MINERVA FOUNDATION & MINERVA FOUNDATION INSTITUTE FOR MEDICAL RESEARCH

Scientific Report 2018

Front page image: A portrait of Professor Ralph Gräsbeck (July 6, 1930 – January 22, 2016), one of the founders of Minerva Foundation and its Research Institute. Painted by Eva Cederström.

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CONTENTS

CONTENTS

Research groups

SUMMARY OF RESEARCH AND ACTIVITIES DURING THE YEAR 2018

Minerva Foundation Institute for Medical Research is a privately owned research institute located at Biomedicum, Academic Medical Center Helsinki, Finland. The Institute, the history of which dates back to 1959, combines basic biomedical research with clinical investigation relevant to common diseases.

The overarching aims of the Minerva Institute are to generate 1) new fundamental knowledge and mechanistic insight, 2) innovations for the development of future diagnostic approaches, and 3) preventive measures and treatments for common diseases such as diabetes and cardiovascular diseases, as well as neurodegenerative and neuropsychiatric disorders. The study objectives, rooted in the fundamental molecular mechanisms of disease, are addressed at the Minerva Institute through a spectrum of approaches ranging from studies employing pure proteins and lipids, cultured cells and genetically manipulated animal models to the investigation of human patients. The research undertaken in the groups of the Institute during 2018 is outlined in this report.

The financial resources of Minerva Foundation are directed at maintaining and further developing a research infrastructure that serves, in the most effective way, the work in the research groups. The groups are responsible for acquiring external funds to cover the costs of special reagents, the stipendium or salary support of doctoral students, and the salaries of other personnel. The amount of external, competitive research funds acquired by the groups exceeded 1 M€ during 2018, covering 56,5% of the total Institute budget.

The year 2018 was highly productive: A total of 53 articles were published, 43 of which were in international peer-reviewed journals, the median impact of the publications being 4.47. In addition, five doctoral theses were defended during the year.

To foster the exchange of scientific ideas and new collaborations, on Aug 28-29, together with the Wihuri Research Institute, the Minerva Institute organized the international symposium 'Stem Cells in Regenerative Medicine' (see pp. 8-9), as well as three special seminars (listed on the right). Medix Prize of the Minerva Foundation was delivered on Sept 17 for the 31st time and received quite remarkable publicity due to enhanced communication to the media (see p. 6). Moreover, the Foundation's first Ralph Gräsbeck Scholarship in Laboratory Medicine was awarded in 2018 (see p. 7). During the spring of 2018, the research at the Institute was evaluated by a panel of international experts, whose recommendations are being implemented to direct the future development of the Institute. To promote cohesion between the groups and the positive atmosphere at the Institute, the Institute organized a summer excursion on June 12, a group leaders' brain storming session on Aug 23 and a Christmas party on Nov 30.

To conclude, the Institute thrived in 2018 both scientifically and financially, and is determined to make the New Year of 2019 even more successful.

EVENTS AT MINERVA 2018

Symposium

MINERVA AND WIHURI RESEARCH INSTITUTES' SYMPOSIUM
Biomedicum Helsinki, August 28 – 29, 2018
Stem Cells in Regenerative Medicine

Read more on pp. 8-9.

Seminars

MINERVA SEMINAR, BIOMEDICUM HELSINKI

Francesca Giordano, Institute de Biologie Intégrative de la Cellule, Gif-sur-Yvette, France: *Role of the OSBP-related proteins ORP5/8 in lipid transport at ER-mitochondria membrane contact sites.* June 14, 2018.

Andrew Brown, School of Biotechnology and Biomolecular Sciences, The University of new South Wales (UNSW, Sydney), Australia: *The control of cholesterol and the fate of fat.* August 24, 2018.

Marion Weber-Boyvat, Charité-Universitätsmedizin, Cluster of Exellence NeuroCure, Berlin, Germany: *Oxysterol binding proteins: brakes for exocytosis?* August 30, 2018.

Prizes and Scholarships

MEDIX PRIZE OF THE MINERVA FOUNDATION
Award Ceremony and Lecture, Biomedicum Helsinki, September 17, 2018.

Johanna Ivaska, Cell Adhesion and Cancer Biology, Turku Center for Biotechnology, University of Turku and the Åbo Akademi University: *SHANKing talin and RAS to regulate cancer proliferation and migration.*

The winning article:

Lilja J, Zacharchenko T, Georgiadou M, Jacquemet G, De Franceschi N, Peuhu E, Hamidi H, Pouwels J, Martens V, Nia FH, Beifuss M, Boeckers T, Kreienkamp HJ, Barsukov IL, Ivaska J. SHANK proteins limit integrin activation by directly interacting with Rap1 and R-Ras. *Nat Cell Biol.* 2017; 19:292-305.

Read more on page 6.

MINERVA FOUNDATION'S RALPH GRÄSBECK SCHOLARSHIP FOR RESEARCH IN LABORATORY MEDICINE
Pirkka-Pekka Laurila, École Polytechnique Fédérale de Lausanne, Switzerland.

Read more on page 7.

