Introduction

I am proud of having been appointed the new head of the Department of Biosciences and Nutrition “BioNut” in August 2015 and I am very inspired and motivated to lead the department into an exciting future within KI, that will be undergoing large structural improvements in the next few years. Historically, BioNut was created in 2006 by merging two departments Biosciences and Medical Nutrition and it has grown to become the largest biomedical department at the KI South Campus with a strong focus on basic research. As you can see in this report of our activities 2013-2015, we cover a wide range of topics in biomedical research ranging from Ageing to Virology, with many prominent research groups. We also run high level educational activities including a master’s programme in Nutrition in collaboration with SU and we contribute to the Biomedicine programme at KI. In the future, we wish to strengthen the quality of research and be attractive for collaboration with the healthcare sector and other partners at KI South Campus. We also aim to strengthen our international environment in basic and applied experimental research and education.

My visions for the next three years (2016-2018)

At the end of 2017, our new research building NEO will be ready in Huddinge. The move to NEO will be a major step for BioNut, since it will provide new conditions for our infrastructure, as well as possibilities to change the contents of our activities, thereby creating better conditions for collaboration across our research groups, with neighbouring departments and across research disciplines. In this context I have three important goals for BioNut:

1. To create a more integrated coherent BioNut Department: We wish to develop a creative and safe work environment, with a constructive collegial atmosphere.

2. To increase and improve our collaborations with our neighbouring Departments and Research Centres in particular NVS, LabMed, MedH, KTH STH and CIMED (SLL) and the Karolinska Hospital in Huddinge: The goal here is to obtain a very open environment for research and education with common areas where all employees can meet and interact.

3. Finally we should not forget ‘Tredje uppgiften’ - our collaboration with Swedish society and enterprise (näringsliv): I am determined to make BioNut a consistently attractive partner in this context by inspiring and enabling higher standards of excellent quality research and education.

Karl Ekwall
The department in brief

Organisation

Finances 2013-2015

INCOME STATEMENT

<table>
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<th></th>
<th>2015</th>
<th>2014</th>
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<td>Revenues from grants</td>
<td>49 668</td>
<td>51 739</td>
<td>47 504</td>
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<td>Revenues from fees</td>
<td>9 598</td>
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<td>Revenues from allowances</td>
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<td>Internal revenues</td>
<td>21 300</td>
<td>17 235</td>
<td>20 075</td>
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<td><strong>Total revenues</strong></td>
<td><strong>226 243</strong></td>
<td><strong>255 068</strong></td>
<td><strong>250 640</strong></td>
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Key financial figures

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<th>2015</th>
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<tbody>
<tr>
<td>External / total financing</td>
<td>72,7%</td>
<td>72,9%</td>
<td>68,4%</td>
</tr>
<tr>
<td>Research and doctoral education</td>
<td>93,9%</td>
<td>95,8%</td>
<td>95,4%</td>
</tr>
<tr>
<td>First and second level education</td>
<td>6,1%</td>
<td>4,2%</td>
<td>4,6%</td>
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Discoveries
There are many examples of key scientific discoveries made at BioNut. This report highlights selected papers from each of the research groups. Here follows some examples from two different research areas i.e. functional genomics and nutrition. Jussi Taipale’s group have uncovered the DNA binding specificities of human transcription factors and mapped the binding of these factors to cohesion sites (Cell 2013; Cell 2015). Marie Löf’s group made an important contribution to childhood obesity research with a mobile phone tool to improve dietary habits (BMC public health 2015; Int J Obesity in press). Please note that our research covers as many as 14 different research areas resulting in many important findings published in 2013-2015.

Renewals
New seminar series started during 2015 include “Chairman’s seminar series”, “Introduction seminars by new BioNut Group Leaders” and “Group leaders journal club”. The chairman’s seminar series aims to highlight selected top scientists at Swedish universities and is designed to specifically promote female scientists. The introduction seminars aim to increase the visibility for new research groups at our department. Group leaders’ journal club has been created to inspire our most junior scientists, the newly registered PhD students, and to increase their academic networks.

New groups and improved gender balance
One of our top priorities is to obtain an improved gender balance in the department. At the beginning of 2015 we had 4 female and 17 male group leaders. During 2015 and the beginning of 2016, five newly established PI’s with research groups, one new Professor with a group, three Guest Professors, and one foreign Adjunct Professor have been recruited. Of these 10 new group leaders 4 are female, which is a significant improvement of the gender balance on the group leader level. The department head is very pleased to see this positive development and to lead such a dynamic department supporting newly established teams and international recruitments. Please note that the activities of seven new PI’s, recruited during 2015 and 2016, will not be presented until the next scientific report (2016-2018).
### Research

Three group leaders have left the Department during the period 2013-2015. Thomas Bürglin (Regulation of cell specialization), Mauro D’Amato (Molecular genetics of gastrointestinal disease) and Dan Segerbäck (UV radiation and DNA damage). Their research is not presented in this report.

<table>
<thead>
<tr>
<th>Name of new group leader</th>
<th>Research area</th>
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<tbody>
<tr>
<td>Martin Bergö</td>
<td>Biochemical and medical importance of CAAX protein processing and the role of reactive oxygen species and antioxidants in cancer</td>
</tr>
<tr>
<td>Piero Carninci (Foreign adjunct professor)</td>
<td>Studies of mammalian transcriptomes</td>
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<tr>
<td>Pekka Katajisto</td>
<td>Tissue homeostasis loss and ageing</td>
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<tr>
<td>Andreas Lennartsson</td>
<td>Epigenetic regulation of acute myeloid leukaemia</td>
</tr>
<tr>
<td>Linda Sofie Lindström</td>
<td>Molecular and genetic cancer epidemiology</td>
</tr>
<tr>
<td>Victoria Menendez Benito</td>
<td>Centrosomes in cell division</td>
</tr>
<tr>
<td>Cecilia Williams (Guest professor)</td>
<td>Hormone signalling and non-coding RNAs in cancer</td>
</tr>
</tbody>
</table>
Genetic mechanisms of premature and healthy ageing

Genetic mechanisms that affect ageing are of high interest to society, yet not well understood. Although genetic variation between individuals has been studied extensively, few studies have investigated genetic variation within an individual and genetic variation acquired during ageing.

Hutchinson-Gilford progeria syndrome (HGPS, progeria) is a very rare genetic disorder with several clinical features reminiscent of premature ageing, including atherosclerosis, osteoporosis, loss of subcutaneous fat and hair, and thinning of the skin.

The overall aim of our research is to identify genetic mechanisms that contribute to the declined tissue homeostasis associated with ageing and disease mechanisms in progeria. In our studies we use next generation sequencing technologies to investigate the genome of human cells and cells from transgenic models of premature ageing to identify disease mechanisms and early targets for treatment. We expect our findings to contribute to the understanding of genetic mechanisms in ageing and age-associated disease, and ultimately the prevention and treatment of these processes.

Selected publications


Prizes/Awards to group members 2013-2015

Nikenza Viceconte: Fernström travel award 2014
<table>
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<tr>
<th>Group members</th>
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<tbody>
<tr>
<td>Agustin Sola Carvajal</td>
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<td>Irene Franco</td>
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<td>Hafdis Helgadottir</td>
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<td>Gwaldys Revechon</td>
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<td>Tomas McKenna</td>
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<tr>
<td>Sofia Rodriguez</td>
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<tr>
<td>Raquel Pala Rodriguez</td>
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<tr>
<td>Charlotte Strandgren</td>
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<tr>
<td>Emelie Wallén Arzt</td>
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<tr>
<td>Nikenza Viceconte</td>
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<tr>
<td>Jean-Ha Baek</td>
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Transcriptomics for gene regulation in development and disease

Our interests focus on the understanding of the molecular basis of gene regulation of diseases through translational research. The key aspects of our work include genome-wide gene expression analysis from human patient samples employing technologies such as RNA-Seq, Cap Analysis of Gene Expression (CAGE) or small RNA sequencing (miRNA).

