The Department of Biosciences and Nutrition

Scientific Report
2016-2019

Karolinska
Institutet

CONTENT

The Department of Biosciences and Nutrition

The Department of Biosciences and Nutrition (BioNut), located in the Neo building on the South Campus of KI in Flemingsberg, performs research in areas of medical science, including molecular endocrinology, cancer biology, functional genomics, epigenetics, structural biology, bioinformatics, cell biology and nutrition. The focus is on experimental research, but we nevertheless provide education at all levels, with subjects covered including biomedicine, molecular techniques, bioinformatics, microscopy and nutrition science.

BioNut provides an international study and working environment, including about 250 scientists, students, administrative and technical personnel. Since 2019, under the new organisation of KI, we have been part of the KI South group of Departments. This group includes BioNut, the Department of Clinical Science, Intervention and Technology (CLINTEC), the Department of Laboratory Medicine (LabMed), the Department of Medicine, Huddinge (MedH), the Department of Neurobiology, Care Sciences and Society (NVS), the Department of Dental Medicine (Dentmed) and the Department of Clinical Science and Education, Södersjukhuset (KI SÖS).

A word from the Head of Department

KI is a two campus medical university with activities in both Solna and Flemingsberg. In 2019 KI launched a new 'Strategy 2030' with the goal that KI shall strengthen its role as one of the world's leading medical universities. As part of the new strategy both campuses *"shall be developed into attractive arenas for life science companies and other actors that strengthen the innovation ecosystem"*. Therefore, BioNut has a key function in Flemingsberg being the only pre-clinical department at KI South. In the past few years major investments have been made in new buildings at KI. In Flemingsberg, Neo and ANA Futura were built in close proximity to Karolinska University Hospital in Huddinge to strengthen experimental-translational research environments. In my opinion it is essential in this context to have basic scientific expertise in molecular biology, biochemistry, genetics and cell biology. This allows us to conduct high quality research projects including collaborations that can improve the quality of clinical research at KI South. Due to changes in the healthcare system in the Stockholm region, large patient groups at the hospital in Huddinge will be available for experimental studies on disease mechanisms in coming years. It has been a challenge for KI to balance infrastructure investments and strategic recruitment between the two campuses. For BioNut such a balance in the area of experimental research will be of key importance in order to strengthen its role at Flemingsberg in this new decade.
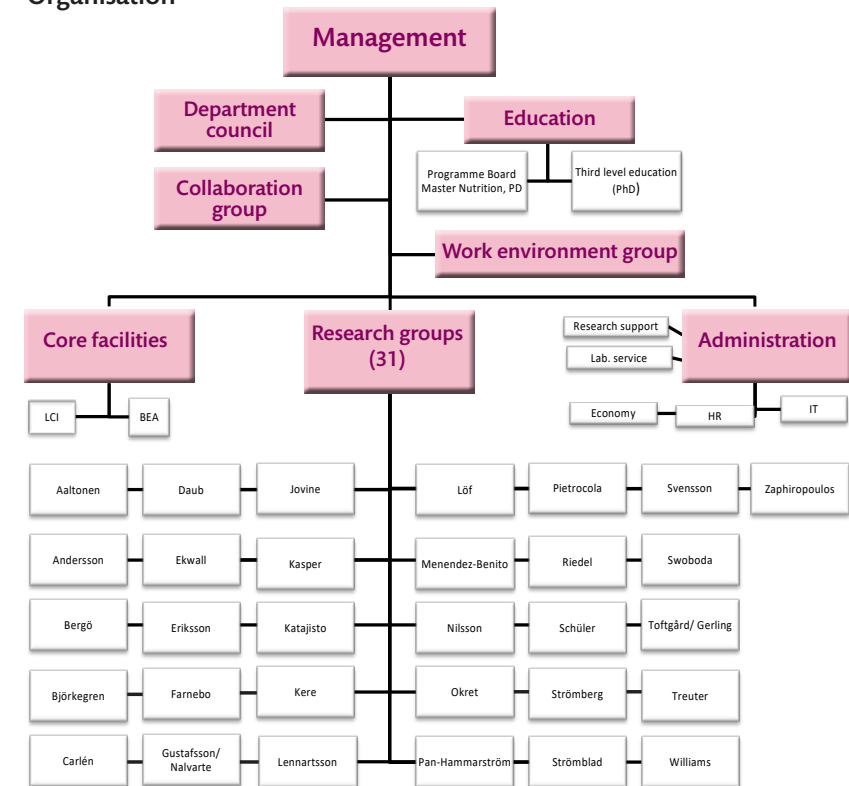
Karl Ekwall,
Head of Department at BioNut (August 2015 - August 2020)

The Department in brief

Organisation

Finances 2016-2019

INCOME STATEMENT	2016	2017	2018	2019
Revenues from Public Grants	43 897	50 315	56 770	49 483
Revenues from Fees	10 436	10 884	10 356	13 293
Revenues from External Grants	153 252	137 853	182 700	135 848
Internal revenues	20 119	16 636	18 050	27 259
TOTAL REVENUES	207 585	215 688	267 876	225 883

Key Financial Figures (%)	2019
External/Total financing	60%
Research and doctoral education	95%
First and second level education	5%

Discoveries

There are numerous examples of key scientific discoveries made at BioNut. This report highlights selected papers from each of the research groups. Here follow some examples from three different research areas, namely ageing, cancer and structural biology. Maria Eriksson's group has discovered that the underlying mechanism responsible for age-related somatic mutagenesis, across most tissues, is the gradual loss of efficiency of DNA repair systems (Franco, Helgadottir *et al.*, *Genome Biology,* 2019, 20:285). Martin Bergö's team has found that dietary antioxidants actually accelerate lung cancer - they activate a protein called BACH1 which forces tumour cells to take up glucose and use it for aerobic glycolysis, which drives metastasis (Wiel C *et al., Cell* 2019 78: 330). Luca Jovine's group has shown the first example in molecular detail of how egg and sperm contact each other at the very beginning of fertilisation (Raj I *et al., Cell* 2017 169:1315). Please note that our research covers more than a dozen different research areas resulting in many important findings published in 2016-2019.

External grants 2016-2019

- 41% The Swedish Research Council
- 19% The Swedish Cancer Society
- 4% Swedish Foundation for Strategic Research
- 11% European Commission
- 8% The Wallenberg Foundation
- 6% Astra Zeneca
- 5% The Swedish Childhood Cancer Fund
- 5% Forte
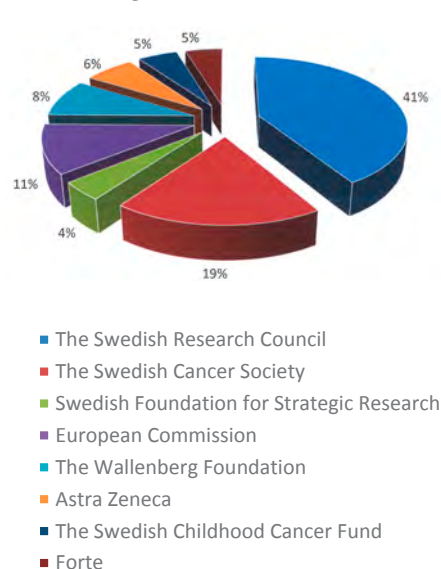
Research

We have currently 31 research groups, 46 doctoral students and around 70 affiliated researchers and postdocs.

- We aim to carry out high quality research projects including collaborations that can improve the quality of clinical research at Campus Flemingsberg.
- We have a key function in Flemingsberg, being the only pre-clinical Department at KI South.
- We emphasise that it is essential to have basic scientific expertise in molecular biology, biochemistry, genetics and cell biology on both KI campuses.
- We are hosting three Core Facilities for experimental research. One of these is the newly established, eHealth, which will not be described in this report.

For more information about the research at BioNut, see our website:
https://ki.se/en/bionut/research-at-bionut

Researchers leaving 2016-2019

During the period eight group leaders left the Department; Joseph Rafter (Bioinformatics), Patrick Cramer (Functional Genomics), Karin Dahlman-Wright (Functional Genomics), Jussi Taipale (Functional Genomics), Hans Hebert (Structural Biology), Lennart Möller (Toxicology), Henrik Garoff (Virology) and Linda Lindström (Cancer epidemiology).

~170 Employees
31 Research groups
46 Doctoral students
60% External Grants 2019
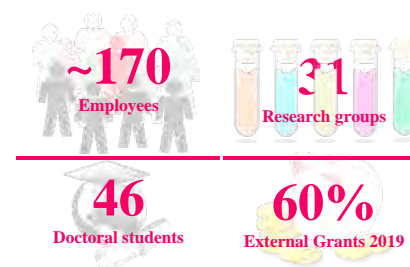
New researchers

We have new group leaders coming in. Their activities will not be presented in this report, but can always be found on our website; www.ki.se/bionut.

NAME OF NEW GROUP LEADER	Research area
Camilla Björkegren	Exploring molecular mechanisms that regulate expression and stability of eukaryotic and viral genomes.
Federico Pietrocola	Cellular responses to stress in ageing and cancer.
Herwig Schüler	Biochemistry and structural biology of ADP-ribosylation - human enzymes and binder domains, and bacterial toxins.
Peter Svensson	We study interactions between viruses – notably HIV-1 and HTLV-1 – and the host cell so as to understand how these interact and to gain insights into both cellular processes and the viral replicative cycle.

Researchers at SciLifeLab

Science for Life Laboratory (SciLifeLab) was established as a joint effort between KI, KTH, Stockholm University and Uppsala University. BioNut has two research group leaders working with Infrastructure Services there; Ellen Sherwood and Max Käller. Their work will not be presented in this report.

Our research groups

On the following pages we will introduce you to our research groups and the important work they do. Contact details for the group leaders are given and you can always look on our website for more information:
https://ki.se/en/bionut/research-at-bionut

RESEARCH GROUP LEADER

Maria Eriksson

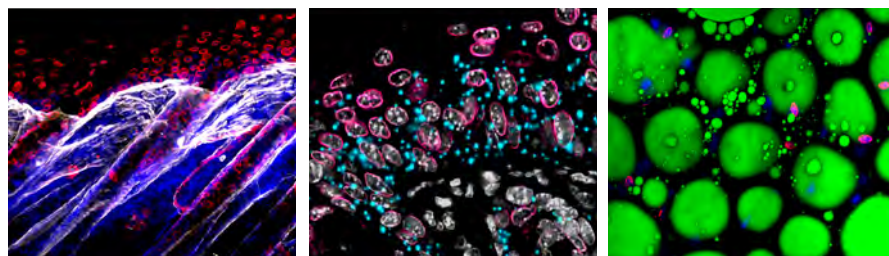Phone: +46 8 524 810 66
Email: maria.eriksson.2@ki.se

Genetic mechanisms of ageing

Our research concerns the genetic mechanisms that contribute to age-related decline of tissues and the development of age-associated disease. We use modern genomic technologies to identify genetic variations, and conditional *in vivo* models to dissect the functional significance of the variants discovered.

When we age, our tissues are characterised by a progressive loss of tissue function and regenerative capacity, which limits our physical performance and general health. The purpose of our research is to increase the knowledge about specific genetic and molecular factors that influence the onset of age-related diseases and affect health and disease. Advances in genomic technologies have made it possible to analyse somatic mutations in the whole genome of human cells and show that all cells accumulate mutations during development and ageing. This ongoing mutagenic process results in a tissue composed of cells with different genetic makeups, and is referred to as somatic mosaicism.

The specific aims include the development of a genetic atlas of somatic mutations across various cells of the human body. This atlas helps us to improve the current understanding of genetic events in cancer development and age-associated diseases, and to better comprehend the mutational processes that lead to differences in the somatic mutation landscape in different cells. Our results may also contribute to the development of therapies that could counteract the propagation of somatic mutagenesis, for example by the activation of DNA repair. Our most recent results indicate that the underlying mechanism responsible for age-related somatic mutagenesis, across most tissues, is the gradual loss of efficiency of DNA repair systems with ageing (Franco, Helgadottir *et al.*, 2019).

Other projects in the lab include the study of the very rare premature ageing disorder Hutchinson-Gilford Progeria Syndrome (HGPS, progeria) and the development of novel treatment strategies. HGPS affects one in 18 million individuals and is caused by a *de novo* point mutation in the lamin A gene, *LMNA c.*1824C>T, leading to mis-splicing and production of a truncated lamin A protein named progerin. Children show typical symptoms of accelerated ageing and die in their teens due to accelerated atherosclerosis and cardiovascular disease. The underlying pathomechanisms remain unclear and clinical trials have shown only limited success.

The impact of our studies may be beneficial for ageing and promote healthy ageing, as well as encouraging the identification of novel treatments that alleviate age-associated diseases.

Confocal microscopy pictures illustrating progerin expression in the skin and adispose tissue of a progeria model. Left; progerin is specifically expressed in epidermal cells (red) as demonstrated by the basement membrane staining (white). Middle; progerin is shown at the protein level by nuclear staining (pink) and at the transcript level by in situ hybridisation (blue). Right; adipocytes are illustrated by bodipy staining (green) and progerin by nuclear laminA/C staining (red).

Photos: Augustin Sola Carvajal, Gwladys Revêchon and Tomas McKenna

Selected publications 2016-2019

1. Franco I, Helgadottir HT, Moggio A, Larsson M, Vrtačnik P, Johansson A, Norgren N, Lundin P, Mas-Ponte D, Nordström J, Lundgren T, Stenvinkel P, Wennberg L, Supek F, Eriksson M.(2019) 'Whole genome DNA sequencing provides an atlas of somatic mutagenesis in healthy human cells and identifies a tumor-prone cell type.' *Genome Biology*, 2019, 20:285. (IF: 14.028)

2. Aguado J, Sola-Carvajal A, Cancila V, Revêchon G, Fern Ong P, Winston Jones-Weinert C, Wallén Arzt E, Dreesen O, Tripodo C, Rossiello F*, Eriksson M*, d'Adda di Fagagna F*. (2019) 'Inhibition of DNA damage response at telomeres improves the detrimental phenotypes of Hutchinson-Gilford Progeria Syndrome.' *Nature Communications,* 2019, 10:4990. *co-last author (IF: 11.880)

3. Osmanagic-Myers S, Kiss A, Manakanatas C, Hamza O, Sedlmayer F, Szabo PL, Fischer I, Fichtinger P, Podesser BK, Eriksson M, Foisner R. (2019) 'Endothelial progerin expression causes cardiovascular pathology through an impaired mechanoresponse.' *Journal of Clinical Investigation* 2019; 129:531-545. (IF: 12.282)

4. Franco I, Johansson A, Olsson K, Vrtačnik P, Lundin P, Helgadottir HT, Larsson M, Revêchon G, Bosia C, Pagnani A, Provero P, Gustafsson T, Fischer H, Eriksson M. (2018) 'Somatic mutagenesis in satellite cells associates with human skeletal muscle aging.' *Nature Communications* 2018, 9:800. (IF: 11.880)

Research Networks 2016-2019

- CIMED translational network in Clinical Physiology
- CIMED translational network in Chronic Kidney Disease
- European Society of Human Genetics
- American Society of Human Genetics

Prizes/Awards 2016-2019

- 2018 Rönnberg's prize in ageing and age-related diseases to Irene Franco
- 2019 Jeansson's foundation to Irene Franco

Group members 2016-2019

- Charlotte Strandgren
- Daniel Whisenant
- Robin Hagblom
- Hafdis Helgadottir
- Peter Vrtačnik
- Emelie Wallen Arzt
- Irene Franco
- Pär Lundin
- Carla Bosia
- Gwladys Revêchon
- Agustin Sola Carvajal

RESEARCH GROUP LEADER

Christian Riedel

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## The mechanisms that regulate age-related decline

Ageing and age-related diseases are central to human health. We study the molecular mechanisms that regulate ageing and try to pharmacologically target them for therapeutic purposes.

These are the major lines of research that we have been pursuing:

The role of DAF-16/FOXO and its binding partners in ageing regulation

A particular focus of ours has been the mechanistic exploration of ageing regulatory transcription factors, in particular of DAF-16/FOXO – a central driver of longevity that integrates many lifespan extending stimuli, namely nutrient deprivation, various stresses and cues of infertility, which it relays into the transcription of a wide range of stress resistance and longevity determining genes. We recently identified multiple binding partners of DAF-16/FOXO and have since been exploring their mechanistic role. Highlights of this research have been 1) our discovery that DAF-16/FOXO acts as a combinatorial transcription factor together with the transcription factor HLH-30/TFEB, and 2) that we observed a crucial role for Protein Phosphatase 4 in promoting initiation of transcription at many DAF-16/FOXO target genes.
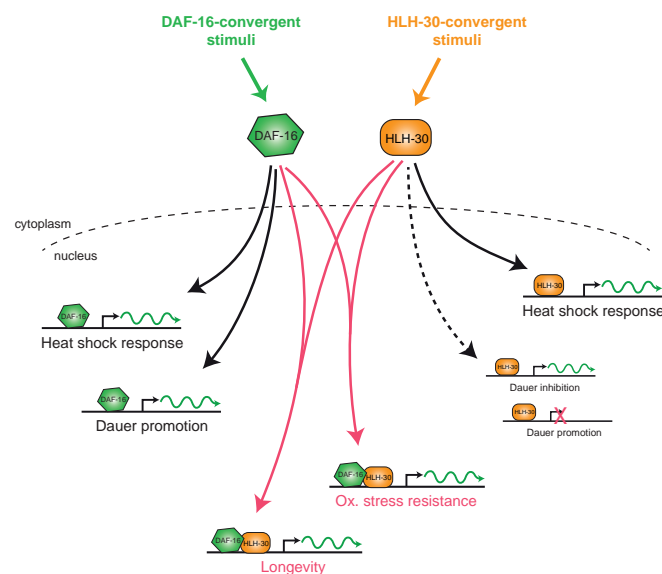
The role of the chromatin landscape in ageing regulation

Transcription is not only controlled by transcription factors but also the chromatin landscape that they interact with. Hence, we have been complementing our work with studies on the role of chromatin states, chromatin remodellers and the epigenome in the context of ageing and age-related disease.

Search for ageing-preventive interventions in humans

In addition to the mechanistic studies from above, we also sought pharmacological interventions against ageing in mammalian systems, including humans. Most importantly, we have developed machine learning-based methods that can predict ageing-preventive compounds on the basis of human transcriptomic data.

We identified the HSP90 inhibitor Monorden as a new ageing-preventive drug. In this graph, one can see how the lifespan of C. elegans is extended upon treatment with Monorden.

Illustration: Christian Riedel

Selected publications 2016-2019

1.   Sen, I., Chernobrovkin, A., Puerta Cavanzo, N., Liu, M., Lin, X.X., Baskaner, B., Brandenburg, S., Zubarev, R.A., Riedel, C.G. (2020) 'DAF-16/FOXO requires Protein Phosphatase 4 to initiate the transcription of stress resistance and longevity promoting genes'. *Nature Communications* 11(1): 138.

2.   Janssens, G.E., Lin, X.X., Millan-Arino, L., Sen, I., Kavsek, A., Seinstra, R.I., Stroustrup, N., Nollen, E.A.A., Riedel, C.G. (2019) 'Transcriptomics-based screening identifies pharmacological inhibition of Hsp90 as a means to defer aging.' *Cell Reports* 27(2): 467-480.

3.   Lin, X.X., Sen, I., Janssens, G.E., Zhou, X., Fonslow, B.R., Edgar, D., Stroustrup, N., Swoboda, P., Yates 3rd, J.R., Ruvkun, G., Riedel, C.G. (2018) 'DAF-16/FOXO and HLH-30/TFEB function as combinatorial transcription factors to promote stress resistance and longevity.' *Nature Communications* 9(1): 4400.

4.   Zhou, X., Sen, I., Lin, X.X, Riedel, C.G. (2018) 'Regulation of age-related decline by transcription factors and their crosstalk with the epigenome.' *Current Genomics* 19(6): 464-482.

Research Networks 2016-2019

- Management committee member of the European COST action "GENiE", BM1408

Group members 2016-2019

- Ilke Sen
- Xin Zhou
- Georges Janssens
- Lluís Millán-Ariño
- Lioba Körner
- Daniel Edgar
- Jérome Salignon
- Naghmeh Rajaei
- Poomy Pandey
- Alan Kavsek
- Marco Lezzerini
- Xin-Xuan Lin
- Andrea Stöhr
- Bora Baskaner
- Sonja Pikkupeura

We identified a new module comprised of the transcription factors DAF-16 and HLH-30 that by combinatorial gene regulation controls the relay of stressful conditions into the appropriate gene-regulatory responses.
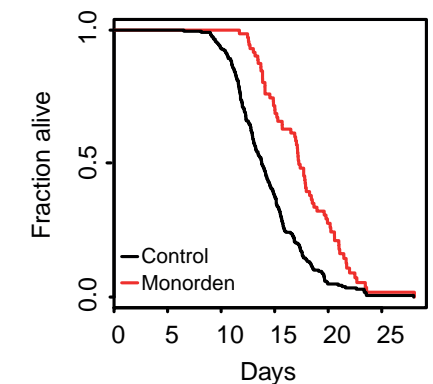
Illustration: Christian Riedel

RESEARCH GROUP LEADER

Carsten Daub

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Molecular basis of gene regulation of diseases

We focus on understanding the molecular basis of gene regulation of diseases, specifically related to inflammation. Our work includes genome-wide gene expression analysis from human patient samples employing various RNA-Sequencing.