Doctoral Dissertations

Susanna Lallukka: Non-alcoholic fatty liver disease: The role of insulin resistance, inflammation and the PNPLA3 I148M variant. University of Helsinki, January 13, 2018. (Endocrinology)

Anna Tikka: Characterization of ANGPTL3 deficiency and molecular mechanisms of ANGPTL3 deficiency-induced hypolipodemia. University of Helsinki, January 19, 2018. ((Lipid Signaling and Homeostasis/Matti Jauhiainen)

Raghavendra Mysore: Novel molecular regulators of adipose tissue metabolism. University of Helsinki, May 18, 2018. (Lipid Signaling and Homeostasis)

Henriikka Kentala: ORP2 – A sterol sensor controlling hepatocellular bioenergetics and actin cytoskeletal functions. University of Helsinki, August 18, 2018. (Lipid Signaling and Homeostasis)

Panu Luukkonen: Heterogeneity of non-alcoholic fatty liver disease – Genetic and nutritional modulation of hepatic lipid metabolism. University of Helsinki, September 7, 2018. (Endocrinology)

ADMINISTRATION

THE MINERVA FOUNDATION

The main purpose of the Foundation is to promote research in medicine and biosciences by maintaining the Minerva Foundation Institute for Medical Research. This scientific review covers the period from January 1 – December 31, 2018. During this period, the board of trustees included the following persons:

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MEDIX PRIZE OF THE MINERVA FOUNDATION

Photo. Never before has SHANK protein been studied in cancer. It has been known that SHANK is related to autism, but the mechanism was unknown. International, multidisciplinary research group at the lobby in Turku BioCity. From left: Ph.D. Maria Georgiadou, Ph.D. Guillaume Jacquemet, Ph.D. Ilkka Paatero, post graduate student Pranshu Sahgal, Ph.D. Hussein Al-Akhrass, Academy professor Johanna Ivaska, Ph.D. Paulina Moreno-Layseca, Ph.D. James Conway, Laboratory technician Jenni Siivonen, Ph.D. Emilia Peuhu, post graduate student Johanna Lilja, Ph.D. Hellyeh Hamidi ja Laboratory technician Petra Laasola. Courtesy of Martti Ahlsten/ Viestintätoimisto Verbi.

The Medix Prize, worth 20,000 €, was this year awarded to the research group of Academy Professor Johanna Ivaska at the University of Turku, for a study elucidating the mechanisms of cell adhesion and cancer. The group works at the Turku Center for Biotechnology maintained by the University of Turku and Åbo Akademi University. The awarded study has been published in the journal *Nature Cell Biology* under the title 'SHANK proteins limit integrin activation by directly interacting with Rap1 and R-Ras.'

Minerva Foundation's Medix Prize is a major annual award for internationally recognized biomedical research in Finland. This prize represents in a way the 'Finnish championship' in biomedicine. In 2018 the Medix Prize was awarded for the 31st time. The prize sum is donated to the University of Helsinki by Medix Ltd. The prize is awarded annually for excellent Finnish scientific research published in the form of one article during the previous year. The research should be from the fields of biomedicine or clinical medicine and performed fully or in its essential parts in Finland. The awardee is selected by a panel consisting of representatives of the universities of Helsinki, Turku, Tampere, Eastern Finland, and Oulu. The panel is nominated for three years at a time.

This year the prize was awarded for research which elucidates the capacity of cells to attach to the surrounding tissues. In this study, the authors found a protein that reduces the ability of cancerous cell to spread in their tissue environment. The SHANK protein under study renders cancer cells less active and prevents their adhesion to tissues. Correspondingly, mutations in this protein impair its anti-adhesive effects.

In addition to their importance in the context of cancer, the present observations are relevant for understanding the nerve cell disturbances occurring in autism.

"SHANK was previously known to be connected with autism. Mutation in SHANK or the absence of this protein predisposes to severe autism, but the underlying mechanism has thus far remained unknown. Out study also provided information on this mechanism," comments Johanna Ivaska.

"This is a good example of basic research at its best. We set out to solve a particular problem, and suddenly found fully unexpected biological connections. The SHANK protein had never before been studied in the context of cancer. When we as cancer researchers began to study these new connections, we unexpectedly also became researchers in autism." However, there is no connection between cancer and autism such that if one lives with autism, one would have an increased risk of cancer, or vice versa.

The group continues its work on the mechanisms underlying cancer and autism. Professor Ivaska does not want to estimate the stage at which the research could possibly be translated to develop new therapies or medications. However, she believes that this will eventually take place. History is full of examples of how medicines have developed based on basic research observations.

Johanna Ivaska's multidisciplinary research group has collaborated with two research groups abroad: Dr. Igor Barsukov's group at the University of Liverpool has elucidated the 3D structure of the SHANK protein, while Dr. Hans-Juergen Kreienkamp's group at the Institute of Human Genetics, Hamburg, has studied the function of SHANK in neurons and cancer cells.

MINERVA FOUNDATION'S RALPH GRÄSBECK SCHOLARSHIP FOR RESEARCH IN LABORATORY MEDICINE

Minerva Foundation has decided to commemorate Professor Ralph Gräsbeck, one of the founders of Minerva Foundation and the associated Medical Research Institute, by establishing a new scholarship in his name. The first scholarship was granted in 2018, the awardee being Dr. Pirkka-Pekka Laurila on the recommendation of an independent panel of experts.

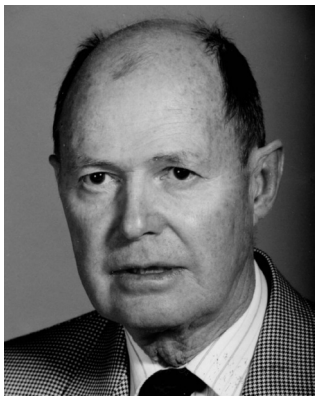
The Ralph Gräsbeck Scholarship totals EUR 10,000 and will be granted every second year starting from 2018 to an outstanding researcher in laboratory medicine who has completed their doctorate within the last seven years. Candidates are assessed on the basis of their application, research plan and merits.

Pirkka-Pekka Laurila works at the École Polytechnique Fédérale de Lausanne in Switzerland. He investigates metabolic routes related to aging and their roles in metabolic and cardiovascular diseases using systems biology approaches. The Ralph Gräsbeck Scholarship was granted to him for this very research, which aims to identify biomarkers and new treatment targets related to such diseases.