Our analysis goes beyond differentially expressed genes and identifies a variety of candidate elements responsible for the observed expression differences in the disease patients and the associated clinical phenotypes. Application of sequencing technology to the transcriptome previously has been utilized to uncover a range of regulatory elements and mechanisms, including regulation through transcription factors (TFs), nearby 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 expressed repeat elements and miRNAs. Subsequent functional validation studies confirm the suggested regulatory relationships.

Selected publications


Research networks 2013-2015

FANTOM5 “Functional Annotation of the Mammalian Genome” coordinated by the Riken Institute, Omics Science Center, Japan

DANIO-CODE Encyclopedia of DNA Elements in Zebrafish

Group members

Tahmina Akhter  Abdul Kadir Mukarram  Niyaz Yoosuf
Olga Hrydziuszko  Enrichetta Miletii  Nancy Yu
Matthias Hörtenerhuber
Understanding the interplay between gut microbiota, gut function and host genes in the generation of gastrointestinal symptoms and disease

The human gut is colonized by billions of microbes, which constitute a complex community known as the gut microbiota. The microbiota exerts positive physiological/nutritional effects, and alterations in its composition are associated with conditions such as inflammatory bowel disease, colon cancer and metabolic disorders.

Our work (collaboration with Mauro D’Amato, BioCruces Institute, Bilbao) attempts to understand how host genes, gut microbiota and gastrointestinal function are interconnected and how they are eventually related to GI disease (IBS, IBD). This involves correlating variation in microbiota composition with variation in gut function and correlating human genetic variation with alterations in microbiota and gut function.

We showed that, in humans, a correlation exists between microbiota and gut function, in that measures of stool frequency and pattern that are associated with gut transit time show a negative correlation with α-diversity indices. We showed that variation in the human genome contributes to shaping the composition of the gut microbiota. We provide preliminary evidence that specific genes/associated pathways may be relevant to the control of bowel movement frequency, and establish a set of candidate targets for follow-up and replication in independent datasets.

Therapies can be considered, where modifications in gut microbiota may be introduced via pharmacological or dietary changes, in order to restore “normal” intestinal flora and human wellbeing.

Selected publications


**Prizes/Awards to group members 2013-2015**

Maria Henström: National Scholar Award (UEG) 2015.

**Research network 2013-2015**

**FP7-KBBE-2007-2A-222720** (CP-IP - Large-scale integrating project)
TORNADO: Molecular Targets Open for Regulation by the gut flora – New Avenues for improved Diet to Optimize European health” (2009 – 2014).

**Group members**

Fatemeh Hadizadeh
Maria Henström
**Bioorganic Chemistry**

Roger Strömberg

+46-8-524 810 24, roger.stromberg@ki.se
http://ki.se/bionut/stromberg

**Targeted oligonucleotides and other alternative approaches for treatment of disease**

The main research aims at chemically enabling novel treatments for inherited, metabolic or infectious disease. This through development of oligonucleotide (ON) therapeutics that target RNA molecules, and in treatment of infections also by triggering our own innate defense molecules and mechanisms.

ON therapeutics can be used to target proteins difficult to modulate with small molecule drugs and also to affect regulatory non-coding RNAs. Advances in ON chemistry can increase potency and provide new therapeutic molecules. The field of ON therapeutics encompass different modes of action, including effects on mRNA, microRNAs, pre-mRNA as well as mRNA therapy.

A key feature is synthetic modified oligonucleotides and their conjugates with other biomolecules that act as signals directing them to the site of action.

Globally, infections are responsible for two thirds all deaths among children of the age 1 month to 4 years. A possible treatment is induction of our own antimicrobial peptides.

Three main directions of the research are:

*Oligonucleotide based artificial nucleases and PNAzymes for biomedical applications and also aiming at treatment of Malaria.*

*Stabilized, cell penetrating and target seeking oligonucleotides for enhanced therapy, aiming at treatment of inherited, metabolic and infectious diseases.*

*Treatment of infections through substances that induce our own innate defense (antimicrobial peptides) against microbes as well as through enhancing autophagy by targeting of microRNA.*

**Selected publications**


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To the left: Confocal microscopy image of uptake of our cell penetrating AECM oligonucleotides in U-2 OS cells treated with a fluorescein-labelled fully AECM modified oligonucleotide (green colour).  

To the right: Graph showing reduction of bacterial count in Shigella infected rabbits after treatment with different doses of an inducer of antimicrobial peptides. Treated rabbits recovered clinically in four days.
Research networks 2013-2015
Swedish Research Council’s “framtidens behandlingar”
MMBIO, EU training network

Group members

Ghidini Alice  Jezowska Herrera Martina  Ottosson Håkan
Honcharenko Dmytro  Maity Joytirmoy
Honcharenko Malgorzata  Murtola Merita
Cell biology of cancer

Our research focuses on key cellular events in cancer progression, with emphasis on cell migration and p21-activated kinase 4 (Pak4). Depending on the properties of the surrounding extracellular matrix, cancer cells can utilize different migration strategies for dissemination. This adaptive behavior 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 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 metastasize.

Pak4 is overexpressed in several human cancers and we previously linked Pak4 to promotion of cancer cell migration and to control of cell growth. To examine the role of Pak4 in cancer progression, our laboratory has in place a number of techniques, including in vitro models, transgenic mice, cancer mouse models, patient database bioinformatics and patient derived material, which will be combined within our comprehensive yet molecularly detailed investigations, stretching also into testing Pak4 pharmacological targeting.

Simultaneous combination of Traction force microscopy (TFM) and a signalling biosensor (RhoA FRET) in a human colon cancer cell. Left: RhoA FRET heat map; Right: Calculated TFM force fields displayed as force heat map. Image: Jianjiang Hu

Selected publications

Research networks 2013-2015

FP7-HEALTH-2010-258068 (NoE)
The KI Breast Cancer theme Center (BRECT); Strömblad serves as vice director.

H2020-PHC-2014- 634107 (RIA)
Multimot: Capture, dissemination and analysis of multiscale cell migration data for biological and clinical applications (2015- ) Strömblad is a partner.

Group members

<table>
<thead>
<tr>
<th>Ulrich Berge</th>
<th>Gabriela Imreh</th>
<th>Helene Olofsson</th>
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<tbody>
<tr>
<td>Tânia Costa</td>
<td>Alexa Kiss</td>
<td>Parisa Rabieifar</td>
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<tr>
<td>Marianne van Dijk</td>
<td>Jacob Kowalewski</td>
<td>Hamdah Shafqat Abbasi</td>
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<tr>
<td>Xiaowei Gong</td>
<td>Zhilun Li</td>
<td>Matthias Spiess</td>
</tr>
<tr>
<td>Sara Göransson</td>
<td>John Lock</td>
<td>Miao Zhao</td>
</tr>
<tr>
<td>Pablo Hernández-Varas</td>
<td>Miriam Masia-Balague</td>
<td>Ting Zhuang</td>
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Hedgehog signalling and tissue stem cells in cancer development

The Hedgehog (Hh) signalling pathway plays a key role in directing cellular growth and tissue patterning during embryonic development. In normal adult physiology the pathway is implicated in stem cell maintenance and tissue repair.

Inappropriate activation of the Hh-signalling pathway is increasingly implicated in human cancer. Mutational inactivation or activation of core components of the Hh-pathway underlie cell autonomous activation in basal cell carcinoma of the skin (BCC), medulloblastomas, meningiomas and rhabdomyosarcomas. In other tumour types, such as colorectal and pancreatic cancer, tumour cells upregulate expression of Hh-ligands that signal to the surrounding tumour stroma.

A major focus of our research is to understand the details of Hh signalling at the genetic, molecular and structural level with emphasis on the key intracellular SUFU and GLI components. Moreover, to elucidate how aberrant activation of this pathway influences cancer development in skin, mammary gland and colon we combine studies of genetically modified models and patient samples.

