. Organ shortage resulting in death on the waiting list.

Sandra's research group has focused on optimizing and improving marginal donor lungs using ex vivo lung perfusion (EVLP) on brain dead donors but also by using Donation after cardio-circulatory determination of death (DCD) donors in the urge to increase the donor pole.

Development of chronic lung allograft dysfunction (CLAD) is a great limitation of long-term survival and quality of life after LTx. Reports show that 45 % to 75 % of patients develop CLAD within the first five years and is a primary cause of death post-transplant. Her research group focusing on finding early biomarkers for organ rejection in blood and in exhaled air. Early detection and early treatment has a large impact on patient survival.

Strengths in lab

- Ex vivo lung perfusion
- Lung transplantation
- Mass spectrometry
- Laser speckle
- Laser doppler

None invasive measurement of particle flow from the small airways using pexa method in vivo and during ex vivo lung perfusion in DCD donation

Objectives
The optimal mechanical ventilations in the different phases in the Lung Transplantation (LTx) Donation after Cardio-circulatory Determination of Death (DCD) donation (in vivo, post mortem and ex vivo) is on debate. Different ventilations modes affect lung preservation and lung regeneration. We use a new method for airway monitoring using mass spectrometric analysis of exhaled particles, particle flow and their size distribution. The exhaled particles are collected onto a substrate and possible for subsequent chemical analysis for biomarkers.

Methods
Particle flow from the airways was monitored none invasive during in vivo ventilation, post mortem ventilation and ex vivo lung perfusion ventilation in six domestic pigs. Different ventilations settings was used volume controlled ventilation (VCV) and pressure controlled ventilation (PCV) with different tidal volumes and different PEEP (Positive End-Expiratory Pressure) and after distribution of different drugs.

Results
In Vivo: the accumulated particle mass in VCV1 was significantly lower than VCV2 ($p = 0, 0186$), and the accumulated particle mass was significantly higher in PCV1 than in the VCV1 ($p = 0, 0322$). Ex Vivo: the accumulated particle mass in VCV1 was significantly higher than PCV1 ($p = 0, 0371$), the accumulated particle mass was significantly higher in PCV2 than in the PCV1 ($p = 0, 0127$). Different levels of phospholipids was detected during the different settings.

Conclusions
We believe this technology will be useful for monitoring mechanical ventilated patients to optimize ventilation and preserve the lung and promote lung regeneration. Furthermore the method might be used to detect new biomarkers in exhaled air.

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Francisca Lottersberger

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Area of interest

Chromatin Mobility and Genome Integrity

Francisca Lottersberger, PhD, Senior Lecturer, studies the molecular pathways that encompass DNA Damage Response (DDR) signaling, with the aim to develop tools for the diagnosis and tailored treatment of cancer.

The integrity of our DNA is continuously threatened by both endogenous and exogenous sources of damage, which have the potential to give rise to mutations and chromosome rearrangements. Eukaryotic cells have evolved DNA Damage Response (DDR) pathways to recognize and repair such damage. The crucial role these pathways play is evidenced by the links between defects in DDR proteins and genome instability, tumorigenesis, and cancer progression. However, defects in DNA repair pathways also provide a therapeutic window that has been successfully exploited by many clinical cancer treatments, such as Topoisomerase Inhibitor (Irinotecan) for metastatic colon/rectal cancer and PARP inhibitor (Olaparib and Rubraca) for ovarian cancer.

We are combining mouse genetics and quantitative time-lapse imaging to dissect the principles of chromatin dynamics and understand its contribution to DNA repair, tumorigenesis and ageing. We also aim to investigate the mechanisms that regulate mobility, identify new molecular factors involved in regulating chromatin dynamics, and to evaluate the consequences of altered mobility on genome integrity in both normal and cancer cells.

I graduated at the University of Milano-Bicocca in 2006, using the budding yeast S. cerevisiae as a model for studying DNA damage response and cell cycle regulation. I joined the laboratory of Professor Titia de Lange at the Rockefeller University in 2008 to investigate the role of chromatin mobility in promoting DNA repair in mammalian cells. In 2017, I was appointed WCMM Fellow at the Linköping University.

Strengths in lab

The experimental techniques applied in the lab are: live-cell imaging and quantification of chromatin mobility, induction of DNA damage by various treatments, detection of chromatin binding proteins by immunofluorescence/FISH, telomere overhang/length detection and chromosomal rearrangements analysis, as well as standard biochemical and cell-biological methods.

53BP1 and the LINC complex promote microtubule-dependent DSB mobility and repair

Increased mobility of chromatin surrounding Double Strand Breaks (DSBs) has been noted in yeast and mammalian cells but the mechanism responsible and its contribution to DSB repair are not understood. We have previously shown that telomeres lacking shelterin protection undergo a 53BP1-dependent increase in their mobility and explore larger territories. Using this telomere-based system, we established that the 53BP1-dependent chromatin mobility required dynamic microtubules and SUN1/2 in the LInker of the Nucleoskeleton and Cytoskeleton (LINC) complex. The data further demonstrated that the excursions promote NHEJ of dysfunctional telomeres. 53BP1/LINC/microtubule-dependent mobility was also evident at IR-induced DSBs and contributed to the mis-rejoining of PARPi-induced DSBs in BRCA1-deficient cells. The data show that DSB mobility can be detrimental in cells with numerous DSBs. In contrast, under physiological conditions where cells have only one or a few lesions, DSB mobility is proposed to prevent repair errors. In a continuation of this published work, we are focusing on the different mechanisms that can promote chromatin mobility. Recent findings on the role of the DNA-binding factor Ku and the nuclear lamina component Lamin A/C are here presented.

Iben Lundgaard

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Area of interest

The Glymphatic System: Glia-Immune Interactions

Despite the brain's high level of metabolic activity the central nervous system (CNS) does not contain any lymphatic vessels. The cerebrospinal fluid (CSF) is driven into peri-vascular spaces where exchange of solutes takes place and this mediates brain-wide clearance. The peri-vascular bulk flow system was named the glia-lymphatic (glymphatic) system due to the crucial role of astrocytes' aquaporin 4 (AQP4) water channels. The glymphatic system is akin to the lymphatic system and also connects with the conventional lymphatic system upon drainage from the CNS. Due to the drainage to lymph nodes, it is believed that the glymphatic system is important for CNS immune function.
Our lab is interested in the glymphatic system due to its function as a macroscopic clearance system. Among specific research topics at the Lundgaard laboratory is the role of the glymphatic system in neurodegenerative diseases, such as Parkinson's disease, and in CNS immunity including the autoimmune disease multiple sclerosis.

Beneficial effects of low alcohol exposure, but adverse effects of high alcohol intake on glymphatic function

Prolonged intake of excessive amounts of ethanol is known to have adverse effects on the central nervous system (CNS). Here we investigated the effects of acute and chronic ethanol exposure and withdrawal from chronic ethanol exposure on glymphatic function, which is a brain-wide metabolite clearance system connected to the peripheral lymphatic system. Acute and chronic exposure to 1.5g/kg (binge level) ethanol dramatically suppressed glymphatic function in awake mice. Chronic exposure to 1.5g/kg ethanol increased GFAP expression and induced mislocation of the astrocyte-specific water channel aquaporin 4 (AQP4), but decreased the levels of several cytokines. Surprisingly, glymphatic function increased in mice treated with 0.5 g/kg (low dose) ethanol following acute exposure, as well as after 1 month of chronic exposure. Low doses of chronic ethanol intake were associated with a significant decrease in GFAP, with little changes in the cytokine profile compared with the saline group. These observations suggest that ethanol has a J-shaped effect on glymphatic system whereby low ethanol doses increase glymphatic function. Conversely, chronic 1.5g/kg ethanol intake induced reactive gliosis and perturbed glymphatic function, which possibly may contribute to the higher risk of dementia observed in heavy drinkers.

Cristina Maglio

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Area of interest

Obesity, inflammation and the development of inflammatory arthritis

Cristina Maglio, MD PhD, and her team aim to understand how obesity and weight loss affect the development and the natural history of inflammatory arthritis, with a focus on the genetic, molecular and cellular mechanisms influencing those interactions.

Obesity is associated with a low-grade, often subclinical, inflammation and increases the risk of developing rheumatic diseases, leading to a worse quality of life and to increased mortality in affected subjects. Moreover, obese subjects suffering from inflammatory joint disorders, such as rheumatoid arthritis and psoriatic arthritis, have a higher disease activity and a lower chance to respond to therapy compared to lean subjects. However, the specific pathophysiological mechanisms underlying the association between obesity and rheumatic diseases are unknown. Moreover, the effect of weight loss on the susceptibility to inflammatory joint diseases and the response to treatment is currently poorly understood.

I am a resident physician in Rheumatology at the Sahlgrenska University Hospital in Gothenburg. Since my defence, I combine clinical practice with research. I am currently working at the Department of Rheumatology and Inflammation at the University of Gothenburg where I am now establishing my own research group. Since my PhD, I am interesting in studying the effect of bariatric surgery-induced weight loss on the developing of diseases commonly associated with obesity. After my defence, I started a collaboration between the Department of Rheumatology and Inflammation and the Department of Molecular and Clinical Medicine at the University of Gothenburg, aiming to study the effect of obesity and weight loss on the development of inflammatory joint disorders.