Laurila presents regularly at international conferences. He has previously received the International Atherosclerosis Society Young Investigator Award (2009), the American Heart Association Early Career Award (2014), the Finnish Atherosclerosis Society Young Investigator Award (2014), and the European Atherosclerosis Society Young Investigator Award (2017) for the best European publication on basic research in the cardiovascular area during 2016.

Dr. Pirkka-Pekka Laurila

Ralph Gräsbeck (July 6, 1930 – January 22, 2016)



Ralph Gräsbeck achieved his MD degree in 1952 at the remarkably young age of 22. His career continued in the Fourth Department of Internal Medicine at the University of Helsinki, where he was inspired by his chief and mentor, Professor Bertel von Bonsdorff, to study the physiology and pathophysiology of vitamin B_{12}. This led to his MD thesis in 1956, in which he described the presence and vitamin B_{12} transporting function of 'intrinsic factor' in human gastric juice.

As a researcher, Ralph Gräsbeck is probably most famous for the discovery and analysis of Imerslund-Gräsbeck syndrome, which is part of the Finnish disease heritage. He made various observations with his colleagues about the metabolism of vitamin B_{12} – also called cobalamin – and its disorders. He also took part in the investigation of tapeworm-induced anemia. Moreover, he introduced the concept of reference value, which replaced the illogical concept of normal value.

In the 1950s, Gräsbeck worked as a biochemistry researcher at Johns Hopkins University, Baltimore, USA, and the Medical Nobel Institute (part of the Karolinska Institute) in Stockholm. Gräsbeck was appointed lecturer (docent) in clinical chemistry at the University of Helsinki in 1959. He was head physician of the central laboratory at Maria Hospital from 1960 to 1990.

Ralph Gräsbeck was a member of several national and international scientific societies and institutional boards. Besides many other honors, he was awarded the Anders Jahre prize for young investigators at the University of Oslo in 1966. He was appointed professor honoris causa in 1982 and doctor of honor at the Poincaré university of Nancy in 1996.

Ralph Gräsbeck was one of the founders of Minerva Foundation and Minerva Foundation Institute for Medical Research in 1959. He played a key role in the founding of the Medix clinical laboratory in 1964 (now Yhtyneet Medix Laboratories) and of the company Medix Biochemica in 1985. Gräsbeck was the director of the Institute from 1971 to 1993 and an active researcher at Minerva almost until his death.

MINERVA AND WIHURI RESEARCH INSTITUTES' SYMPOSIUM

The joint symposium on Stem Cells in Regenerative Medicine was hosted by Minerva and Wihuri Research Institutes on August 28–29, 2018. The meeting was sponsored by the Minerva Foundation, the Jenny and Antti Wihuri Foundation, and the Helsinki University Doctoral Program in Biomedicine, and had more than 200 participants.

The program, focusing on the first day on cardiovascular and on the second day on neuronal diseases, consisted of an impressive list of international speakers at the frontiers of the field, supplemented with national stem cell researchers. It was an innovative idea to combine these two research areas in order to learn from the approaches employed in the two different fields. In the end, the main challenges in both fields are similar, such as how to culture mature iPSC-derived cells in a reasonable time window and how to transplant them into the body so that they survive and regenerate the tissue of interest.

The symposium started with an impressive keynote talk given by **Hans Clevers** (Utrecht University, the Netherlands). The Clevers group has developed a new technology to grow cancer organoids. They can grow the organoids in 4-6 weeks and then test which anti-cancer drugs are most effective in killing each individual cancer type.

Christine Mummery (Leiden University Medical Center, the Netherlands) pointed out that many rodent and human tissues, such as those in the heart or brain, significantly differ between the species. Therefore, studying human proteins in rat tissue is not always feasible or it can lead to incorrect conclusions. Thus, her group is developing human cells on chips to test drugs, find new drug targets and identify patients at risk of heart failure.

Hans Clevers

Christine Mummery





Photos on the top, from left: Joseph Wu, Oliver Brustle, Thomas Eschenhagen

Photos below, from left: Benedikt Berninger, Zaal Kokaia

Joseph Wu (Stanford University, CA, USA) highlighted the problem that cancer treatment often causes acute heart failure or other cardiac problems later in life. To predict who will suffer heart failure, they test chemotherapeutics on patients' iPS cells. The problem in their approaches to repairing the heart with iPSC is that the iPSCs finally die. The major questions are why they die and how their maintenance can be better supported.

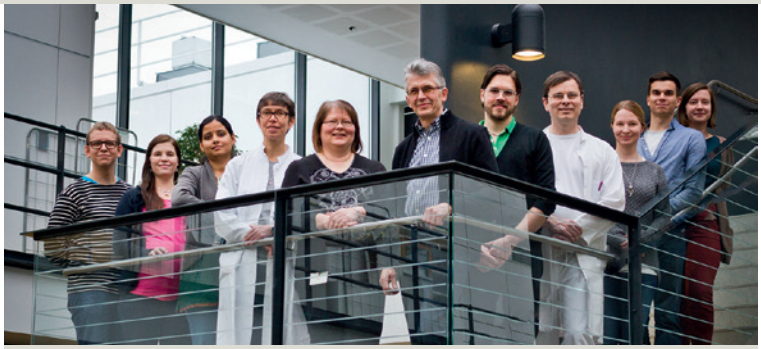
Thomas Eschenhagen (University Medical Center Hamburg-Eppendorf, Germany) also discussed attempts to repair damaged heart tissue using human pluripotent stem cell derived artificial tissue. Their main problem is that only a small portion of the transplanted stem cells adhere to the original heart tissue.

The neuroscience session on Aug 29 was started by **Zaal Kokaia** (Lund University, Sweden). Zaal Kokaia´s group carries out cutting-edge research on transplanting iPSC-derived neurons into the brain. Currently they are transplanting human neurons into the mouse brain and have shown that the transplanted human neurons can wire with the endogenous mouse neurons.