To understand cancer biology and how to best eradicate tumour cells it is necessary to know also the biology of normal tissues, the nature of tissue stem and progenitor cells and their ability to serve as cancer cells of origin. With this aim lineage tracing and cell fate mapping is used to investigate the presence and functional properties of tissue stem cells marked by expression of Lgr5 and Lgr6 in the skin and mammary gland.

Confocal 3D projection of mammary gland alveoli from a pregnant mouse. A network of contractile myoepithelial cells (green) encloses milk-producing luminal cells (blue). Mammary progenitor cells expressing Lgr6 were genetically labelled during puberty and their progeny (red) traced into mid-pregnancy.

Selected publications


**Prizes/Awards to group members 2013-2015**

Marco Gerling: 3-year Postdoctoral Fellowship Cancerfonden 2015
Romina Croci: 2-year Postdoctoral Fellowship Barncancerfonden 2015

**Research networks 2013-2015**

Breast Cancer Theme Center (BRECT), Karolinska Institutet (Member PI)
Strategic Research Programme on Cancer (StratCan), Karolinska Institutet (Director)
Center for Innovative Medicine (CIMED), Karolinska Institutet (Director)

**Group members**

<table>
<thead>
<tr>
<th>Name</th>
<th>Mohammed Ferdous-Ur Rahman</th>
<th>Fabian Schneider</th>
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<tr>
<td>Agneta Andersson</td>
<td>Csaba Finta</td>
<td>Stephan Teglund</td>
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<td>Marco Gerling</td>
<td>Elin Tüksammel</td>
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<td>Maria Hölzl</td>
<td>Sandra Falck</td>
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<td>Biljana Jovanovic</td>
<td>Victoria Villegas</td>
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<tr>
<td>Romina Croci</td>
<td>Uta Rabenhorst</td>
<td>Peter Zaphiropoulos</td>
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<td>Yumei Diao</td>
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Genetic and environmental control of embryonic development

Our group studies the genetic underpinnings of disease, and how genes interact with the environment to produce specific phenotypes. Within this, our lab has two main focuses:

1. Alagille syndrome pathogenesis with a focus on biliary and vascular development.

2. Development of ultrasound-guided in utero nanoinjection as a powerful tool to manipulate gene expression during development.

Alagille syndrome is a pediatric disorder caused by mutations JAGGED1 or NOTCH2, which leads to liver defects, heart defects, vertebral and ocular malformations and stereotypic facial features. We investigate the role of Notch signaling in bile duct development, liver regeneration and liver malignancy in a mouse model for Alagille syndrome and in human patient material using RNA sequencing of liver and biliary organoids. We also investigate the role of Notch signaling in the vasculature, since a large portion of Alagille patients in fact die from vascular accidents.

In order to rapidly manipulate gene expression in the developing embryo, to answer basic biological questions in various organ systems, we have collaborated with Elaine Fuchs’s group and further developed ultrasound-guided nanoinjection to target other organ systems than the skin. We use this technology to screen gene libraries for roles in cancer or normal development of various organ systems, with a focus on the nervous and hepatic system.
Prizes/Awards to group members 2013-2015

Emma R Andersson: Sven and Ebba Christina Hagberg’s prize 2014
Simona Hankeova: Best Technique Presentation, From Basic to Clinic, March 2015, Sweden; title: Imaging of 3D structures using resin casts and µC 2015
Best Poster Presentation, From Basic to Clinic, March 2014, Sweden ; title: Notch Signalling and Alagille Syndrome 2014

Research networks 2013-2015

Center for Innovative Medicine (CIMED), Karolinska Institutet
Understanding the role of cilia in human brain conditions

We work on the biology of cilia, crucial signal reception and transduction organelles present on many different eukaryotic cell types. Cilia stick out from the cell surface, akin to antennae. Thereby cells can communicate with their immediate environment.

Many components of cilia are controlled by RFX transcription factors. With their unique DNA binding domain RFX factors bind to the X-box promoter motif (RFX = Regulatory Factor binding to the X-box). In this way they directly regulate their target genes. In animals RFX factors regulate genes involved in the immune response and in cilia development and function.

By searching for X-boxes in several animal genomes (C. elegans, Drosophila, mouse and humans) we have identified numerous direct RFX targets. We confirmed many of these targets to function in cilia by using various assays in C. elegans worms and in human (neuronal) cell lines. Accordingly we assigned a number of these cilia genes – upon malfunction – to being at the root of a human disease class termed ciliopathies. We focus on the cell biological underpinnings of human brain-related, suspected ciliopathies, like dyslexia (reading disorder). We attempt to tie together the different biological functions (in ciliogenesis) of direct RFX targets by cross-comparing a large number of candidate X-box regulated genes in various different genomes. With these approaches we will be able to track RFX target gene modules from basic biological function to disease states in humans.

The head of the worm C. elegans is shown. Two bilaterally symmetrical “salt-tasting” neurons are marked with GFP. Through cell-specific genetic rescue experiments the neuron at the top has regained a fully functional sensory cilium (arrowhead) and thus is able to “taste” salt (cf. calcium imaging trace on the left). The neuron at the bottom remains mutant for cilia development and thus is not able to “taste” salt (cf. calcium imaging trace on the left).

Selected publications


**Prizes/Awards to group members 2013-2015**

Gilbert Lauter: Fellowship award from Hjärnfonden (HF), Fellowship award from Svenska Sällskapet för Medicinsk Forskning (SSMF) 2015.

**Research networks 2013-2015**

KI Neurosciences network

Nordic C. elegans researcher network (Nord-Forsk)

Nordic Cilia and Centrosome network (Nord-Forsk)

European C. elegans researcher network (EU COST Action)

**Group members**

Johan Dethlefsen  
Karin Fürtenbach  
Ida Klang  
Gilbert Lauter  
Prasad Phirke  
Flavie Soubigou  
Debora Sugiaman-Trapman
Basic research on epigenetic mechanisms and cancer epigenetics

My group is carrying out both basic research in epigenetics and applied research in cancer epigenetics. We are studying yeast cells (S. pombe) and human cell lines for the basic research and we are using human blood cells as a model to study cell differentiation and cancer.

Our recent work is focused on chromatin remodelling mechanisms, gene regulation and genome stability.

See also http://ki.se/bionut/ekwall

Selected publications

Prizes/Awards to group members 2013-2015
Karl Ekwall: Distinguished Professorship at Karolinska Institute (2010-2014)
Punit Prasad: Award from Åke Olssons foundation for hematology 2013

Research networks 2013-2015
Member of the NordForsk Network "Chromatin, Transcription, and Cancer" (2010-14)
Member of the NordForsk Network "Non-coding RNA" (2011-14)
The FANTOM5 project coordinated by the Riken Institute, Omics Science Center (2013-2015)
Principal investigator for the KAW project ‘Clinical epigenetics of acute leukemia’ involving three research groups at KI (S Lehmann, R Ohlsson and K Ekwall (2012-17)

Group members
Ulrika Axelsson Olga Khorosjutina Michelle Rönnerblad
Galina Bartish Andreas Lennartsson Laia Sadeghi
Jiang Cheng Victoria Menendez-Benito Lee Siggens
Lina Cordeddu Jenna Persson Babett Steglich
Wenbo Dong Punit Prasad Peter Svensson
Alexander Julner
Coregulators, epigenomes and metaflammation

Our research attempts to better understand how alterations of the epigenome control metaflammation, i.e. inflammation in the context of metabolic diseases such as obesity, type-2 diabetes and atherosclerosis. Thereby, we hope to identify novel epigenomic targets and chromatin-based strategies for future prevention and treatment of these diseases.

Epigenome alterations linked to gene expression are fundamental reprogramming processes of the chromatin landscape that are associated with 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 transcription factors. Our search for candidates involved in metaflammation revealed a key role of a fundamental corepressor complex linked to histone deacetylation and demethylation. We suspect that inappropriate function of the complex in adipose tissue triggers epigenomic reprogramming and thereby enhances the susceptibility to develop inflammatory disturbances, insulin resistance and type-2 diabetes. To dissect the underlying mechanisms, we apply a multidisciplinary approach including conditional corepressor knockout mice, genomic and epigenomic profiling, and translational studies.