Strengths in lab (technologies, methods):

So far, my research group includes a post-doc with a background in molecular and cellular biology of the immune system. She has hands-on experience of a variety of cellular and genetic techniques, including among others immunoprecipitation, immunofluorescent/immunohistochemistry staining, confocal microscopy, ELISA, multiplex assay, zymography, flow cytometry analysis, cell migration/invasion assays (2D or 3D), proliferation/apoptosis assays, siRNA transfection, mammalian cell culture, animal handling and surface plasmon resonance. I have experience in collecting, analysing and interpreting data from big patient cohorts as well as interpretation of data from genome- and exome-wide association study, Mendelian-randomization studies, clinical trials etc. I have expertise in a variety of statistical methods, including univariate/multivariate methods, power analysis, effect size, survival analysis etc.

Bariatric surgery and the prevention of inflammatory arthritis in obese individuals

Obesity is a risk factor for inflammatory joint diseases. Bariatric surgery, also known as obesity surgery, is a powerful treatment to achieve sustained weight loss and to prevent the development of obesity-associated disorders. Bariatric surgery-induced weight loss has been associated with improvement of inflammatory joint diseases; however, the role of bariatric surgery on the long-term prevention of those diseases is not yet clear.

The Swedish Obese Subjects (SOS) study is a longitudinal clinical trial including about 2000 individuals affected by obesity who underwent bariatric surgery and about 2000 matched controls who were conventionally treated. By exploiting the potential of the SOS study, we showed that bariatric surgery prevents the incidence of gouty arthritis in obese individuals over a 25-year follow up. Moreover, we showed that obese subjects undergoing bariatric surgery have a lower risk to develop psoriasis, an inflammatory systemic disease characterized by cutaneous lesions. About 30% of patients with psoriasis develop arthritis. We could not demonstrate a preventive effect of bariatric surgery on the incidence of psoriatic arthritis, although our results suggest a trend towards a lower risk of psoriatic arthritis in obese subjects undergoing bariatric surgery. We now aim to understand if bariatric surgery prevents the incidence of rheumatoid arthritis and study possible factors influencing the development of that inflammatory joint disease.

Martin Magnusson

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Area of interest

The core of our research is to bridge the surprisingly under-explored gap between the "omics" of epidemiology (e.g. genomics, metabolomics and proteomics) and biological and clinical function. Thus, a major component our research is to enhance the understanding of causes to progressing diabetes and cardiovascular disease (CVD) where we invest large efforts in metabolomics and proteomics. However, a central issue is that we do not stop at finding metabolites/proteins and metabolomics/proteomic patterns associated with risk of progressing disease, but we also examine the importance of genetic predisposition behind such relationship to find causal association and we also aim to explore the underlying mechanisms (by in vivo/vitro experiments and even human trials if applicable).

Here we have already discovered two novel candidates in the amino acids isoleucine, phenylalanine, and tyrosine but also in dimethylglycine, which will be further tested to shed light on the biochemical underlying mechanisms. It is conceivable to assume that our causality assessment of biomarkers of disease will provide guidance on whether or not drug development targeted at the biomarker in question is worthy to pursue. Apart from this, we will generate substantial clinical value by accurately describing the utility of all known common and rare genetic diabetes and CVD susceptibility variants as well as metabolites and proteins in clinical diabetes and CVD risk prediction and risk stratification in some of the largest population based cohorts in the world

Exploration of Biomarkers for Incident Diabetes Using a Targeted Proteomics Chip – The Malmö Preventive Project

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Background
Multiplex proteomic platforms provide excellent tools for investigating associations between multiple proteins and disease (e.g., diabetes) with possible prognostic, diagnostic, and therapeutic implications. In this study, we examined 92 proteins and their association with incident diabetes in a population-based cohort.

Methods
92 proteins from the Proseek Multiplex CVD III 96×96 (Olink Bioscience, Sweden) were analyzed in 1737 participants from a subsample of the population-based Malmö Preventive Project (mean age 67 years, 29 % women, 28% with prevalent diabetes). Subjects with prevalent diabetes (n=483) and missing data (n=22) were excluded. 1232 subjects (348 incident cases vs. 884 controls) remained for the analysis of incident diabetes (median follow up time 8.0 years). Cox regression models and Harrell's concordance index were used to calculate hazard ratios and predictive accuracy.

Results
After adjusting for traditional diabetes risk factors, we confirmed five proteins (Scavenger receptor cysteine rich type 1 protein M130, Fatty acid binding protein, adipocyte, Growth-differentiation factor 15, Plasminogen activator inhibitor 1 and Insulin-like growth factor-binding protein 2) with a previously established association with incident diabetes. Furthermore, we found novel associations with incident diabetes for five proteins (Cathepsin D, Galectin-4, Interleukin receptor-1 type 2, Cathepsin Z, Paraoxonase type 3). When including plasma glucose in the multi-variable model Galectin-4 and Paraoxonase type 3 remained significantly associated with incident diabetes.

Conclusion
In a prospective community sample of 1232 individuals without diabetes we confirmed five proteins with established association and identified five proteins with novel associations with incident diabetes, two of which were independent of glucose.

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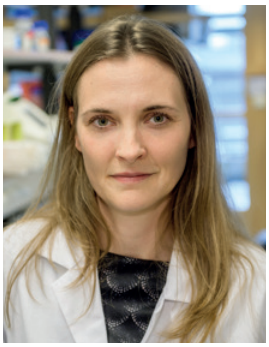

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Area of interest

Cardiovascular disease such as heart attack, stroke, and peripheral vascular disease, is the number-one health problem in the world. Despite remarkable progress in diagnosis and prevention, cardiovascular diseases cause disability and death at an astounding rate. The best opportunities to develop and implement new strategies for preventing and treating cardiovascular disease lies in the understanding of its underlying mechanisms. Our research aims to isolate novel therapeutic targets that effectively prevent and most importantly, also reverse complications mediated by cardiovascular risk factors such as hypertension.

Specifically, we are interested in sphingosine-1-phosphate (S1P) signaling and its role in the regulation of the vascular and the immune system. We recently described a novel role for S1P and its generating enzyme SphK2 in the pathogenesis of experimental hypertension, whereby hematopoietic Sphk2 activity crucially regulates the hypertension-induced elevation of plasma S1P. Remarkably, elevated plasma S1P levels have also been reported in human hypertension. Thus far, our earlier work provides ample evidence that S1P plays a key role in immune cell recruitment, cytokine production and vascular tone regulation during experimental hypertension and heart failure. Therefore, we strongly believe that its signaling axis will prove to be an attractive therapeutic target in cardiovascular complications.

Strengths in lab

- Vascular biology (dissection of small vessels of different tissues, immune-staining, myography, vessel culture)
- Immunology (FACS, animal models – adoptive transfer, bone marrow chimerism)
- Molecular Biology
- Animal work (mouse models of hypertension, cerebral small vessel disease and stroke, laser speckle and laser Doppler)

SphK2-S1P Signaling and Inflammation in Experimental Hypertension

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Introduction
Hypertension (HTN) is a complex condition involving functional and structural alterations of the microvasculature, and an activation of the immune-system. We recently reported a critical contribution of the bioactive phospholipid sphingosine-1-phosphate (S1P) to the pathogenesis of experimental HTN, whereby the activity of its generating enzyme SphK2 crucially affects blood pressure (BP) responses to Angiotensin II (AngII) by regulating S1P plasma levels and hence, T cell mobilization from secondary lymphoid organs. Based on these findings, we presently investigated the role of SphK2-S1P signaling in T-cell responses and vascular inflammation during HTN.

Methods
In a murine model of AngII-induced HTN, S1P levels were determined using mass spectrometry. Using FACS and ELISA approaches, we analyzed T-cells and cytokines. Standard qPCR and immune-histochemistry were applied to analyze endothelial activation and inflammation.

Results
In contrast to plasma, splenic S1P concentration drastically elevated with AngII treatment only when SphK2 activity was reduced. Ultimately, T- cells accumulated in the spleen with an overall Th2 phenotype. On the contrary, T-cells of untreated hypertensive WT mice predominantly presented an elevated circulating T-cell count with a Th17 phenotype. Thus, typical hypertension-associated accumulation of immune-cells in small arteries was devoid in mice where SphK2-S1P signaling was inhibited. Similarly, AngII-induced elevation of plasmatic and vascular S1P levels was accompanied by enhanced endothelial activation and impaired vasodilatory response to S1P and acetylcholine only in WT mice. Intriguingly, pharmacological inhibition of SphK2 lowered BP, and reduced vascular inflammation.

Conclusion
These results point to a critical contribution of SphK2-S1P signaling in immune-cell responses and vascular inflammation during AngII-induced HTN.

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Lili Milani

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Area of interest

Pharmacogenomics and epigenomics

My research group has focused on pharmacogenomics and epigenomics by developing next-generation sequencing based methods for targeted bisulfite sequencing of genes involved in drug absorption, distribution, metabolism and excretion (ADME). In collaboration with scientists at Karolinska Institutet we have developed several methods (Ivanov et al 2013, Nucleic Acids Research; Ivanov et al 2016, Nucleic Acids Research) and published a study on the ontogeny, distribution and potential roles of 5-hydroxymethylcytosine in human liver function (Ivanov et al 2013, Genome Biology). As the principal investigator, I also coordinated a study of the genetic and epigenetic regulation of gene expression in fetal and adult human livers, with collaborators from Sweden and the Netherlands (Bonder and Kasela et al 2014, BMC Genomics). The study allowed us to calculate the proportion of variation in gene expression that could be explained by common single nucleotide polymorphisms and DNA methylation.