Benedikt Berninger (King's College London, UK) continued partially on the same topic, however using a different approach. In the Berninger group, astrocytes are converted to neurons directly in the brain to rescue neuronal loss.

Oliver Brüstle (Universität Bonn, Germany) brought up an important question about using iPSC technology in studying neurodegenerative diseases: In many such disorders the disease phenotype often appears only after 60 years of age. How can we mimic the aging process when using iPSC-derived cells or tissue?

In addition to these high-end talks, 22 posters were presented at the symposium.



Group Members

Ilkka Tikkanen, M.D., Dr.Med.Sci., Professor, Head
Päivi Lakkisto, M.D., Dr.Med.Sci., Docent, Co-Head
Mika Laine, M.D., Dr.Med.Sci., Docent
Jere Paavola, M.D., Dr.Med.Sci.
Hong Wang, Ph.D.
Heli Segersvärd, M.D.
Juuso Siren, M.D.
Karri Kalervo, M.D.
Mikko Hänninen, M.D.
Suneeta Narumanchi, M.Sc.
Katariina Immonen, B.Sc., Laboratory technician
Riikka Kosonen, M.Sc., Laboratory technician
Sanni Perttunen, B.Sc., Laboratory technician

External funding

The Aarne Koskelo Foundation
The Finnish Cultural Foundation
The Finnish Foundation for Cardiovascular Research
The Finnish Foundation for Laboratory Medicine
The Finnish Society of Clinical Chemistry
The Finska Läkaresällskapet
The Liv och Hälsa Foundation
Research Funding of the Helsinki-Uusimaa Hospital District
(state funding for university-level health research)

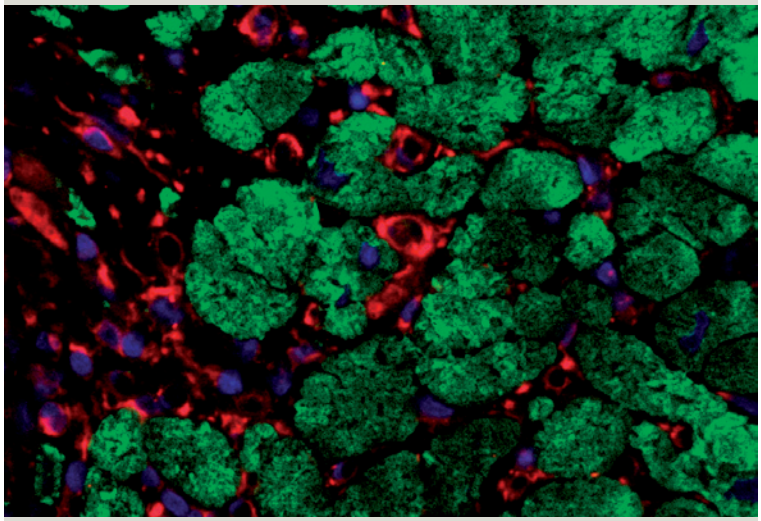


Figure. Immunohistochemistry of human heart showing septin-7 expressing cells (red), cardiomyocytes (green) and nuclei (blue) (courtesy of Katariina Immonen).

CARDIOVASCULAR RESEARCH

Main research activities

Our research group studies mechanisms of end organ damage in cardiovascular and renal diseases. In addition, we evaluate the cardiovascular and renal protective properties of new cardiovascular drugs and treatments. During recent years, the group's research has focused on exploring the molecular mechanisms of cardiac injury and repair after myocardial infarction (MI) and in heart failure, to identify potential targets for cardiovascular medicines.

In these studies, a translational approach is applied, combining methods and findings from both basic science and clinical research in order to improve the evaluation and treatment of cardiovascular diseases. The main projects worked on during 2018 are presented below.

The role of heme oxygenase-1 (HO-1) in cardiovascular diseases

HO-1 and its reaction products, carbon monoxide (CO), biliverdin, and bilirubin, have a variety of cardiovascular protective properties. Our findings demonstrated that treatment with a specific CO-donor, CORM-3, improves both structural and functional cardiac recovery after MI in rats. These effects were associated with altered expression of myocardial miRNA molecules involved in cardiac remodeling and repair. The modulation of the HO-1-CO pathway may prove to be a novel tool to facilitate cardiac recovery after myocardial injury and protect against the development of heart failure after MI.

In collaboration with Adj. Prof. Hannele Laivuori, University of Helsinki (HU), the association of HO-1 gene (HMOX1) polymorphisms and risk of preeclampsia was studied. The long allele of *maternal* microsatellite GTn repeat seems to predispose to a late-onset, less severe form of preeclampsia, whereas the long *fetal* GTn repeat may instead increase the mother's risk of severe and early-onset preeclampsia.

We continued the collaboration with Prof. Per-Henrik Groop and the FinnDiane Study Group, HU, Helsinki University Hospital (HUCH), and the

Folkhälsan Institute of Genetics, to study the possible involvement of HO-1 and HO-1 gene polymorphisms in the development of cardiovascular and renal complications in type 1 diabetes.

Molecular mechanisms of cardiac failure, hypertrophy, and repair

The prognosis of chronic cardiac failure is still poor despite optimal therapy with currently available cardiovascular drugs. Thus, deeper understanding of cellular and molecular mechanisms of cardiac failure and repair is needed.

Septins are small GTPases that are associated with actin and are important in the organization of the cytoskeleton. We have shown in collaboration with Prof. Sanna Lehtonen, HU, that septin7b, the zebrafish ortholog of human septin7, is essential for the subcellular organization of cardiomyocytes and cardiac function in zebrafish. Moreover, knock-down of septin7b diminished the expression of retinaldehyde dehydrogenase 2 (raldh2), which catalyzes the synthesis of retinoic acid shown to modulate ischemic injury and stimulate cardiac regeneration. Our studies elucidating the role of septins in cardiac recovery after myocardial injury continued during 2018.