Model of how obesity-associated epigenome alterations caused by inappropriate corepressor function trigger insulin resistance. In metabolically healthy adipose tissue, a GPS2-containing complex represses transcription of pro-inflammatory genes encoding chemokines such as CCL2 (known as chemo-attractant protein MCP-1), thereby preventing macrophage infiltration. In metabolically unhealthy adipose tissue (e.g. in obese humans and mice), loss of the subunit GPS2 causes inappropriate function of the entire complex, resulting in epigenome alterations (e.g. histone H3K27 acetylation at enhancers) and increased signal responsiveness of transcription to propagate an inflammatory disease environment.

Selected publications


**Research networks 2013-2015**

**FP7 HEALTH F5-2013-602757** (SME-targeted collaborative project)
HUMAN: Health and the understanding of metabolism, aging and nutrition (2013-2018)

**FP7 PEOPLE ITN-2013-606866** (Marie Curie Initial Training Network)

**Group members**

<table>
<thead>
<tr>
<th>Serena Barilla</th>
<th>Marco Giudici</th>
<th>Ning Liang</th>
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<tr>
<td>Anastasios Damdimopoulos</td>
<td>Saioa Goñi</td>
<td>Huang Zhiqiang</td>
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<td>Rongrong Fan</td>
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Functional Genomics
Lauri Aaltonen
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http://ki.se/bionut/aaltonen

Tumor genomics
Since June 2015 I have been a visiting Professor at the Department of Biosciences and Nutrition, KI. My research revolves around genomics of benign and malignant tumors. The work scrutinizes both hereditary and acquired genetic mutations and variations that can cause uncontrolled cell growth.

The genomics of colorectal cancer and uterine leiomyoma are long-term interests of mine with the focus on the role of the non-coding regions of the DNA in susceptibility and somatic genesis of the disease. Whole genome sequencing and genome wide association studies have made this poorly characterized part of the genome visible to researchers, but how variation in this region can lead to uncontrolled growth remains difficult to predict. In collaboration with Professor Jussi Taipale, we are exploring its role in these two tumor types, in order to provide a more profound understanding on the underlying mechanisms.

Sample materials are important in this type of research. A collection of fresh leiomyoma samples is planned to start in May 2016. The collection will be performed at Danderyds hospital in collaboration with doctor Helena Kopp-Kallner. My group has recently revealed that different leiomyoma subtypes have distinct driver pathways and biomarkers (Mehine et al., 2016). To build on this finding we will use the prospective sample collection to investigate possible associations of the leiomyoma subclasses to treatment responses.
Selected publications


Research networks 2013-2015

Academy of Finland project "Finnish Center of Excellence in Cancer Genetics Research" (2012-2014). This is a research consortium where Lauri Aaltonen serves as the director, funded by the Academy of Finland (12M€). Major goal: To unravel the genetic components of human cancer susceptibility using systems biology approaches and to translate the molecular findings into clinical benefits.

**FP7-HEALTH-2010-258236** (CP-IP)
**Functional Genomics**

Patrick Cramer  
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http://ki.se/bionut/cramer

**Genome regulation**

The goal of our research is to understand the molecular mechanisms of gene transcription and the principles of genomic regulation in eukaryotic cells. To this end we develop functional genomics techniques and computational approaches. Eventually we wish to understand the functional genome as a regulatory network based on the underlying sequence determinants and molecular mechanisms.

We maintain a guest professor team at the Department whereas our main laboratory is located at the Max Planck Institute for Biophysical Chemistry in Goettingen, Germany (https://www.mpibpc.mpg.de/cramer). There we also use integrated structural biology (electron microscopy, X-ray crystallography, mass spectrometry) to investigate the molecular basis of gene transcription.

Recent highlights from the laboratory include the three-dimensional structure of the RNA polymerase II transcription initiation complex and its coactivator Mediator (Plaschka et al., Nature 2015 and unpublished data) and the development of transient transcriptome sequencing (TT-Seq), a method that uses metabolic RNA labeling to map the entire range of RNA species in cells, including very short-lived non-coding RNAs (Schwalb, Michel, Zacher, et al., Science 2016). In the future we wish to collaborate with various research groups in Stockholm and aim at using TT-Seq to address several biological questions, including the mechanisms of gene activation during hedgehog signalling and the deregulation of gene transcription in cancer cell lines.
Selected publications


Prizes/Awards to group members 2013-2015


Research networks 2013-2015

German Research Council (DFG) SFB 860 “Integrative structural biology of dynamic macromolecular complexes”

German Research Council (DFG) SPP 1935 “Deciphering the mRNP code”

Group members

Katja Frühauf
Michael Lidschreiber
Functional Genomics
Karin Dahlman-Wright
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Functional genomics of breast cancer

Patients with estrogen receptor (ER)-positive breast cancer are usually treated with anti-hormone therapies such as tamoxifen or aromatase inhibitors. However, many of these patients are resistant to these drugs at diagnosis or develop resistance during treatment resulting in treatment failure. In addition, patients with triple-negative breast cancer (TNBC) have limited treatment options.

Our group is using functional genomics approaches towards unravelling mechanisms of drug resistance in ER positive breast cancer and identifying molecular determinants of malignant cell behaviors in TNBC. The ultimate goal is to develop novel and improved prognostic tools and therapies for patients with these breast tumors.

Recent published results from the group showed the first evidence that the AP-1 transcription factor Fra-1 is overexpressed in TNBC and has prognostic value. This work provided novel insights into the mechanisms through which TNBC cells acquire invasive and proliferative properties. Currently there are three main projects in focus 1) Characterization of the role of AP-1 in regulating the invasive phenotype of TNBC and in a breast cancer mouse model. 2) Identification of the ER cistrome associated proteome in response to different ligands in ER-positive breast cancer cells. With the term “the ER cistrome associated proteome” we refer to the global identification of proteins associated with primarily the DNA bound ER. 3) Identification of the ER cistrome associated proteome in tamoxifen resistant compared to tamoxifen sensitive breast cancer.

The group is approaching the genomic alterations responsible for drug resistance and malignant cell behaviors in breast cancer combining phenotypic and functional genomics data with the ultimate goal to identify novel diagnostic criteria and drug targets.
Selected publications


Group members

Lucia Bialešová  Huan He  Yichun Qiao
Gábor Borbély  Malin Hedengran-Faulds  Indranil Sinha
Peik Brundin  Min Jia  Li Xu
Hui Gao  Amirhossein Kharman Biz  Chunyan Zhao
Marcela González-Granillo  Ju Luan  Jian Zhu
Lars-Arne Haldosén
The first week of human development

The earliest stages of human development before embryo implantation at 5-7 days after fertilization remain poorly charted. The development starts with individual transcriptome activation (Embryo Genome Activation, EGA) accompanied by the degradation of mRNA brought along by the egg cell, to be followed with new waves of transcriptional activation.

These steps can be approached by transcriptomic analysis, but they pose also challenges such as ≈30-fold changes in cellular mRNA content. In order to understand these steps, we performed single-cell transcriptome sequencing of over 340 cells, including oocytes, zygotes and single blastomeres from 4-cell and 8-cell embryos, obtained by informed consent as donations after in vitro fertilization treatments. Comparison of the transcriptomes of oocytes and 4-cell stage blastomeres identified the first 32 embryonally transcribed genes, including previously uncharacterized transcripts and promoters, as well as the significant reduction of thousands of maternal transcripts. At the 8-cell stage, 129 additional genes were upregulated compared to the 4-cell stage. Our transcription start site targeted data allowed also the identification of critical regulators of EGA as 36 bp and 35 bp conserved promoter elements at the two stages of EGA, respectively. These data constitute a resource for understanding the earliest steps of human embryonal development and provide new genes of interest for study of pluripotency and stem cell technologies.

Analysis of RNA changes during the first 3 days after fertilisation. The embryo cells, blastomeres, become successively smaller with each round of cell divisions, with a corresponding reduction in total mRNA content. Massive mRNA degradation takes place in the zygote to 4-cell stage transition, when there is a fourfold degradation effect on top of a fourfold cell division effect.