Bioinformatics analysis identifies elements responsible for the observed expression differences in the diseased patients and the associated clinical phenotypes. Examples include transcription factors (TFs), closely related but distinct alternative promoters resulting in the same protein but employing different sets of regulatory TFs, expression of anti-sense RNA to modulate the sense-RNA and the regulatory role of enhancers, expressed repeat elements and miRNAs. We are also involved in several genome annotation consortia.

Development of sequencing technologies and sequencing library methods for genome, metagenome, transcriptome and epigenome data is moving at a breathtaking pace. We are working with the development of corresponding bioinformatics data analysis technologies for these genomics data. For example, our group identified gene enhancers in transcriptome data and assigned gene regulatory roles to these enhancers in diseases and development.
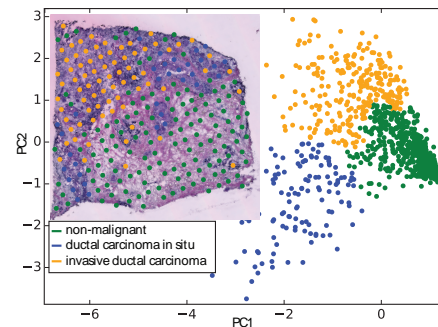
Spatial Transcriptomics data was used to identify cancer gene expression signatures and to classify cancer subtypes in breast tissue.

Illustration: Niyaz Yoosuf
Image modified from the original article, open access under the terms of Creative Commons Attribution 4.0 International Licence.

Understanding the molecular basis of perturbed gene regulation in diseases is one aspect of our research. We are using genome-wide analysis technologies based on high-throughput sequencing extensively. Developing the necessary bioinformatics tools together with best-practice analysis methods constitutes an important aspect.

For the last ten years, we have been working on obesity-related type 2 diabetes and on asthma. Close collaboration with clinical research groups has been of key importance.

We usually join the projects during the design phase where we contribute to the experimental design in terms of cohort stratification, statistical power, selection of tissue types, annotation of samples and data as well as selecting the high-throughput analysis technologies used. Addressing the specific biomedical questions of the projects by analysing the sequencing data together with the clinical data constitutes one of the main aspects of our work. Very close interaction with the clinicians is of outmost importance in connecting the findings of the data analysis to the biology underlying the disease.

We contributed to genome annotation projects for the zebrafish as part of the DANIO-CODE consortium and for the dog as part of the DoGA consortium. We first developed a sample and data annotation framework since both consortia are consolidating data from various sources. Main goals include improved genome annotation and adding gene enhancers. We work with Spatial Transcriptomics (ST) data, where we used the ST data in a gene independent way and employed machine learning methods to identify breast cancer signatures.

Selected publications 2016-2019

1. Sugiaman-Trapman D, Vitezic M, Jouhilahti EM, Mathelier A, Lauter G, Misra S, Daub CO, Kere J, Swoboda P. (2018) 'Characterization of the human RFX transcription factor family by regulatory and target gene analysis.' *BMC genomics* 2018 19;1 181-

2. Baillie JK, Arner E, Daub C, De Hoon M, Itoh M, Kawaji H, Lassmann T, Carninci P, Forrest ARR, Hayashizaki Y, Consortium F, Faulkner GJ, Wells CA, Rehli M, Pavli P, Summers KM, Hume DA.(2017)'Analysis of the human monocyte-derived macrophage transcriptome and response to lipopolysaccharide provides new insights into genetic aetiology of inflammatory bowel disease.' *PLOS GENETICS* 2017 13;3 e1006641-

3. Rydén M, Hrydziuszko O, Mileti E, Raman A, Bornholdt J, Boyd M, Toft E, Qvist V, Näslund E, Thorell A, Andersson DP, Dahlman I, Gao H, Sandelin A, Daub CO, Arner P. (2016) 'The Adipose Transcriptional Response to Insulin Is Determined by Obesity, Not Insulin Sensitivity.' *Cell reports* 2016 16;9 2317-26

Research Networks 2016-2019

- SYSMIC
- RP-Diabetes
- DANIO-CODE
- DoGA

Group members 2016-2019

- Enrichetta Mileti
- Matthias Hörtenhuber
- Filip Läärä
- Johanna Labate
- Abdul Kadir Mukarram
- Amitha Raman
- Eunkyoung Choi
- Wenjing Kang
- Ho Man Kelvin Kwok
- Mickael Dong
- Marine Tessarech
- Jacqueline Nowak
- Tahmina Akhter
- Irene Stevens
- Jiarui Mi
- Kubra Altinel
- Rasha Fahad
- Niyaz Yoosuf
- Marta Dias

RESEARCH GROUP LEADER

Roger Strömberg

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Unit for Organic and Bioorganic Chemistry

The current research is largely focused on nucleic acids and peptides for potential use in therapy. We are working with novel concepts in pharmaceutical development, i.e. "new modalities" as they are known, especially development of methodology that enables synthesis of these classes of molecules.

This also involves synthesis of biomolecules with new modifications that provide beneficial properties and oligonucleotide and peptide conjugates that equip the molecules with entities that enhance catalysis, delivery and/or targeting. Over the past ten years we have become more and more involved in translational research where new concepts show promise towards being moved further towards the clinic.

Stabilised, cell penetrating and target seeking oligonucleotides for enhanced therapy

Oligonucleotide (ON) therapy is limited by inefficient *in vivo* delivery. To address this, we are developing methods for conjugation to enable constructs of oligonucleotide equipped with different entities, including multiple conjugation of different classes of molecules to ONs. We are developing "cell penetration oligonucleotides", in order to address both cellular uptake and reduction of phosphorothioate modifications. We are looking at ON conjugates with entities for the targeting of specific tissues, e.g. heart and muscle cells where we collaborate with academic and industrial partners on antisense and splice switching ON therapy.
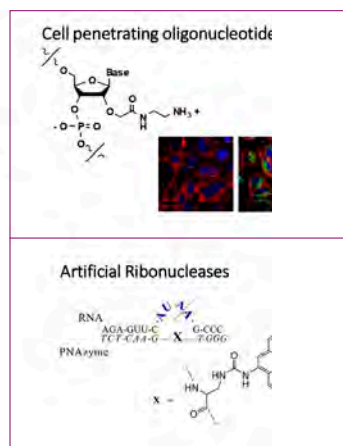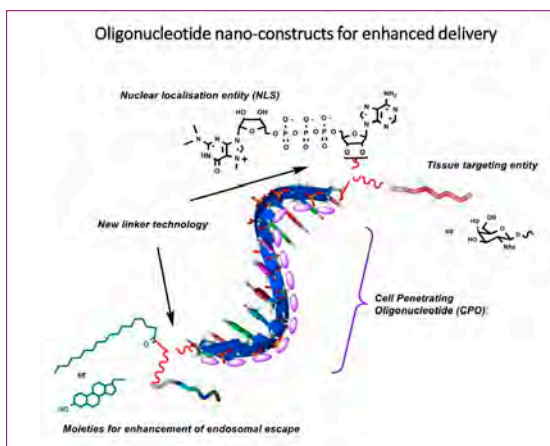
Oligonucleotide-based artificial nucleases and PNAzymes

A special part of modified ONs for potential therapeutic use is oligonucleotide-based artificial nucleases (OBANs). We have developed these to the state of being potentially useful tools, e.g. as artificial RNA restriction enzymes. We aim to make these biocompatible and efficient enough for use in a cellular environment and to explore potential for disease therapy. Recent peptide nucleic acid (PNA) based zinc ion dependent nucleases (PNAzymes) are highly efficient for cleavage of RNA and once crystal structures with substrate analogues are obtained, further development will follow.

Treatment of infections by means of substances that induce our own defense against microbes and Aβ-peptide ligands for potential treatment of Alzheimer's Disease (AD)

Over the past years we have developed substances for the treatment of infections through induction of body-own antimicrobial peptides. Potent inducers of antimicrobial peptides are currently being looked at for further development within a company. Ligands that stabilise the Aβ peptide and prevent toxicity of Aβ aggregates may hold promise for treatment of AD and this is now also in the hands of a pharmaceutical company.

Selected publications 2016-2019

1. Honcharenko M, Honcharenko D, Strömberg R. (2019), 'Efficient Conjugation to Phosphorothioate Oligonucleotides by Cu-Catalyzed Huisgen 1,3-Dipolar Cycloaddition.', *Bioconj. Chem.* , 2019, 30, 6, 1622-1628.

2. Luige O, Murtola M, Ghidini A, Strömberg R. (2019) 'Further Probing of Cu2+-Dependent PNAzymes Acting as Artificial RNA Restriction Enzymes.' *Molecules* 2019, 24, 672

3. Honcharenko D, Juneja A, Roshan F, Maity J, Galan-Acosta L, Biverstal H, Hjort E, Johansson J, Fisahn A, Nilsson L, Stromberg R (2019), 'Amyloid-β Peptide Targeting Peptidomimetics for Prevention of Neurotoxicity.', *ACS Chemical Neuroscience* 2019, 10.1021/acschemneuro.8b00485.

4. Ottosson H, Nylen F, Sarker P, Miraglia E, Bergman P, Gudmundsson GH, Raquib R, Agerberth B, Strömberg R. (2016), 'Potent Inducers of Endogenous Antimicrobial Peptides for host Directed Therapy of Infections.', *Sci Rep.*, 2016, 6:36692. DOI: 10.1038/srep36692.

Research Networks 2016-2019

- Molecular Tools for Nucleic Acid Manipulation for Biological Intervention (MMBio), EU network
- Delivery of Antisense RNA Therapeutics (DARTER) COST action, EU network
- IS3NA International Society for Nucleosides, Nucleotides and Nucleic Acids

Group members 2016-2019

- Håkan Ottoson
- Olivia Luige
- Dmitri Ossipov
- Malgorzata Honcharenko
- Rouven Stulz

- Merita Murtola
- Dmytro Honcharenko
- Kristina Druceikaite
- Partha Bose

RESEARCH GROUP LEADER

Martin O. Bergö

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Cancer, rapid ageing and nutrition

Our group is interested in how free radicals and antioxidants interact with nutritional and metabolic needs of tumour cells during cancer development. Contrary to popular wisdom, antioxidants stimulate cancer metastasis and we are now exploring this finding to develop anti-metastatic drugs and to be able to give well-informed nutritional advice to cancer patients.

We are also developing a new medicine for children with progeria – an accelerated ageing syndrome. We found a new enzyme involved in progeria and discovered that inhibiting this enzyme might increase life quality and life span for these children.

Research on *CAAX*-proteins raised exciting new possibilities

We perform curiosity-driven basic and translational research into cancer, arthritis, atherosclerosis, heart disease, and ageing. Our research begins with a biochemical pathway by which hundreds of *CAAX*-proteins, as they are known, are enzymatically modified by a cholesterol-like molecule – which is believed to activate *CAAX*-proteins by stimulating their interaction with membranes. When these *CAAX*-proteins (e.g. RAS and prelamin A) are dysfunctional they can cause cancer, inflammation, and ageing-like diseases. Our goals are to define the biochemical importance of the *CAAX*-protein modifications and thereby identify new strategies to treat these diseases.

Our studies have led to exciting and surprising discoveries and below are two examples.
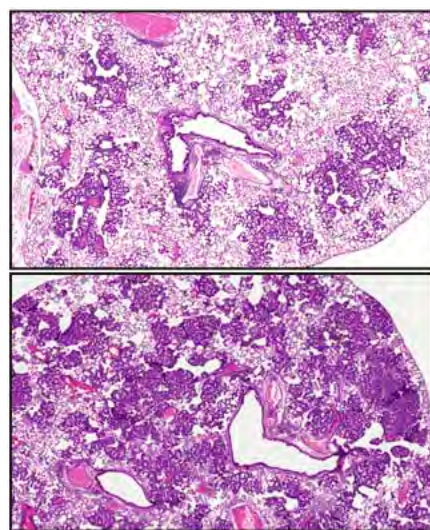
H&E–stained lung sections from mice with KRAS-induced lung cancer (top, untreated; bottom, mouse whose drinking water was supplemented with NAC). Sayin et al., Science Transl. Med. 2014

Photo: Bergö lab

Antioxidants stimulate cancer progression

Healthy people and cancer patients alike use antioxidant supplements, including vitamins A, C, and E, as a daily cancer-fighting strategy despite lack of convincing scientific evidence. We discovered that dietary antioxidants actually accelerate lung cancer growth and metastasis. Antioxidants activate a protein called BACH1 which forces tumour cells to take up glucose and use it for aerobic glycolysis – i.e. the Warburg effect – which drives metastasis. Antioxidants produce similar effects in malig-

nant melanoma and pancreatic cancer. The results suggest that cancer patients should avoid antioxidant supplements and that we may now design drugs that inhibit BACH1-induced glycolysis as a strategy to block metastasis.

A new treatment strategy for children with progeria

Progeria is a rare disease caused by a dysfunctional form of the *CAAX*-protein prelamin A. Dysfunctional prelamin A causes hair loss, slow growth, osteoporosis, muscle weakness, and death from heart attack or stroke in the teenage years. We discovered that inhibiting ICMT, an enzyme that modifies prelamin A, increases body weight and muscle strength, eliminates osteoporosis, and prevents death in mice with progeria; it also stimulates the

growth of cells from children with progeria. We are now developing drugs that inhibit ICMT and preliminary data indicate that our strategy could be successful. But first we have to optimise the drug so it can be tested in children with progeria.

Left, a mouse with progeria-like disease (e.g. hair loss, low body weight, muscle weakness, bone fractures). Right, a sibling whose disease was prevented by inhibiting the enzyme ICMT.

Photo: Bergö lab

Selected publications 2016-2019

1. Bandaru S, Ala C, Salimi R, Akula MK, Ekstrand M, Devarakonda S, Karlsson J, Van den Eynden J, Bergström G, Larsson E, Levin M, Borén J, Bergo MO, Akyürek LM (2019), 'Targeting Filamin A Reduces Macrophage Activity and Atherosclerosis', *Circulation. 2019 Jul 2;140(1):67-79*. doi: 10.1161/CIRCULATIONAHA.119.039697. Epub 2019 Apr 24.

2. Wiel C, Ibrahim MX, Le Gal K, Jahangir CA, Ziegler DV, Kashif M, Xu X, Mondal T, Kanduri C, Lindahl P, Sayin VI, and Bergo MO. (2019) 'BACH1 stabilization by antioxidants stimulates lung cancer metastasis.' *Cell* 78: 330–345

3. Akula MK, Ibrahim MX, Ivarsson EG, Khan OM, Kumar IT, Erlandsson M, Karlsson C, Xu X, Brisslert M, Brakebusch C, Wang D, Bokarewa M, Sayin VI, and Bergo MO. (2019) 'Protein prenylation restrains innate immunity by inhibiting RAC1 effector interactions.' *Nature Commun.* 10: 3975

4. Cisowski J, Liu M, Sayin V, Karlsson C, and Bergo MO. (2016) 'Oncogene-induced senescence underlies the mutual exclusive nature of oncogenic KRAS and BRAF.' *Oncogene* 35: 1328–1333

Research Networks 2016-2019

*   MBE is a member of the Nobel Assembly at Karolinska Institutet since 2018
*   MBE is a member of the board and chair of the research working group for the strategic research area cancer - Cancer Research KI

Group members 2016-2019

*   Xiufeng Xu
*   Anna-Karin Gustavsson
*   Sarah Schmidt
*   Kristell Le Gal
*   Elin Tüksammel
*   Sama Sayin
*   Yiran Liu

*   Murali Akula
*   Clotilde Wiel
*   Xue Chen
*   Christian Karlsson
*   Emil Ivarsson
*   Muhammad Kashif
*   Ting Wang

*   Mohamed Ibrahim
*   Ella Äng
*   Haidong Yao
*   Chowdhury Jahangir
*   Jaroslaw Cisowski

RESEARCH GROUP LEADER

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RNA-guided repair of DNA double-strand breaks

Our goals are to characterise the involvement of RNA and associated proteins in response to DNA damage and cancer.

Although evidence that RNA regulates DNA repair and thereby genome stability is accumulating, the underlying mechanism(s) is not well understood. Our goals are to characterise the involvement of RNA-modifying enzymes and guide RNAs in response to DNA damage and the role of associated modification of RNA in repairing this damage.

Recently, we demonstrated that the RNA-binding protein WRAP53β, initially discovered in our own laboratory, regulates repair of DNA double-strand breaks and that RNA plays a critical role in this context. Our preliminary findings reveal that silencing RNAs associated specifically in small Cajal bodies with WRAP53β (scaRNAs) impairs recruitment of repair factors to DNA breaks, which results in defective repair. Moreover, scaRNAs, enzymes that modify RNA and modified RNAs all accumulate at sites of damage, indicating that these are involved in DNA repair.

Currently we are exploring these observations, initially by characterising the RNA-modifying enzymes dyskerin and fibrillarin, subunits of the H/ACA and C/D complexes, respec-
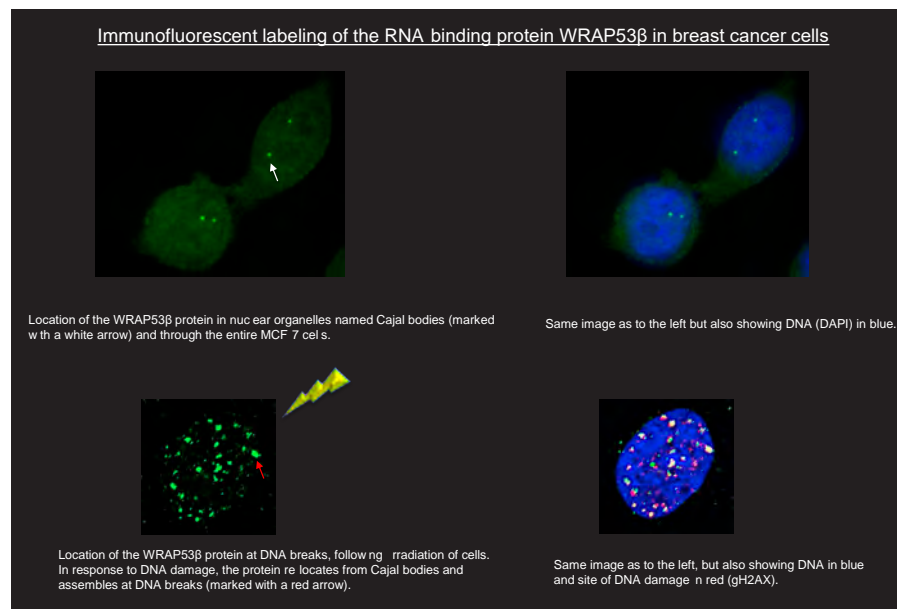
tively, and identifying novel RNAs involved in their action at DNA breaks. In parallel, we will elucidate the targets of scaRNAs at sites of DNA damage as well as their involvement in DNA repair. In addition, the role of RNA modifications in the DNA damage response will be investigated by identifying pseudouridinylated RNAs immunoprecipitated from chromatin fractions of UV-treated cells with antibodies that specifically recognise pseudouridine and/or dyskerin. Moreover, the factors that recognise modified RNAs present

at DNA breaks and the involvement of these factors in DNA repair will be examined.

These studies will provide novel insights into the role of noncoding RNA in the repair of DNA under both physiological and pathological conditions. Unravelling the underlying mechanism(s), the primary objective of our research, may allow the development of novel approaches to the treatment of diseases such as cancer.

Immunofluorescent labeling of the RNA binding protein WRAP53β in breast cancer cells

Location of the WRAP53β protein in nuclear organelles named Cajal bodies (marked with a white arrow) and through the entire MCF 7 cells.

Same image as to the left but also showing DNA (DAPI) in blue.

Location of the WRAP53β protein at DNA breaks, following irradiation of cells. In response to DNA damage, the protein relocates from Cajal bodies and assembles at DNA breaks (marked with a red arrow).

Same image as to the left, but also showing DNA in blue and site of DNA damage in red (gH2AX).

Photo and illustration: Marianne Farnebo

Selected publications 2016-2019

1. 1Dueva R, Akopyan K, Pederiva C, Trevisan D, Dhanjal S, Lindqvist A and Farnebo M. (2019), 'Neutralization of the positive charges on histone tails by RNA promotes and open chromatin structure.' *Cell Chemical Biology*, Aug 20. pii: S2451-9456(19)30248-X. doi: 10.1016/j.chembiol.2019.08.002.

