National Molecular Medicine Fellows Program

Francesca Aguilo

Wallenberg Centre for Molecular Medicine, Umeå University
Associate Senior Lecturer at the Department of Medical Biosciences
francesca.aguilo@umu.se
www.medbio.umu.se/om-institutionen/personal/aguilo-francesca/

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.

Alexey Amunts

SciLifeLab/Stockholm University
Group leader at Stockholm University
amunts@scilifelab.se
www.su.se/english/profiles/aamun-1.219419

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

Wallenberg Centre for Molecular Medicine, Umeå University
Associate Senior Lecturer at the Department of Clinical Microbiology
marta.bally@umu.se

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.

Photo: Stefan Zimmerman

Magda Bienko

SciLifeLab/Karolinska Institutet
Assistant Professor at the Department of Medical Biochemistry and Biophysics
magda.bienko@ki.se
bienkocrosettolabs.org

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.

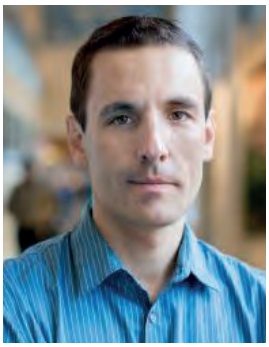
It is well established that, inside the human cell nucleus, chromatin is spatially organized in a non-random manner that is believed to have profound consequences on how genetic information is read. In the case of human DNA, a two-meter long molecule is compressed into a volume whose linear size is five 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.



Jeremie Boucher

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Adjunct Senior Lecturer, Institute of Medicine
Principal Scientist, Associate Director, AstraZeneca
jeremie.boucher@astrazeneca.com
jeremie.boucher@gu.se
wcmtm.gu.se/research-groups/boucher

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.

Paul Bourgine

Wallenberg Centre for Molecular Medicine, Lund University
Assistant Senior Lecturer
paul.bourgine.fr@gmail.com

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

Fabien Burki

SciLifeLab/Uppsala University
Systematic Biology Program, Department of Organismal Biology,
Associate senior lecturer
fabien.burki@ebc.uu.se
www.burki-lab.net

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).

Björn Burmann

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Associate Senior Lecturer at Institute of Chemistry and Molecular Biology
bjorn.marcus.burmann@gu.se
wcmtm.gu.se/research-groups/burmann

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.

Emma Börgeson

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Associate Senior Lecturer, Institute of Medicine
emma.borgeson@gu.se
wcmtm.gu.se/research-groups/borgeson
www.borgesonlab.org

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.

Claudio Cantù

Wallenberg Centre for Molecular Medicine, Linköping University
Senior Lecturer at the Department of Clinical and Experimental Medicine (IKE)
Faculty of Medicine and Health Sciences
claudio.cantu@liu.se
liu.se/en/employee/claca29

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.

Lars-Anders Carlson

Wallenberg Centre for Molecular Medicine, Umeå University
Associate Senior Lecturer at the Department of Medical Biochemistry and Biophysics
lars-anders.carlson@umu.se
www.carlsonlab.se

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).

Jens Carlsson

SciLifeLab/Uppsala University
Associate senior lecturer
Dept. of Cell and Molecular Biology, Uppsala University
jens.carlsson@icm.uu.se
www.carlssonlab.org

Area of interest

Strategies for structure-based drug discovery

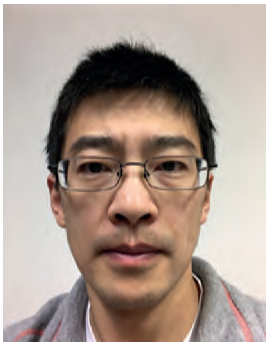
The goal of my research is to improve atomic level understanding of protein-ligand interactions with the vision to develop new strategies for early phase drug discovery and identify novel mechanisms for target modulation. We have mainly focused our efforts on G protein-coupled receptors (GPCRs), which 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.



Changchun Chen

Wallenberg Centre for Molecular Medicine, Umeå University
Associate Senior Lecturer at Umeå Center for Molecular Medicine
changchun.chen@umu.se

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*

Erika Comasco

SciLifeLab/Uppsala University
Associate senior lecturer, Uppsala University
Erika.Comasco@neuro.uu.se
www.scilifelab.se/researchers/erika-comasco/

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.