Selected publications


**Group members**

<table>
<thead>
<tr>
<th>Nathalie Acevedo</th>
<th>Linda Lindström</th>
<th>Debra Sugiaman-Trapman</th>
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<tr>
<td>Andrea Bieder</td>
<td>Elo Madissoon</td>
<td>Cilla Söderhäll</td>
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<td>Gayathri Chandrasekar</td>
<td>Hans Matsson</td>
<td>Isabel Tapia</td>
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<td>Elisabet Einarsdottir</td>
<td>Myriam Peyrard</td>
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<td>Hong Jiao</td>
<td>Suvi Renkonen</td>
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<td>Eeva-Mari Jouhilähti</td>
<td>Gustaf Rosin</td>
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<td>Shintaro Katayama</td>
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Finding the genes that drive cancer

The main scientific questions addressed in our laboratory relate to the understanding of molecular mechanisms that control gene regulation through the use of high-throughput biology to characterize transcription factor (TF) binding specificities and sites in human cancer cells. TFs are analysed both alone, and in combination with other TFs and scaffolding proteins such as the mediator complex.

The resulting knowledge is then applied to the interpretation of large data sets such as whole cancer genomes, and genome-wide association studies that have revealed genomic regions associated with a wide variety of diseases, including heart disease, diabetes and different types of cancer. The work in the laboratory is interdisciplinary, and has an impact both on basic scientific understanding of gene regulation, and on mechanisms of formation of cancer and other diseases.

The specific objectives of our research are the following:

1 To identify mechanisms that govern transcription factor binding in vitro and in live cells
2 To use the resulting information in the interpretation of cancer genomes and genome wide-association studies
3 To validate the findings in mouse genetic models

PWM motif similarities between the heterodimer motifs (green bars) and monomeric and homodimeric representative motifs from Jolma, A. et al. DNA-binding specificities of human transcription factors. Cell 152, 327–339 (2013). Barcode logos for each factor are shown, and background colour of name indicates TF structural family.
Selected publications


Prizes/Awards to group members 2013-2015

Jian Yan: The Chinese Government Annual Award for Outstanding Self-financed Graduate Students Abroad 2014

Research networks 2013-2015

**FP7-HEALTH-2010-258236** (CP-IP)

**FP7-HEALTH-2010-258068** (NoE)

The Centre of Excellence (CoE) in Cancer Genetics, funded by the Academy of Finland (2012-2017), will take advantage of the powerful synergistic combination of advancing technologies, unique national materials, and sophisticated data analyses to create and validate disease models.

Group members

Sandra Augsten  
Lijuan Hu  
Emma Inns  
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Arttu Jolma  
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Inderpreet Sur  
Minna Taipale  
Kashyap Dave  
Sandeep Botla  
Alex Minidis  
Yimeng Yin  
Bei Wei  
Ning Wang
Effects of estrogen and glucocorticoid hormones on normal and malignant cells of the immune system

Hormonal effects on cells of the immune system are more or less well known. An example is the killing of thymocytes by glucocorticoids (GCs). A less known topic is the role and regulation of the de novo synthesis of GCs locally in the thymus, where it seems to have a paracrine role regulating thymocyte homeostasis and T cell development.

Less established is the effect of estrogens on cells of the immune system and particularly on tumors originating from lymphoid cells. The research projects of the group aim to elucidate molecular mechanisms that are involved in regulating physiological GC and estrogen effects on lymphoid cells. Two main areas have been studied.

A) The role and regulation of GCs locally produced in the thymus for T cell development and homeostasis. We and others have demonstrated a de novo synthesis of GCs in the thymus. Furthermore, we demonstrate that GC-regulated thymocyte homeostasis is controlled by ACTH, which exerts a tropic effect on the thymus.

B) Lymphomas are generally not considered as endocrine-related malignancies. However, epidemiological data clearly demonstrate a gender difference in incidence and prognosis and a possible impact of estrogens. We showed that several lymphomas are highly sensitive to ERβ agonists that cause an inhibition of tumor growth in vivo, reduce tumor vascularization (Fig) and inhibit dissemination. On the contrary, inhibition of estrogen synthesis promotes lymphoma progression. We are now studying the molecular mechanism responsible for this tumor inhibiting effect by ERβ agonists and its prognostic value in clinical lymphomas. The results suggest that estrogen signaling through the ERβ is an interesting future therapeutic target for treatment of lymphomas.

Selected publications

**Group members**

<table>
<thead>
<tr>
<th>Konstantin Yakimchuk</th>
<th>Mattias Berglund</th>
<th>Jiyu Guan</th>
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<td>Gergely Talabér</td>
<td>Muhammad Sharif Hasni</td>
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Childhood obesity: Risk factors, prevention and intervention in early life

According to WHO, childhood obesity is one of the most serious public health challenges of the 21st century. Marie Löf’s research group studies early-life factors important for the establishment of childhood obesity with special emphasis on physical activity.

Marie has established two birth cohorts in which body composition are measured continuously during infancy and childhood in order to identify early life determinants of obesity. A follow up at 9 years of age will be initiated during 2016. Another area of Marie’s research concerns development and evaluation of methodology important for nutritional assessments. This work includes methodology to assess intake of foods and energy, physical activity and body composition. Recently this interest has primarily focused on the possibilities of using telecommunication technologies, such as mobile phones, to improve dietary and physical activity assessments and to deliver interventions (mHealth). Marie has developed a mobile phone tool to assess intake of foods in preschool children. One of her recent studies is also the so called MINISTOP (Mobile-based intervention Intended to STop Obesity in Preschoolers) trial which is a mobile phone based intervention aiming at improving dietary habits, increasing physical activity and decreasing sedentary behavior in four-year-old children (Delisle et al BMC public health 2015; 15: 95, Delisle et al Nutrients 2016; 8: 50; Leppänen et al, Int J Obesity, in press).
Selected publications


Research networks 2013-2015

Member of NEON: the Network in Epidemiology and Nutrition which is a Swedish national network for scientists and practitioners with an interest in nutritional epidemiology and methodological issues related to studies of diet and health, funded by Forte, Sweden.

Member of NRCycle: the Network of Nutrition during the Reproductive Cycle – impact on maternal, fetal and infant health. A national network for scientists in nutrition and reproduction, funded by Forte, Sweden.

Member and Report Card Leader for Sweden within the international network: Active Healthy kids Global Alliance [http://www.activehealthykids.org/](http://www.activehealthykids.org/). The network consists of a large number of countries that gather data on physical activity in children within their own country that are then summarized and presented in a global summit.

Group members

Christine Delisle
Bettina Ehrenblad
Eva Flinke Carlsson
Gunilla Hennermark

Hanna Henriksson
Lena Martin
Francisco Ortega

Eric Poortvliet
Sara Rapaso
Jonatan Ruiz
The physiological and pathophysiological significance of the nuclear receptors Estrogen receptor beta and Liver X receptor beta

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

We are particularly interested in Estrogen receptor beta (ERbeta) and Liver X receptor beta (LXRbeta), two receptors which we discovered in the middle of the 90’ies. ER beta is antiproliferative in many tissues including mammary gland and the prostate whereas its relative ERalpha often enhances proliferation of cells, e.g. in the mammary gland. ERbeta is of great interest as an antitumor agent in breast and prostate cancer and we work with various ERbeta ligands which we hope will qualify as drugs against breast and prostate cancer. Furthermore, both ERbeta and LXRbeta have important functions in the developing and adult brain. For example, ERbeta is anxiolytic and LXRbeta is important for cholesterol metabolism in the CNS, and is involved in Parkinson’s disease by influencing dopamine signaling. ERbeta and LXRbeta ligands hold great promise as drugs against neuropsychiatric diseases. LXRbeta is also antiproliferative in many tissues, e.g. the lung. Double knockout of LXRbeta and its relative LXRA in mice results in squamous cell lung cancer, a new and surprising finding that we hope will generate breakthrough knowledge about the etiology of lung cancer.