In collaboration with Prof. Pärt Peterson's team at the Institute of Biomedicine and Translational Medicine (University of Tartu), we have studied purified immune cells of Estonian Biobank participants, and determined the epigenetic changes that occur with age (Tserel et al 2015, Scientific Reports) and in Graves' disease (Limbach et al 2016, J Autoimmun). I lead a larger study on the regulation of gene expression in purified immune cells in collaboration with Prof. Lude Franke's group at the University of Groningen and Prof. Julian Knight's group at the University of Oxford (Kasela et al 2017, PLoS Genetics). I have also participated in several multi-site genome-wide association studies within large international consortia. In these multi-center studies I have mostly contributed to eQTL studies regarding the regulation of gene expression in immune cells. I have also been in charge of providing data, cleaning data, and carrying out GWAS analyses on the Estonian samples.

Currently my research focuses on the genetics of adverse drug reactions by analyzing whole genome/exome sequence or genotype data combined with electronic health records, both in the Estonian biobank and Swedegene biobank. We recently received funding from SciLifeLab (in collaboration with prof Mia Wadelius - PI) to sequence the genomes of 1000 individuals with clinically confirmed adverse drug reactions from the Swedegene biobank.

Strengths in lab

My lab is becoming more and more computational, with extensive experience in analysis of genomes and large datasets including electronic health records (structured and free-text) and drug prescriptions. I also stay on track with the latest technology developments for genotyping and next-generation sequencing, as well as development of sample preparation protocols to serve specific purposes.

Abstract

Despite recent advances in pharmacogenomic research, interindividual variability in drug metabolism and sensitivity for drug toxicity persists as a major problem for drug treatment. Recent research has highlighted the large extent of rare variants in genes with importance for drug metabolism. Our team aims to identify common and rare genetic variants related to suboptimal drug metabolism and adverse drug reactions (ADRs) in the Estonian and Swedish populations. We are currently analyzing the genome or exome sequences of 5000 and genotype data of 50,000 individuals combined with extensive health records regarding drug prescriptions and ADR diagnoses. Using this approach, we were able to validate previously documented pharmacogenetic associations and detect new independent variants in known gene-drug pairs. Specifically, we found that CTNNA3 associated with myositis and myopathies among individuals taking non-steroidal anti-inflammatory oxicams (OR 1.8, p-value 7.9×10^{-7}), which replicated in an extended cohort of 706 individuals (OR 2.02, p-value 6×10^{-4}). These findings thus illustrate that electronic health records coupled to genome data can be useful for biomarker discovery. Currently, we are extending this study by sequencing the whole genomes of 1000 individuals with confirmed ADRs in the Swedegene biobank, and we are also testing the extent of relevant pharmacogenetic guidelines that can be extracted from existing genotype data as compared to sequence data, and designing tools for its automation.

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Bright Nwaru

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Area of interest

Allergy and asthma – from epidemiology to prevention and management

The overarching aim of Nwaru's research is to investigate the distribution, risk factors, and causes of allergy and asthma in the population and seek to advance potential preventive approaches for these conditions. One of the current research programs focuses on deciphering the role of sex steroid hormones in asthma in women. Although endogenous and exogenous sex steroids have been suspected to largely explain observed gender-related differences in asthma for many decades, a putative answer has so far been elusive. By assembling cross-country population cohorts and using a combination of epidemiological and mechanistic approaches, his group collaborates with national and international experts in the field to provide a definitive answer on the role of sex steroids in asthma in women. The research also seeks to understand whether sex steroid-based therapy can be developed for the management of asthma.

A second research program is to understand the potential mechanisms and predictors of asthma-COPD overlap disease phenotype. The group also capitalizes on the various population routine data (generated from clinical encounters, administrative and social care, and behavioral data) to better understand the network of factors influencing allergy and asthma in the population. In collaboration with national and international colleagues, Nwaru continuously undertakes important evidence syntheses to aid understanding of scientific findings and healthcare decisions.

Asthma, women, and sex steroids: from exploration to definitive understanding

Over the past four decades, the role of sex steroid hormones in the development of asthma and manifestation of clinical outcomes has been investigated but the evidence has only been speculative. In this poster abstract, I will demonstrate the approach now established by my group towards reaching a definitive understanding. From an initial exploratory study (which showed up to 55% reduction in asthma exacerbations in women using hormonal contraceptives), we proceeded to conduct a comprehensive synthesis of the underlying evidence. This evidence synthesis showed that women who used hormone replacement therapy (compared to those who did not use) had up to 85% and 40% increased risk of having asthma and wheeze, respectively. However, the risk of asthma was greater in non-obese versus obese and non-smoking versus smoking women who used hormone therapy, an indication that body mass and smoking may modify the putative impact of hormone therapy on asthma. The evidence synthesis also highlighted key limitations in the underlying evidence. I will highlight these findings and present the current investigations we are undertaking, combining both population epidemiology and mechanistic approaches, aimed at a better understanding and to seek whether exogenous sex steroids have any therapeutic potentials.

Antonios Pantazis

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Area of interest

The Molecular Determinants of Cellular Excitability

Ion channels are fascinating macromolecular complexes that endow our cells with the ability to sense and generate electrical signals. The Pantazis laboratory will combine cutting-edge experimental and computational approaches to understand how the intricate molecular architecture of ion channels relates to their function and regulation; and how ion channel function or dysfunction governs cellular excitability in health and disease.

I am thrilled to soon be starting my appointment as a WCMM Fellow at the Department of Clinical and Experimental Medicine (IKE), at the University of Linköping. My main area of research is on ion channels, which are fascinating membrane proteins governing cellular excitability: that is, the ability of cells to generate, sense, and respond to, the electrical signals used in nerves, muscles and the heart. I am particularly interested in neuronal voltage-gated calcium (CaV) channels, which couple electrical messages to the potent Ca^{2+}-mediated cytosolic signaling system, responsible for neurotransmitter release, synaptic tuning and even gene expression. CaV channels possess a highly intricate molecular structure, uniquely suited to their varied biophysical properties: my laboratory will study how the CaV channel dynamic structure responds to electrical signals, to ensure the precise amplitude and timing of the Ca^{2+} signal. Importantly, neuronal CaV channels are critical, and largely underused, drug targets, for many familial and acquired neurological disorders including epilepsy, ataxia and chronic pain. Therefore, our research is not only important for understanding how our bodies work at the molecular level, but also for the development of next-generation drugs with superior potency and selectivity.

Strengths in lab

The Pantazis laboratory will combine cutting-edge and innovative experimental and computational approaches to (i) unravel the complex activation and regulation mechanisms of ion channels; (ii) discover how their intricate structure and conformational rearrangements relate to their functional properties; and (iii) understand how ion channel function (and dysfunction) regulates physiological electrical signaling or causes aberrant excitability and disease. The structural and functional properties of normal, and disease-causing, ion channel macromolecular complexes will be interrogated in heterologous expression systems using voltage clamp fluorometry, and functional and structural modeling. Ion channel role in neuronal excitability and diseases such as epilepsy will be evaluated in cultured cells and excised tissues using hybrid electrophysiological-computational approaches (dynamic clamp) and Ca^{2+} imaging.

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Area of interest

Neuroprotective & neuroregenerative therapies- from experimental models to clinical trials

Being a neurologist, my vision is to contribute to discovery, development and clinical implementation of novel therapies for neurological disorders such as Parkinson's disease, Huntington's disease and stroke. I work with patients with all neurological disorders, but have a specialized profile in Parkinson's disease. As such, I am head of the clinical movement disorder team and elected board member of the Swedish Movement Disorder Society (Swemodis), the Swedish Parkinson Academy and the Network of European CNS Transplanation and Restoration. As a GCP- trained clinician, I have considerable experience in clinical studies, with a focus on not just therapeutic improvement but structural regeneration.

Having also a background in basic science, I lead a preclinical research group, which allows me to work with research questions using a translational approach. We examine disease mechanisms of neurodegenerative disorders, in particular how neurovascular changes contribute to neurodegeneration, with a special focus on pericytes as key players in inflammation and neurodegeneration and potential target cells for brain repair.

Strengths in lab

We work with disease modeling and target identification in vitro (cell cultures) and in vivo (several disease models) and utilize different patient samples (post mortem tissue, CSF, blood). We apply morphological and behavioral analysis as well as gene expression, proteome and secretome analysis to identify novel molecules and pathways involved in disease progression, neuroprotection and regeneration.

Clinical trials: I am also clinical investigator in an EU financed clinical multicenter trial using fetal-cell derived dopaminergic neurons for cell replacement in Parkinson's disease (www.Transeuro.org.uk) and in two clinical trials investigating the neurorestorative effect of the intracerebral administration of growth factors in Parkinson's disease. We are currently preparing the first clinical trial using embryonic stem-cell derived dopaminergic neurons for patients with Parkinsons disease.