2. 2Coucoravas C, Dhanjal S, Böhm S, Henriksson S and Farnebo M. (2017) 'Phosphorylation of the Cajal protein WRAP53β by ATM promotes its involvement in the DNA damage response.' *RNA Biology*, 2017 Jun 3; 804-813. doi: 10.1080/15476286.2016.1243647

3. 3Rassoolzadeh H, Böhm S, Hedström E, Gad H, Helleday T, Henriksson S and Farnebo M. (2016) 'Overexpression of the scaffold WD40 protein WRAP53β enhances repair of DNA double-strand breaks and survival after DNA damage.' *Cell death & Disease*, Jun 16;7:e2267. doi: 10.1038/cddis.2016.172

4. Pederiva C, Böhm S, Julner A, Farnebo M. (2016) 'Splicing controls the ubiquitin response during DNA double-strand break repair.' *Cell death & Differentiation*, Jun 17. doi: 10.1038/cdd.2016.58

Research Networks 2016-2019

- Member of research Network "Karolinska Institute's Breast Cancer Theme Center" (BRECT)

Prizes/Awards 2016-2019

- 2018 Senior Investigator Award, Swedish Cancer Society (Marianne Farnebo)
- 2017 Senior Research Award, Karolinska Institutet (Marianne Farnebo)
- 2017 Senior Investigator Award, Strategic Research Programme in Cancer (Marianne Farnebo)
- 2016 Junior Investigator grant, Center for innovative medicin (CIMED) (Marianne Farnebo)
- 2016 Selected to represent Karolinska Institutet (as 1 of 5 scientists) in Osaka (Osaka University), Japan, for a joint scientific symposium and future collaborations

Group members 2016-2019

- Soniya Dhanjal
- Chiara Pederiva
- Rosi Dueva
- Sofie Bergstrand
- Panos Maragozidis
- Christos Coucoravas
- Dominika Hrossova
- Stefanie Böhm
- Eleanor O'Brien

RESEARCH GROUP LEADER

Staffan Strömblad

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Cell Biology of Cancer

Our research focuses on key cellular events in cancer development and progression, including how cancer cells interact with and respond to their extracellular matrix (ECM), a protein network surrounding all tissue cells.

Cancer cells attach to and can migrate within the ECM, ultimately leading to life-threatening metastasis. We study the process of cancer cell migration with the purpose of unravelling new molecular mechanisms governing this process. We also study intracellular signalling stemming from cell-matrix interactions and from other sources and how these signals govern cancer cell behaviour.

Depending on the properties of the surrounding extracellular matrix, cancer cells can utilise different migration strategies for dissemination. This adaptive behaviour expands the range of tissue contexts under which cancer cells can efficiently invade. Expanding on this knowledge, we recently identified two distinct modes of mesenchymal migration and the fact that perturbing cell-ECM interactions or tensile forces caused switching between these modes. We combine different quantitative microscopy techniques, including traction force microscopy and FRET signalling biosensors, aiming to reveal mechanisms of migration mode switching and how distinct temporal phases are controlled and executed. These studies are expected to provide novel treatment opportunities targeting the most malignant aspect of any cancer, the ability to metastasise.
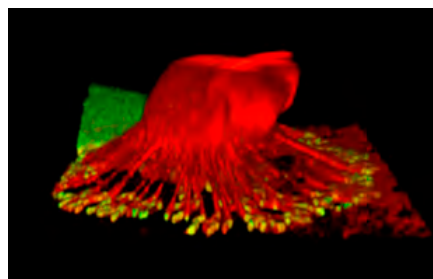
Reticular adhesions attach cells during mitotic round-up.
Confocal image of a U2OS cell rounded up to undergo mitosis. The cell body is labelled by a membrane dye in red, while integrin β5 in green marks the position of reticular adhesions.
*From Lock et al., Nat Cell Biol 2018. Image by John Lock.*

Cells attach to the ECM via multi-molecular adhesion complexes. We recently identified a novel class of adhesion complexes with a unique composition, including an enrichment in PIP2-binding and clathrin-associated proteins. We tentatively named these complexes "Reticular adhesions" and found a function of these complexes in cell division (mitosis) to attach the cells to the ECM while other adhesion complexes disassembled. We continue to study the function of this new class of adhesion complexes. We also study how the mechanical properties of the ECM affect breast cancer progression.

We also recently identified a novel signalling pathway in breast cancer, where we found p21-activated kinase 4 (PAK4) to be overexpressed in breast cancer and to correlate to poor patient outcome. We found that PAK4 overexpression in mammary cells overcomes the major barrier to cancer development called cellular senescence, which blocks cancer cell growth. Once breast cancer had developed, we were able to restore senescence selectively in the cancer cells by inhibition of PAK4, while untransformed cells were not affected. We have expanded these investigations to pancreatic adenocarcinoma and continue to elucidate the molecular underpinnings to how PAK4 may overcome the senescence barrier to cancer.

A new signalling pathway controlling the senescence barrier in breast cancer. In normal cells with low PAK4 expression levels (grey cells), oncogenes cause oncogene-induced senescence (OIS, blue cells), a major barrier to cancer development. We found that PAK4 overexpression can override the OIS barrier, indicating, consistent with the commonly observed PAK4 overexpression in cancer (purple cells). PAK4 inhibition in established breast cancer elicits a senescent-like growth arrest, indicating that PAK4 may be targeted for the development of therapy. We also defined a novel senescence regulatory pathway involving PAK4 phosphorylation of RELB. Based on Costa et al., Nat Commun 2019. Figure from Costa & Strömblad, Mol Cell Oncol 2020. Illustration by Tania Costa.
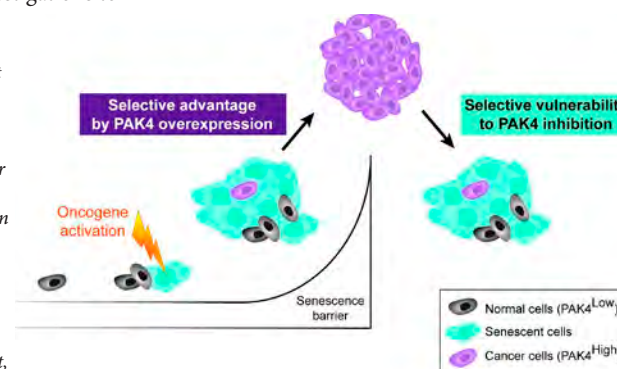
Selected publications 2016-2019

1. Costa, TDF., Zhuang, T., Lorent, J., Turco, E., Olofsson, H., Masia-Balague, M., Zhao, M., Rabieifar, P., Robertson, N., Kuiper, R., Sjölund, J., Spiess, M., Hernández-Varas, P., Rabenhorst, U., Roswall, P., Ma, R., Gong, X., Hartman, J., Pietras, K., Adams, PD., Defilippi, P., & Strömblad, S. (2019). 'PAK4 suppresses RELB to prevent senescence-like growth arrest in breast cancer.' *Nature Commun* 10, 3589-

2. Spiess M., Hernandez-Varas, P., Oddone A., Blom, H., Olofsson, H, Waithe, D., Lock, J.G., Lakadamyali, M., & Strömblad, S. (2018). 'Active and inactive β1 integrins segregate into distinct nanoclusters in focal adhesions.' *J Cell Biol* 217, 1929-1940

3. Gong, X., Didan, Y., Lock, JG. & Strömblad, S. (2018) 'KIF13A-regulated RhoB plasma membrane localization governs membrane blebbing and blebby amoeboid cell migration.' *EMBO J.* 37: e98994

4. Lock, J.G., Jones, M.C., Askari, J.A., Gong, X., Oddone, A., Olofsson, H., Göransson, S.A., Lakadamyali, M., Humphries, M.J., & Strömblad, S. (2018) 'Reticular adhesions are a distinct class of adhesion complex that mediates cell matrix attachment during mitosis.' *Nature Cell Biol* 20, 1290-1302

Research Networks 2016-2019

-   Member of research Network "Karolinska Institute's Breast Cancer Theme Center" (BRECT)
-   Systems microscopy pan-university network: sysmic.ki.se

Group members 2016-2019

-   Tania Costa
-   Miriam Masia-Balague
-   Xiaowei Gong
-   Xavier Serra Picamal
-   Sara Göransson
-   Matthias Spiess
-   Jianjiang Hu
-   Feifei Yan
-   Veronica Larsson
-   Miao Zhao
-   Helene Olofsson
-   Parisa Rabieifar

RESEARCH GROUP LEADER

Rune Toftgård

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From Jan.1st 2020: **Marco Gerling**
Email: marco.gerling@ki.se

Signalling and cellular heterogeneity in cancer

Our group tackles tumour complexity from different angles, focusing on signalling pathways, cellular heterogeneity and cellular interactions in cancer development and progression.

Tumours are complex tissues, in which there are constant interactions between many different cell types. Consequently, a multitude of factors determine how rapidly and aggressively a tumour grows. We study the heterogeneity of solid tumours with a focus on breast and gastrointestinal cancers.

We were able to show that Hedgehog signalling, a major developmental pathway, is diminished in the stroma of colorectal cancer. Using mouse models, we found that Hedgehog activation in the tumour microenvironment can attenuate tumour growth, unveiling a novel mechanism to target colorectal tumours via their surrounding stromal cells.

In breast cancer, different subtypes exist that have a direct impact on prognosis. We have discovered a novel population of mammary gland progenitor cells, which are marked by the stem cell gene Lgr6 and serve as the cells-of-origin for luminal breast cancers.

Hedgehog signalling, tissue stem cells, and cancer development

Mutational inactivation or activation of core components of the Hedgehog pathway underlies tumourigenesis in basal cell carcinoma of
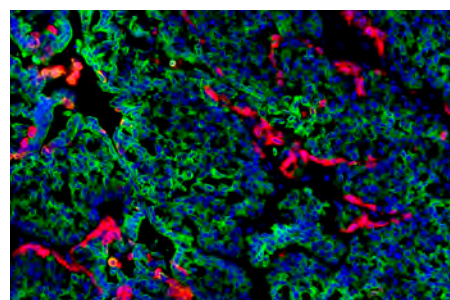
Breast tumour sample stained for basal (red) and luminal (green) cell markers. Photo: Leander Blaas

the skin (BCC), medulloblastoma and additional tumour types. A major focus of our research is to understand the molecular details of Hedgehog signalling and to devise new methods aimed at pharmacological inhibition of the Hedgehog signalling pathway at the level of the GLI transcriptional effectors.

## Tumour-microenvironment interactions in gastrointestinal cancer

Metastases are the main cause of death for cancer patients. Based on the finding that the tumour microenvironment has great impact on tumour growth, we study tumour-microenvironment interactions in metastases. How do metastases co-opt the stroma of the host organ, and what are the molecular mechanisms that allow tumour cells to replace the resident cells of their new host organ? We tackle these questions with mouse models, *ex vivo* culturing models and analyses of patient samples.

Cancer cells-of-origin and tumour heterogeneity

Breast cancer comprises an array of diseases with remarkable genetic and phenotypic diver-

sity, which are believed to originate from mutations in different stem cells or progenitor cells. Our research focuses on identifying and studying the cells-of-origin for different breast cancer subtypes. We use human organoid technology and mouse models to unravel how mutations affect the behaviour and plasticity of normal breast epithelial cells and how these factors contribute to breast cancer heterogeneity.
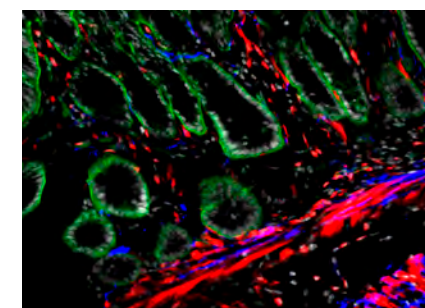
Mouse colon stained with CD49f (green, epithelial cells), ASMA (blue, stromal cells), and endogenous tdTomato (red, expressed in stroma cells). Nuclei in grey. Photo: Marco Gerling

Selected publications 2016-2019

1. Fernandez Moro, C., Bozoky, B., and Gerling, M. (2018). 'Growth patterns of colorectal cancer liver metastases and their impact on prognosis: a systematic review.' *BMJ Open Gastroenterol* 5, e000217.

2. Blaas, L., Pucci, F., Messal, H.A., Andersson, A.B., Josue Ruiz, E., Gerling, M., Douagi, I., Spencer-Dene, B., Musch, A., Mitter, R., *et al.* (2016). 'Lgr6 labels a rare population of mammary gland progenitor cells that are able to originate luminal mammary tumours.' *Nature cell biology* 18, 1346-1356.

3. Gerling, M., Buller, N.V., Kirn, L.M., Joost, S., Frings, O., Englert, B., Bergstrom, A., Kuiper, R.V., Blaas, L., Wielenga, M.C., *et al.* (2016). 'Stromal Hedgehog signalling is downregulated in colon cancer and its restoration restrains tumour growth.' *Nat Commun* 7, 12321.

4. Raducu, M., Fung, E., Serres, S., Infante, P., Barberis, A., Fischer, R., Bristow, C., Thezenas, M.L., Finta, C., Christianson, J.C., *et al.* (2016). 'SCF (Fbxl17) ubiquitylation of Sufu regulates Hedgehog signaling and medulloblastoma development.' *Embo J* 35, 1400-1416.

Research Networks 2016-2019

- Cancer Research KI
- Breast cancer theme group (Rune Toftgård, Leander Blaas)
- European Network for Breast Development and Cancer (Leander Blaas)

Prizes/Awards 2016-2019

- SSMF (Svenska Sällskapet för Medicinsk Forskning) Stora Anslag (Marco Gerling)
- Vetenskapsrådet, 6 years start-up grant (Marco Gerling)
- KI-funded Assistance Professor ("FoAss") position (Leander Blaas)
- Start-up grant from Swedish Research Council (Leander Blaas)

Group members 2016-2019

- Leander Blaas
- Xiaoze-Li Wang
- Csaba Finta
- Maryam Saghafian
- Romina Crocci
- Pablo Fernández-Pernas
- Iva Sutevski
- Katharina Gegenschatz-Schmid
- Natalie Geyer
- Anne-Franziska Guthörl
- Maria Hölzl
- Agneta Andersson
- Jens-Henrik Norum
- Ewa Dzwonkowska
- Arash Chitsazan
- Uta Rabenhorst
- Rosan Heijboer

RESEARCH GROUP LEADER

Victoria Menéndez Benito

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Protein inheritance in asymmetric cell division

Our goal is to understand the principles of asymmetric cell division (ACD). By dividing asymmetrically, a cell can produce two cells with different fates from a common genetic blueprint. ACD is a universal strategy for cellular diversification in most organisms, ranging from bacteria to humans.

ACD provides the basis for embryonic development, where different cell types need to arise from a single cell – the fertilised egg. In adulthood, ACD helps to maintain the correct number of stem cells and prevent cancer and tissue degeneration. Therefore, understanding the general mechanisms of ACD is of great medical importance.

We use the model organism budding yeast, *Saccharomyces cerevisiae*. Budding yeasts divide asymmetrically to produce two cells (mother and bud) that differ in size, composition, and age. While the mother cell progressively ages with each division, the daughters are born with a full replicative lifespan. Thus, budding yeast offers a tractable system to study ACD and rejuvenation. Our strategy is to develop technology to birth-date and follow proteins over time at single-cell resolution in combination with genome-wide approaches. Our main research lines are:

Mapping the inheritance of the yeast proteome

A hallmark of ACD is the unequal segregation of cellular components between the two daughter cells. By doing so, cells propagate specific traits and fitness to individual progeny. However, we do not have a global view of which proteins are asymmetrically inherited and their link with cellular fitness. In this project, we aim to fill this gap of knowledge by mapping the inheritance of the complete proteome of budding yeast.

Deciphering the mechanism of centrosome inheritance

Each cell division, the centrosome duplicates to form the mitotic spindle that segregates the chromosomes. Centrosome duplication is a conservative process that generates two different centrosomes: one is old and the other is new. Interestingly, many asymmetrically dividing cells, including yeast and stem cells, segregate their centrosomes in an age-dependent manner. To explore the mechanisms of centrosome inheritance, we developed a method to label old/new centrosomes differentially. We are combining these tools with yeast genetics, microscopy, and mass spectrometry to identify regulators of centrosome inheritance.

Prizes/Awards 2016-2019

- 2018-2021 The Swedish Research Council (VR-NT), Project grant, 'Mapping the inheritance of the yeast proteome to discover mechanisms of aging and rejuvenation´ (Reg no. 2017-04536)
- 2018-2021 Doctoral grant (KID-funding) 'Mapping the inheritance of the yeast proteome to discover mechanisms of ageing and rejuvenation' (Reg no. 2018-00878)
- 2015-2019 Doctoral grant (KID-funding) 'Deciphering the role of centrosomes in asymmetric cell division' (Reg no. 2-5586/2017)
- 2017-2018 Carl Trygger Stiftelse, Project grant
- 2015-2017 Åke Wiberg Stiftelse, Project grant
- 2014-2018 The Swedish Research Council (VR-NT), Project Grant Junior Researcher
- 2014-2018 Faculty funded Research Associate Position

Group members 2016-2019

- Alexander Julner-Dunn
- Jana Lalakova
- Marjan Abbasi

RESEARCH GROUP LEADER

Emma R. Andersson

Phone: +46 8 524 873 60
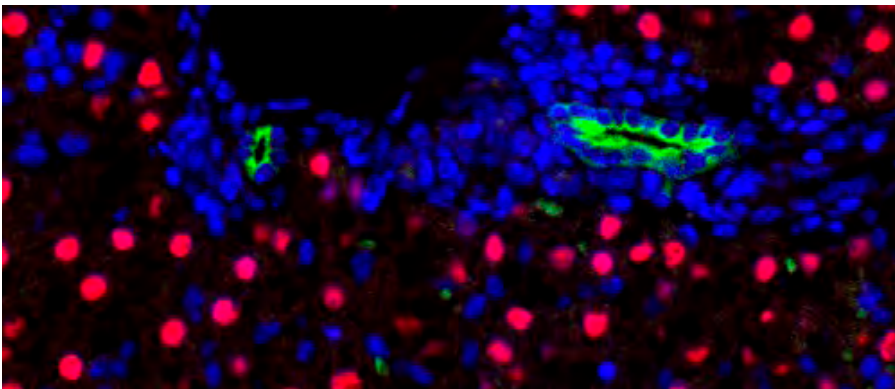Email: emma.andersson@ki.se

Developmental Biology

The Andersson lab aims to understand how a multicellular organism, such as a human, develops specialised organs (a nervous system, a circulatory system, etc.) from a single fertilised egg.

As developmental biologists, we use mouse models, 3D cell culture, CRISPR cell lines, single cell omics, and patient samples to address fundamental questions with relevance for human health. For example, how are cellular proliferation and differentiation during embryogenesis coordinated with morphogenesis to achieve organs with the right function and shape to accomplish their jobs?

The liver is a highly versatile organ, with a shifting identity and function during embryogenesis and after birth. In the adult state, it is our largest internal organ and is responsible for hundreds of functions, from production of coagulation factors, and detoxification, to production of bile so we can digest fats and absorb fat-soluble vitamins. During embryogenesis, the liver is transiently composed of cells that will become liver cells, as well as cells that will become red and white blood cells. The embryonic liver has a well-developed tree of blood vessels that acts as a scaffold for development of the future bile duct system and is innervated by nerves whose cell bodies reside outside the liver. Thus, the embryonic liver is a nexus of cell types and organ systems, whose interaction during embryogenesis has not yet been fully understood. Deciphering the interaction of cell types and understanding the programmes that lead to acquisition of the right cell fate, or establishment of the bile duct system, may allow us to design therapies or devise cures for the large number of diseases that affect the liver.

Alagille syndrome is a genetic disease usually caused by mutations in the gene JAG1, which encodes a ligand in the Notch signalling pathway. Children with this disease are often diagnosed when they have persistent jaundice (are yellow) after birth, revealing liver dysfunction due to an absence of well-developed bile ducts. Alagille syndrome also causes several other problems from heart defects to spontaneous bleeds. Our lab studies the role of Notch signalling in liver development, to better understand how bile ducts develop and in order to ultimately devise therapies for Alagille syndrome, and other diseases affecting the biliary system. Using a variety of technical approaches, as well as developing new methods when existing technology is insufficient, we aim to understand the interactions of Notch components in the embryonic liver, and decipher the interactions of liver cells with vasculature, hematopoietic cells and the nervous system during embryogenesis. By resolving developmental principles, our aim is to develop therapies for congenital disorders, including Alagille Syndrome and neurodevelopmental disorders. In parallel, we are focused on devising high throughput gene-manipulation techniques to reduce the number of animals used in science, while improving the versatility and speed of scientific inquiry.

Selected publications 2016-2019

1. Sjöqvist M & Andersson ER† (2019), 'Do as I say, Not(ch) as I do: lateral control of cell fate', *Developmental Biology,* 2019 447;1 58-70

2. Bush JO†, Andersson ER†, (2019) 'Signaling pathways instruct the blueprint of life', *Developmental Biology.* 2019 447;1 1-2

3. Andersson ER†*, Chivukula IV, Hankeova S, Sjöqvist M, Tsoi YL, Ramsköld D, Masek J, Elmansuri A, Hoogendoorn A, Vazquez E, Storvall H, Netušilová J, Huch M, Fischler B, Ellis E, Contreras A, Nemeth A, Chien KC, Clevers H, Sandberg R, Bryja V, Lendahl U. (2018), 'Mouse Model of Alagille Syndrome and Mechanisms of Jagged1 Missense Mutations' *Gastroenterology.* 2018 Mar;154(4):1080-1095.