Deficiency of LXRA and LXRβ induced progressive lipid accumulation in pneumocytes and macrophages. The lung parenchyma was injured by the lipid-toxicity, chronic M1-predominant lung inflammation and oxidative stress. Before 12 months of age, type 2 pneumocytes which are the alveolar progenitor cells tried to repopulate the damaged tissue...
the epithelial lining, but after 12 months of age, when type 2 pneumocytes failed to repair the lung parenchyma, p63+CK14+ basal cells moved into lung parenchyma from the terminal bronchioles to repair. Dysregulation of the p63+CK14+ cells (likely because of loss of LXRs) led to development of peripheral squamous cell lung cancer.

Selected publications


Prizes/Awards to group members 2013-2015

Jan-Åke Gustafsson: Benning Lecture, School of Medicine, Salt Lake City, Utah 2015
The Schueler Distinguished Lecture in Pharmacology, Tulane, University School of Medicine, New Orleans, Louisiana 2014
Distinguished Professor of Dalian Medical University, China 2015
Honorary Doctor in Medicine, University of Athens, Greece 2015
Honorary Fellow at South Australian Health and Medical Institute, Adelaide 2014

Research network 2013-2015

Center for Nuclear Receptors and Cell Signaling, Department of Biology and Biochemistry, University of Houston, Houston, Texas

Group members

- Ivan Nalvarte
- Per Antonson
- Knut Steffensen
- Annemarie Witte
- Patricia Humire
- Liselotte Vedin
- Margaret Warner
- Christina Thulin-Andersson
- Mukesh Varshney
- Marion Korach-André
- Marcela González-Granillo
- Amenä Archer
- Tomas Jakobsson
- Kirsten Remen
Skin stem cells in health, wound repair and cancer initiation

The murine skin is an excellent model organ to study the cellular and molecular interplay in tissue homeostasis and cancer formation, as the skin is one of the best-studied adult stem cell systems and cancer is believed to arise from deregulated stem and progenitor populations.

Stem cells of the skin’s epithelium are located in distinct niches of the hair follicle, the sebaceous gland, and the interfollicular epidermis and their respective progeny are normally restricted to defined areas. However, injuries like acute wounds disturb the balance of homeostasis and allow stem cell progeny to repopulate new areas. Cancer also disturbs – or needs a disturbed – homeostasis, thus it is not surprising that wound healing and cancer formation are closely linked processes.

To build a comprehensive picture of skin homeostasis and cancer initiation we are addressing three different yet tightly linked key questions:

1. What is the cellular plasticity and diversity of epithelial (stem) cells in skin homeostasis?
2. How does wound healing concert reprogramming of epithelial (stem) cells?
3. What roles do (stem cell) niches play during tissue maintenance and cancer initiation?

In summary, our aim is to unravel stem cell diversity and plasticity in adult tissue maintenance, and to reveal how wound repair and stem cell reprogramming influence the development of non-melanoma skin cancer.

Selected publications


**Prizes/Awards to group members 2013-2015**

Maria Kasper: Future Research Leader (FFL5), Swedish Foundation for Strategic Research (2013)
Center for Innovative Medicine (CIMED) Young Investigator (2014)

**Research network 2013-2015**

TARGET (http://ki.se/en/onkpat/starget-a-cancer-research-network), a cancer research network (Linné center), supported by the Swedish Research Council.

**Group members**

Alexandra Are  Simon Joost  Unnikrishnan Sivan
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Structural studies of biomolecular complexes using cryo electron microscopy

Molecular complexes mainly involved in biosynthesis of mediators of inflammation, epigenetic modification, neuro- and synaptic plasticity, formation of the mucus layer and having chaperone function are being studied.

The overall aim is to understand how these structures govern actions in systems, balanced under normal circumstances, can strongly affect diseases. The structures are studied using high resolution cryo electron microscopy (cryoEM) following protein production and isolation to homogeneity. By utilizing and taking advantage of recent major advances in the field of cryoEM, primarily the advent of new detectors, we are aiming for structures which can be interpreted in terms of atomic models. The structural information will be merged with results from complementary studies such as activity measurements and proteomics to elucidate structure – function relationships. In addition to these applications of cryoEM we are also performing method developments with the aim of being able to study smaller objects than those normally subjected to analysis.

Huntingtin is a large protein, normally having more than 3100 amino acid residues in humans, with 6 to 35 glutamine residues close to the N-terminus. In patients with the neurodegenerative disorder Huntington’s disease the number of polyglutamine repeats exceeds this number and the longer the repeat the earlier the onset of the disease as shown in the diagram. The insets show 3D maps of huntingtin having 23 and 78 glutamines respectively as obtained by electron microscopy. The scale bar is 5 nm. For more information see: Vijayvargia R. et al. (2016). eLife, Mar 22;5. Pii: e11184. Doi: 10.7554/eLife.11184.
Selected publications


Research network 2013-2015

Korea – Sweden Research Corporation (STINT/NRF)

Group members

Philip Koeck, PhD  
Caroline Jegerschöld  
Pasi Purhonen, PhD  
Carsten Mim, PhD  
Harriet Nilsson, PhD  
Ji-Joon Song, PhD  
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Structural Biology

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How life begins: egg-sperm interaction at fertilization

By marking the beginning of a new life, adhesion between female and male gametes at fertilization is one of the most crucial steps of development. Although this key event has been studied since the seventeenth century, its molecular basis remains unknown.

Our laboratory uses mammalian cells to express in recombinant form the highly post-translationally modified molecules that mediate egg-sperm recognition, for both biochemical and X-ray crystallographic studies. By determining the 3D structure of ZP3, a major glycoprotein component of the extracellular coat of the egg that first contacts sperm at conception, we gained insights into the evolution of fertilization proteins from invertebrates to human. Recently we also unveiled the architecture of Juno, a mammalian egg protein that is essential for triggering the fusion of gamete plasma membranes. Ongoing work aims at visualizing how gamete recognition proteins bind to each other at the atomic level, with possible future application to the understanding of human infertility and the design of targeted non-hormonal contraceptives. In parallel, we are investigating medically relevant human proteins that share structural similarity with egg coat components but are important for the control of urinary tract infection and tumor angiogenesis. Cancer is also at the core of a long-term collaboration with the group of Rune Toftgård, with whom we solved the structure of tumor suppressor SUFU, a key regulator of the human hedgehog signaling pathway.

Crystal structure of Juno, an egg plasma membrane-anchored glycoprotein. This is the first structure to be determined of a molecule essential for triggering the fusion between mammalian gametes.

Selected publications


**Prizes/Awards to group members 2013-2015**

Luca Jovine: Hugo Theorell Prize for Biophysics 2013

**Group members**

<table>
<thead>
<tr>
<th>Marcel Bokhove</th>
<th>Kaoru Nishimura</th>
<th>Hamed Sadat</th>
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<tr>
<td>Elisa Dioguardi</td>
<td>Isha Raj</td>
<td>Takako Saito</td>
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<td>Ling Han</td>
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Simulating the behavior of proteins and nucleic acids

Intrinsically disordered protein regions, which are implicated in a number of diseases, are commonly found in transcription factors. Based on our previous simulation studies of the effect of ligands, which were designed to bind to, and stabilize, the disordered amyloid \( \beta \)-peptide in a helical conformation, we are currently characterizing disordered regions in the glucocorticoid receptor and c-myc transcription factors, correlating modeled structural stability with activity data for mutants.

In the ribosomal decoding center we study the role of modified nucleotides in the recognition between tRNA and mRNA. These systems contain many modified nucleotides (110 naturally occurring modified nucleotides are known), and we have developed a force field for these nucleotides adopting the same rigorous methodology as has been used for the CHARMM force fields.

From simulations of the internal motions of the apical stem loop RNA of human hepatitis B virus, we computed dynamical properties of the RNA and found them to be in good agreement with NMR experiments.