Neurorestorative effects of Platelet-derived growth factor in Parkinson's disease

In the majority of neurodegenerative disorders there is also vascular dysfunction, pointing towards an important cross talk between vasculature and neurons.

We analysed microvascular changes in a rodent model of Parkinson's disease and demonstrated that specifically pericytes, perivascular cells lining microvessels, are activated as part of the blood vessel changes seen in Parkinson's disease. Treatment with platelet-derived growth factor (PDGF-BB), a growth factor binding with high affinity to the PDGF-Receptorβ (PDGFRβ) on pericytes, normalizes these blood vessel changes, and leads to partial neurorestoration and behavioral recovery in models of Parkinson's disease.

Stimulation of the PDGF-BB/PDGFRβ pathway not only leads to vascular stabilization, but also to the release of regenerative molecules and microvesicles suggesting a possible dual mechanism in the regenerative effect of PDGF-BB on the nigrostrial system in Parkinson's disease.

In a phase I/IIa first-in-men clinical trial i.c.v. administration of rhPDGF-BB is safe and well tolerated. PDGF-BB induces significant improvement in dopamine transporter (DAT) binding, a marker of DA fibers as measured by PET-Scan (10) in patients receiving the highest dose, whereas the signal declines in placebo patients indicating ongoing neurodegeneration.

Vicent Pelechano

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Area of interest

Genome-wide study of gene expression

One of the biggest challenges in biology is to understand how apparently identical cells respond differently to the same stimulus. Our group develops and applies novel genomic technologies to study the appearance of divergent gene expression programs in clonal populations of cells. We are especially interested in the case of drug-tolerant cancer persister cells that, although genetically sensitive to a drug, do not respond to it. To deliver an integrated view of the mechanisms driving their appearance, as well as to refine our knowledge of the basic process of gene expression, we study: the epigenetic status, transcript isoform usage and post-transcriptional mRNA regulation. In the last few years, the biomedical field has suffered a revolution thanks to the development of the massive parallel sequencing technologies. We have contributed by developing a diversity of approaches to study eukaryotic gene expression. By simultaneously sequencing both the 5' and 3' ends of each RNA molecule (TIF-Seq), we showed that the complexity of overlapping transcript isoforms had been greatly underestimated. More recently, we have shown how the existence of widespread co-translational mRNA degradation allows studying ribosome dynamics by sequencing mRNA degradation intermediates (5P-Seq). In addition, we have developed approaches for the study of other relevant biological questions, such as chromatin structure, single-cell transcriptomics or mRNA isoform-specific interactions with RNA binding proteins.

Strengths in lab

Our group, combining experimental and computational work, aims to develop and apply novel genome-wide techniques to study eukaryotic transcription to address fundamental biological questions with medical implications. We are experts in the development of genome-wide methods based on massive parallel sequencing. To develop those approaches we use budding yeast and human cell lines. We are interested in: Chromatin and RNA Inmunoprecipitation (ChIP and RIP), transcript isoform measurement, alternative transcription start and polyadenylation site, ribosome profiling, RNA stability measurement, single-cell approaches and the development of novel clinical genomic tools.

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Area of interest

Cell Reprogramming in Hematopoiesis and Immunity

The focus of my laboratory is to understand the molecular determinants underlying cell reprogramming and hematopoietic specification. In humans, the 200 differentiated cell states are normally stable and inherited through cell division. Under certain conditions, cell fate can, however, be modified or reversed. Cell reprogramming can be achieved experimentally in different ways, including nuclear transfer, cell fusion or expression of transcription factors. The emergent ability to directly reprogram any human cell into desired hematopoietic cell-types is opening avenues to the discovery of new therapies for immune and blood diseases.

The main goals of our research are:

1. To understand at the molecular level how hematopoietic cellular identities are specified during development employing cellular reprogramming.
2. To use this knowledge to manipulate genes and pathways that ultimately may allow the generation of patient-specific hematopoietic and immune cells for regenerative medicine and immunotherapy.

Our research will increase the understanding of the minimal intrinsic determinants underlying hematopoietic cell diversity, allowing us to delve into the mechanistic regulation of progenitor and effector cell developmental specification. This knowledge may allow the re-creation of these unique cell identities from any human cell. In the long-term we believe that our research will contribute to personalized hematopoietic regeneration as well as to develop novel cancer immunotherapies for leukemia, melanoma and other aggressive cancers.

Strengths in lab

We use a variety of experimental approaches to understand hematopoietic reprogramming, including: lentiviral gene transduction, flow cytometry, single cell gene expression and chromatin profiling, directed differentiation of mouse embryonic stem cells, Crispr/Cas9-based gene editing, cellular transplantation, high-content automated image acquisition and analysis and mouse genetics. Alongside with the understanding of the basic biology of hematopoietic specification, we aim to apply our findings to the treatment of human diseases. Our translation efforts include: a) development of new viral vectors and reprogrammed cells for gene as cell therapy, b) use these new sources of patient-specific cells for the identification of small molecules using chemical screens, c) analysis of patient cohorts with haematological and solid cancers that have received immunotherapies.

Programming antigen-presenting dendritic cells from fibroblasts

Fábio F. Rosa[1], Cristiana F. Pires[1], Ilia Kurochkin[2], Luís G. Palma[1], Andreia Gomes[1], Oliver Schulz[3], Dmitri Papatsenko[2], Caetano Reis e Sousa[3] and Carlos-Filipe Pereira[1]

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Cell fate reprogramming of adult cells towards pluripotency or unrelated somatic cell-types has been explored in the context of regenerative medicine and cell replacement therapy. Dendritic cells (DCs) are professional antigen presenting cells (APCs) specialized in the recognition, processing and presentation of antigens to T-cells, inducing adaptive immunity. We hypothesized that the unique properties of DCs could be induced by cell reprogramming allowing the direct control of immune responses.

Here, the requirements to induce DCs were investigated using combinatorial overexpression of Transcription Factors (TFs) in Clec9a-tdTomato mouse fibroblasts. This reporter system specifically marks the conventional DC lineage. We have identified three TFs sufficient to induce reporter activation, establish DC morphology and activate a DC transcriptional program. Reporter activation occurs within 48 hours and its efficiency increases with additional TFs. Induced DCs (iDCs) express surface MHCII, CD40, CD80 and CD86, which are essential for antigen presentation. iDCs engulf particles, proteins, dead cells and upon stimulation of toll-like receptors, secrete inflammatory cytokines. Remarkably, iDCs capture, process and present exogenous antigens to CD4+ T and CD8+ T cells, a hallmark of DCs. Finally, transduced human fibroblasts acquire DC morphology, surface markers and competence to engulf beads, proteins and dead cells. Hence, we provide evidence that antigen presentation can be programmed in unrelated cell types by a small combination of TFs.

Collectively, our results provide insights into DC specification and cellular identity, opening avenues for inducing immune responses with autologous-engineered cells. This strategy may underlie the development of powerful cancer immunotherapies.

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Area of Intrest

Hematopoietic cell transplantation (HCT) is often considered a last treatment resort for a number of serious diseases. At the Pediatrics Department in Lund, parental donors are often used in such setting, referred to as haploidentical (haplo-) HCT. In our research, we aim to study a number issues concerning haplo-HCT with the overall aim to increase efficacy and decrease treatment related complications.

First, in Haplo-HCT cells are transferred across large age boundaries; does this come at a price? Therefore, we study aging within our blood cell system, with a focus on hematopoietic stem cells. We study the mechanisms that drive these changes and aim to evaluate if haplo-HCT recipients present with signs a premature hematopoietic aging?
Second, as parental donors are only 50% HLA-identical, these children are at risk for graft-versus-host disease, whilst potentially benefitting from graft-versus-tumor actions. Future work will detail clinical outcome of such pediatric haplo-HCTs. Further, we will use a murine model to study hematological regeneration following haplo-HCT and evaluate how extended graft manipulation impacts graf-versus-tumor actions.

Cornelis Jan Pronk received his medical degree in 2001 from Utrecht University, The Netherlands. He completed his training in pediatrics at the Skåne University Hospital and currently works as a permanent staff member at the Department of Pediatric Oncology/Hematology in Lund. Dr. Pronk received his PhD in stem cell biology at Lund University (2008). Parallel to his clinical work, his research activities focus on hematopoietic and immunologic regulation in the context of aging and following hematopoietic cell transplantation at the Division of Molecular Hematology and Department of Pediatrics. Since 2017, Pronk holds a Clinical Researcher fellow-position within the Wallenberg Center for Molecular Medicine at Lund University, with a focus on the hematopoietic system.

Anders Rosengren

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Area of interest

Type 2 diabetes - from basic science to clinical trials

Anders Rosengren, MD, Associate Senior Lecturer (Assistant Professor), integrates clinical investigations, bioinformatics and experimental studies and aims to better understand the pathophysiology of type 2 diabetes and to identify more specific treatment targeted at the underlying disease mechanisms.

He is PI for the "Detailed Mapping of Type 2 Diabetes" (DIACT) study, which is a longitudinal patient study that investigates how the major pathophysiological components in type 2 diabetes are interlinked and develop over time. This is combined with global genetic, gene expression and metabolite data to identify biomarkers associated with pathophysiological components.