Vezf1 encodes a nuclear protein containing six zinc finger motifs of the C2H2-type (krüppel-like) and a proline-rich transcriptional transactivation domain. The role of Vezf1 in stress-induced cardiac hypertrophy and development of heart failure in embryonic zebrafish was studied in collaboration with Prof. Risto Kerkelä, University of Oulu. We employed loss of function methods using antisense oligomer molecules that block the translation or splicing of Vezf1. We were able to demonstrate that Vezf1 regulates the development of stress-induced cardiac hypertrophy by modulating βMHC expression and cardiac contractile function by stabilizing cardiomyocyte calcium cycling. Our results indicate a clinically relevant role for Vezf1 in the heart.

MicroRNAs are short noncoding RNA molecules widely involved in the regulation of gene expression. The role of miRNAs after cardiac injury and in heart failure was studied utilizing both experimental and clinical materials. Based on initial microarray screening, followed by quantitative RT-PCR, several novel cardiovascular miRNAs of interest were identified. We were able to show, in collaboration with Adj. Prof. Veli-Pekka Harjola, HUCH, and Dr. Yvan Devaux, the Luxembourg Institute of Health, Luxembourg, that high plasma levels of miR-423-5p predict mortality in patients with acute cardiogenic shock.

Päivi Lakkisto was nominated as a management committee member of COST Action CA17129 "Catalysing transcriptomics research in cardiovascular disease" (CardioRNA).

Clinical hypertension

High blood pressure is the leading risk factor for death worldwide. Despite developments in antihypertensive therapies during recent years, treatment results are still unsatisfactory.

Our clinical hypertension research has focused on new treatment strategies for resistant hypertension, notably renal denervation and baroreflex activation therapy. In addition, we have participated in international collaboration to elucidate the blood pressure lowering and vascular effects of sodium glucose co-transporter 2 (SGLT2) inhibitors, novel glucose-lowering drugs with cardiovascular and renal protective properties, in the treatment of type 2 diabetes.

Publications 2018

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Tikkanen I. Verenpainetavoitteet tiukentuivat ja hypertensiodiagnoosin raja laski uusissa yhdysvaltalaisissa suosituksissa: Paranevatko kohonneen verenpaineen hoitotulokset tavoitetasoja alentamalla? *Duodecim.* 2018; 134:1869-1871.

CELLULAR NEUROSCIENCE

Group members

Pirta Hotulainen, Ph.D., Docent, Head
Rimante Minkeviciene, Ph.D.
Enni Bertling, Ph.D. (on study leave September-December)
Merja Joensuu, Ph.D. (at University of Queensland, Australia, 2-month visit to Helsinki)
Amr Abouelezz, M.Sc.
Iryna Hlushchenko, M.Sc.
Pushpa Khanal, M.Sc.
David Micinski, B.Sc.
Maria Anastasiadou, B.Sc.

External funding

The Academy of Finland
The Instrumentarium Foundation
The Liv och Hälsa Foundation
Päivikki and Sakari Sohlberg foundation
University of Helsinki Brain and Mind graduate school (Amr Abouelezz)
Alfred Kordelin foundation (Iryna Hlushchenko)

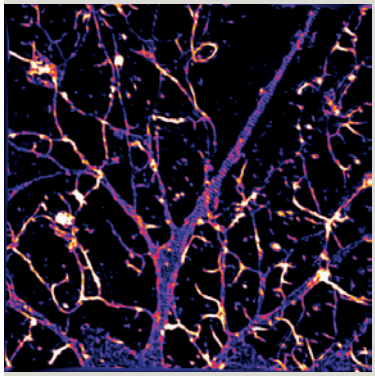


Figure. Periodic actin rings of the rat hippocampal neuron axon visualized using SIM-super resolution imaging (courtesy of Amr Abouelezz).

Main research activities

Disorders of the central nervous system (CNS) are some of the most prevalent, devastating, and yet poorly treated illnesses. The development of new therapies for CNS disorders could significantly improve patients' quality of life, as well as reducing the future burden on healthcare systems. However, few truly innovative CNS drugs have reached the market in recent years. Defective regulation of the neuronal cytoskeleton underlies many neurological diseases, making the neuronal cytoskeleton a perfect target for drug innovation.

A neuron typically extends a long thin axon to transmit information to target cells and several shorter dendrites that receive input from other cells through specialized connections known as synapses. The axon initial segment (AIS) is the site of action potential initiation. At same time, the AIS serves as a barrier between dendrites and axons, by sorting vesicles and proteins to the axon or somatodendritic compartment. The majority of excitatory synapses in the central nervous system exist on small bulbous structures on dendrites known as dendritic spines. The dendrites of a single neuron can contain hundreds to thousands of spines. During learning, new spines will appear. At the same time, other spines and synapses will be removed. Thus, dendritic spines can be considered 'memory units' or 'stuff that memories are made of.' Through adding or removing, or strengthening or weakening, these units, the brain modulates its function. By reorganizing synaptic pathways, new skills are stored in the brain. Precise control of the dendritic spine morphology and density as well as the length and location of AISs are critical for normal brain function. Accordingly, both aberrant spine mor-

phology and non-functional AISs are linked to many neurological diseases. The actin cytoskeleton is a structural element underlying the proper morphology of dendritic spines as well as the proper structure of the AIS.

Goal: We are aiming to develop a comprehensive model of actin cytoskeleton regulation in dendritic spines and the axon initial segment during neuronal development as well as in neurological diseases. So far we have elucidated the molecular mechanisms underlying dendritic spine initiation (Saarikangas et al., 2015), dendritic filopodia elongation (Hotulainen et al., 2009), spine head growth (Hotulainen et al., 2009), and spine head maintenance (Koskinen et al., 2014).