We model nucleic acid complexes, in particular DNA triplex structures, for use in gene therapy, where we optimize the composition (including the use of modified or novel nucleotides) and sequence of triplex forming oligonucleotides to bind with high affinity and specificity to double stranded DNA and function as an anchor for functional groups decorating a plasmid carrying genetic material to be introduced in the nucleus.

Influence of locked nucleic acids (LNA, which have a rigid sugar moiety) on the structure of DNA duplexes with and without a bound triplex forming oligonucleotide (TFO). The LNA sugars are blue and the TFO strands are orange. In the top-view only the duplex strands are shown.

Selected publications


**Research networks 2013-2015**

EU COST Action CM1402 “From molecules to crystals - how do organic molecules form crystals”

CHARMM core developer group ([www.charmm.org](http://www.charmm.org))

**Group members**

- Yossa Dwi Hartono
- Evdokiya Salamanova
- Mikael Gillner
- Arzu Uyar
- Alok Juneja
- Alessandra Villa
- You Xu
Environmental cancer risk and oxidative damage on DNA

The research within the laboratory group has had a long-term collaboration with several networks. The focus has been consistently on oxidation of DNA. Oxidation of DNA leads to DNA breaks, misincorporation and dysfunction of DNA. Several substances interact with metal-atoms in the body and in most cases there is a repair process, but there are also situations with consequences related to the environment – health axis.

It could be metal particles that interact with cells that can induce inflammatory effects. An example of this is metal nano-flakes interacting with tissues that induce recycling. A normal matter like cycling on a bicycle is good for the health, but if we add anti-oxidants we might manipulate with the redox-cycling so we either increase or decreases oxidation. This is complicated since the body uses both. Free radicals, exposure to nano-particles, both a premature child and food can interact with these and give adverse effects. We have seen differences in different countries as well as laboratory experiments. This leads to much collaboration to understand oxidation as a normal process and/or a direct effect that can affect a tissue.

Selected publications


Group members

Karine Ehlin  Johanna Kain  Ylva Rodhe
Clara Ersson  Siiri Latvala
Activation of the spike proteins of enveloped viruses for membrane fusion

Enveloped viruses like Zica, dengue, influenza, HIV-1, Ebola and SARS enter into cells by fusing their membrane with that of the host cell. For this they use spike proteins on their surface. We are interested in how the spikes work and how they are neutralized by antibodies.

We use two retrovirus, murine leukemia virus (MLV) and HIV-1 as our models. The spikes of both viruses are trimeric proteins, where each protomer is composed of a surface (SU) and a transmembrane subunit (TM). The latter can interact with the target membrane by its fusion peptide and drag the viral and the cell membranes together for fusion by zippering its polypeptide into a hairpin (panels E and F in Fig.). The SU binds to the viral receptor and triggers the TM. Although the major features of the activation process have been established, the reaction intermediates of the trimeric spike have remained elusive. We have developed novel ways for solubilizing the native spike oligomer for biochemical studies and for structural studies by cryo-EM. Recently we showed that the MLV spike protomers are sequentially activated, i.e. one after each other, forming two intermediates with one, and two activated protomers, respectively (panels B-D in Fig.). The spikes are transmembrane proteins and a major problem has been to solubilize them in a natural milieu. To alleviate the problem we have introduced the human spingolipid activator protein saposin A as a way to solubilize spikes into small nanomembranes (Nature Methods 2016, 13:345).

Sequential activation model for the retrovirus spike protomers. The SU subunits are grey and the TM subunits colored. In the native spike the fusion peptide (FP) of TM is reversibly exposed in all SU-TM protomers (panel A). Receptor binding facilitates interaction of the exposed FP with the cell membrane (panel B). This activates the isomerization of the SU-TM disulfide of the protomer and the release of SU (panel C). The spike is now
bound to the cell membrane by the FP of the first activated protomer. This facilitates the interaction of the FP of the second protomer with the cell membrane and its activation (panel D). When the third protomer also has reacted the N-terminal helical regions of the TM subunits (red) complete a trimeric coiled coil, upon which the C-terminal parts (blue) are zippered (panels E-F). This leads to a trimer of TM hairpins, where the FPs and the transmembrane segments of the TM subunits are juxta positioned in a fused viral and cell membrane.

Selected publications


Research network 2013-2015

**FP7-PEOPLE-ITN-2008-235649 (MC-ITN)**


Group members

Henrik Garoff

Robin Löving

Birgitta Lindqvist

Mathilda Sjöberg
Core Facilities

BEA - the core facility for Bioinformatics and Expression Analysis

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Fredrik Fagerström Billai
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BEA, the core facility for Bioinformatics and Expression Analysis, www.bea.ki.se, provides access to a wide variety of genomic technologies. With more than 10 years of operating experience, BEA has extensive experience of implementing and maintaining genomic technologies. The core facility services are based on microarrays, next generation sequencing (NGS) and quantitative PCR (qPCR) platforms from Affymetrix, Agilent, Illumina and ABI.

The strategy of BEA is to provide a broad repertoire of genomic technologies to support individual research projects thereby contributing to the success of those projects. Specifically, this involves supporting the implementation of new technologies and maintaining standardized genomic services in the rapidly developing field of genomic research.

Importantly, BEA offers comprehensive solutions from experimental design to completion of data analysis. BEA aims to provide high quality and internationally competitive services within the described fields including associated data analysis. BEA also provides education and information, including PhD student courses, workshops and seminars.

BEA services and competences are highly requested by researchers at the Karolinska institute and other Swedish academia. BEA has status as “SciLifeLab Regional facility of national interest” and operates with a strict "fee-for-service" principle with customer fees covering costs for reagents, smaller operating investments and service agreements.

Group members

David Brodin, Bioinformatician
Fredrik Fagerström Billai, Head of facility
Susanne Fält, Laboratory engineer

Malin Liljebäck, Laboratory engineer
Patrick Muller, Laboratory engineer
Marika Rönnholm, Laboratory technician
At the CryoEM facility transmission electron microscopy (TEM) is being used for applications mainly in structural biology. Large purified molecules or complexes are subjected to analysis by single particle methods while smaller systems like membrane proteins may require crystallization and electron crystallography data collection and processing. Specimens are often initially characterized by negative staining for high contrast imaging followed by preparation of frozen hydrated specimens (cryo).

One of the TEMs is used for initial studies, while the other is dedicated for data collection. It has recently been equipped with a direct electron detector. The improvements on the detector side have had a major impact on recent progress of cyroEM. Furthermore, the facility has all the necessary equipment for specimen preparation. Processing of data can be performed on a Linux cluster with most of the common software for single particle and crystallography procedures.

At the cryoEM facility projects are run on specimens originating from other groups at the Stockholm south campus, KI main campus, other universities in Sweden and through international contacts. Most of the projects can be characterized as structural biology at the molecular level, but applications towards cell biology and biotechnology are also ongoing. The last category also involves a non-academic user.

2D crystal of a potassium channel (image by Qie Kuang). The inset shows reconstructed density at the channel position and an adapted atomic model with a K⁺-ion.

Group members

Hans Hebert, PhD, professor, group leader
Philip Koeck, PhD, associate professor
Caroline Jegerschöld, PhD, lab manager

Pasi Purhonen, PhD, lab manager
Carsten Mim, PhD, assistant professor
Harriet Nilsson, PhD, researcher
The Live Cell Imaging facility is a large microscopy core platform that offers high-end image acquisition and analysis equipment and expertise to its users. The facility covers most areas of microscopy applied to live sciences: live cell imaging, super resolution microscopy, fast microscopy, confocal and widefield microscopy, high throughput 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 workshop. Students get the chance to get feedback on how to prepare and image their own sample.

Started in 2008, the facility was opened up to all researchers at KI and other universities in 2014. The same year it also became a Nikon Center of Excellence, one of only a handful in the world. This label is attributed to facilities with a special collaboration with Nikon Instruments.

The Live Cell Imaging facility currently has 60 active users who share 6 microscopy systems and 4 analysis computers.