Network analysis and other bioinformatics approaches are used to integrate genetic and gene expression data from the patients and to identify disease genes. Candidate genes identified from these analyses are studied experimentally to investigate underlying disease mechanisms. Moreover, a method for drug repositioning is used that compares the gene networks that are perturbed in T2D with a large library of gene expression signatures from drugs to identify potential anti-diabetic compounds.

Anders Rosengren has extensive international collaborations, which includes e.g. Sage Bionetworks in Seattle and University of Oxford. Anders Rosengren was appointed a Ragnar Söderberg researcher in Medicine 2013. He has also recently been awarded a 5-year Future Research Leader grant by the Swedish Foundation for Strategic Research.

Anders Rosengren is also PI for PriusHealth, a study aiming to develop new research-based web tool for patients with type 2 diabetes. This tool will integrate biological and lifestyle aspects of type 2 diabetes and aims to improve patient self-management and is developed in close collaboration with patients in a research study.

Strengths in lab

We have an experimental and a translational arm in the lab. The experimental techniques we work with are: electrophysiology, Ca^{2+} imaging, in vivo metabolic challenges of mice and rats as well as standard biochemical and cell-biological methods.

The translational arm integrates bioinformatics methods, especially network analysis of gene expression data and statistical analysis of genetic, gene expression and patient phenotypes, with patient studies using various metabolic challenges.

Abstract

The presentation will discuss how to combine bioinformatics with cell-physiological techniques and clinical studies to identify new disease mechanisms and therapies for type 2 diabetes (T2D). We have recently identified Sox5 as a regulator of beta-cell phenotype. Sox5 knockdown induced gene expression changes similar to those observed in T2D and diabetic animals and had profound effects on insulin secretion, including reduced depolarization-evoked Ca2+-influx and beta-cell exocytosis. SOX5 overexpression reversed the expression perturbations observed in a mouse model of T2D, increased the expression of key beta-cell genes and improved glucose-stimulated insulin secretion in human islets from donors with T2D. The findings suggest that human islets in T2D display changes reminiscent of dedifferentiation and highlight SOX5 as a regulator of beta-cell phenotype and function. The presentation will also discuss recent findings on sulforaphane as a new potential anti-diabetic compound that reduces hepatic gluconeogenesis, including a translation to T2D patients.

Rolf B. Saager

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Area of interest

Quantitative Optical Imaging of Skin

Rolf Saager, PhD, develops methods and instrumentation that advance spectroscopy, light transport modeling, and imaging of tissue; creating non-invasive tools for the clinical detection, monitoring or treatment of skin diseases and injuries. Primarily, I work with Spatial Frequency Domain Imaging (SFDI), a wide-field, spectral imaging technique that can quantify functional properties of tissue (e.g. hemodynamics) via tissue absorption and structural properties via light scattering as well as adapt these techniques to include additional sources of light-tissue interaction (e.g. fluorescence).

Spatial Frequency Domain Imaging/Spectroscopy (SFDI/S) is a relatively new technique that has several appealing attributes: low cost, quantitative, depth selective, and scalable. I have developed strategies to quantify and localize macroscopic tissue structures, heterogeneities and functional biologic parameters. This creates a substantial opportunity to study a broad range of depth specific skin conditions (e.g. melanoma and nonmelanoma skin cancers, burn/pressure wound assessment and dermal therapeutics and regeneration) and/or models of localized disease in small animals (e.g. breast cancer models).

Strengths in lab

I hope to provide the biomedical field with novel tools to conduct disruptive research, while also providing a means to translate it into clinical settings; positively impacting the practice of healthcare:

Diagnostics: I aim to develop non-invasive imaging tools with increased sensitivity and specificity to actual biological processes, thereby developing new, quantitative platforms to study disease rather than just establishing metrics to differentiate it from surrounding tissue.

Light based therapies: This platform can impact Photodynamic Therapy (PDT) as SFDI can monitor three critical aspects of this treatment modality through quantitative, spatially resolved determination of 1) therapeutic light dosimetry, 2) tissue oxygenation, 3) photosensitizer uptake and concentration. In the context of Photothermal Therapy (PTT), this same measurement platform can determine 1) therapeutic light delivery and convert to the thermal load within sub-volumes of tissue, 2) nanoparticle concentration and distribution and 3) spectral signature changes in response to treatment.

Monitoring longitudinal response to therapy/wound healing: Phases of the wound healing (i.e. Hemostasis, Inflammation, Proliferation/Granulation, and Tissue Remodeling) can be non-invasively identified by the quantitative optical methods I have developed. This platform not only allows for predictive therapeutic response, but also invites collaborations to study interventions that may promote and/or accelerate wound healing; expediting drug development in regenerative medicine.

Michael Schöll

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Area of interest

Early detection of neurodegenerative diseases

Neurodegenerative diseases are notoriously difficult to diagnose early and there is still no cure available for disorders such as Alzheimer's disease (AD). Biomarkers derived from imaging modalities such as positron emission tomography (PET) and magnetic resonance imaging (MRI), as well as biomarkers based on the analysis of cerebrospinal fluid (CSF) or blood, have become immensely important especially for the early identification of individuals who are likely to develop neurodegenerative disorders, since an established notion is that potentially successful treatments should be deployed as early as possible in the disease process.

This early identification of neuropathological processes using adequate biomarkers currently not only supports reliable clinical diagnoses but also serves the recruitment of suitable candidates for clinical treatment trials, and renders possible the application of these biomarkers as outcome measures in treatment trials.

In particular the recent development of methods to map the accumulation of conformationally faulty forms of proteins and the subsequent synaptic impairment in vivo using PET has profoundly changed the way these processes can be identified at an early, pre-symptomatic disease stage. The Schöll group is using the most recent developments in molecular imaging by means of PET in combination with other neuroimaging- and fluid-based biomarkers, as well as neuropsychological profiling to develop holistic, validated, and usable tools for such an early identification.

Strengths in lab

Our group uses a truly multidisciplinary approach to create prediction models for neurodegenerative diseases. We combine advanced imaging- and fluid-based biomarker analyses with neuropsychological assessment and statistical modelling to validate both the predictive and diagnostic properties of each modality and combinations of modalities as well as to establish and validate novel, more accessible tools for the early, pre-symptomatic detection of pathogenic processes.

Spatial correspondence of tau pathology and grey matter atrophy distribution in Alzheimer's disease with intrinsic functional brain networks

Neuropathological studies have shown that typical tau pathology in Alzheimer's disease (AD) preferentially affects specific brain regions whereas others remain relatively spared. The distinct regional spread of tau pathology in AD may be a consequence of the intrinsic network structure of the human brain and underlie regional grey matter (GM) atrophy. The spatially distributed brain regions that are most affected by the spread of tau pathology or atrophy may hence reflect an interconnected neuronal system. We characterized the distribution profiles of tau pathology and GM atrophy in AD using positron emission tomography (PET) and structural magnetic resonance imaging (MRI), and studied these patterns in relation to the functional network organization of the human brain in two independent samples of prodromal and manifest AD cases (Swedish BioFINDER and ADNI) with functional brain networks characterized by large-scale resting state functional magnetic resonance imaging (rs-fMRI) data in healthy subjects. In the BioFINDER cohort, the tau pattern involved predominantly regions overlapping primarily with the dorsal attention, and to some extent with higher visual, limbic and parts of the default-mode network. PET-evidenced tau pathology in the ADNI replication sample, which represented a more prodromal group of AD cases, was less pronounced but showed a highly similar spatial distribution profile, suggesting an earlier-stage snapshot of a consistently progressing regional pattern. Preliminary analyses of atrophy patterns in the BioFINDER sample suggested less cortical involvement than with tau spread. Our results indicate that the regional deposition of tau aggregates in AD predominantly affects higher-order cognitive over primary sensory-motor networks, but does not appear to be specific for the default-mode or related limbic networks. Moreover, GM atrophy seems to involve significantly fewer cortical regions than tau pathology in AD.

Mikael Sellin

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Area of interest

Gut infections constitute a leading cause of morbidity worldwide, with estimates of up to two billion disease cases annually. Enterobacteria, such as *Salmonella*, *Escherichia*, and *Shigella* species account for more than half a billion of these infections. Pathogenic enterobacteria are characterized by the ability to bind and/or invade the epithelium of the intestinal mucosa, thereby triggering an inflammatory tissue response. Antibiotic treatment has proven remarkably inefficient at clearing these infections and may in some cases even increase bacterial shedding from the infected individual. Moreover, the heavy use of antibiotics in healthcare and agriculture has led to a fast spread of resistance mechanisms among enterobacterial isolates. Hence, we have both curiosity-driven and clinical incentives to better understand the relevant microbe – host interactions that drive progression of intestinal inflammatory disease.

The mechanisms of pathogen - host cell interplay have traditionally been studied in simplified cell culture settings, where pure bacteria and tumour-derived cell lines are mixed in a culture medium. Such experiments continue to uncover a wealth of potential biochemical interactions between microbe and host cell. However, to understand the relevant molecular and physiological underpinnings of a "real" gut infection, additional approaches are needed. Recent developments in high-resolution microscopy techniques and experimental models now allow us to tackle how enterobacterial disease progresses on the cellular and molecular level also under more physiological conditions. The Sellin lab employs comparative cell biology, organotypic tissue culture, analysis of intact infected tissues, state-or-the-art microscopy, and clinically relevant pathogens (*i.e. Salmonella* and *Shigella* species), to explore the mechanisms sparking enterobacterial gut disease. The ambition is that our fundamental work will form the basis for future therapeutic approaches against these challenging infectious agents.