The main publication of the group in 2018 was a study elucidating the effects of genetic mutations linked to autism spectrum disorder on dendritic spine density and morphology as well as on inhibitory synapses (Hlushchenko et al., 2018). In addition, a many-year collaboration with Leonard Khirug´s group, and follow-up study for actin phosphorylation project (Bertling et al., 2016), was published (Pryazhnikov et al., 2018). To bring the recent neuroscience knowhow to medical doctors, Pirta Hotulainen, together with Juha Saarikangas, wrote a review (in Finnish) about synaptic mechanisms in learning (Duodecim). At the end of the year, this publication was celebrated as one of the best five Duodecim articles in 2018.

In our current projects, we are revealing the roles of the actin-regulating proteins Rif, gelsolin, and myosin XVI in neurons. We have continued studies with MIM with a broader behavioral test pattern and more detailed analysis of brain structures. We have also started a project aiming to identify new initiating factors for dendritic spines. Moreover, we are clarifying the special actin regulation underlying the structure of the axon initial segment. In addition, we aim to improve the culturing of neurons derived from human-induced pluripotent cells (iPSC) so that they resemble mature neurons, e.g. exhibit dendritic spines. As dendritic spine morphology and/or density has been altered in many neurological diseases, these mature-looking neurons with dendritic spines could be used for screening novel CNS drugs, using dendritic spines as a readout.

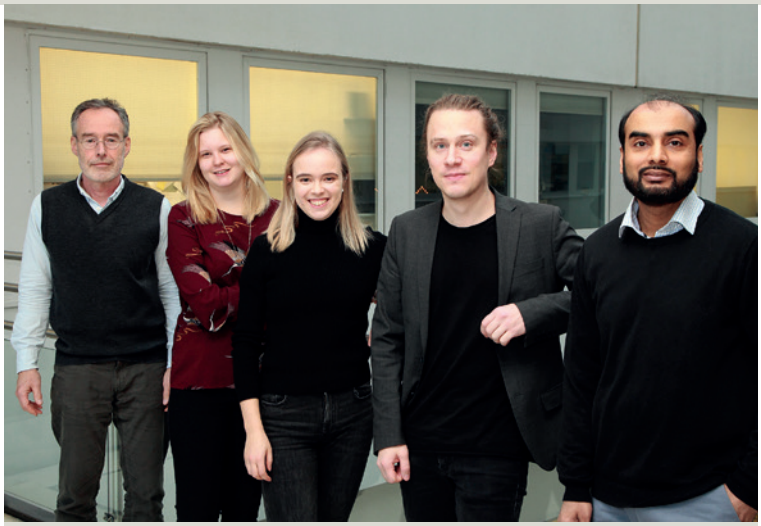
Dendritic spine density and morphology are altered in various neurological diseases. The actin cytoskeleton is a structural component regulating dendritic spine density and morphology. Manipulation of the dendritic spine actin cytoskeleton provides a means of changing dendritic spine morphology and density. Thus, manipulating the actin cytoskeleton could be used to redress the altered dendritic spine density and morphology in neurological diseases.

Publications 2018

Hlushchenko I, **Khanal P**, **Abouelezz A**, Paavilainen VO, **Hotulainen P**. ASD-associated *de novo* mutations in five actin regulators show both shared and distinct defects in dendritic spines and inhibitory synapses in cultured hippocampal neurons. *Front Cell Neurosci*. 2018; 12:217. eCollection 2018.

Pryazhnikov E, Mugantseva E, Casarotto P, Kolikova J, Fred SM, Toptunov D, Afzalov R, **Hotulainen P**, Voikar V, Terry-Lorenzo R, Engel S, Kirov S, Castren E, Khiroug L. Longitudinal two-photon imaging in somatosensory cortex of behaving mice reveals dendritic spine formation enhancement by subchronic administration of low-dose ketamine. *Sci Rep*. 2018; 8:6464.

Saarikangas J, **Hotulainen P**. Hermosolujen synapsien muovautumismekanismit oppimisen, muistin ja aivojen rappeumasairauksien taustalla**.** *Duodecim*. 2018; 134:1226-34.



CELLULAR PHYSIOLOGY

Group members

Kid Törnquist, Ph.D., Professor, Head
Muhammad Yasir Asghar, Ph.D.
In addition, the following researchers were working at Åbo Akademi University:
Ilari Pulli, M.Sc.
Taru Lassila, M.Sc.
Fanny Erkkilä, Phil.Stud.

External funding

The Sigrid Juselius Foundation
The Liv och Hälsa Foundation

Main research activities

Our research group investigates calcium and lipid signaling in thyroid and other human tumor-derived cancer cells. At present, we are interested in the importance of stromal interacting molecule 1 (STIM1) and Orai1, two important proteins regulating intracellular calcium storage and signaling. Furthermore, we are also investigating the interactions between calcium signaling and the sphingomyelin metabolite sphingosine 1-phosphate (S1P) on the regulation of thyroid cancer cell migration and invasion. Preliminary results indicate that knock-down of either STIM1 or Orai1 potently modulates the behavior of thyroid cancer cells (e.g. attenuation of invasion, migration and also proliferation). These results were presented at the 15th International meeting of the European Calcium Society in Hamburg. Furthermore, knock-down of these proteins also modulates the expression of S1P receptors. Our results also suggest that knock-down of STIM1 or Orai1 results, in part, in similar actions as were previously shown for the knock-down of the transient receptor potential canonical 1 (TRPC1) ion channels. A manuscript is presently being compiled on the results.