Sebastian Deindl

SciLifeLab/Uppsala University
Associate senior lecturer, Associate Professor at the Department of Cell and Molecular Biology
sebastian.deindl@icm.uu.se
www.deindl-lab.com

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.).

Lucie Delemotte

SciLifeLab/KTH
Assistant Professor, KTH
lucie.delemotte@scilifelab.se
delemottelab.theophys.kth.se

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

João Duarte

Wallenberg Centre for Molecular Medicine, Lund University
Associate Senior Lecturer
joao.duarte@med.lu.se
www.lunduniversity.lu.se/lucat/group/v1001219

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.

Simon Elsässer

SciLifeLab/Karolinska Institutet
Assistant Professor, Department of Medical Biochemistry and Biophysics, Karolinska Institutet
simon.elsasser@scilifelab.se
www.elsaesserlab.org

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.

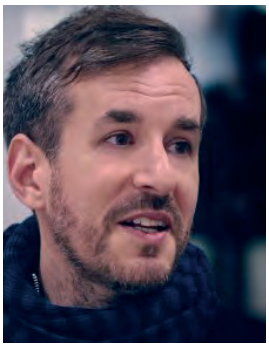
Our main interest is gene expression regulation at the transcriptional and translational level. We are, for example, controlling and probing chromatin proteins using light-activated and bioorthogonal chemistries. These methods, combined with quantitative, high-throughput, proteomic and genomic read-outs, 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).



Marc Friedländer

SciLifeLab/Stockholm University
Head of Quantitative RNA Biology Group
Assistant Professor at Department of Molecular Biosciences,
The Wenner-Gren Institute (MBW), Stockholm University
marc.friedlander@scilifelab.se
friedlanderlab.org

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.

Daniel Globisch

SciLifeLab/Uppsala University
Associate Professor at the Department of Medicinal Chemistry
Daniel.globisch@scilifelab.uu.se
www.ilk.uu.se/research/afk_en/biomarker-discovery/

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.

Markus Hansson

Wallenberg Centre for Molecular Medicine, Lund University and
Skåne University Hospital
Senior consultant, Department of Hematology
Markus.Hansson@med.lu.se
www.med.lu.se/wcmm/researchers

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.

Frank J. Hernandez

Wallenberg Centre for Molecular Medicine, Linköping University
Research Fellow at the Department of Physics, Chemistry and Biology (IFM)
Faculty of Science and Engineering
frank.hernandez@liu.se
liu.se/en/research/nucleic-nacids-technologies-lab

Area of interest

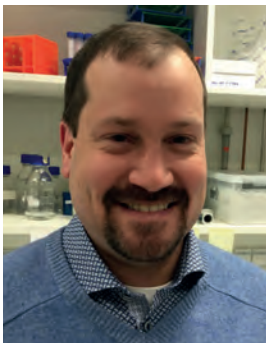
At Linköping University, Frank is a WCMM fellow in the Department of Physics, Chemistry and Biology (IFM) and the Group Leader of the Nucleic Acids Technologies Lab (NAT-Lab). His lab is exploring the utility of nucleases as biomarkers of disease. The ultimate goal of the NAT-Lab is to develop diagnostic 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.



Walker S. Jackson

Wallenberg Centre for Molecular Medicine, Linköping University
Senior Lecturer at the Department of Clinical and Experimental Medicine (IKE)
Faculty of Medicine and Health Sciences
walker.jackson@liu.se
liu.se/en/employee/walja90

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

Gauti Jóhannesson

Wallenberg Centre for Molecular Medicine, Umeå University
Associate Senior Lecturer at the Department of Clinical Sciences
Senior consultant, Ophtalmology, University Hospital of Umeå
gauti.johannesson@umu.se

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.