Strengths in lab

Organotypic tissue culture, Intestinal pathology analysis, Bacterial infection biology, Bacterial genetics, Mammalian cell line culture, Murine models of gut infection, Live microscopy

Bacterial gut infections

It has likely not escaped anyone's notice that bacterial infections constitute a re-emerging global health threat. Invasive gut bacteria comprise a prevalent and challenging group of infectious agents that can spark intestinal inflammatory disease and are often surprisingly resilient to antibiotic therapy. The Sellin laboratory is embedded in the department IMBIM at Uppsala University and affiliated with SciLifeLab and Uppsala Antibiotics Center. We study the molecular warfare between invading gut bacteria, for example Salmonella and Shigella species, and the epithelium of the hosts intestinal mucosa. We conduct bacterial infection experiments both under simplistic cell line culture settings, in cultured organotypic 3D-mimics of the gut mucosa, and in murine in vivo models of gut disease. Our overarching aim is to understand the physiologically relevant mechanisms that explain each step of bacterium – host cell interplay during development of inflammatory gut disease. Here, we give an overview of ongoing activities in our laboratory.

Karolina Skibicka

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Area of interest

Obesity - Neural Substrates of Energy Balance; From Molecule to Circuit to Behavior

Karolina Skibicka, PhD, Associate Senior Lecturer in Physiology, investigates the behavioral and neuroendocrine processes that govern fundamental homeostatic and reward controls of food intake, and ultimately how these systems fail in obesity. She aims to identify a more effective obesity treatment targeting the neural circuits underlying overeating.

By integrating careful experimental decomposition of behavior with neuropharmacology, genetic manipulations, and molecular methods we aim to gain insight into how food and feeding behavior affects the brain, and in turn how the brain regulates feeding and food choices.

Recent discoveries by my group include findings that satiety or hunger hormones, for example glucagon-like peptide 1 or ghrelin, which are altered by nutritional status, affect far more than feeding behavior and body weight. They profoundly affect reward derived from food but also alcohol, emotionality and decision-making. This impact on behavior is paralleled by neurochemical and molecular changes in brain circuits regulating them. These findings are now pursued in clinical trials. I have extensive international collaborations, which include researchers from University of Pennsylvania, University of Southern California, Cambridge University, University of Freiburg, and Karolinska Institute, in addition to multiple local collaborative projects. I was appointed a Ragnar Söderberg Fellow in Medicine 2015. I have also been awarded the Fernström Prize in Medicine 2016 for young investigators.

Strengths in lab

CNS microinjections and microinfusions; optic stimulation and DREADD manipulation of genetically selected neuronal population; brain, BAT, & WAT histology and immunohistochemistry; virally-mediated neural tract tracing and si/shRNA neuroanatomically selective gene knockdown; energy expenditure measurements (telemetric core and BAT temperature measurement, infrared thermography, spontaneous activity); ingestive behavior measures (meal size, frequency, macronutrient preference); motivated behavior (operant conditioning paradigms, place preference); impulsive behavior (delay discounting, go-no go, DRL); emotionality and sociability tests (depression and anxiety-like behaviors, novel cage mate interaction-based tests).

Additionally we are also collaborating with Chalmers (an engineering university; group of Ann-Sofie Cans), to develop novel implantable microfabricated sensors for in vivo real time analysis of neurotransmitter release.

Doubling adiposity and robust hyperphagia with increased food reward after loss of lateral hypothalamic GLP-1R

Lorena López-Ferreras, Jennifer E Richard, Emily E Noble, Kim Eerola, Rozita H Anderberg, Kajsa Olandersson, Lilly Taing, Scott E Kanoski, Matthew R Hayes, Karolina P Skibicka

Increased motivation for highly rewarding food is a major contributing factor to obesity. Here we hypothesize that manipulating glucagon-like peptide-1 receptor (GLP-1R) activity selectively in the lateral hypothalamus (LH) can profoundly affect food reward behavior, ultimately leading to obesity. Progressive ratio operant responding for sucrose was used to examine food reward in male and female rats, following GLP-1R activation and pharmacological or genetic GLP-1R blockade in the LH. Ingestive behavior, metabolic parameters, as well as molecular and efferent targets of the LH GLP-1R activation were also evaluated. Food motivation was reduced by activation of LH GLP-1R. Conversely, acute pharmacological blockade of LH GLP-1R increased food motivation, but only in male rats. GLP-1R activation also induced a robust reduction in food intake and body weight. Chronic knockdown of LH GLP-1R induced by intraparenchymal delivery of an AAV-shRNA construct was markedly and persistently elevated ingestive behavior, body weight and ultimately resulted in a doubling of fat mass in males and females, in only four weeks. Increased food reinforcement was again found only in males. We also found a great degree of adaptive plasticity in the CNS GLP-1 system, likely an unsuccessful attempt to counteract the stunning weight gain. Collectively, our data identify the LH GLP-1R as an indispensable element of normal food reward, food intake, and body weight regulation. These findings also show, for the first time, that brain GLP-1R manipulation can result in a robust and chronic body weight gain. The broader implications of these findings are that the LH differs between females and males in its ability to control motivated and ingestive behaviors.

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Area of interest

Molecular Epidemiology and Cardiology

Heart failure is the end-stage of all heart disease, characterized by inability of the heart to maintain sufficient output of blood for the demands of the body, and arguably constitutes the major unmet clinical need in cardiovascular medicine today.

In our research, we aim to improve understanding of the causes and mechanisms underlying heart failure, to identify novel therapeutic targets and facilitate individually tailored treatment strategies. My research group applies and integrates a range of omics tools to large cohorts with blood and heart tissues from heart failure cases, recipients of heart transplants and mechanical circulatory support, and the general population.

Anders Ståhlberg

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Area of interest

Translational Genomics Platform

Anders Ståhlberg, Associate Professor, working as principal investigator at Sahlgrenska Cancer Center, University of Gothenburg. He is also Head of the Translational Genomics Platform at Clinical Pathology and Genetics, Sahlgrenska University Hospital.

Our research group's goal is to increase the survival of patients suffering from breast cancer or sarcomas characterized by specific fusion oncogenes. To accomplish this we are identifying and targeting cancer stem cell (CSC) specific features associated with therapy resistance and monitoring treatment efficiency using blood plasma. To achieve these goals we have access to (i) advanced single-cell methodologies to study CSCs, (ii) experimental systems that allow us to study the role of the microenvironment, and (iii) ultrasensitive mutation detection techniques, enabling treatment monitoring using blood plasma.

The Translational Genomics Platform is a research initiative with the attempt to bring innovation into healthcare. Ultrasensitive techniques allow individual DNA molecules related to diseases like cancer to be detected. Tumor DNA enters the blood in cancer patients and by analyzing the amount of these disease-specific DNA sequences the tumor burden is assessed. Thereby the method not only opens up the possibility for early diagnostics, but also to customize the treatment for patients before tumors are observed through traditional imaging methods. Today, we apply our platform and techniques in several national and international research projects in cancer and beyond.

We have developed several strategies for gene expression profiling and rare molecule analysis, especially at the single-cell and single-molecule level. Anders is also a co-founder of TATAA Biocenter and iScaff Pharma.

Strengths in lab

Our translational research includes in vitro and in vivo systems as well as handling and using clinical samples. We are applying a wide range of methods related to cell and molecular biology. We have also developed several technologies related to DNA, RNA and protein analysis. Our expertise includes the whole workflow from sample collection to final data analysis with a focus on single-cell analysis and liquid biopsies. We have also expertise in experimental systems related to the microenvironment and 3D-bioprinting.

Translational Genomics Platform for Ultrasensitive Allele Variant Analysis

Detection of extremely rare variant alleles within a complex mixture of DNA molecules is becoming increasingly relevant in many areas of clinical and basic research. The limitations of most technologies are that they are not sensitive enough to reliable detect rare allele variants or that they only interrogate a few pre-defined variants. Simple, multiplexed, PCR-based barcoding of DNA for sensitive allele variant detection using sequencing (SiMSen-seq) was developed to meet these needs. SiMSen-Seq has an easy workflow that allows flexible multiplexing options and the method can be applied on minimal DNA input (< 5 ng DNA). SiMSen-seq enables detection and quantification of individual DNA molecules with single-bp resolution covering several kilobases of DNA. Data analysis is standardized and can be performed with freely available software. Suitable sample types include cytological aspirates, fixed tissues and liquid biopsies like blood, urine, saliva, cerebrospinal fluid, and pleural fluid. Applications include cancer diagnostics, prenatal testing, immunology, and detection of organ rejection, forensics, and pathogen detection among others. Liquid biopsy analysis and the SiMSen-Seq methodology is available through the Translational Genomics Platform at the GeneCore, Clinical Pathology and Genetics, Sahlgrenska University Hospital.