We have shown that in anaplastic thyroid cancer cells, S1P potently attenuates the expression and secretion of matrix metalloproteinases 2 and -9 (MMP2/9). This effect occurs through the activation of S1P receptor 2 (S1P2). Furthermore, activation of S1P2 also inhibits calpain activity, and inhibiting calpain pharmacologically attenuates the expression and activity of MMP2/9. These results unveil a novel function for the S1P2 receptor in attenuating thyroid cancer cell invasion. This observation may also be important in the search for novel pharmacological tools to curtail cancer.

On-going work in our group also aims to understand compartmentalized calcium signaling in different types of cells. Since compartmentalized calci-

um signaling results in ion hot spots in cells, it may affect specialized signaling pathways or organelles. Of special interest are calcium signals in the caveolae, endoplasmic reticulum, mitochondria, and endosomes. Our current investigations aim at understanding how sphingolipids and related proteins modulate organellar calcium homeostasis. Together with Prof. Vesa Olkkonen, we have investigated the importance of oxysterol-binding protein related-protein 5 and 8 (ORP5/8) in regulating compartmentalized calcium signals. These proteins are localized to the membrane contact sites (MCS) of the endoplasmic reticulum and the mitochondria, as well as to the ER-plasma membrane MCS. The MCS are considered important in regulating signaling events in cells, including calcium signaling. We observed that agonist-evoked stimulation of cells overexpressing ORP5/8 enhanced calcium signaling in both the mitochondrial matrix, as well as in the caveolar subdomain of the plasma membrane. Interestingly, overexpression of ORP5/8 did not affect cytosolic calcium signals. We speculate that the ORP5/8 mediated calcium signaling events may be of importance in regulating mitochondrial respiration and cell proliferation. We are also revising a manuscript regarding sphingosine kinase 1-modulated calcium signaling in the mitochondria.

Ilari Pulli participated in a project to screen for the action of mineral particles on fibroblasts. This project resulted in a report entitled *The influence of mineral particles on fibroblast behaviour: A comparative study* by Soto Velitz D, Luoto JC, Pulli I, and Toivakka M, published in Colloids Surf B Biointerfaces 167:457-468 (2018). Our group has on-going collaborations with Prof. Vesa Olkkonen (Minerva), Prof. John Eriksson (ÅAU), Assoc. Prof. Diana Toivola (ÅAU), and Prof. Jessica Rosenholm (ÅAU).

Taru Lassila's Master's thesis entitled *Påverkan av Dicer i regleringen av sköldkörtelspecifica proteiner samt proliferation och migration I ML-1 celler* was accepted at Åbo Akademi University (ÅAU,Turku). She will now continue as a graduate student.

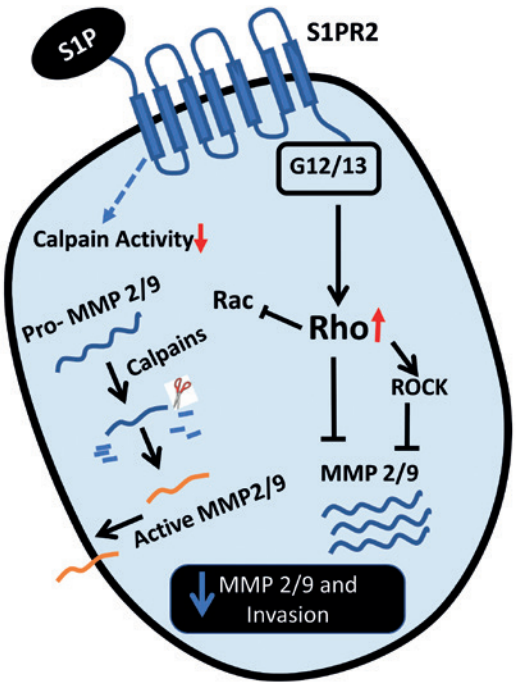


Figure. S1P, through S1P2 and Rho and ROCK pathways, attenuates the expression, secretion and activity of MMP2 and MMP9 and the calpain activity. This leads to the inhibition of thyroid cancer cells migration and invasion.

Publications 2018

Asghar MY, Kemppainen K, Lassila T, **Törnquist K**. Sphingosine 1-phosphate attenuates MMP2 and MMP9 in human anaplastic thyroid cancer C643 cells: Importance of S1P2. *PLoS One*. 2018; 13:e0196992. eCollection 2018.

Pulli I, **Asghar MY**, Kemppainen K, **Törnquist K**. Sphingolipid-mediated calcium signaling and its pathological effects. *Biochim Biophys Acta* (*Mol Cell Res*). 2018; 1865:1668-1677.

Pulli I, Lassila T, Pan G, Yan D, **Olkkonen VM**, **Törnquist K**. Oxysterol-binding protein related-proteins (ORPs) 5 and 8 regulate calcium signaling at specific cell compartments. *Cell Calcium*. 2018; 72:62-69.

Törnquist K, Kemppainen K. Transient Receptor Potential Cation Channel, Subfamily C, Member 2, Pseudogene. *Ensyclopedia of Signaling Molecules*. pp. 5675-5679. Edited by Choi S. © 2018 Springer Science+Business Media LLC.