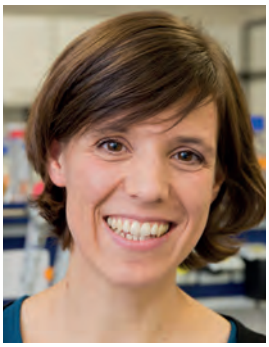
The main thread of my research has been glaucoma. Through my career I have studied glaucoma with respect to its prevalence, follow-up and enhanced drug delivery with nanoparticles. Taking the next step in glaucoma research, I have gotten increasingly more interested in the pathophysiology of glaucoma. 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.



Kristina Jonas

SciLifeLab/Stockholm University
Assistant professor (Bitr. lektor) at Stockholm University
Kristina.Jonas@su.se
www.jonaslab.org

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

Stefan Koch

Wallenberg Centre for Molecular Medicine, Linköping University
Senior Lecturer at the Department of Clinical and Experimental Medicine (IKE)
Faculty of Medicine and Health Sciences
stefan.koch@liu.se
liu.se/en/research/cell-signaling-in-intestinal-inflammation

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.

Claudia Kutter

SciLifeLab/Karolinska Institutet
Assistant Professor, Karolinska Institutet
Claudia.kutter@ki.se
ki.se/en/mtc/claudia-kutter-group

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

Wallenberg Center for Molecular Medicine, Lund University and Skåne University Hospital
Senior Consultant in Cardiothoracic surgery
sandra.lindstedt_ingemansson@med.lu.se
www.med.lu.se/wcmm/researchers

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

Francisca Lottersberger

Wallenberg Centre for Molecular Medicine, Linköping University
Senior Lecturer at the Department of Medical and Health Sciences (IMH)
Faculty of Medicine and Health Sciences
francisca.lottersberger@liu.se
liu.se/en/employee/fralo26

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.

Iben Lundgaard

Wallenberg Centre for Molecular Medicine, Lund University
Associate Senior Lecturer
Iben.lundgaard@med.lu.se
lundgaardlab.com/

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.

Cristina Maglio

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Resident physician at Department of Rheumatology and Inflammation
Researcher at Institute of Medicine
cristina.maglio@gu.se
wcmtm.gu.se/research-groups/maglio

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.

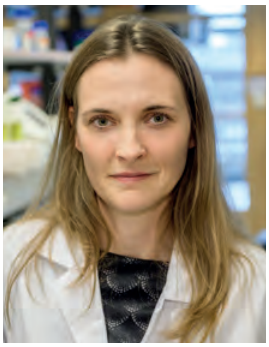
Martin Magnusson

Wallenberg Centre for Molecular Medicine, Lund University and Skåne University Hospital
Senior Consultant, Department of Clinical Sciences, Malmö and Department of Cardiology
martin.magnusson@med.lu.se
www.med.lu.se/wcmm/researchers/fellows#magnusson

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



Anja Meissner

Wallenberg Centre for Molecular Medicine, Lund University
Associate Senior Lecturer,
anja.meissner@med.lu.se
portal.research.lu.se/portal/en/persons/anja-meissner(6a464116-a3b7-4cd2-b418-2206a3f2d1b0).html

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)

Lili Milani

SciLifeLab/Uppsala University
Associate senior lecturer at the Department of Medical Sciences, Uppsala University
lili.milani@medsci.uu.se

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.

Bright Nwaru

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Association Senior Lecturer at Institute of Medicine
bright.nwaru@gu.se
wcmtm.gu.se/research-groups/nwaru

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.

Antonios Pantazis

Wallenberg Centre for Molecular Medicine, Linköping University
Assistant Researcher, University of California at Los Angeles
Group Leader at the Department of Clinical and Experimental Medicine (IKE)
Faculty of Medicine and Health Sciences
apantazis@ucla.edu
www.researchgate.net/profile/Antonios_Pantazis

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.

Gesine Paul-Visse

Wallenberg Centre for Molecular Medicine, Lund University and Skåne University Hospital
Senior Consultant, Department of Clinical Sciences, Neurology
gesine.paul-visse@med.lu.se
www.med.lu.se/english/klinvetlund/translational_neurology_group

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.

Vicent Pelechano

SciLifeLab/Karolinska Institutet
Assistant Professor, Karolinska Institutet
vicent.pelechano@scilifelab.se
pelechanolab.com

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.