4. Oliva-Vilarnau N, Hankeova S, Vorrink SU, Mkrtchian S, Andersson ER and Lauschke VM (2018), 'Calcium Signaling in Liver Injury and Regeneration', *Frontiers in Medicine,* 2018: 5, July

5. Masek J & Andersson ER† (2017), 'The developmental biology of congenital Notch disorders', *Development,* 2017; 144: 1743-1763

Prizes/Awards 2016-2019

- 2019/2020; ERC Starting Grant Ranked A & recommended for funding, but unfunded:
- Awarded the Swedish Foundations' Starting Grant
- 2017; The Daniel Alagille Award, *This prize for one internationally competitive young scientist (under 40) in Europe is awarded by the European Association for the Study of the Liver (EASL), for research in the field of genetic cholestatic liver disorders (€ 25,000).*
- 2017; EASL Mentoring Program recipient, *This European mentorship program awards two mentees per year with a mentor, in international competition and provides funds for visits and networking. I was selected and matched with Mario Strazzabosco, Yale, USA.*
- 2016; Knut and Alice Wallenberg Foundation Project Grant, co-applicant with Katja Petzold (KI)

Group members 2016-2019

- Sandra De Haan
- Afshan Iqbal
- Jan Masek
- Simona Hankeova
- David Kosek
- Bettina Semsch
- Jingyan He
- Katrin Mangold
- Noemi Van Hul
- David Kosek
- Linus Christerson
- Ileana Guzzetti
- Marika Sjöqvist
- Aiman Elmansuri
- Emine Cilek
- Dimitri Schritt
- Elenae Vazquez
- Rob Driessen
- Anita Hoogendoorn
- Cherie Vervuurt
- Francien Grotenhuijs
- Sanne Stokman
- Naomi Hensens
- Elvira Verhoef

Liver is stained for Hnf4a (hepatocytes, red nuclear marker), and CK19 (Green bile duct marker). DAPI in blue labels all nuclei. Photo: Afshan Iqbal

RESEARCH GROUP LEADER

Peter Swoboda

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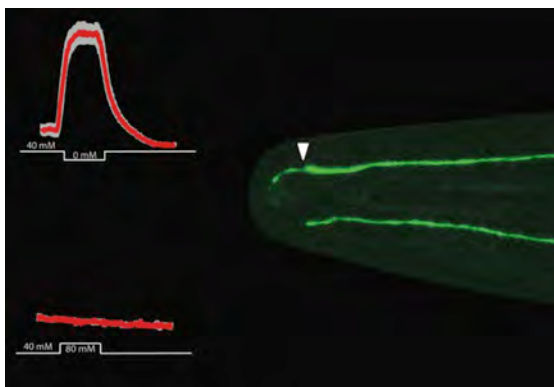## Cilia in the brain – and their connections to human brain disorders

Cilia are sensory or signalling structures projecting off cell surfaces like an antenna. In humans, many different cell types are ciliated, including neurons in the brain.

Neuronal cilia as signalling hubs are involved in shaping and maintaining functional neuronal circuits. These circuits are crucial for orchestrating behavioural output. Ciliopathies are characterised by defective cilia and comprise various disease states, including brain phenotypes. We have uncovered highly relevant connections between (i) cilia, ciliary genes and cilia-based signalling and (ii) (candidate genes for) different human brain conditions or disorders, like dyslexia or schiz-

ophrenia. The biological pathways behind these brain phenotypes are largely unknown. And our understanding of neuronal cilia is still rudimentary.

Fundamental questions about ciliary involvement in brain development, function and behavioural output in normal and disease states remain. What are the mechanisms by which cilia orchestrate cellular signalling in neuronal development? When and how does ciliary signalling control cell fate during expansion of the neural progenitor cell pool and their differentiation and organisation into neurons during brain development? Addressing these questions is crucial for understanding disease aetiology and for eventually developing treatment regimens for brain disorders.

Our work lets us hypothesise that proper cilia function impacts differentiation of neural progenitor cells and early-stage neurons, including polarisation and neurite outgrowth, and thereby neuronal migration and circuit formation later on. Different non-lethal cilia

malfunctions may thus cause different brain phenotypes (or disease states) depending on the affected neuron type and its location in the brain.

We address these hypotheses by:

* Determining in cultured human neurons and a whole-animal model, the worm *C. elegans*, causative connections between cilia formation, structure and function and aspects of neuronal development.

* Analysing transcriptomes of differentiating (human) neurons, including bioinformatics-based cross-correlations with ciliary gene lists and human candidate genes for various brain phenotypes.

* Analysing in the worm *C. elegans* behavioural output of disease-associated mutations in evolutionarily conserved (human and worm) ciliary genes connected to brain phenotypes.

Our goal is to create proper spatiotemporal information about ciliary localisation and function of proteins encoded by disease genes to better understand human brain development in the context of neural progenitor cells, and differentiating and mature functional neurons.

Behavioural output: In the head of the worm C. elegans two bilaterally symmetrical salt-tasting neurons are marked with GFP. The neuron at the top has a fully functional sensory cilium (arrowhead) and thus is able to "taste" salt (see calcium imaging trace on the left). The neuron at the bottom is defective for cilium development and thus cannot "taste" salt (see calcium imaging trace on the left).

Image: Swoboda group

Selected publications 2016-2019

1. Lauter G, Swoboda P, Tapia-Páez I. (2018), 'Cilia in brain development and disease.' *Cilia: Development and Disease.* 2018 May 31 (ed. P. Goggolidou, CRC Press, Taylor and Francis Publishers, Boca Raton, Florida, USA); ch. 1:pp. 1-35.

2. Sugiaman-Trapman D, Vitezic M, Jouhilahti EM, Mathelier A, Lauter G, Misra S, Daub CO, Kere J, Swoboda P. (2018) 'Characterization of the human RFX transcription factor family by regulatory and target gene analysis.' *BMC Genomics.* 2018 Mar 6;19:181.

3. Tammimies K, Bieder A, Lauter G, Sugiaman-Trapman D, Torchet R, Hokkanen ME, Burghoorn J, Castrén E, Kere J, Tapia-Páez I, Swoboda P. (2016) 'Ciliary dyslexia candidate genes DYX1C1 and DCDC2 are regulated by Regulatory Factor X (RFX) transcription factors through X-box promoter motifs.' *FASEB J.* 2016 Oct;30(10):3578-3587.

4. Ezcurra M, Walker DS, Beets I, Swoboda P, Schafer WR. (2016), 'Neuropeptidergic signaling and active feeding state inhibit nociception in *Caenorhabditis elegans.' J Neurosci.* 2016 Mar 16;36(11):3157–3169.

Research Networks 2016-2019

* KI Neurosciences network
* European *C. elegans* researcher network (EU COST Action Network BM1408)
* Swedish-Korean research cooperation network (VR and STINT, Korean NRF)

Prizes/Awards 2016-2019

* Mariangela Pucci: Visiting scholarships from the CM Lerici and Henning & Johan Throne-Holst Foundations (2017 and 2019).

Group members 2016-2019

* Andrea Coschiera
* Debora Sugiaman-Trapman
* Gilbert Lauter
* Soungyub Ahn
* Xin Xuan Lin
* Mariangela Pucci
* Shalini Sethurathinam

RESEARCH GROUP LEADER

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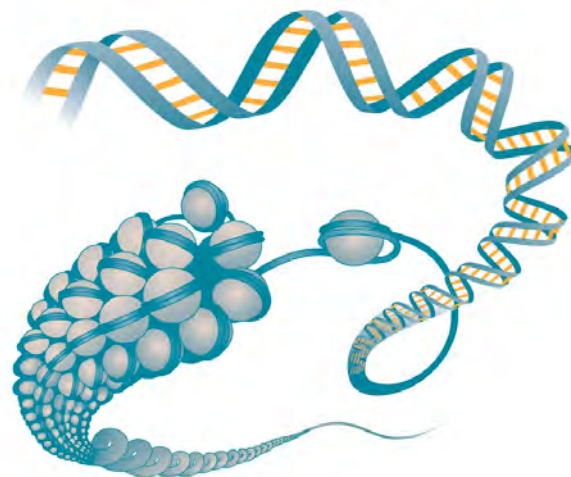
Epigenetics - basic mechanisms and disease

We are studying epigenetic modification mechanisms in fission yeast and human cell lines as model systems. In our basic research we focus on how these mechanisms contribute to cell cycle, cell differentiation and cellular quiescence.

We also carry out applied collaborative clinical epigenetic projects especially in the areas of cancer and obesity. We have extensive expertise in chromatin analysis by genome-wide methods using our cellular model systems and samples from the clinic.

Epigenetics is a rapidly expanding research field ranging from basic research to clinical applications. The term epigenetics comes from developmental biology and is a theory developed by Conrad Waddington in the 1940s to explain how genes are used during the process of morphogenesis and development of a multicellular organism (the process of epigenesis). Since all somatic cells of an organism, with very few exceptions, contain exactly the same DNA sequence, epigenetics can possibly explain how the same DNA sequence can be used to express different genes in different cell types and tissues. A more modern definition of epigenetics is 'nuclear inheritance' which is not based on differences in the DNA sequence. With this we now consider all modifications of the chromatin template that together establish and propagate different stable patterns of gene expression.

Epigenetic modifications: Covalent chemical modifications to the DNA and to histones, histone variants, nucleosome positions, non-coding RNAs and the level of chromatin compaction all contribute to chromosomal structure and to the activity or silencing of genes. These chromatin-level alterations are defined as epigenetic when they are heritable from mother to daughter cell. Histone acetylation and methylation are the most common modifications and they occur at specific lysines mainly in the NTER region of histones H3 and H4. The modifications lead to functional changes in gene promoters and enhancers because they confer altered accessibility to transcriptional regulatory complexes, thus impacting on gene expression. Nucleosome remodelling activity of SNF2 enzymes results in nucleosome sliding, modulation of histone turnover, spacing of nucleosomes, histone eviction and histone exchange. These activities are central in epigenetic regulation and control accessibility to the DNA for a large number of factors involved in processes involving recognition of the DNA sequence i.e. RNA transcription, DNA replication, repair and recombination.

The powerful molecular genetic analysis in fission yeast *(Schizosaccharomyces pombe)* is important for dissecting the detailed molecular function of several epigenetic mechanisms including histone acetylation, histone methylation and SNF2 chromatin remodelling. Our work in human cell lines allows for identification of conserved epigenetic mechanisms and the clinical epigenetics projects show a relevance of epigenetic mechanisms in disease.

Chromosome structure in eukaryotic cells. The DNA helix (yellow/blue) is wrapped approximately two turns around each nucleosome (grey spheres). Each nucleosome consists of eight histone proteins that can be epigenetically modified.

Illustration: Karl Ekwall

Selected publications 2016-2019

1.   Ait-Saada A, Khorosjutina O, Chen J, Kramarz K, Maksimov V, Svensson JP, Lambert S, Ekwall K. (2019) 'Chromatin remodeler Fft3 plays a dual role at blocked DNA replication forks.' *Life Sci Alliance.* 2019 Oct 1;2(5):e201900433. doi: 10.26508/lsa.201900433. eCollection 2019 Oct. PMID:31579888

2.   Oya E, Durand-Dubief M, Cohen A, Maksimov V, Schurra C, Nakayama JI, Weisman R, Arcangioli B, Ekwall K. (2019) 'Leo1 is essential for the dynamic regulation of heterochromatin and gene expression during cellular quiescence.' *Epigenetics Chromatin.* 2019 Jul 17;12(1):45. doi: 10.1186/s13072-019-0292-7.

3.   Ekwall, K. and G. Thon (2017). 'Genetic Analysis of *Schizosaccharomyces pombe.*' *Cold Spring Harb Protoc* 2017(8): pdb top079772.

4.   Persson J, Steglich B, Smialowska A, Boyd M, Bornholdt J, Andersson R, Schurra C, Arcangioli B, Sandelin A, Nielsen O and Ekwall K. (2016) 'Regulating retrotransposon activity through the use of alternative transcription start sites' *EMBO reports* 2016 May;17(5):753-68. doi: 10.15252/embr.201541866.

Research Networks 2016-2019

- Principal investigator for the KAW financed project 'Clinical epigenetics of acute leukemia' involving three research groups at KI (S Lehmann, R Ohlsson and K Ekwall; 2012-2017)

Prizes/Awards 2016-2019

- Appointed as visiting Professor at Nagoya City University (NCU) in Japan 2016-2017

Group members 2016-2019

- Eriko Oya
- Mickaël Durand-Dubief
- Olga Khorosjutina
- Vladimir Maksimov
- Lee Siggens
- Marc Laurent
- Lina Cordeddu
- Yasaman Zahedi

RESEARCH GROUP LEADER

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Epigenetic regulation of leukemia and normal blood development

We are identifying key mechanisms that cause epigenetic and transcriptional perturbation in AML in order to be able to find new ways to treat the disease.

Acute myeloid leukaemia (AML) has a poor prognosis in both, adults and children. There is therefore an urgent need for new novel therapeutics. Dramatic improvements in treatment and outcome have been made, with well characterised biology. For acute promyelocytic leukaemia (APML) the long-term survival now exceeds 90%, demonstrating that a better understanding of AML biology is a pre-requisite for the development of novel therapies to improve treatment outcomes. AML is characterised by early mutations and chromosomal aberrations in epigenetic regulators and transcription factors. Therefore, we are focusing our research on epigenetic regulation and epigenetic treatment of AML.

We are using cutting edge genome-wide technologies, biochemistry and molecular biology methods, novel model-systems and primary patient material, to obtain an increased knowledge of the molecular mechanisms that drive AML. The results are used to identify new drugs and drug combinations to develop improved treatments for AML.
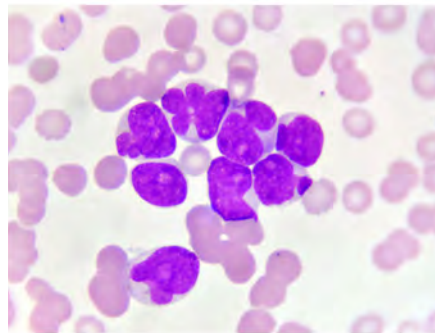
AML is characterised by an abnormal enrichment of immature blood progenitor cells that have lost their potential to differentiate to mature blood cells.
Illustration: https://stock.adobe.com/se/ License to Andreas Lennartsson

We are working together with several international research groups who are developing technologies to be able to analyse transcriptomics and epigenomics in new ways and in small cell populations, such as the leukemic stem cells. In addition, we have close collaborations with clinical haematologists to be able to ask the clinically important research questions. Within this network of technical know-how, clinical expertise and scientific drive, we have the tools to make major advances in the treatment of AML.
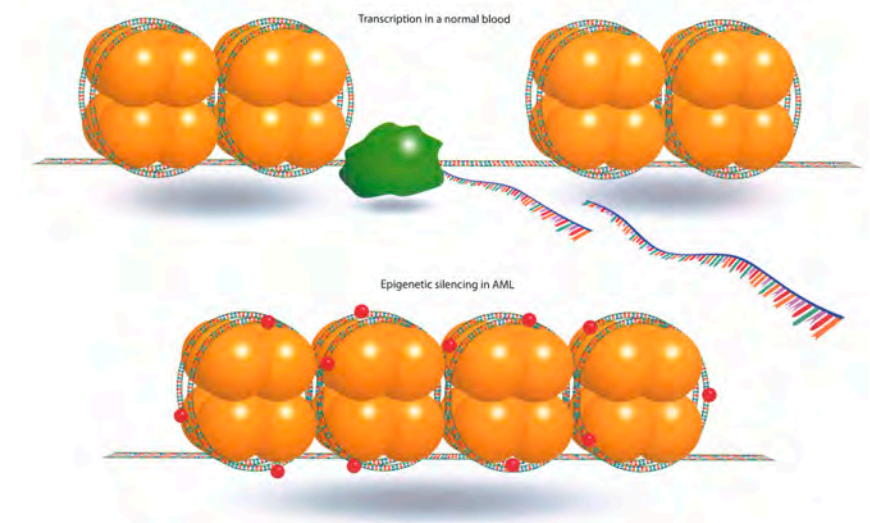
Disturbed epigenetic regulation in AML can lead to silencing of tumour suppressor genes and development and maintenance of AML.
Illustration: by deusin. https://stock.adobe.com/se/   License to Andreas Lennartsson

Selected publications 2016-2019

1. Huthayfa Mujahed, Sophia Miliara, Anne Neddermeyer , Sofia Bengtzén, Christer Nilsson, Stefan Deneberg, Lina Cordeddu, Karl Ekwall, Andreas Lennartsson*, Sören Lehmann* (2020) 'AML Displays Increased CTCF Occupancy Associated to Aberrant Gene Expression and Transcription Factor Binding' *Blood*, 2020 in press.

2. Shahin Varnoosfaderani F, Palau A, Dong W, Persson J, Durand-Dubief M, Svensson JP, Lennartsson A. (2020) 'A regulatory role for CHD2 in myelopoiesis.' *Epigenetics*. 2020 Jan 10:1-13. doi: 10.1080/15592294.2019.1710913

3. Qu Y, Siggens L, Cordeddu L, Gaidzik VI, Karlsson K, Bullinger L, Döhner K, Ekwall K, Lehmann S, Lennartsson A. (2017) 'Cancer specific changes in DNA methylation reveal aberrant silencing and activation of enhancers in leukemia.' *Blood*. 2017 Feb 16;129(7):e13-e25. doi: 10.1182/blood-2016-07-726877

Research Networks 2016-2019

• FANTOM 6

Prizes/Awards 2016-2019

• Appointed as visiting Professor at Nagoya City University (NCU) in Japan 2016-17

Group members 2016-2019

• Sophia Miliara
• Sylvain Mareshal
• Anna Palau de Miguel
• Annarita Scialdone
• Xiangfu Zhong

• Elisabetta Cozzi
• Farzaneh Shahin Varnoosfaderani
• Stina Betts
• Wenbo Dong

RESEARCH GROUP LEADER

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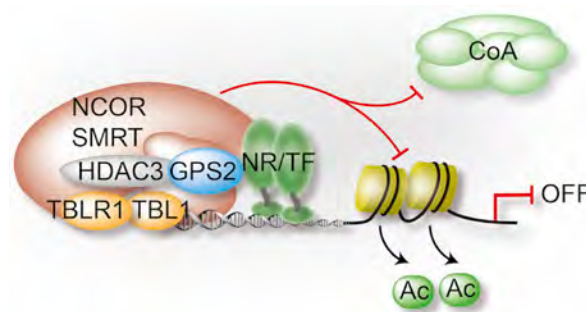## Epigenetic control of metabolism and inflammation by transcriptional coregulators

Our research attempts to better understand how the epigenome controls metabolic and inflammatory pathways in the context of obesity, type 2 diabetes, fatty liver disease and atherosclerosis.

Epigenetic alterations that trigger changes in epigenome activity and gene expression are fundamental reprogramming events that contribute to the development of these diseases. However, the underlying regulatory mechanisms, the critical components, and the causal relationship of these associations are currently poorly defined. We address these issues with an emphasis on coregulators, proteins that modify chromatin and cooperate with tran-

scription factors. Thereby, we hope to identify novel epigenome-based strategies for the prevention and treatment of these diseases.

Transcription factors (>1500) and associated coregulators (>300) play central roles in linking epigenome alterations to transcriptional reprogramming, as they shape the chromatin/enhancer landscape (i.e. the epigenome) and determine signal responses. Although these processes are well studied for many transcription factors and coactivators, our understanding of the precise roles of corepressors is currently lagging behind. It is also poorly understood whether and how the dysregulation of specific coregulators contributes to, or potentially even causes, disease.

Our search for candidates that might be involved in metabolic and inflammatory disease pathways revealed a potential key role of a fundamental corepressor complex, consisting of the core subunits histone deacetylase HDAC3, G-protein pathway suppressor 2 (GPS2), and the related corepressors NCOR and SMRT. Although these subunits were originally identified as nuclear receptor-associated

proteins, we know today that the complex controls many other transcription factors and multiple cellular pathways.

Our studies have demonstrated the involvement of the complex in the regulation of cholesterol metabolism and transport, in anti-inflammatory crosstalk mechanisms, in adipose tissue inflammation and hypertrophy, and in hepatic fatty acid oxidation and lipogenesis. For example, knockout mice that lack the subunit GPS2 specifically, either in macrophages or in adipocytes, display hall-

marks of metaflammation (i.e. elevated systemic inflammation and insulin resistance). In contrast, hepatocyte-specific knockout mice are protected from developing obesity-associated fatty liver disease, highlighting the role of cell type and signalling differences. Intriguingly, alterations of GPS2 expression in adipocytes and macrophages associate with systemic inflammation and diabetic risk in obese humans, suggesting the identified pathways to be conserved and clinically relevant.

The GPS2-containing corepressor complex associates with transcription factors (TF, including nuclear receptors, NR) at promoters and enhancers to regulate chromatin modification states and transcription. Expression and function of individual subunits is modulated by multiple signals, which in the context of immuno-metabolic diseases can result in the epigenetic reprogramming of gene expression.