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Area of interest

Molecular aspects of synapse formation and mechanisms of neurometabolic disease

The human brain is a remarkably complex structure: Nearly 100 billion neurons wire together via some 1015 synapses to form the neural circuits that underlie its function. The formation, specification and maturation of synaptic connections are thought to depend on specific cell adhesion molecules that span the synaptic cleft to form physical interactions between pre- and postsynaptic neurons. The details of these processes are not well understood, but their impairment predispose to neurodevelopmental and psychiatric disorders including autism and schizophrenia.

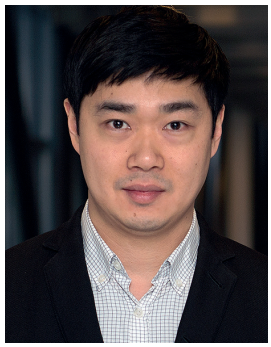
We are interested in the molecular mechanisms that regulate the formation and specification synaptic connections. By using a combination of protein biochemistry and genetic models, we are addressing the role of two carbonic anhydrase-related proteins that may regulate synaptic cell adhesion via the well-known Neurexin family of adhesion receptors. We are also interested in the intracellular pathways involved in synapse formation and are setting up a reduced system to study this. Furthermore, we aim to apply reverse genetic modeling in human ES-derived neurons to address mechanisms of disease, for example to study if patient-derived mutations that impair cellular metabolism could cause synaptic dysfunction and explain the patients' neuropsychiatric symptoms.

Strengths in lab

- Protein biochemistry and proteomics
- Production and transduction of lentivirus and adeno-associated virus (AAV)
- Genetically modified mice
- Mouse primary neurons
- Genetic modification of human embryonic stem cells (by CRISPR-Cas9 and/or AAV)
- Direct lineage-conversion of human ES/iPS-cells to neurons
- Confocal microscopy

Molecular Arcitecture of Synapses and Mechanisms of Rare Neurodevelopmental Disease

Our everyday thoughts and actions are mediated by the flow of information across synapses. Pre- and post-synaptic cell adhesion molecules are believed to play a role in the assembly, validation and plasticity of synaptic connections; a well-known example are presynaptic neurexins and their interactions with diverse post-synaptic ligands. Consistent with a critical role of neurexin-1 in the human brain, exonic deletions affecting the NRXN1 gene are associated with risk for developing autism spectrum disorder or schizophrenia. The carbonic anhydrase-related protein CA10, an evolutionarily conserved, secreted glycoprotein with unknown function, has been found to bind neurexins in a cis configuration. This interaction can result in the formation of an intermolecular disulfide bond between conserved cysteine residues in neurexins and CA10 to form a stable and stoichiometric complex. Upon forced expression of CA10 in neurons, surface-levels of various neurexin isoforms are specifically enhanced. We are now studying the in vivo function of CA10 as well as the mechanism whereby CA10 can promote neurexin surface-levels using a combination of protein biochemistry, mass spectrometry and knockout mice. This research will expand our understanding of protein complexes that shape our synapses and the basis for diseases that result from their dysfunction.



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Area of interest

Tumour virology - Virus genes essential for tumour maintenance and mutational landscapes during tumour development

Ka-Wei is a resident physician in Clinical Microbiology with research time within Wallenberg Centre. He aims to identify novel targets for the treatment of Epstein-Barr virus associated malignancies.

The majority of adults in the world are infected by Epstein-Barr virus (EBV). Following a primary infection during childhood or adolescence, EBV remains latent in our B-lymphocytes for the rest of our lives. For most of us this latent infection will go unnoticed. But for approximately 200,000 patients world-wide each year EBV-infection turns into a fatal disease in the form of hematological (Hodgkin's lymphoma, Burkitt's lymphoma and post-transplantation lymphoproliferative disease) and epithelial malignancies (gastric adenocarcinoma and nasopharyngeal carcinoma). However, no specific treatment is currently available for EBV-associated malignancies.

Recently it has been shown that EBV-associated gastric adenocarcinomas mainly express a single EBV-gene, RPMS1 (Tang KW et al. 2013). RPMS1 encodes a 4 kilobase-pair long non-coding RNA, and expression levels are in the top seven percent of all cellular genes expressed in gastric adenocarcinoma. Interestingly, despite being one of few putative targets for EBV-associated malignancies, this transcript has been completely neglected and the function is not yet known.
Our projects encompass clinical and molecular studies of the EBV-associated malignancies with particular focus on viral gene expression and mutational landscapes. We study clinical samples from pre-malignant and malignant stages as well as cell lines. We employ genetic manipulation techniques as well as standard clinical assays to affirm potential targets as clinically significant markers and important factors for proliferation.

Strengths in lab

We use a wide range of molecular and cell biological techniques including variations of massive parallel sequencing and chromatin immunoprecipitation. Our proximity to the clinical laboratory allows us to easily identify samples suitable for ex vivo translational studies.

Long non-coding RNA RPMS1 is essential for proliferation of Epstein-Barr virus transformed lymphoma cells

Epstein-Barr virus (EBV) is the causative agent for 200'000 cases of neoplasia worldwide every year. The virally encoded long non-coding RNA RPMS1 is detected in all types of EBV-infected cells. Recently it has been shown that RPMS1 is the main EBV-encoded gene in EBV-associated gastric adenocarcinoma, indicating a significant role for RPMS1 in tumour maintenance. EBV-transformed lymphoma cells transfected with plasmids encoding GFP, Cas9 and guide-RNA were enriched using FACS, and cell proliferation was quantified during a period of nine days. Cells transfected with guide-RNA against the RPMS1-promoter displayed a 30-fold reduction in expression levels of RPMS1 compared to cells transfected with a guide-RNA targeting a scramble sequence. Interestingly, the total number of cells in the control experiment increased 200-fold after nine days, while the cells with RPMS1 knock-out only increased 14-fold. Our results suggest that RPMS1 may be a potential drug target for treating EBV-associated malignancies.

Ilaria Testa

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Area of interest

Advanced light microscopy techniques

My research interest is focused on the establishment and development of advanced light microscopy techniques and its application to the life sciences.

Fluorescence microscopes, and especially their confocal and two-photon variants, are unique in their ability to directly observe morphological changes and molecular reactions in living cells. However, due to diffraction of light, the lateral resolution of conventional light microscopes is limited to about 200-300 nm. This limitation is overcome with great success by the field of super-resolution microscopy. Here, fluorescence molecules do not only act as probes to highlight features of interest, but their photophysical properties are used for overcoming the diffraction limit of light. By controlling those properties in space or time with light it is possible to improve the spatial resolution of an optical microscope down to the molecular scale (10-20nm).

My overarching scientific objective is to develop novel paradigms and concepts based on super-resolution microscopy to address contemporary challenges in biophysics and molecular biology. To achieve these goals I will push forward the quantitative aspect of live cell imaging by setting-up and applying different concepts of super-resolution microscopy based on single molecule detection (PALM/STORM/GSDIM) and targeted switching (STED/RESOLFT). These next generation microscopes will allow the precise identification of populations of biomolecules depending on their localization, abundance and dynamics inside their native environment. A special effort will be dedicated to investigate neuronal proteins, especially in synapses, where trafficking organelles and protein complexes are packed so tight in space that resolving them requires high resolution in space and time.

Live cell imaging at the nanoscale

Lens-based microscopy was unable to discern fluorescently labeled features closer than 200 nm for decades, until the recent breaking of the diffraction resolution barrier by sequentially switching the fluorescence capability of adjacent features on and off quickly made nanoscale imaging routine. Reported nanoscopy variants switch these features either in a target manner with intense laser beams, or molecule by molecule followed by computation in a stochastic fashion. Here, we show that emergent MoNaLISA (Molecular Nanoscale Live Imaging with Sectioning Ability) fluorescence nanoscopy enables fast and continuous imaging of living cells and tissues in super resolved detail by producing raw data images using only ultralow levels of light. This advance has been facilitated by the generation of fluorescent proteins (rsFP) that can be reversibly photoswitched numerous times. Distributions of functional rsFP-fusion proteins in living bacteria and mammalian cells are imaged at < 40 nm resolution. Using a fast-switching rsFP variant, we increased the imaging speed over our first reported RESOLFT schemes, which in turn enabled us to record spontaneous and stimulated changes of dendritic actin filaments and spine morphology occurring on time scales from seconds to hours. Furthermore, 3D and adaptive scanning implementation of our concept enable precise localization of synapses by recording neuronal proteins located in the pre and post synaptic side as well as in the axon initial segment directly inside 3D tissues. Our powerful next generation super resolution technique represents a new paradigm for non invasive induction and monitoring of ultrastructural dynamics of synaptic plasticity at the nanoscale.

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Area of interest

Molecular mechanisms underlying protein function in health and disease

I am interested in examining at the molecular level how alterations in the sequence and structure of proteins affect their function. Combining techniques such as X-ray crystallography with NMR and solution scattering techniques allows us to explore the structure and dynamics of proteins and complexes of varying size and complexity. By integrating these techniques with biochemistry, biophysics and cell biology allows us to probe their function and regulation at the molecular as well as cellular level.

In particular, we aim to employ these integrated structural biology techniques to explore the evolutionary relationship and functional repurposing of human proteins acquired by picornaviruses (through horizontal gene transfer).