Felipe Pereira

Wallenberg Centre for Molecular Medicine, Lund University
Associate senior lecturer
filipe.pereira@med.lu.se
www.med.lu.se/labmedlund/molecular_medicine_and_gene_therapy/research_groups/filipe_pereira

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.

Cornelis Jan Pronk

Wallenberg Centre for Molecular Medicine, Lund University and Skåne University Hospital
Senior Consultant, Dept. Clinical Science Lund, Divisions of Molecular Hematology and Pediatrics
kees-jan.pronk@med.lu.se
http://portal.research.lu.se/portal/en/persons/keesjanpronk(375363ae-33af-48ad-8aec-bf233f98a046).html

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

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Senior Lecturer at Institute of Neuroscience and Physiology
anders.rosengren@gu.se
wcmtm.gu.se/research-groups/rosengren

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.

Rolf B. Saager

Wallenberg Centre for Molecular Medicine, Linköping University
Senior Lecturer at the Department of Biomedical Engineering (IMT)
Faculty of Science and Engineering
rolf.saager@liu.se
https://liu.se/en/employee/rolsa28

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

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Associate Senior Lecturer, Institute of Physiology and Neuroscience
michael.scholl@neuro.gu.se
wcmtm.gu.se/research-groups/scholl

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.

Mikael Sellin

SciLifeLab/Uppsala University
Associate Senior Lecturer, IMBIM, Uppsala University
mikael.sellin@imbim.uu.se
imbim.uu.se/Research/Microbiology-immunology/sellin-mikael/

Twitter: @SellinLab

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

Karolina Skibicka

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Senior Lecturer at Institute of Neuroscience and Physiology
karolina.skibicka@neuro.gu.se
wcmtm.gu.se/research-groups/skibicka

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.

Gustav Smith

Wallenberg Centre for Molecular Medicine, Lund University and Skåne University Hospital
Resident in cardiology, Department of Cardiology
gustav.smith@med.lu.se
www.med.lu.se/english/klinvetlund/cardiology/research/project_leaders/smith

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

Wallenberg Centre for Molecular and Translational Medicine,
University of othenburg
Head of Translational Genomics Platform within WCMTM at
Clinical Pathology and Genetics, Sahlgrenska University Hospital
Associate Professor at Department of Pathology and Genetics
anders.stahlberg@gu.se
wcmtm.gu.se/research-groups/genomics-platform
cancercenter.gu.se/svenska/forskargrupper/anders-stahlberg

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.

Fredrik H. Sterky

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Resident physician at Department of Clinical Chemistry,
Sahlgrenska University Hospital
Researcher at Institute of Biomedicine
fredrik.sterky@gu.se
wcmtm.gu.se/research-groups/sterky

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

Ka-Wei Tang

Wallenberg Centre for Molecular and Translational Medicine,
University of Gothenburg
Resident physician at Department of Clinical Microbiology,
Sahlgrenska University Hospital
Researcher at Institute of Biomedicine
kawei.tang@gu.se
wcmtm.gu.se/research-groups/tang-group

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.

Ilaria Testa

SciLifeLab/Kungliga Tekniska Högskolan
Assistent Professor, Department of Applied Physics at the School of Engineering Science, Kungliga Tekniska Högskolan
ilaria.testa@scilifelab.se
www.scilifelab.se/researchers/ilaria-testa/

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.

Eleonore von Castelmur

Wallenberg Centre for Molecular Medicine, Linköping University
Research Fellow at the Department of Physics, Chemistry and Biology (IFM)
Faculty of Science and Engineering
eleonore.von.castelmur@liu.se
liu.se/en/employee/elevo74

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.

Darcy Wagner

Wallenberg Centre for Molecular Medicine at Lund University
Associate Senior Lecturer at the Department of Experimental Medical Sciences
darcy.wagner@med.lu.se
tinyurl.com/lungbiogen

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.

Daniel Öhlund

Wallenberg Centre for Molecular Medicine, Umeå University
Associate Senior Lecturer at the Department of Radiation Sciences
Resident physician, Oncology, University Hospital of Umeå
daniel.ohlund@umu.se
www.radsci.umu.se/forskning/onkologi/daniel-ohlund/

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.