Illustration: Tomas Jakobsson and Eckardt Treuter

Selected publications 2016-2019

1. Liang, N., Damdimopoulos, A., Goni, S., Huang, Z., Vedin, L. L., Jakobsson, T., Giudici, M., Ahmed, O., Pedrelli, M., Barilla, S., Alzaid, F., Mendoza, A., Schroder, T., Kuiper, R., Parini, P., Hollenberg, A., Lefebvre, P., Francque, S., Van Gaal, L., Staels, B., Venteclef, N., Treuter, E. (co-correspondence), and Fan, R. (2019) 'Hepatocyte-specific loss of GPS2 in mice reduces non-alcoholic steatohepatitis via activation of PPARalpha.' *Nature Communications* 10, 1684

2. Huang, Z., Liang, N., Damdimopoulos, A., Fan, R., and Treuter, E. (2019) 'G protein pathway suppressor 2 (GPS2) links inflammation and cholesterol efflux by controlling lipopolysaccharide-induced ATP-binding cassette transporter A1 expression in macrophages.' *FASEB Journal* 33, 1631-1643

3. Drareni, K., Ballaire, R., Barilla, S., Mathew, M. J., Toubal, A., Fan, R., Liang, N., Chollet, C., Huang, Z., Kondili, M., Foufelle, F., Soprani, A., Roussel, R., Gautier, J. F., Alzaid, F., Treuter, E. (co-correspondence), and Venteclef, N. (2018) 'GPS2 deficiency triggers maladaptive white adipose tissue expansion in obesity via HIF1A activation. ' *Cell Reports* 24, 2957-2971 e2956

4. Fan, R., Toubal, A., Goni, S., Drareni, K., Huang, Z., Alzaid, F., Ballaire, R., Ancel, P., Liang, N., Damdimopoulos, A., Hainault, I., Soprani, A., Aron-Wisnewsky, J., Foufelle, F., Lawrence, T., Gautier, J. F., Venteclef, N., and Treuter, E. (2016) 'Loss of the co-repressor GPS2 sensitizes macrophage activation upon metabolic stress induced by obesity and type 2 diabetes.' *Nature Medicine* 22, 780-791

Research Networks 2016-2019

Prizes/Awards 2016-2019

Group members 2016-2019

- Serena Barilla
- Saioa Goñi
- Rongrong Fan
- Zhiqiang Huang
- Oihane García-Irigoyen
- Ning Liang
- Marco Giudici

RESEARCH GROUP LEADER

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Tumour genomics

Our research revolves around genomics of benign and malignant tumours. The work scrutinises both hereditary and acquired genetic mutations and variations that can cause uncontrolled cell growth. The overall aim is to create, integrate, and interpret information on human tumourigenesis to facilitate cancer prevention, diagnosis, and treatment. At KI, our research team has so far focused on two types of tumours; uterine leiomyomas and colorectal cancer.

Uterine leiomyoma

Uterine leiomyomas are extremely common benign tumours that arise from the smooth muscle layer of the uterus. Although benign they can cause a variety of symptoms, such as excessive bleeding and abdominal pain, and negatively affect fertility and pregnancy.

Recent work from our research group at the University of Helsinki has revealed that although uterine leiomyomas are widely regarded a single entity, there are at least four distinct subgroups of leiomyomas with characteristic genetic driver mutations.

Using patient samples collected in collaboration with clinicians at Danderyds Sjukhus, we are now further characterising the features of the identified subgroups and exploring if and how the subtype specific features may affect the tumour's sensitivity to drug treatment.

Colorectal cancer

Colorectal cancer is our long-term interest, and the group has contributed to several key discoveries along the way. Although a number of genetic variations (mutations) have been linked to colorectal cancer, we still do not know the full set of mutations that are necessary and together sufficient to cause this type of cancer. One of the aims with our research is to identify novel mutations/genetic aberrations that contribute to colorectal cancer and to explore how these contribute to tumourigenesis.

In a recent high-throughput effort to characterise structural genetic changes in a large number of human colorectal cancer samples (Palin *et al., Nature Communications* 2018), a set of plausible candidate targets were identified. We are currently functionally validating one of the most striking findings to see if and how the putative driver gene contributes to colorectal cancer.

Lauri Aaltonen is a Visiting Professor (Cancer Genetics) at KI, and his main position is at the University of Helsinki where he is the Director of the Center of Excellence in Tumour Genetics Research.
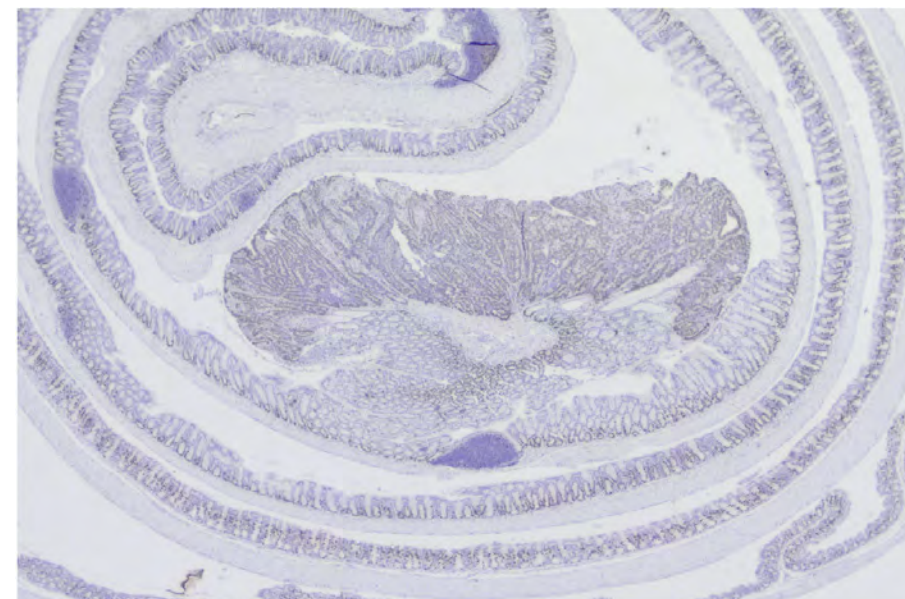
Histological section of a mouse colon with adenoma, stained with the proliferation marker Ki67 (brown).
Photo: Åsa Kolterud

Selected publications 2016-2019

1. Kaasinen E, Kuismin O, Rajamäki K, et al. (2019) 'Impact of constitutional TET2 haploinsufficiency on molecular and clinical phenotype in humans.' *Nat Commun* 2019;10:1252.
2. Palin K, Pitkänen E, Turunen M, et al. (2018) 'Contribution of allelic imbalance to colorectal cancer.' *Nat Commun* 2018;9:3664.
3. Kämpjärvi K, Mäkinen N, Mehine M, et al. (2016) 'MED12 mutations and FH inactivation are mutually exclusive in uterine leiomyomas.' *Br J Cancer* 2016;114:1405-11.
4. Mehine M, Kaasinen E, Heinonen HR, et al. (2016) 'Integrated data analysis reveals uterine leiomyoma subtypes with distinct driver pathways and biomarkers.' *Proc Natl Acad Sci U S A* 2016;113:1315-20.

Research Networks 2016-2019

- Swedish Colorectal Cancer Study Group
- Uterine Leiomyoma clinical network

Group members 2016-2019

- Åsa Kolterud
- Agneta Andersson
- Asal Fotouhi
- Birgitta Lindqvist
- Sara Shakeri Manesh

RESEARCH GROUP LEADER

Juha Kere

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Embryonal, foetal and brain development

Our knowledge of the very first few days of human life is still poor. We address questions such as: How does the embryo get started? How is the oocyte changed after fertilisation to gradually become mother of all different cell types in the body? Which genes regulate these earliest molecular mechanisms and how? What can we learn of stem cells and cellular reprogramming?

At the other end of foetal development, we study preeclampsia, a severe complication of pregnancies threatening both the mother and the baby. We look for diagnostic methods and therapy to better manage and prevent this serious disorder.

Early embryonic development and stem cells

Human embryo development starts by fertilisation of the egg cell (oocyte). The fertilised oocyte (zygote) will start to divide once a day, so that on day 2 the embryo has reached the 4-cell stage and on day 3, the 8-cell stage. The earliest events include the rapid but transient expression of the DUX4 gene in zygotes; the rapid degradation of a large number of oocyte-specific transcripts; and the activation of the embryo's first own genes at the 4 and 8-cell stages. Recently, we have focused on the role of the DUX4 gene in regulating these processes. Our results have revealed multiple roles for DUX4, including a major effect in making the embryo genes accessible to regulatory proteins (chromatin opening) and activating a large number of enhancers, regulators of gene expression.
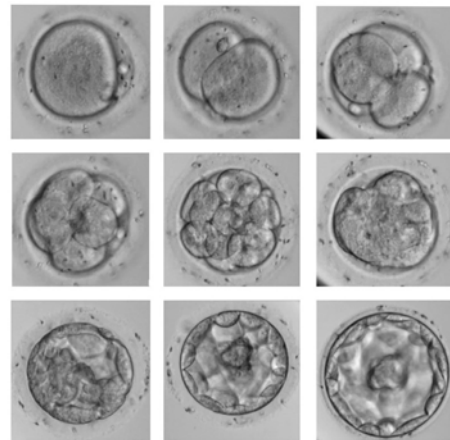
Microscope images of the stages of foetal development. (Published in: Kere J & Sariola H. Duodecim 135:2391-2399, 2019)

Preeclampsia, a severe complication of pregnancy

Preeclampsia is a serious pregnancy complication that starts during the last trimester of pregnancy and threatens the wellbeing of both the mother and the foetus. It is worldwide a leading cause of prematurity or even death during pregnancy. The aim of our project is to develop blood sample based sensitive methods to predict and diagnose threatening preeclampsia weeks before symptoms start. Our results show that an essential mechanism of preeclampsia involves a compromised genetic ability of the foetus to protect itself against maternal attack against the foreign body of placental cells. Our results have also suggested a therapy based on a well-known and safe medication.

Developmental dyslexia, a specific disorder of human brain development

Developmental dyslexia (DD), or specific reading disability, is an unexpected difficulty in learning to read despite normal intelligence and senses, and normal school teaching and social environment. DD is the most common learning disability, affecting between 5 and 10% of school-age children.

Epidemiological studies have shown that DD has a strong genetic background. The aim of our project is to continue our groundbreaking research on the biological background of DD. After many gene discoveries, we now study gene functions in cell models. A key mechanism in DD involves signalling by neuronal cilia, antenna-like organelles that guide neuronal development.

Selected publications 2016-2019

1. Hirabayashi S, Bhagat S, Matsuki Y, Takegami Y, Uehata T, Kanemaru A, Itoh M, Shirakawa K, Takaori-Kondo A, Takeuchi O, Carninci P, Katayama S, Hayashizaki Y, Kere J, Kawaji H, Murakawa Y. (2019) 'NET-CAGE characterizes the dynamics and topology of human transcribed cis-regulatory elements.' *Nature Genet* 51:1369-1379, 2019

2. Madissoon E, Damdimopoulos A, Katayama S, Krjutškov K, Einarsdottir E, Mamia K, De Groef B, Hovatta O, Kere J*, Damdimopoulou P*. (2019) 'Pleomorphic Adenoma Gene 1 is needed for timely zygotic genome activation and early embryo development.' *Sci Rep* 9:8411, 2019

3. Weltner J, Balboa D, Katayama S, Bespalov M, Krjutškov K, Jouhilahti E-M, Trokovic R, Kere J*, Otonkoski T*. (2018) 'Human pluripotent reprogramming with CRISPR dCas9 activators.' *Nature Commun* 9:2643, 2018

4. Jouhilahti E-M, Madissoon E, Vesterlund L, Töhönen V, Krjutshkov K, Plaza Reyes A, Petropoulos S, Månsson R, Linnarsson S, Bürglin T, Lanner F, Hovatta O, Katayama S, Kere J. (2016) 'The human PRD-like homeobox gene LEUTX has a central role in embryo genome activation.' *Development* 143:3459-3469, 2016

Research Networks 2016-2019

- EU Consortia: MAARS, SARM, NANOSOL, BIOMAP, MATER
- Other international consortia (coordinator country): FANTOM6 (Japan), FINNPEC (Finland)

Prizes/Awards 2016-2019

- Juha Kere: The Royal Society Wolfson Research Merit Award (UK)

Group members 2016-2019

- Tiina Skoog
- Hong Jiao
- Shintaro Katayama
- Shruti Bhagat
- Masahito Yoshihara

RESEARCH GROUP LEADER

Cecilia Williams

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# Hormone signalling and non-coding RNAs in cancer

Our research focuses on understanding key molecular mechanisms in cancer. Each cancer is unique and there is an urgent need for precision medicine, diagnostic tools and novel treatment approaches to reduce cancer mortality.

We use a combination of large-scale omics together with focused mechanistic experiments and *in vivo* studies. Our goal is to understand critical cancer pathways so that we can suggest better cancer treatments and preventive approaches, as well as biomarkers, to be developed for clinical use.

Non-coding RNA molecules are RNAs that do not encode for proteins. The family includes microRNAs which regulate translation of target mRNAs and long non-coding RNAs (lncRNAs) which can have active functions such as 3D-RNA molecules. Both types can function as biomarkers or therapeutic targets. We study how non-coding RNAs are impacted by cell differentiation, hormone signalling and cancer, and their corresponding functions.

Oestrogen signalling and sex differences in cancer

Some cancers (such as colorectal and liver) are more common in men, and others (breast and thyroid) are more common in women. We explore how the hormone oestrogen influences this and, for example, increases the growth of breast cancer while protecting against colorec-
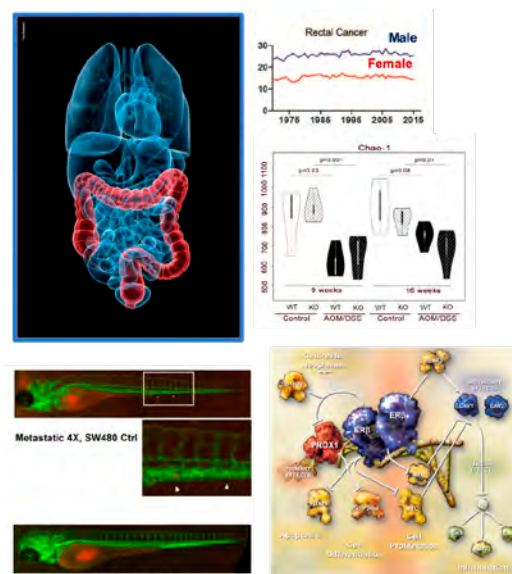

Colorectal cancer (top left) is more common in men (top right, Zheng et al., BMC Cancer, 2019). Tumour development reduces the diversity of the microbiome which is further compounded if intestinal ERbeta is deleted (middle right, Ibrahim et al., Int. J Cancer 2019). Omics data proposes mechanisms (bottom right, Cover, Molecular Endocrinology), and expression of ERbeta reduces the cells' migratory capacity per in vivo micrometastasis (zebrafish asssay, bottom left, Nguyen-Vu et al., 2016).

tal cancer. The effect of oestrogen is mediated by three oestrogen receptors: ERα, ERβ and GPER1. These are expressed to various extent in different tissues in both women and men. ERα and ERβ are ligand-activated nuclear receptors and are excellent therapeutic targets. GPER1 is a G protein-coupled transmembrane receptor with promising therapeutic potential. Using technologies like RNA-Seq, ChIP-Seq, microbiota analysis, and proteomics, along

with cell models, tissue-specific knockouts and clinical samples, we explore how these three receptors, and their ligands, such as dietary oestrogens or endocrine disruptors, impact cancer. We are interested in understanding how this contributes to sex differences in cancer incidences and outcomes, as well as the intricate connection with diet/obesity, inflammation and carcinogenesis.
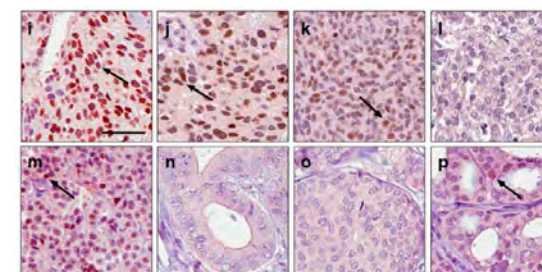
Cancer tissues

Tissue-microarrays (TMA) using validated antibody (PPZ0506) demonstrate expression of nuclear ERbeta protein in (i–l) 3 out of 4 granulosa cell tumours, (m) one case of melanoma, and (p) one case of thyroid cancer. All other cancers, including (n) colorectal and (o) breast tumours, were negative (Andersson et al., Nature Communications 2017).

Selected publications 2016-2019

1. Ibrahim A, Hugerth LW, Hases L, Saxena A, Seifert M, Thomas Q, Gustafsson JÅ, Engstrand L, Williams C. (2019) 'Colitis-induced colorectal cancer and intestinal epithelial estrogen receptor beta impact gut microbiota diversity.' *Int J Cancer.* 2019. 144(12):3086-3098.

2. Wang J, Aydoğdu E, Mukhopadhyay S, Helguero LA, Williams C. (2019) 'A miR-206 regulated gene landscape enhances mammary epithelial differentiation.' *J Cell Physiol.* 2019. 234(12): 22220-22233.

3. Berger AC, Korkut A, Kanchi RS, Hegde AM, Lenoir W, Liu W, Liu Y, Fan H, Shen H, Ravikumar V, Rao A, Schultz A, Li X, Sumazin P, Williams C, Mestdagh P, Gunaratne PH, Yau C, Bowlby R, Robertson AG, Tiezzi DG, Wang C, Cherniack AD, Godwin AK, Kuderer NM, Rader JS, Zuna RE, Sood AK, Lazar AJ, Ojesina AI, Adebamowo C, Adebamowo SN, Baggerly KA, Chen TW, Chiu HS, Lefever S, Liu L, MacKenzie K, Orsulic S, Roszik J, Shelley CS, Song Q, Vellano CP, Wentzensen N; Cancer Genome Atlas Research Network, Weinstein JN, Mills GB, Levine DA, Akbani R. (2018) 'A Comprehensive Pan-Cancer Molecular Study of Gynecologic and Breast Cancers.' *Cancer Cell.* 2018. 33(4):690-705.e9.

4. Andersson S, Sundberg M, Pristovsek N, Ibrahim A, Jonsson P, Katona B, Clausson CM, Zieba A, Ramström M, Söderberg O, Williams C, Asplund A. (2017) 'Insufficient antibody validation challenges oestrogen receptor beta research.' *Nature Communications* 2017. 8:15840.

Research Networks 2016-2019

• Pan-Gynecologic Cancers Analysis Working Group, The Cancer Genome Atlas
• VR Research environment Interdisciplinary research (QuantumSense 2018-2025)
• American Association for Cancer Research (AACR)

Prizes/Awards 2016-2019

• Career Development Award (VINNOVA/ Marie-Curie Actions GROWTH 291795, Cecilia Williams, 2014-2018)
• National Cancer Institute / NIH USA (R01 CA172437, 2013-2019)

Group members 2016-2019

Amena Archer	Ahmed Ibrahim	Linnea Pettersson Hases
Rajitha Indukuri	Dandan Song	Madeleine Birgersson

RESEARCH GROUP LEADER

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# We study human B cells in health and disease

We focus on two main areas of research: primary immunodeficiency and B cell malignancy.

Regulation of immunoglobulin gene diversifications in human B cells

This project is aimed at understanding the complex molecular mechanisms involved in DNA editing, repair and recombination during immunoglobulin class switch recombination (CSR) and somatic hypermutation (SHM) and their involvement in the pathophysiological processes leading to immunodeficiency, genome instability and cancer development in humans.

Induced pluripotent stems cells - a platform for study human B cell development and personalised therapy in patients with primary immunodeficiency

The project is aimed at reprogramming the fibroblasts derived from primary immunodeficiency patients into pluripotent stem (iPS) cells and re-differentiating these iPS cells into antibody-producing B cells. If successful, this study will provide a methodological platform for the study of human B cell development and for development of new therapies aiming at editing genes/cells in patients with a variety of other primary immunodeficiency diseases.
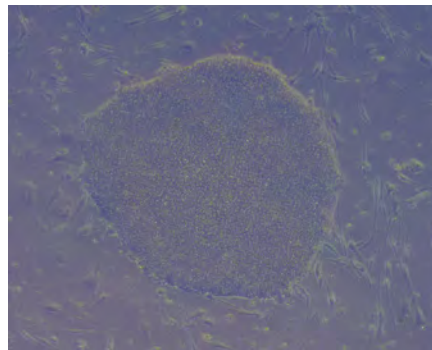
An iPSC colony derived from IgAD patient's fibroblast cells. Photo: Pan-Hammarström's group

Discovery of therapeutic targets in B cell lymphoma by next generation sequencing

The project is aimed at identifying potentially treatable molecular targets in mature B cell lymphomas (with focus on diffuse large B cell lymphoma, follicular lymphoma and mantle cell lymphoma) by applying high-throughput, next generation-sequencing technologies such as whole genome and whole exome sequencing, immune repertoire sequencing, RNA sequencing and single-cell RNA sequencing. The multiomic sequencing data will be further integrated with clinical data as well as functional assays to identify genes/pathways that can be used for disease classification and prediction and for the development of new targeted therapy.