**Group members**

Straffan Strömblad, Director  
Sylvie Le Guyader, Manager  
Gabriela Imreh, Research Engineer  
Tobias Nyberg, Research Engineer
KHTC - Karolinska high throughput center
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KHTC is a core facility with an extensive collection of state-of-the-art instrumentation and research tools for functional genomics studies, including integrated liquid and microplate handling, high-throughput screening (HTS) and Next Generation Sequencing (NGS) capabilities. KHTC is among the most advanced centers of its kind in Europe and operates as an investigator-assisted facility, where user training in experimental design and operation of the instruments is an important part.

Services at KHTC include: (i) Genome editing using pooled CRISPR/Cas9 screening followed by NGS readout and initial data analysis, (ii) Assay miniaturization, optimization and validation from 96- to 384 or 1536-well formats. (iii) HTS of siRNAs and compounds in various assays. In addition, we provide access to collections of CRISPR guide RNA libraries, siRNA libraries, human ORFeome clones and comprehensive sets of small molecule compounds.

The equipment at the facility comprises the following detection instruments: (i) HiSeq2000 and 4000 sequencers, (ii) BD pathway 855 automated microscope, (iii) Acumen Cellista high-content imager, (iv) CyAn ADP flow cytometer, (v) EnVision multilabel plate reader and (vi) LightCycler 480 qPCR device.

KHTC is a national infrastructure as part of the Functional Genomics platform at SciLifeLab. During the past three years, we have assisted more than 80 research groups from five Swedish Universities, seven international Universities and several non-academic institutions.

Analysis of lipid content in human fat cells

Group members
Jussi Taipale, Facility Director
Anders Eriksson, Head of Facility
Jianping Liu, Laboratory Manager
Natalia Nekhotiaeva, Research Engineer
Minna Taipale, Senior Scientist
Dissertations 2013-2015

2013

Susanna Kugelberg, Public health nutrition in Europe: Workforce development and policy change

Ammad Khan, Transcriptional regulation and evolution of kindlins

Tove Sandberg, Urinary thymine dimer as a biomarker of exposure to ultraviolet radiation

Lise-Lotte Vedin, The antiproliferative role of the liver X receptor in breast and colorectal cancer

Ali Sorosh, A 6 month physical activity intervention in university staff: Effectiveness and health outcomes – The ASUKI step study

Johanna Kain, Toxicity of metal containing micro- and nanoparticles – Studies from an inhalation perspective

Tina Jurén, DNA adducts as biomarkers of exposure to some dietary carcinogens

Jenna Persson, Chromatin remodeling and DNA topology in transcription and genome stability

Li Xu, Molecular characterization of estrogen receptor beta variants: Cancer cell proliferation and invasion

2014

Sofía Rodríguez Vásquez, The genetic mechanism that links Hutchinson-Gilford progeria syndrome to physiological aging

Michelle Rönnerblad, Dissecting the epigenetic landscapes of hematopoiesis and fission yeast

Jian Yan, Deciphering the transcriptional regulation code in colorectal cancer genome

Santhosh Kumar Gudise, The functional organization of nuclear envelope proteins

Assoc. Prof. Dan Segerbäck, Opponent Prof. dr. Frederik-Jan van Schooten, Maastricht University, and defendant Tove Sandberg.

2015

Tomas McKenna, Epithelial stem cells in Hutchinson-Gilford progeria syndrome

Ida Klang, Effects of pharmaceutical modulation of protein aggregation on lifespan in Caenorhabditis elegans

Ylva Rodhe, Toxicity and biocompatibility of nanoparticles, and studies on oxidative stress and DNA damage

Babett Steglich, Interplay of chromatin remodeling, transcriptional regulation, and nuclear organization

Ulrika Axelsson Norman, DNA topoisomerases and nucleosome dynamics in fission yeast

Muhammed Sharif Hasni, Estrogens and lymphoma growth

Jian Zhu, Post-translational modification of estrogen receptor alpha and p53 in breast cancer cells

Alice Ghidini, Mimicking the action of ribonucleases: Studies on RNase A and design of PNA based artificial enzymes

Ting Zhuang, Post-translational modifications in mammary gland development and mammary tumor progression

Hamdah Shafqat Abbasi, Systems microscopy analysis of cell migration

Laia Sadeghi, Modulating chromatin by transcription and nucleosomal turnover. A genome-wide study in fission yeast

Arttu Jolma, Determination of transcription factor binding specificities
Undergraduate teaching

At the Department of Biosciences and Nutrition research and education go hand in hand. Although research constitutes the larger part of the Department’s undertakings, education is an important and central part of the department’s activities. This is exemplified by the participation of the Departmental Educational Coordinator in the Departmental management group.

The Department has its main competence in basic 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 programs given by the Department become knowledgeable, skilled and trustworthy professionals with high credibility within their respective educational areas.

The Department of Biosciences and Nutrition’s main educational engagements are within the bachelor and master’s programs in Biomedicine and bachelor and master’s programs in Nutrition, the latter two which the Department gives in collaboration with Stockholm University. The Department has the overall responsibility for the bachelor and master’s programs in Nutrition. In addition, the Department gives a few freestanding courses in Nutrition at Karolinska Institutet. Teachers at the Department also participate in teaching activities at other programs at the Karolinska Institutet e.g. the Medicine program with lectures/seminars in Nutrition.

Within the Biomedicine programs, the Department is responsible for several courses both at the bachelor and master’s levels comprising a total of 58 credits (10 at the bachelor level, 48 at the master’s level) with approximately 44 annual performance equivalents (HÅP). For the 3 year bachelor program in Nutrition, the Department is responsible for courses corresponding to 105 credits and for 90-120 credits (depending on the length of the degree project) on the master’s program in Nutrition. All together this corresponds to approximately 72 annual full time student equivalents (HÅS) and 66 total annual performance equivalents in the bachelor and master’s programs in Nutrition in 2015. The bachelor courses in Nutrition given at the Department are taught in Swedish while all courses at the master’s level given at the Department are taught in English. More than 50% of the students at the master’s level are non-Swedes, making it highly international. Courses given at the bachelor level within the Biomedicine program include “Cell Biology and Genetics”. At the master’s program in Biomedicine, they include courses in Applied Communication in Biomedicine 1, 2, 3, and 4 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. The Department is also responsible for the Degree projects at the master’s programs in Biomedicine. All courses at both the bachelor and master’s level are taught in English making the student composition of the classes highly international.
The education in Nutrition in collaboration with Stockholm University was initiated more than 40 years ago. The education programs in Nutrition are the only Swedish academic educations with nutrition as their major. The bachelor program deals with nutrition from many different perspectives - medical, biochemical, molecular, epidemiological and public health perspectives. Evidence based relationships between food and health are main topics. It differs from “Dietician education” as the students obtain a deep knowledge in natural sciences, including chemistry (45 credits), cell biology (30 credits), physiology and molecular biology. The broad profile of the program gives the students a lot of possible professional roles to choose between after completing their training. Among other things, they work with health education, health administration or development of new consumer products.

The master program in Nutrition is based on the bachelor program and offers additional research interaction and possibilities to go both deeper and broader into studying questions related to food and health. The master’s program also includes courses in communication, philosophy of science, pedagogics and environmental aspects on food production and consumption. In the evaluation of all national university programs by the Swedish National Agency of Higher Education in 2013, both the bachelor and master’s program in Nutrition were approved. In 2015 Stockholm University announced its interest to transfer full responsibility of the master’s program to Karolinska Institutet. The Department is positive to this idea and is working for it’s implementation.

Examples of freestanding courses given are “Basic Nutritional Physiology” partly given as a distance course on-line and “Body composition and disease”.

Some courses on the postgraduate program given by the department were also offered as elective courses to the undergraduate students, e.g. in bioinformatics and nuclear receptors and metabolism.

Finally, the Department 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.
Contact

The Department of Biosciences and Nutrition is situated at NOVUM in Flemingsberg, adjacent to Karolinska University Hospital, Huddinge. We will move into a new house in the same area called “Neo” during 2017.

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Omslagsfoto: Tomas McKenna, Karolinska Institutet, Biovetenskaper och Näringslära

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