Picornaviruses are a major cause of infections in humans and as such, it is of great interest to identify and characterise "host factors" (cellular proteins) necessary for viral infection, as well as their viral homologs. We want to understand whether the viruses have acquired these proteins to become independent of the cellular variant, and how these proteins have evolved in the viruses to fulfil new functions in short evolutionary time-frames. Such discoveries provide target candidates for the development of novel antiviral therapeutics and help us gain a better understanding of the lifecycle of these biomedically important viruses.

In the future, I'd also like to explore whether we can evolve these proteins further, e.g. for applications in biotechnology.

Strengths in lab

In my lab we have extensive experience in all aspects of protein crystallography, from construct design and (high-throughput, LIC) cloning, protein expression and purification, crystallization, data collection and processing, phasing using both molecular replacement as well as experimental phasing techniques (for novel structures), model building and analysis.

We also use general biochemistry and biophysics techniques to characterize protein stability and function as well as protein–protein as well as protein-ligand interactions.

Understanding Viral Entry Mechanisms Through Multi-Level Structural Analysis

Picornaviruses are a major cause of infections in humans and animals, including common cold, poliomyelitis, hepatitis A, and foot-and-mouth disease. To identify and characterise novel viral host factors will help us gain a better understanding of the lifecycle of these biomedically important viruses, and hopefully yield candidates for the development of novel antiviral therapeutics. By employing insertional mutagenesis in haploid human cells, we identified a poorly-studied phospholipid-modifying enzyme, PLA2G16, as a common host factor for multiple picornaviruses. We could show that this enzyme is required in the early steps of viral entry, enabling virion-mediated genome delivery into the cytoplasm (ahead of a viral pore-formation triggered clearance pathway involving the autophagy machinery). Remarkably, there is a group of picornaviruses whose 2A proteins share conserved sequence motifs with the human protein host factor, which led us to ask whether these viruses had acquired and evolved the host protein so as to become independent from the host factor.

We are currently characterising representative examples of this protein from all branches of the phylogenetic tree of viral 2AH-box proteins, to try and trace the possible evolutionary steps of this protein. The crystal structures of H-box containing proteins we have elucidated to date reveal a remarkable structural plasticity. Addressing how this structural plasticity correlates with the functional repurposing of the protein in the different picornaviruses will help answer still open questions on the molecular details of the picornavirus life cycle, contribute to our basic understanding of protein folding and function, and help guide rational enzyme design efforts.

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Area of interest

Over three million people die each year and over 60 million people suffer worldwide from chronic lung diseases (CLDs). At present, there is no cure for CLDs, including chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and pulmonary fibrosis. Lung transplantation is the only option at end-stage disease and is further complicated by shortage in organs available for transplantation and low efficacy. Five-year survival rate has remained at 50% for the last decade. New options are desperately needed for these patients.

Our lab focuses on understanding the role of the extracellular environment for endogenous and exogenous lung tissue regeneration in healthy and diseased lung. In particular, our work focuses on the design and use of biologic and synthetic scaffolds to bioengineer new lung tissue for transplantation. We further aim to build new models of human lung tissue to reduce animal usage, better understand how regeneration processes are deranged in CLDs, and for use as drug discovery and therapeutic screening platforms.

Strengths in lab

My lab has a translational approach which uses techniques ranging from the cell level to in vivo animal models and ex vivo human models. In addition to standard cell and molecular biology techniques, we have established the following techniques:

The bioengineering arm of my lab has established techniques for whole organ perfusion decellularization, physiologic recellularization in 2 and 3-dimensions, and ex vivo bioreactor culture (including whole native organs). The lab also studies repair and regeneration and has established expertise in precision cut tissue slices, organoid culture of primary stem and progenitor cells, and mechanotransduction (stretch and stiffness studies). We have experience in chronic lung disease murine models of fibrosis (bleomycin) and emphysema (elastase induced), as well as measuring lung mechanics using the Flexivent. The lab also utilizes bioinformatics approaches such as gene set enrichment analysis applied towards understanding chronic lung diseases.

Development of a hybrid alginate-ECM hydrogel as a potential bioink for 3D bioprinting

Background

Lung transplantation is the only curative approach for end stage lung disease, but tissue shortage remains a problem. Generating lung tissue ex vivo could overcome tissue shortages. Synthetic and biologic scaffolds have been explored, yet both have limitations. Biologic scaffolds have low reproducibility, while synthetic scaffolds lack biologically inductive properties. Hybrid materials, comprised of both, have been used for tissue engineering, but have been limited to simple shapes. Recent advances in 3D printing may permit for complex shapes, but potential bioinks are unknown. We hypothesized that a hybrid hydrogel generated by combining a synthetic polymer with lung derived extracellular matrix (ECM) could be a suitable bioink for 3D bioprinting lung tissue.

Methods

We generated hybrid hydrogels from a synthetic polymer, alginate, and ECM derived from decellularised mouse lungs to make hybrid hydrogels. Different combinations of ECM and alginate hybrid pre-hydrogel solutions and crosslinked hydrogels were characterised by rheology, spectrophotometry for turbidity, histological stainings and scanning electron microscopy (SEM). Viability and proliferation of distal lung epithelial cell lines (MLE12 and A549) encapsulated in the hydrogel were measured via immunofluorescence (Ki67+) and flow cytometry (EdU+) after 7 days.

Results

A hybrid ECM gel was successfully generated from alginate and decellularised mouse lung ECM. Percentages of ECM and alginate in pre-gel solutions impacted viscosity. Both MLE12 and A549 cells remained viable and were distributed homogenously within manufactured hydrogels of various shapes. MLE12s in ECM-alginate hybrid hydrogels were significantly more proliferative (30% increase) than MLE12 cells seeded in an alginate hydrogel as assessed by flow cytometry.

Discussion

A hybrid hydrogel generated from alginate and decellularised lung derived ECM supports proliferation of lung epithelial cell lines and can be manufactured in a variety of shapes. The hybrid alginate-ECM solution is thus a promising candidate as a bioink for 3D bioprinting but processing parameters need to be further optimized to generate constructs more closely resembling lung tissue.

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Area of interest

Novel therapies for Pancreatic Cancer

The research in Daniel Öhlund's laboratory aims to identify and explore novel therapeutic strategies for pancreatic ductal adenocarcinoma (PDAC) by targeting the tumor-associated stroma of this highly treatment resistant disease.

PDAC is characterized by a pronounced fibrotic stroma that surrounds clusters of cancer cells. The cancer cells are known to trigger both the recruitment and activation of heterogeneous populations of cells, such as cancer-associated fibroblasts (CAFs), immune cells, and neurons, and to stimulate the production of extracellular matrix (ECM). Many studies have suggested that certain stromal cells, and the ECM they produce, provide the cancer cells with essential signals that regulate cancer cell growth and survival, modulate drug response and contribute to therapy resistance. But recent data have also shown that nonselective approaches to target the stroma can give undesirable and unpredicted results. This highlights the complexity of the tumor-associated stroma and underlines the need for a better understanding of the stromal heterogeneity to be able to develop more precise drugs targeting the stroma. The hypothesis developed in the lab predicts that the stroma contains subpopulations of stromal cells, and ECM proteins, with different pathophysiological roles. Some stromal components are induced by the cancer cells to serve pro-tumorigenic roles, and others are driven by host defense mechanisms to serve anti-tumorigenic purposes. By deciphering the stromal composition and by developing strategies that selectively target the pro-tumorigenic elements of the stroma, or that is enhancing the efficacy of the anti-tumorigenic stromal elements, we believe that tumor inhibitory effects can be achieved.

Strengths in lab

To reveal the full complexity of the stroma, we are applying mass spectrometry-based methods, single cell sequencing techniques, and different in situ RNA sequencing techniques, on cancer tissue from genetically engineered mouse models (GEMMs) of pancreatic cancer and human pancreatic cancer tissue from biobanks with detailed clinical data available. To further identify which of the components in the stroma that serve as potential drug targets, we have developed organoid based co-culture systems where both neoplastic cells and different stromal cells are represented. Promising findings are tested in vivo in pre-clinical drug trials at our animal hospital. The team of scientists in the laboratory have different background and expertise, and the scientific questions are approached with a multidisciplinary mindset.

Targeting Tumor-stromal Interactions in Pancreatic Cancer

Pancreatic cancer is resistant to all available adjuvant therapies, indicating that novel strategies to tackle the disease are needed. The pancreatic tumor is characterized by a pronounced tumor stroma that surrounds the cancer cells, containing extracellular matrix and cancer-associated fibroblasts that provide the cancer cells with important signals that regulate cancer cell growth and survival, and contribute to therapy resistance. The overall goal of this project is to get a deeper understanding in the stromal heterogeneity, and to reveal and explore potential drugable targets hidden within the stroma. First, we will decipher the composition of the extracellular matrix by applying mass spectrometry-based methods, then resolving the phenotypic diversity found in cancer- associated fibroblasts embedded within the tumor by utilizing fluorescent in situ RNA sequencing techniques. Next, we aim to determine which stromal elements that are important in regulating cancer cell growth, survival, immune escape, and drug resistance by using genetically engineered mouse models of pancreatic cancer and organoid based co-culture systems. Finally, we will develop and test drugs that target the most pro-tumorigenic stromal interactions with the aim to discover and explore novel therapeutic strategies.

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