Overview of DLBCL genetic alterations
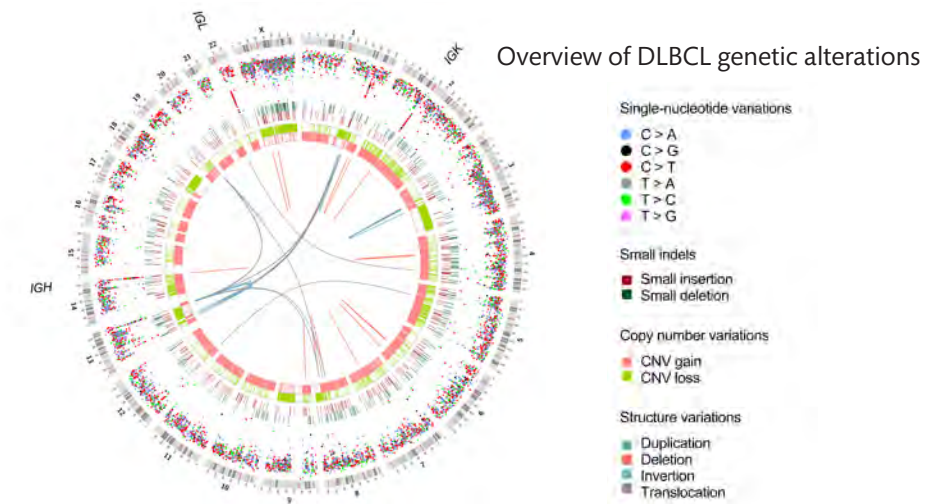
Selected publications 2016-2019

1. Ren W, Ye X, Su H, Li W, Liu D, Pirmoradian M, et al (2018), 'Genetic landscape of hepatitis B virus-associated diffuse large B-cell lymphoma.' *Blood* 2018 06;131(24):2670-2681

2. Björkman A, Du L, van der Burg M, Cormier-Daire V, Borck G, Pié J, et al (2018), 'Reduced immunoglobulin gene diversity in patients with Cornelia de Lange syndrome.' *J. Allergy Clin. Immunol.* 2018 01;141(1):408-411.e8

3. Abolhassani H, Edwards ES, Ikinciogullari A, Jing H, Borte S, Buggert M, et al (2017), 'Combined immunodeficiency and Epstein-Barr virus-induced B cell malignancy in humans with inherited CD70 deficiency.' *J. Exp. Med.* 2017 01;214(1):91-106

4. Bronson PG, Chang D, Bhangale T, Seldin MF, Ortmann W, Ferreira RC, et al (2016), 'Common variants at PVT1, ATG13-AMBRA1, AHI1 and CLEC16A are associated with selective IgA deficiency.' *Nat. Genet.* 2016 11;48(11):1425-1429

Research Networks 2016-2019

- Cancer Research KI (https://ki.se/en/cancerresearchki/cancer-research-ki)
- Kiim, KI inflammation and immunology network (https://ki.se/en/research/kiim-ki-inflammation-and-immunology-network)

Prizes/Awards 2016-2019

- Cancerfonden, 2018 - Bo Zhang, postdoc position awarded
- Wenner-Gren Foundation, 2017 - Yingqing Li, postdoc position awarded
- CIMED senior research grant, 2016, Qiang Pan-Hammarström

Group members 2016-2019

- Likun Du
- Hui Wan
- Rozina Caridh
- Jonathan Arias Fuenzalida
- Jingwei Yu
- Rosa Romano

- Valentyn Oksenych
- Bo Zhang
- Wei Li
- Weicheng Ren
- Mohammad Pirmoradian
- Yinqing Li

- Chunli Yang
- Konstantinos Georgiou
- Xiaofei Ye
- Radhika Kamdar

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Nuclear receptors in health and disease

Our research group studies the field of nuclear receptors, a family of transcription factors of very high physiological and pathophysiological significance. They regulate expression of several hundreds of genes and are often activated or inactivated by low molecular weight ligands, e.g. steroid hormones or intermediary metabolites.

Our main focus lies on two nuclear receptor (NR) transcription factors that were discovered in our laboratory in the middle of the 90's; the Oestrogen receptor beta (ERβ) and the Liver X receptor beta (LXRβ). We study their implications in neurodevelopment, neurodegeneration, cholesterol homeostasis, fertility, and cancer.

ERβ is antiproliferative in many tissues including mammary gland and the prostate, which is of great interest since it may be an antitumour agent in breast and prostate cancer. We work with various ERβ ligands which we hope will qualify as drugs against breast and prostate cancer. Furthermore, both ERβ and LXRβ have important functions in the developing and adult brain. For example,

ERβ is anxiolytic and is needed for proper corticogenesis, and LXRβ is important for brain cholesterol metabolism, and is involved in Parkinson's disease by influencing dopamine signalling. Loss of either ERβ or LXRβ results in increased vulnerability to neurodegeneration, where in particular disrupted ERβ signalling may be of relevance to the sex differences observed in Alzheimer's disease. Therefore, ERβ and LXRβ ligands hold great promise as drugs against neurological diseases.
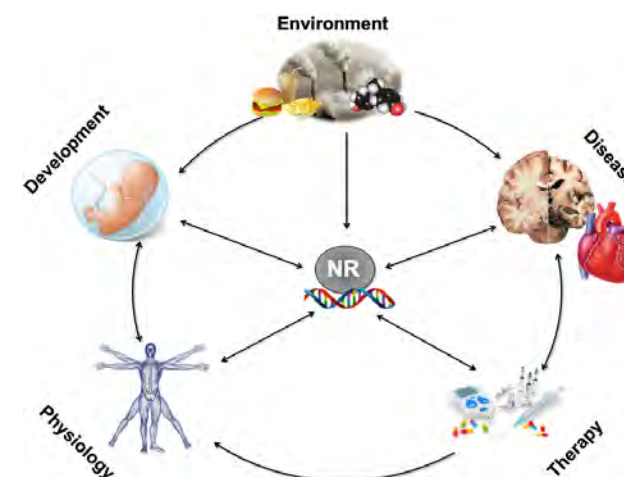
NRs are ligand activated nuclear transcription factors. They function downstream of endocrine processes to mediate the response to external and internal stimuli, thereby controlling the expression of genes involved in homeostasis, metabolism, growth and development. Since they often bind low molecular weight ligands they pose promising targets for therapeutic interventions. Our research group study a subset of nuclear receptors, the oestrogen receptors (ERs) and the liver X receptors (LXRs) that are involved in inflammation, metabolism, proliferation and development.

Illustration: Ivan Nalvarte

Selected publications 2016-2019

1. Varshney MK, Yu NY-Y, Katayama S, Li X, Liu T, · Wu W-W, Töhönen V, Krjutškov K, Kere J, Fan X, Inzunza J, Gustafsson JÅ, Nalvarte I. (2020) 'Motor function Deficits in the estrogen receptor beta knockout mouse: Role on excitatory neurotransmission and myelination in the motor cortex.' *Neuroendocrinology* 2020, Jan 28, https://doi.org/10.1159/000506162

2. Zhao L, Gimple RC, Yang Z, Wei Y, Gustafsson JÅ, Zhou S. (2019) 'The immune regulatory functions of nuclear receptors: mechanisms and therapeutic implications.' *Trends in Endocrinology and Metabolism*, 2019, Nov 6. pii: S1043-2760(19)30205-X. doi: 10.1016/j.tem.2019.10.002.

3. Zhao L, Zhou S, Gustafsson JÅ. (2019) 'Nuclear receptors: recent drug discovery for cancer therapies.' *Endocr. Rev*. 2019 Mar 14. pii: er.2018-00222. doi: 10.1210/er.2018-00222

4. Thomas DG, Doran AC, Fotakis P, Westerterp M, Antonson P, Jiang H, Jiang XC, Gustafsson JÅ, Tabas I, Tall AR. (2018) 'LXR Suppresses Inflammatory Gene Expression and Neutrophil Migration through cis-Repression and Cholesterol Efflux.' *Cell Reports*. 2018 Dec 26;25(13):3774-3785.e4. doi: 10.1016/j.celrep.2018.11.100.

5. Varshney MK, Inzunza J, Lupu D, Ganapathy V, Antonson P, Rüegg J, Nalvarte I, Gustafsson JÅ. (2017) 'Role of estrogen receptor beta in neural differentiation of mouse embryonic stem cells.' *Proc Natl Acad Sci U S A*. 2017 Nov 28;114(48):E10428-E10437. doi: 10.1073/pnas.1714094114

Group members 2016-2019

- Per Antonsson
- Peik Brundin
- Mukesh Varshney
- Leticia Montanholi
- Mohamed Shamekh
- Patricia Humire
- Ivan Nalvarte

RESEARCH GROUP LEADER

Sam Okret

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Endocrine and age aspects of lymphoma biology

Lymphomas are not generally considered as endocrine-regulated malignancies but epidemiological information and experimental data collected by us strongly suggest they are, particularly by sex hormones.

The incidence of most adult lymphoma is higher in males than in females. Furthermore, male sex generally confers a worse prognosis. The sex difference in incidence is even more pronounced for lymphomas in children and young adults. The cause of this difference is not understood and so far not well studied. The aims of our projects are to identify molecular mechanisms and biological processes involved in the sex and age differences of lymphomas with a focus on sex hormones. For example, we have shown that transplanted lymphoma tumours grow faster in male than female mice, a difference that was removed following ovariectomy. Furthermore, we showed that several lymphomas are highly sensitive to compounds that bind to oestrogen receptor β (ERβ) subtype, highly expressed in lymphoma cells, and cause an inhibition of tumour growth *in vivo,* reduce tumour vascularisation and inhibit dissemination. Contrary to this, inhibition of oestrogen synthesis promotes lymphoma progression (4). ERβ

expression in lymphomas may also have a prognostic value (3). We also show that xenoestrogens (food and other compounds in the environment with oestrogen activity) administered to mice inhibit lymphoma growth in grafted mice (1). Taken together this indicates that oestrogens do indeed play a role in lymphoma development. Future research aims to identify molecular mechanisms involved in sex and age dependent differences in lymphoma development and with this knowledge to identify molecular targets for new and more personalised treatment which takes sex and age into consideration.

In addition, we have also studied mechanisms of drug resistance on lymphoma by the tumour microenvironment and how this resistance can be overcome (2).
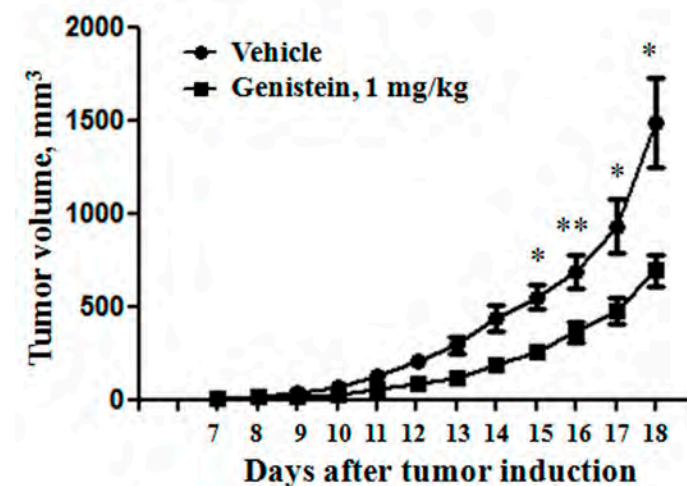
Intake of the food derived compound Genistein inhibits lymphoma growth

The figure shows the effect on lymphoma growth following intake of Genistein (1mg/kg body weight), an isoflavonide present in food products, especially soy, which harbours some oestrogen activity. To note is that intake of 1mg/kg body weight can be reached by normal food intake, especially in a diet rich in soy products (Yakimchuk et al., Endocrine Connections 2018).

Selected publications 2016-2019

1.   Yakimchuk, K. Bangalore Revanna, C., Huang, D., Inzunza, J. and Okret, S. (2018) 'Suppression of lymphoma growth by the xenoestrogens bisphenol A and genistein.' *Endocrine Connections*, 7(12): 1472–1479, 2018.

2.   Guan, J., Huang, D., Yakimchuk, K. and Okret, S. (2018) 'p110α inhibition overcomes stromal cell-mediated ibrutinib resistance in mantle cell lymphoma.' *Mol. Cancer Therap.* 17, 1090-1100, 2018.

3.   Hasni, M.S., Berglund, M., Yakimchuk, K., Guan, J., Linderoth, J., Amini, R.M., Enblad, G. and Okret, S. (2017) 'Estrogen receptor β1 in diffuse large B-cell lymphoma growth and as a prognostic biomarker.' *Leukemia & Lymphoma*, 58, 418-427, 2017.

4.   Talabér, G., Yakimchuk, K., Guan, J., Inzunza, J. and Okret, S. (2016) 'Inhibition of estrogen biosynthesis enhances lymphoma growth in mice.' *Oncotarget*, 7, 20718-20727, 2016.

Group members 2016-2019

- Konstantin Yakimchuk
- Dan Huang
- Chandrachekar Bangalore Revanna
- Jiyu Guan
- Mattias Berglund

RESEARCH GROUP LEADER

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Photo: Johan Miderberg. © Ragnar Söderbergs stiftelse 2012.

Neuronal circuits of cognition

The overall purpose of our research is to map the structure and function of circuitry underlying cognition, and provide causal evidence for how specific neuronal cell types contribute to network processes and computations underlying cognition.

Our research has a strong focus on the prefrontal cortex (PFC) and we are particularly interested in cognitive functions known to be changed in psychiatric disorders such as schizophrenia or autism spectrum disorder.

Prefrontal cortex

The prefrontal cortex (PFC) is pivotal to the integration and coordination of internally generated information and information received from the external world. The PFC is most important when behaviour must be guided by internal intentions (often referred to as goal-directed behaviour), and in line with this the PFC is required for cognitive processes such as attention, working memory, planning and decision-making. Disturbed prefrontal function underlies many cognitive and behavioural deficits associated with neuropsychiatric disorders such as schizophrenia, ADHD, autism and drug-addiction.

Neuronal circuits

The structure and composition of neuronal networks are integral to their functions. Tracing and mapping of neuronal circuits can therefore inform of function. In line with
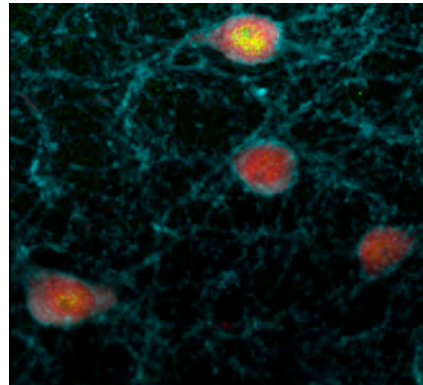
Prefrontal inhibitory interneurons expressing parvalbumin (red), Cre-recombinase (yellow), ChR2-mCherry (cyan). Photo: Sofie Ährlund-Richter

this, we have developed tools enabling whole-brain tracing of circuits. The efferent and afferent connectivity of genetically defined cell types can be mapped, identifying both local and long-range synaptic partners. These neuronal circuit building blocks can be identified, and manipulated, using electrophysiology and optogenetic tools in behaving mice and rats, providing a means for causal demonstration of the role of specific circuit motifs in cognition and behaviour.

Large-scale electrophysiological recordings of neuronal activity in behaving animals

In order to elucidate how complex computations are implemented in neuronal networks, we perform large-scale recordings of neuronal activity (action potential (AP) and local field potential (LFP)) using high-density silicon probes (Neuropixels) or tetrodes in freely moving or head-restrained behaving rodents.

Real-time imaging of neuronal activity in behaving animals

Transiently co-active assemblies of neurons, known as neuronal ensembles, are hypothesised to serve a crucial role in neuronal computation. However, the mechanisms guiding ensemble formation or the dynamic inclusion of single neurons into different ensembles still remain elusive. In order to gain insight into these processes, we perform real-time calcium imaging of large, genetically-defined populations of neurons (>500) using 2-photon microscopy in head-restrained behaving mice.

Mechanisms underlying psychiatric disorders

Ongoing research in the lab aims to understand how brain activity and neuronal networks are affected or altered in psychiatric disorders characterised by changed cognition. We use transgenic animals modelling aspects of mental disorders, as well as pharmacology and optogenetics to decipher how changed brain activity relates to changes in behaviour. This line of research aims to identify novel cellular and molecular targets for pharmacological interventions in psychiatric disorders.

A mouse with implanted optical fibre for optogenetic studies.

Selected publications 2016-2019

1. Ährlund-Richter S* / Xuan Y*, van Lunteren JA, Kim H, Ortiz C, Pollak Dorocic I, Meletis K, Carlén M (2019) 'A whole-brain atlas of the monosynaptic input targeting four different cell-types in the prefrontal cortex of the mouse.' *Nature Neuroscience.* Apr;22(4):657-668.

2. Lazaridis I, Tzortzi O, Weglage M, Märtin A, Xuan Y, Parent M, Johansson Y, Fuzik J, Fürth D, Fenno LE, Ramakrishnan C, Silberg G, Deisseroth K, Carlén M, Meletis, K . (2019) 'A hypothalamus-habenula circuit controls aversion' *Molecular Psychiatry*. Feb 12;24:1351-1368.

3. Carlén, M. (2017) 'What constitutes the prefrontal cortex?' *Science*. Oct 27;285(6362):478-82. Review

4. Kim H, Ährlund-Richter S, Wang X, Deisseroth K, Carlén M. (2016) 'Prefrontal parvalbumin neurons in control of attention.' *Cell.* Jan 14;164(1-2):208-218.   *) *equal contribution*

Prizes/Awards 2016-2019

- Wallenberg Scholar (medicine). 2019 (5 yrs) (Marie Carlén)
- Karolinska Institutet Senior Researcher. 2017 (5 yrs) (Marie Carlén)
- Wallenberg Academy Fellow (medicine) Prolongation. 2017 (6 yrs) (Marie Carlén)
- Consolidation grant from Swedish Research Council. 2016 (6 yrs) (Marie Carlén)
- CIMED Junior Investigator. 2016 (5 yrs) (Marie Carlén)
- NARSAD Young Investigator Award 2019 (Pierre le Merre)

Group members 2016-2019

- Hans Brünner
- Sofie Ährlund-Richter
- Pierre le Merre
- Nicolas Guyon
- Xinming Wang
- Ana Crestani
- Felix Jung
- Yang Xuan
- Hoseok Kim
- Josina van Lunteren
- Martin Hägglund

RESEARCH GROUP LEADER

Marie Löf

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Innovative use of mobile phones to promote physical activity and nutrition across the lifespan

(the IMPACT research group)

Digitalisation has dramatically changed communication and information seeking in our everyday lives. The use of mobile technology (such as the Internet and smartphone applications), referred to as 'Mobile Health' or mHealth, is becoming popular in assisting, informing and guiding people to a healthy lifestyle and is used for primary and secondary prevention of disease.

Our research group utilises mobile phones to develop and evaluate new methods for dietary and physical activity assessments as well as to deliver obesity prevention and physical activity interventions. Our research covers studies in children, pregnant women and adults in general.

MINISTOP and HealthyMoms

Key projects in our research group include the MINISTOP and HealthyMoms trial (led by Marie Löf). In the MINISTOP trial we developed a mobile based (mHealth) obesity prevention programme targeting parents of preschool aged children. The programme is based in social cognitive theory and includes
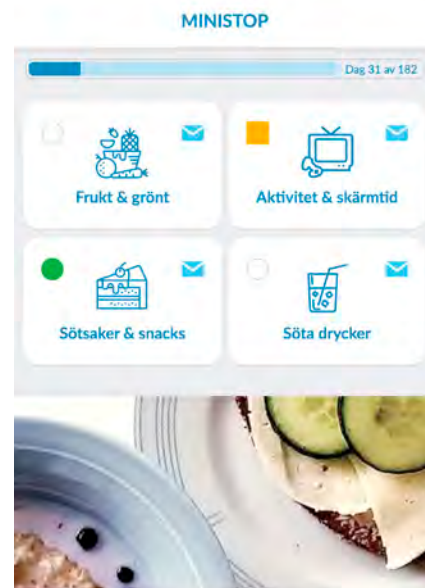
Tema 3: Frukost

Välkommen till tema 3! Det här temat är fullspäckat med tips på bra frukostar och strategier för bra morgonrutiner. Du kommer även att få svar på frågor som varför en del barn inte vill äta frukost eller varför barn helt plötsligt blir petiga med mat de tidigare gillat och hur du som förälder kan tänka och göra.

A screenshot from one of our apps; the MINISTOP app.

information, registration of health behaviours with feedback and parental strategies. The programme has been evaluated in a randomised controlled trial and is currently being implemented in child health care (implementation study). Correspondingly, the HealthyMoms trial is an mHealth programme aiming to promote healthy gestational weight gain, diet and physical activity in pregnant women.

BigO -13 partners – 5 countries

https://bigoprogram.eu/

Obesity rates in children are studied in the EU-funded H2020 project BigO (in continuation of the EU project SPLENDID). Collecting and analysing big data on children's obesogenic behavioural patterns and their environment (smartphones and smartwatches), BigO extracts evidence on which local factors are involved and how they influence childhood obesity. Led by Ioannis Ioakeimidis, KI has formalised the requirements for the BigO system and coordinates all the BigO research trials, with focus on school-based data collection.

i-Prognosis – 11 partners – 7 countries

www.i-prognosis.eu

i-PROGNOSIS aims to advance early prognostics for Parkinson's disease by combining technology with medical expertise. Through technology-based solutions, iPrognosis gathers data from the general population and patients in order to better inform doctors of the onset and development of the disease. Led by Ioannis Ioakeimidis, KI focuses on the behavioural analysis of eating behaviours, using hand-gesture from smartwatches and automatic meal video analysis.

Selected publications 2016-2019

1. Henriksson P, Henriksson H, Tynelius P, Berglind D, Löf M, Lee I-M, Shiroma E, Ortega FB. (2019) 'Fitness and body mass index during adolescence and later life disability: A cohort study of 1 million male military conscripts.' *Ann Intern Med.* 2019 Feb 19;170(4):230-239.

2. Langlet B, Fagerberg P, Delopoulos A, Papapanagiotou V, Diou C, Maramis C, Maglaveras N, Anvret A, Ioakimidis I. (2019) 'Predicting Real-Life Eating Behaviours Using Single School Lunches in Adolescents.' *Nutrients.* 2019 Mar;11(3):672.

3. Fagerberg P, Langlet B, Oravsky A, Sandborg J, Löf M, Ioakimidis I.(2019) 'Ultra-processed food advertisements dominate the food advertising landscape in two Stockholm areas with low vs high socioeconomic status. Is it time for regulatory action?' *BMC Public Health.* 2019 Dec;19(1):1-0.

4. Nyström CD, Sandin S, Henriksson P, Henriksson H, Trolle-Lagerros Y, Larsson C, Maddison R, Ortega FB, Pomeroy J, Ruiz JR, Silfvernagel K, Timpka T, Löf M. (2017) 'Mobile-based intervention intended to stop obesity in preschool-aged children: the MINISTOP randomized controlled trial.' *Am J Clin Nutr.* 2017 Jun;105(6):1327-1335.

Research Networks 2016-2019

- Active Healthy Kids Global Alliance https://www.activehealthykids.org/
- SUNRISE https://sunrise-study.com/

Group members 2016-2019

- Christine Delisle Nyström
- Johanna Sandborg
- Emmie Söderström
- Eric Poortvliet
- Magdalena Rosell
- Lena Martin
- Bettina Ehrenblad
- Ioannis Ioakeimidis
- Francisco Ortega
- Pontus Henriksson
- Petter Fagerberg
- Jonatan Ruiz
- Maria Henström
- Billy Langlet
- Serina Wehbe
- Christina Alexandrou

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Circular RNAs in cancer development

Circular RNAs in eukaryotes were discovered more than twenty years ago, with our Department pioneering in these early studies (PNAS, 93:6536-41). Initially, RNA circles were thought of as rare by-products of the splicing machinery.

However, the advent of next generation sequencing has provided compelling evidence that circular RNAs can be quite abundant, in fact more abundant than the mRNAs originating from the same gene. Additionally, an increasing body of evidence has linked circular RNA expression with human biology, including brain function and cancer development.

Our current research efforts centre on the impact of RNA circles in the biology of the most common paediatric cancer in the brain, medulloblastoma.

Mechanism of circular RNA biogenesis

RNA circles are produced via a back-splicing mechanism, where the 3´ end of an exon is spliced to the 5´ end of an upstream exon. This can be facilitated by inverted repeats in the introns that flank the back-spliced exons, as highlighted in the diagram on the next page.

Function of circular RNA

RNA circles are mostly known to act as molecular traps for microRNAs. This is in-line with their increased stability, which relates to the inability of exonucleases to attack a circular species. Additionally, emerging evidence is linking circular RNAs with protein interactions and with the capacity to encode peptides via internal ribosome entry sites.

Circular RNAs and cancer

There is convincing evidence that circular RNA expression is de-regulated in cancer. Moreover, in colorectal, hepatic, prostate and bladder cancer, the de-regulated circular RNAs have been demonstrated to act as oncogenes/tumour suppressor genes by sponging tumour suppressor/oncogenic microRNAs.

However, little is known on how circular RNAs impact medulloblastoma development. To fill this gap, RNA-sequencing approaches that can detect back-spliced junctions, the marker of RNA circles, are implemented in a large collection of human cerebellar and medulloblastoma samples. It is hypothesised that differentially expressed circular RNAs in normal versus cancerous tissue may not simply be "passenger molecules" but actually functionally impact disease development, and we aim to provide clarity in this direction.
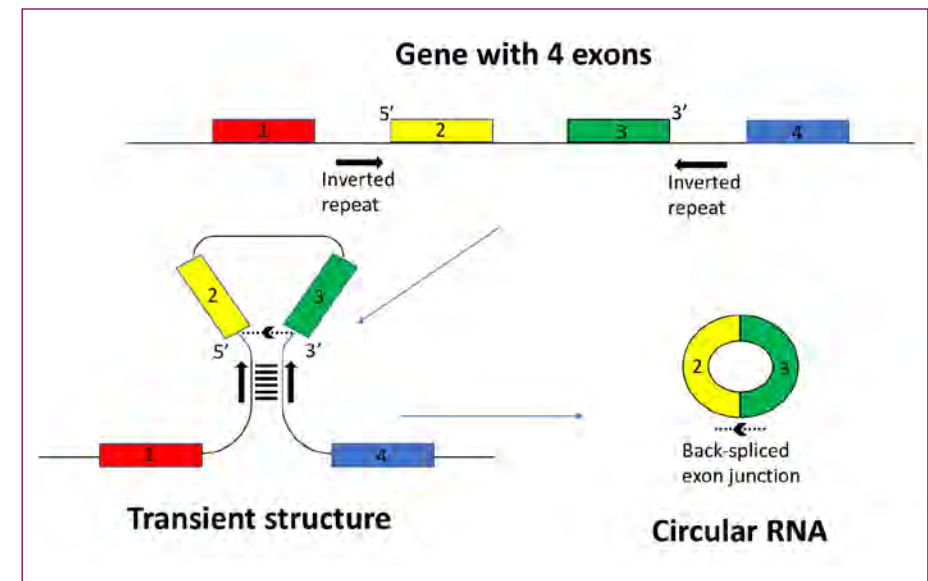
Selected publications 2016-2019

1. Azatyan, A., Gallo, G., Diao, Y., Selivanova, G., Johnsen, J.I., and Zaphiropoulos, P.G. (2019) 'RITA downregulates Hedgehog-GLI in medulloblastoma and rhabdomyosarcoma cells via JNK-dependent but p53-independent mechanism.' *Cancer Letters* 442, 341-350; doi: 10.1016/j.canlet. 2018.11.005.

2. Zaphiropoulos P.G. (2018) 'Circles in action, circles in function.' *AME Medical Journal* 3, 81; doi:10.21037/amj.2018.07.08.

3. Diao, Y., Rahman, M.F-U., Vyatkin, Y., Azatyan, A., St Laurent, G., Kapranov, P., and Zaphiropoulos, P.G. (2018) 'Identification of GLI1 target genes and regulatory circuits in human cancer cells.' *Mol. Oncology* 12, 1718-1734; doi:10.1002/1878-0261.12366

Group members 2016-2019

- Ani Azatyan
- Yumei Diao
- Ting Wang

RESEARCH GROUP LEADER

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Skin at single-cell resolution: molecular and cellular mechanisms during homeostasis, cancer initiation and tissue regeneration

Our skin is the largest organ of the body and contains an intricate variety of cell types that assure proper tissue architecture and function, which includes barrier formation, thermoregulation and hair growth.

An imbalance of cell types and/or molecular signalling often results in disease. We, the Kasper Lab, use modern techniques such as single-cell transcriptomics, *in vivo* lineage-tracing, spatial mapping *in situ* and computational biology, to uncover the cellular behaviour and molecular signals of individual cells in skin during health, repair and cancer development. The overall aim is to understand skin disorders, improve early cancer detection and uncover new regenerative strategies to restore skin.

With our research – rooted within the fields of skin and stem cell biology – we aim to answer fundamental questions about tissue homeostasis, repair and regeneration. We uncover regulatory mechanisms at the cellular and molecular level that dictate stem cell renewal, cell-fate specification and differentiation combining state-of-the-art methodology and interdisciplinary expertise.

Our ongoing projects are:

Decoding the molecular anatomy of skin

We have just completed a molecular (scRNA-seq) and spatial (smRNA-FISH) cell atlas of mouse skin during hair growth and rest (Joost *et al., Cell Stem Cell* 2020) where we defined 56 cell types and states and uncovered how they coordinate hair growth. We also unveiled associated progenitor commitment and lineage differentiation, spatiotemporal fibroblast heterogeneity, and potential epithelial-stromal interactions. Using the expertise and knowledge gained, we are expanding towards human skin analyses with the goal of generating a detailed cell atlas across the human body to propel our molecular understanding of skin in health and disease.

Identifying regulatory mechanisms controlling epithelial stem-cell activation and differentiation

We study when stem cells commit ("lock-in") towards differentiation and if stem-cell activation can be controlled by non-epithelial cell types and cell-extrinsic niche factors, using *in vivo* lineage tracing and cell depletion, *in utero* gene knock down and computational analyses.

Improving skin restoration by studying wound healing and cancer initiation

We investigate how wounding and certain tissue niches promote cancer formation, and how modulation of signalling pathways in the epithelium and stroma can shift a tumour fate into a developmental programme.

Selected publications 2016-2019

1. Dalessandri T, Kasper M. (2019) 'TREMendous Macrophages Inhibit Hair Growth.' *Cell Stem Cell.* 2019 Apr 4;24(4):501-502.
2. Mok KW, Saxena N, Heitman N, Grisanti L, Srivastava D, Muraro MJ, Jacob T, Sennett R, Wang Z, Su Y, Yang LM, Ma'ayan A, Ornitz DM, Kasper M, Rendl M. (2019) 'Dermal Condensate Niche Fate Specification Occurs Prior to Formation and Is Placode Progenitor Dependent.' *Developmental Cell.* 2019 Jan 7;48(1):32-48.e5.
3. Newton PT, Li L, Zhou B, Schweingruber C, Hovorakova M, Xie M, Sun X, Sandhow L, Artemov AV, Ivashkin E, Suter S, Dyachuk V, El Shahawy M, Gritli-Linde A, Bouderlique T, Petersen J, Mollbrink A, Lundeberg J, Enikolopov G, Qian H, Fried K, Kasper M, Hedlund E, Adameyko I, Sävendahl L, Chagin AS. (2019) 'A radical switch in clonality reveals a stem cell niche in the epiphyseal growth plate.' *Nature.* 2019 Mar;567(7747):234-238.
4. Joost S, Jacob T, Sun X, Annusver K, La Manno G, Sur I, Kasper M. (2018) 'Single-Cell Transcriptomics of Traced Epidermal and Hair Follicle Stem Cells Reveals Rapid Adaptations during Wound Healing.' *Cell Reports.* 2018 Oct 16;25(3):585-597.e7.
5. Joost S, Zeisel A, Jacob T, Sun X, La Manno G, Lönnerberg P, Linnarsson S, Kasper M. (2016) 'Single-Cell Transcriptomics Reveals that Differentiation and Spatial Signatures Shape Epidermal and Hair Follicle Heterogeneity.' *Cell Systems.* 2016 Sep 28;3(3):221-237.e9.

Prizes/Awards 2016-2019

- 2017 LEO Foundation GOLD Award (international award to young scientists for exceptional advances within skin research) to Maria Kasper
- 2017 Poster Award (33rd Ernst Klenk Symposium in Molecular Medicine: Tissue regeneration, wound healing and fibrosis: Translating basic discoveries into patient survival) to Tina Jacob
- 2018 Rising Star Lecture (International Investigative Dermatology Meeting 2018, Florida), awarded by the European Society for Dermatological Research (declined due to birth of our son) to Maria Kasper
- 2018 Poster Award (2nd prize; From Basics to Clinics 2018 - An interdisciplinary winter conference) to Tina Jacob
- 2019 Karolinska Institutet Consolidator Grant to Maria Kasper

Group members 2016-2019

- Karl Annusver
- Simon Joost
- Alexandra Are
- Unnikrishnan Sivan
- Tim Dalessandri
- Xiaoyan Sun
- Tina Jacob

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Tissue Stem Cells and Ageing

Tissue resident stem cells (a.k.a. adult stem cells) renew and repair our tissues. However, generation of new stem cells via self-renewal and their differentiation into functional cells must be carefully balanced. During ageing, multiple types of alterations directly in stem cells, or in their tissue neighbourhood can disturb this balance.

Our laboratory studies both stem cell intrinsic, and extrinsic mechanisms altering tissue renewal capacity, and how such mechanisms ultimately result in ageing.

Asymmetric cell division

At least some stem cells can divide asymmetrically to generate a new stem cell and a differentiating cell in a predetermined fashion. This raises the question of the nature of factors that are asymmetrically segregated between the two daughter cells, and how ageing affects this segregation. We are developing methods to analyse whether stem cells apportion their organelles selectively upon asymmetric divisions, and studying the role of related mechanisms in tissue repair.

Cellular metabolism and cell fate

Stem cells have distinct metabolic features. However, whether cellular metabolism facilitates other cellular programmes (self-renewal
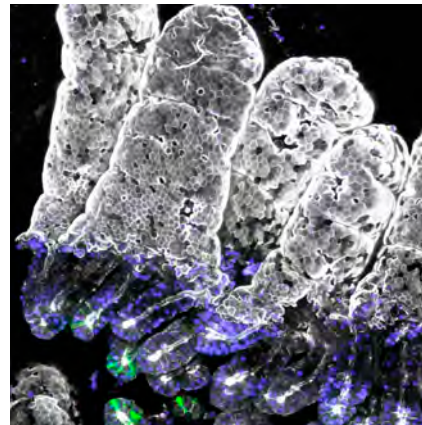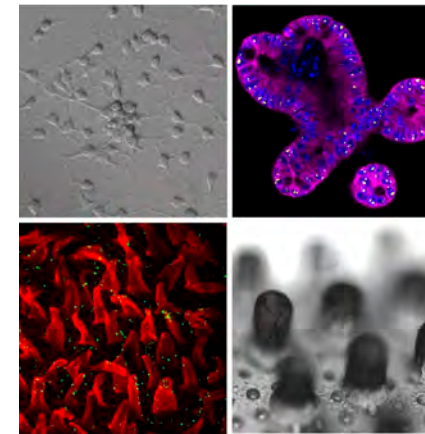

Isolated intestinal crypts and villi. The intestinal stem cells are visible in green. The intestinal stem cells and their niche are one of the models used in our lab.
Picture by Rodrigo Lozano

and differentiation), or whether certain metabolic features can initiate and maintain stemness remains unknown. We study how external cues, such as nutrition, can change stem cell metabolism, and influence their function. Moreover, as mitochondria are a central organelle to cellular metabolism, we probe the hierarchy between cellular metabolism and cell fate by concentrating on the specific case of asymmetric cell division.

Impact of the stem cell niche on ageing

Stem cells are surrounded, nurtured, and protected by their stem cell Niche. The Niche consists of the neighbouring cells, and extracellular matrix, that jointly inform stem cells

on the state of the tissue and organismal physiology. Consequently, age-associated changes in the niche can dramatically impact stem cell activity. We study multiple novel ageing associated niche factors, and develop strategies to increase renewal and repair of old tissues by targeting such stem cell extrinsic factors. Our studies span niche features such as cell-cell contacts, tissue topology, and ECM composition.

Isolated oligodendrocyte progenitor cells (top left) are used to study asymmetric cell divisions and cellular metabolism (Picture by Ana Amaral). Isolated intestinal stem cells and their niche form organoids in vitro (top right), providing a functional assay for niche interactions (Picture by Sandra Scharaw). Decellularised extracellular matrix can be co-cultured with isolated cells to analyse cell-type specific ECM interactions (bottom left, picture by Anna Webb). Organoids can also be cultured in artificial scaffolds (bottom left). This allow us to test different biomaterials or different niche architectures effect stemness (Picture by Rodrigo Lozano).

Selected publications 2016-2019

1. Pentinmikko N, Iqbal S, Mana M, Andersson S, Cognetta AB 3rd, Suciu RM, Roper J, Luopajärvi K, Markelin E, Gopalakrishnan S, Smolander OP, Naranjo S, Saarinen T, Juuti A, Pietiläinen K, Auvinen P, Ristimäki A, Gupta N, Tammela T, Jacks T, Sabatini DM, Cravatt BF, Yilmaz ÖH, Katajisto P. (2019), 'Notum produced by Paneth cells attenuates regeneration of aged intestinal epithelium.', *Nature*. 2019 Jul;571(7765):398-402. doi: 10.1038/s41586-019-1383-0. Epub 2019 Jul 10

2. Tammela T, Sanchez-Rivera FJ, Cetinbas NM, Wu K, Joshi NS, Helenius K, Park Y, Azimi R, Kerper NR, Wesselhoeft RA, Gu X, Schmidt L, Cornwall-Brady M, Yilmaz ÖH, Xue W, Katajisto P, Bhutkar A, Jacks T. (2017), 'A Wnt-producing niche drives proliferative potential and progression in lung adenocarcinoma.' *Nature*. 2017 May 18;545(7654):355-359. doi: 10.1038/nature22334. Epub 2017 May 10.

Research Networks 2016-2019

-   Centre of Excellence in Stem Cell Metabolism - Metastem

Prizes/Awards 2016-2019

-   Fellowship for postdoctoral scholars from SSMF (Svenska Sällskapet för Medicinsk Forskning). (Sandra Scharaw)

Group members 2016-2019

-   Agustín Sola Carvajal
-   Anna Webb
-   Ana Amaral
-   Daniel Borschagovski
-   Sandra Scharaw
-   Tomás McKenna
-   Rodrigo Lozano

RESEARCH GROUP LEADER

Luca Jovine

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Structural studies of fertilisation and zona pellucida module proteins

From microscopic algae to gigantic blue whales, the beginning of every sexually reproducing organism on the planet is sealed by the encounter between female and male gametes, egg and sperm, at fertilisation.

Due to its fundamental role in ensuring the transmission of genetic information between generations, this crucial event has become a true icon of biology that has captivated mankind for centuries. But how does this process actually take place at the molecular level? By harnessing the power of structural biology, our laboratory has started to shed light on the molecular recognition events that underlie the origin of a new life.

The first interaction between gametes happens when sperm contacts the surface of the egg coat, called zona pellucida (ZP) in mammals and vitelline envelope (VE) in non-mammals. This is followed by a second recognition event that triggers fusion of the gametes after sperm has penetrated the VE/ZP and contacted the plasma membrane of the oocyte. By determining 3D structures of ZP2 and ZP3 (major egg coat components that have long been implicated in sperm

binding) as well as structurally characterising Juno and Izumo (counterpart proteins on egg and sperm whose interaction is required for gamete fusion), our group has yielded the first atomic-resolution information on molecules essential for both steps of fertilisation in mammals. By also solving structures of mollusc sperm receptor VERL in complex with its binding partner on sperm, protein lysin (figure), we provided a first example of how gametes contact each other at the very beginning of fertilisation and revealed that - despite being separated by 600 million years of evolution - invertebrate and vertebrate egg coat proteins use the same basic molecular architecture to interact with sperm.

In parallel with these studies, our group is also investigating a family of biomedically important human proteins – such as urinary Tamm-Horsfall protein/uromodulin (UMOD) and endothelial glycoprotein endoglin (ENG)/CD105 – that are similar in structure to fertilisation molecules but which perform completely different functions in the body. While our work on fertilisation proteins has important implications for both understanding human infertility and informing the future development of targeted non-hormonal contraceptives, structural studies on UMOD, ENG and related proteins allowed us to interpret a large number of human mutations linked to severe pathologies, such as urinary and vascular diseases, non-syndromic deafness and cancer. For more information, please visit:

http://jovinelab.org
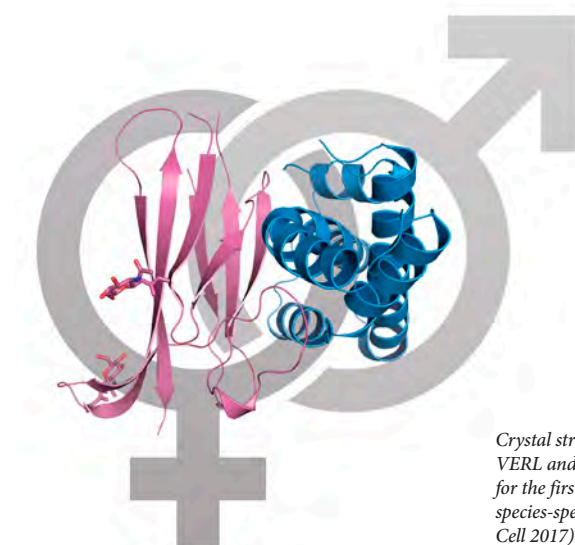
Crystal structure of the complex between egg coat protein VERL and sperm protein lysin. This structure showed for the first time how gametes recognise each other in a species-specific way at the onset of fertilisation (Raj et al., Cell 2017).

Selected publications 2016-2019

1. Nishimura K., Dioguardi E., Nishio S., Villa A., Han L., Matsuda T. and Jovine L. (2019) 'Molecular basis of egg coat cross-linking sheds light on ZP1-associated female infertility' *Nat. Commun*. 10:3086

2. Raj I., Sadat Al Hosseini H., Dioguardi E., Nishimura K., Han L., Villa A., De Sanctis D. and Jovine L. (2017) 'Structural basis of egg coat-sperm recognition at fertilization.' *Cell* 169:1315-1326

3. Saito T., Bokhove M., Croci R., Zamora-Caballero S., Han L., Letarte M., De Sanctis D. and Jovine L. (2017) 'Structural basis of the human endoglin/BMP9 interaction: insights into ALK1 signaling and HHT1' *Cell Rep*. 19:1917-1928

4. Bokhove M., Nishimura K., Brunati M., Han L., de Sanctis D., Rampoldi L. and Jovine L. (2016) 'A structured interdomain linker directs self-polymerization of human uromodulin.' *Proc. Natl. Acad. Sci. USA* 113:1552-1557

Prizes/Awards 2016-2019

- EMBO member (Luca Jovine, 2018-)
- Member of the Nobel Assembly at Karolinska Institutet (Luca Jovine, 2019-)

Group members 2016-2019

- Marcel Bokhove
- Ling Han
- Hamed Sadat
- Romina Croci
- Kaoru Nishimura

- Takako Saito
- Eileen Dietzel
- Shunsuke Nishio
- Alena Stsiapanava
- Dirk Fahrenkamp

- Isha Raj
- Sara Zamora Caballero
- Elisa Dioguardi

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## Conformational dynamics, flexibility and recognition in biological macromolecules

We investigate interactions between proteins and nucleic acids using computer simulations.

Most cellular functions, and thus the survival of the cell, are critically dependent on the ability of the many components of the cell to interact properly and in a controlled fashion, forming more or less stable complexes that may involve dozens of protein and nucleic acid components. Some of these complexes are high-affinity, but in many cases they are transient, and the binding reactions, as well as conformational rearrangements of individual components, which may be partially disordered, exhibit complex kinetics. The focus of our studies is the kinetics of such conformational distributions in nucleic acids and proteins.

We use computational methods, mainly molecular dynamics (MD) simulation, to shed light on the balance between different interactions that stabilise the structural elements as well as the complexes, and to understand how small sequence changes or changes in the environment can modulate function, by affecting structural and dynamic properties. In the last decade computer hardware has evolved to a point where it is possible to perform meaningful studies of flexible and partially disordered biomolecules, and go beyond analyses of the native state(s) to collect data on structural distributions. In parallel with this development, theoretical advances have been made that allow us to compute quantitative descriptions of the kinetics of transitions between intermediates and other (meta)stable states in such distributions using so-called Markov-State-Models (MSMs).

The purpose of these investigations is to provide insight in atomistic detail into the role of structural flexibility and kinetics in proteins and DNA/RNA in relation to their biological function, and to suggest methods to affect pathological states using small molecules.
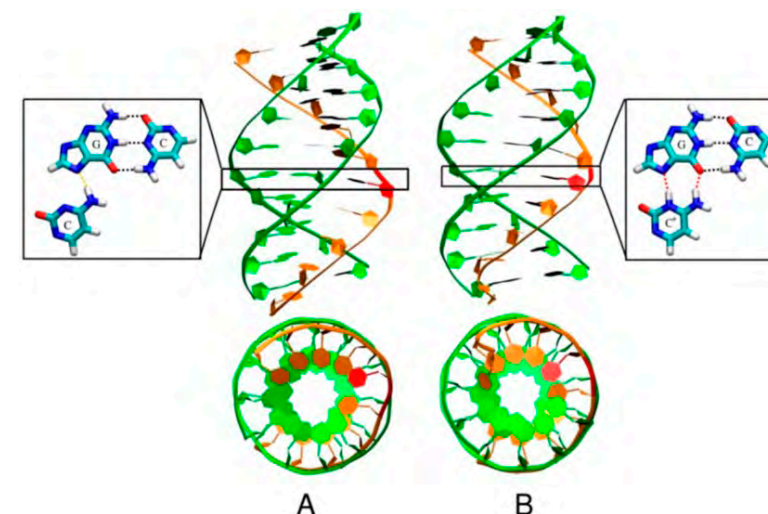
Snapshots from simulation of DNA triple helix, showing stabilising effect of protonation on Cytosine in the third strand. Left: Standard Cytosine. Right: Protonated Cytosine.

Illustration: Lennart Nilsson's group

Selected publications 2016-2019

1. Morgunova, Ekaterina, Yimeng Yin, Pratyush K. Das, Arttu Jolma, Fangjie Zhu, Alexander Popov, You Xu, Lennart Nilsson, and Jussi Taipale. (2018). 'Two distinct DNA sequences recognized by transcription factors represent enthalpy and entropy optima', eLife, 7: e32963.

2. Salamanova, Evdokiya, Joana Costeira-Paulo, Kyou-Hoon Han, Do-Hyoung Kim, Lennart Nilsson, and Anthony P. H. Wright. (2018). 'A subset of functional adaptation mutations alter propensity for α-helical conformation in the intrinsically disordered glucocorticoid receptor tau1core activation domain', Biochimica et Biophysica Acta (BBA) - General Subjects, 1862: 1452-61.

3. Pabon-Martinez, Y. Vladimir, You Xu, Alessandra Villa, Karin E. Lundin, Sylvain Geny, Chi-Hung Nguyen, Erik B. Pedersen, Per T. Jørgensen, Jesper Wengel, Lennart Nilsson, C. I. Edvard Smith, and Rula Zain. (2017). 'LNA effects on DNA binding and conformation: from single strand to duplex and triplex structures', Scientific Reports, 7: 11043.

Prizes/Awards 2016-2019

- CHARMM program development group www.charmm.org

Group members 2016-2019

- Joana Costeira-Paulo
- Evdokiya Salamanova
- Mikael Gillner
- AlessandraVilla
- Yossa Dwi Hartono
- Arzu Uyar
- Marzieh Saeedimasine
- You Xu

RESEARCH GROUP LEADER

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## BEA - the core facility for Bioinformatics and Expression Analysis

BEA - the core facility for Bioinformatics and Expression Analysis is a genomic analysis service facility that provides a broad repertoire of technologies to ongoing research projects at Karolinska Institutet and other Swedish universities.

This includes services for genomic analysis based on the Illumina, Affymetrix, Agilent, and ABI platforms for massive parallel sequencing, microarray analysis and qPCR. BEA aims to provide high quality and internationally competitive infrastructure and service including associated data analysis. Importantly, BEA offers comprehensive pay-for-service solutions at all stages of the analysis from experimental design to bioinformatic support.

BEA provides resources and services to support research needs for high-throughput genomics. The analyses are performed with different sequencing and microarray platforms which support a number of different applications. Among new applications that have been tested and implemented recently are the 10X chromium platform for genomic analysis in single cells and RRBS, reduced representation bisulfite sequencing, for analysing genomic DNA methylation patterns. BEA operates as a core facility offering services with a strict "fee-for-service" and "first-come-first-served" principle. The overall principle for financing the operations at BEA is that customer fees cover costs for reagents, smaller operating investments, service agreements and KI indirect costs (INDI).

BEA advertises the services on the BEA website, www.bea.ki.se, where information about the platforms, the different assays provided and updated pricelists for the different types of analysis can be found. A project can be initiated usually after consultation and information about the different available analysis methods and after an order form is formally signed. The queue time for a project at BEA will start when samples are handed to the core facility.
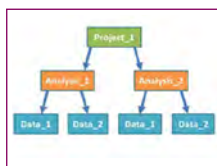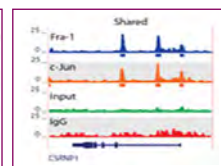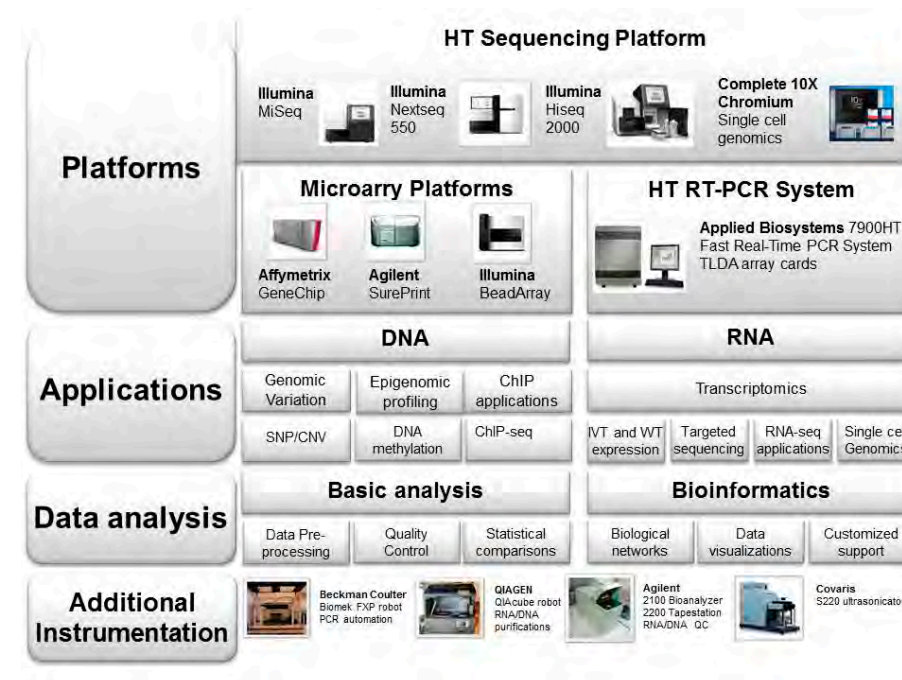

Experimental Planning

Sample Preparation QC

Processing Data accumulation

Data analysis Bioinformatics

Overview of BEA platforms and applications.

Group members 2016-2019

- Susann Fält
- Carolina Bonilla
- Ashwini Gajulapuri
- Anastasius Damdimopoulos
- Marika Rönnholm
- David Brodin
- Patrick Müller

CORE FACILITY MANAGER
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The Live Cell Imaging facility at KI, Huddinge: an advanced microscopy facility with high-end equipment and expertise.

The Live Cell Imaging facility is a large microscopy core facility that offers equipment and expertise for high-end image acquisition and analysis. The facility covers most areas of microscopy applied to live sciences: live cell imaging, super resolution microscopy, fast microscopy, confocal, widefield and light sheet microscopy, high-throughput/content microscopy as well as high-end automated image analysis in multiple dimensions.

Every year an advanced microscopy course is held at the facility, with lectures and workshops. Students get the chance to get personalised feedback on how to prepare and image their own sample.

Group members 2016-2019

- Staffan Strömblad (Director)
- Tobias Nyberg (Research Engineer)
- Sylvie Le Guyader (Core Facility Manager)
- Gisele Miranda (Image Analyst)
- Gabriela Imreh (Research Engineer)

Started in 2008 as a local facility, the LCI opened to all researchers at KI and at other universities in 2014. The same year the LCI also became the Nikon Center of Excellence, one of only a handful in the world. This label is attributed to facilities with a special colla-boration with Nikon Instruments.

The Live Cell Imaging facility currently has 70 active users who share 9 microscopy systems and a powerful analysis server.
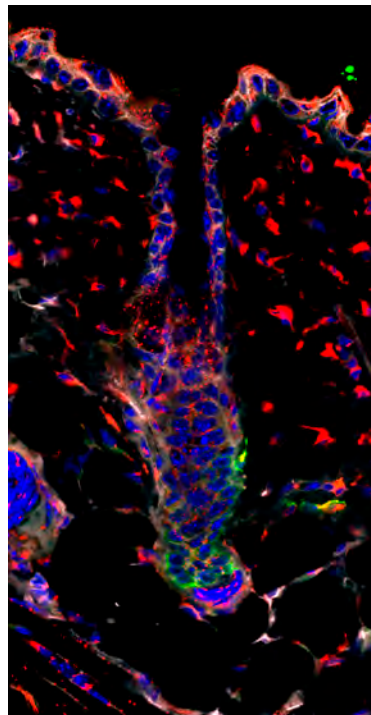
"Hair follicle in telogen: The stem cells on the hair bulge are labelled with GFP (green) and the secretory pathway in red".
Photo: Agustín Sola Carvajal (Pekka Katajisto's group)

Photo: Camilla Svensk

Dissertations 2016-2017

2016	2017
Yichun Qiao; Exploring the genome-wide impact of transcription factor AP-1 in breast cancer	**Maria Hölzl;** Stem cells and development: Studies on SUFU and LGR5
Elo Madissoon; Transcriptional regulation of the human pre-implantation embryo	**Jiyu Guan;** The role of estrogens and the microenvironment in lymphoma progression and drug sensitivity
Anja Füllgrabe; Epidermal stem cells in physiological tissue regeneration, wound healing and cancer	**Charlotte Strandgren;** Analysis of phenotype reversibility in Hutchinson-Gilford progeria syndrome in mice
Mohammed Ferdous-Ur Rahman; Mechanisms of hedgehog signaling activation in cancer development	**Ramakrishnan Kumar;** Insights into 5-lipoxygenase biocatalysis and interaction with membrane components
Martina Jezowska; Towards smart antisense and antigene therapeutics - design & synthesis of novel oligonucleotide based bioconjugates	**Yossa Hartono;** Understanding structural features of biomolecular interactions: From classical simulations to *ab initio* calculations
Hamed Sadat; A crystallographic view of egg-sperm interaction	**Christine Delisle Nyström;** A web and mobile phone-based obesity prevention intervention in 4-years olds: A population-based randomized controlled trial
Amirhossein Kharman Biz; Potential novel molecular targets for breast cancer diagnosis and treatment	**Miao Zhao;** Role of PAK4 in pancreas development and breast cancer
Ghazaleh Assadi; Identification and functional characterization of gastrointestinal disease genes	**Fatemeh Hadizadeh;** Understanding the interplay between gut microbiota, gut function and host genes in the generation of gastrointestinal symptoms and disease
You Xu; Molecular modeling and thermodynamics simulation of nucleic acids	
Yumei Diao; GLI1 modulation of the output of hedgehog signaling in human cancer	

Dissertations 2018-2019

2018	2019
Maria Henström; Genetics of irritable bowel syndrom and associated gastrointestinal symptoms	**Simon Joost;** Decoding the heterogeneity of skin in homeostasis and regeneration at single-cell resolution
Elisa Dioguardi; Structural studies of proteins essential for fertilization	**Ning Liang;** Transcriptional control of liver metabolism and disease by nuclear receptor-corepressor networks
Debora Sugiaman-Trapman; The role of RFX transcription factors in neurons and in the human brain	**Xin-Xuan Lin;** Discovering and targeting the mechanisms that govern age-related decline
Andrea Bieder; Function and regulation of ciliary dyslexia candidates genes	**Gwaldys Revêchon;** Molecular insights into Hutchinson-Gildford progeria syndrome and age-associated disease - From mechanisms to treatment strategy
Billy Langlet; Objective quantifications and analysis of eating behaviours associated with obesity development - from lab to real life	**Hafdis Helgadottir;** Somatic mutations in healthy cells and age-associated diseases
Zhiqiang Huang; Role of GPS2 in epigenome alterations linked to metaflammation	**Huan He;** A multi-omics approach to uncover estrogen receptor (ER) and activator protein 1 (AP-1) signalling networks in breast cancer
	Tânia Costa; Modulating cellular function: PAK4 signaling in development and cancer

Nailing of thesis November 2019, Tânia Costa

Tânia Costa's disseration December 2019

Undergraduate Teaching at BioNut

At the Department of Biosciences and Nutrition (BioNut), research and education go hand in hand. Although research constitutes the larger part of BioNut's undertakings, education is an important and central part of the department's activities.

BioNut has its main competence in basic and experimental biosciences and nutrition and it is also within these educational areas the department is mainly involved. Our goal is that all our educational activities are scientifically based and closely connected to ongoing research. Furthermore, we think that education is an important way to communicate the latest scientific standpoints so that students completing the courses or programmes given by BioNut become knowledgeable, skilled and trustworthy professionals with high credibility within their respective educational areas.

BioNut's main educational engagements are in the global Bachelor and Master's Programmes in Biomedicine, in the global Master's Programme in Molecular Techniques in Life Sciences (run together by the Karolinska Institutet, Stockholm University and the Royal Institute of Technology) and in a one-year global Master's Programme in Nutrition Science, the latter of which we run. All the courses within these programmes are given in English. A majority of the students are non-Swedes, making the programmes highly international. We also run a Bachelor's programme in Nutrition, in collaboration with Stockholm University. In this programme BioNut is in charge of 105 out of 180 credits, mainly courses related to human physiology and nutrition. In addition, BioNut offers a few freestanding courses in nutrition at Karolinska Institutet. Teachers at BioNut also participate in teaching activities on other programmes at Karolinska Institutet, including the Medicine Programme with lectures/

seminars in nutrition. These latter courses are taught in Swedish.

Within the Biomedicine Programmes, BioNut runs several courses both at the bachelor and master's levels with approximately 44 annual full-time student equivalents. The one-year global Master's Programme in Nutrition Science embraces approximately 30 full-time student equivalents, while the 3-year Bachelor's Programme in Nutrition, encompasses approximately 40 annual full-time student equivalents.

Courses given at the bachelor level within the Biomedicine Programme include "Genetics, Genomics and Functional Genomics". The Master's Programme in Biomedicine includes courses in Applied Communication, where the students learn how to communicate science in speech and writing to colleagues, the media and to the public and how to write grant applications. The courses also include philosophy of science and bioethics. BioNut also runs a 30 credit Degree project on the Master's Programmes in Biomedicine, as well as in the Master's Programme in Molecular Techniques in Life Sciences.

The aim of the one-year global Master's Programme in Nutrition Science is to give the student an in-depth understanding of the scientific basis of the subject of nutrition and related research methodology. Areas covered include how relationships between diet and health are studied and what the basis is for various recommendations in diet and physical activity, including sustainability aspects, as well as exploration of molecular mechanisms underlying the link between diet and health. Assessment methodologies in nutrition research are addressed in depth and the students are also trained in designing intervention studies based on eHealth and mHealth (internet and mobile phone technology). Global perspectives and comparisons are included in all of the courses. In the second semester, the students do a 30

credit degree project, which can be carried out in many different areas of nutritional research.

The education in nutrition in collaboration with Stockholm University was initiated more than 40 years ago. The Bachelor's Programme in Nutrition given in collaboration with Stockholm University is the only Swedish academic education at bachelor level with human nutrition as the major subject. This programme deals with nutrition from many different perspectives - molecular, biochemical, physiological, medical, epidemiological and public health. Evidence-based relationships between food and health are main topics. These topics are taught at Karolinska Institutet by BioNut. It differs from dietician education as the students obtain an in-depth knowledge of natural sciences, including chemistry (45 credits) and cell and molecular biology (30 credits). These latter topics are taught by Stockholm University.

The broad profile of the programme, with an emphasis on natural science, gives the students a lot of possible professional roles to choose among after completing their training. Among other things, they work with health promotion at both individual and community level, information and education, research and development, quality work, control and evaluation, and product development. Examples of work places

are universities, authorities, county councils, food and pharmaceutical companies and international organisations. The broad education also enables the students to continue their education at an advanced level within several topics.

During 2007-2017 a Master's Programme in Nutrition was offered in collaboration with Stockholm University and since the autumn 2018 students have had the possibility of continuing studies in nutrition at advanced level by joining the Global Master's Programme in Nutrition Science at Karolinska Institutet, run by BioNut.

Examples of freestanding courses offered are "Basic Nutritional Physiology", partly run as a distance course on-line and "Body composition and disease".

Finally, BioNut works hard to develop the pedagogical skills of the departmental teachers by offering seminars in pedagogical techniques.

Contact:

Professor Sam Okret

Departmental Educational Coordinator and Vice Chairman at the Department of Biosciences and Nutrition

Photo: Ulrich Schulte

Contacts

The Department of Biosciences and Nutrition is situated in the Neo building in Flemingsberg, next to Karolinska University Hospital, Huddinge.

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Photolist

Cover photos: From left to right; Agustín Sola Carvajal, Gwladys Revêchon and Tomás McKenna, Dept. of Biosciences and Nutrition, KI; and picture from Neo: Sara Bruce

Photos of research group leaders: Anders Lindholm, Dept. of Biosciences and Nutrition, KI, with the following exceptions:

Photos of groupleaders:

Lauri Aaltonen: Veikko Somerpuro for Helsinki University

Carsten Daub: Matthias Hörtenhuber, Dept. of Biosciences and Nutrition, KI

Marianne Farnebo: Jacob Farnebo

Luca Jovine: Stefan Zimmerman, UF, KI

Andreas Lennartsson: Fotograf Håkan Flank AB

Christian Riedel: Daniela Später

Martin Bergö: Oskar Allerby/Folkuniversitetet

Emma Andersson: Linda Lindell, Dept. of Cell and Molecular Biology, KI

Roger Strömberg: Staffan Larsson, KTH

Pekka Katajisto: Staffan Larsson, KTH

Marie Löf: Adam Löf

Marie Carlén: Johan Miderberg. © Ragnar Söderbergs stiftelse 2012

Karolinska Institutet is one of the world's leading medical universities. Our vision is to advance knowledge about life and strive towards better health for all. Karolinska Institutet accounts for the single largest share of all academic medical research conducted in Sweden and offers the country's broadest range of education in medicine and health sciences. The Nobel Assembly at Karolinska Institutet selects the Nobel laureates in Physiology or Medicine.