Group members

Hannele Yki-Järvinen, M.D., Dr.Med.Sci., F.R.C.P, Professor, Head
Panu Luukkonen, M.D., Dr.Med.Sci. autumn 2018
Kimmo Porthan, M.D., Dr.Med.Sci.
Susanna Lallukka, M.D., Dr.Med.Sci. spring 2018
Sanja Sädevirta, M.D.
P.A. Nidhina Haridas, Ph.D.
You Zhou, Ph.D.
Jenni Hyysalo, M.D., Dr.Med.Sci.
Elina Isokuortti, M.D., Dr.Med.Sci.
Laura Ahtiainen, Medical student
Mari Lahelma, Medical student
Iida Tuokkola, Medical student
Markus Kallio, Medical student
Aila Karioja-Kallio, Laboratory technician, Research nurse
Päivi Ihamuotila, Laboratory technician, Research nurse

External funding

The Academy of Finland
Biomedicum Helsinki Foundation
EU/ EFPIA: Innovative Medicines Initiative Joint Undertaking (EMIF), 2013–2018 (grant 116125-2)
EU H2020: Elucidating Pathways of Steatohepatitis (EPoS), 2015–2019 (project 634413)
EU H2020: Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS), 2017–2022 (project 777377)
Orionin Tutkimussäätiö
The Paulo Foundation
Research Funding of Helsinki-Uusimaa Hospital District (state funding for university-level health research)
The Sigrid Jusélius Foundation
Suomen Lääketieteen Säätiö

ENDOCRINOLOGY

Main research activities

During 2018, we have continued our studies addressing the pathogenesis of subtypes of non-alcoholic fatty liver disease (NAFLD) in humans. In her thesis Susanna Lallukka showed that coagulation factor activities and production from the liver are increased in NAFLD attributable to metabolic syndrome and insulin resistance ('Metabolic NAFLD'). This contrasts with subjects with increased liver fat content due to the PNPLA3 I148M variant ('PNPLA3 NAFLD') who do not have increased activity of coagulation factors compared to those without the variant. Thus, obesity/insulin resistance rather than an increase in liver fat per se is associated with a procoagulant plasma profile. Dr. Lallukka also showed that adipose tissue is inflamed in Metabolic NAFLD but not PNPLA3 NAFLD. In addition, Dr. Lallukka determined that baseline liver fat content predicts NAFLD and advanced fibrosis after an 11-year period more accurately than metabolic measurements.

Dr. Luukkonen has completed his thesis, which characterized the molecular heterogeneity of NAFLDs in the human liver. His article, which described for the first time that the human liver triglycerides are markedly polyunsaturated in PNPLA3 NAFLD but markedly saturated in Metabolic NAFLD was amongst the top 1% most cited studies in the field of clinical investigation during the first year after its publication. This article also showed that ceramides but not other bioactive lipids are markedly increased in Metabolic NAFLD but not PNPLA3 NAFLD. We therefore examined whether overfeeding of polyunsaturated as compared to saturated fat or carbohydrate (which if consumed in excess is converted into saturated fat) influences the pathways, bioactive mediators of insulin resistance, and magnitude of overfeeding-induced changes in intrahepatic triglycerides in 38 overweight subjects. We used a combination of state-of-the-art in vivo (imaging, stable isotope tracers and hyperin-

sulinemic-euglycemic clamp) and ex vivo (plasma lipidome, adipose tissue transcriptome and gut microbiome) techniques. Three weeks of overfeeding of saturated fat increased hepatic TGs more than that of unsaturated fat by increasing adipose tissue lipolysis. Moreover, the saturated fat-enriched diet increased insulin resistance, circulating ceramides and gram-negative gut bacteria. Simple sugars increased hepatic TGs by stimulating hepatic de novo lipogenesis. Each diet had distinct effects on the adipose tissue transcriptome. These results showed that the effect of overfeeding on the hepatic metabolism depends on the dietary macronutrient composition. Saturated fat may be metabolically more harmful than unsaturated fat or simple sugars. The data support the hypothesis that insulin resistance in Metabolic NAFLD is a consequence of a saturated fat-induced increase in ceramides.

We are currently a partner in three EU-funded projects:

EU H2020: Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS)

A project to develop better tests for liver disease, this is a pioneering European research project (total funding €34 million), which aims to lead to new diagnostic tests to assess patients with non-alcoholic fatty liver disease (NAFLD) and identify those most at risk for developing severe inflammation and liver scarring.

EU H2020: Elucidating Pathways of Steatohepatitis (EPoS)

EPoS is a 48-month project funded by the European Commission within the Horizon 2020 Framework Program.

EU/ EFPIA: Innovative Medicines Initiative Joint Undertaking (EMIF)

EMIF is a project studying the metabolic consequences of obesity. These consequences include NAFLD.

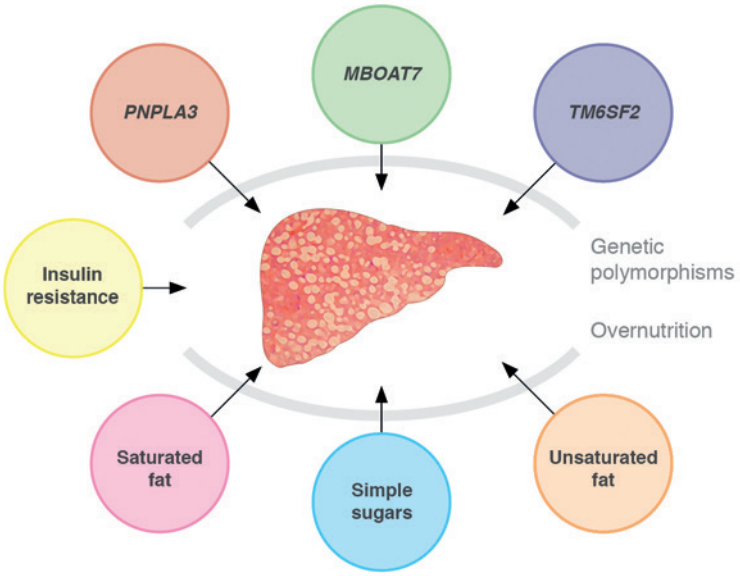


Figure. Heterogeneity of non-alcoholic fatty liver disease is mediated by multiple factors including dietary macronutrient composition, insulin resistance and common genetic polymorphisms in genes such as PNPLA3, MBOAT7 and TM6SF2 (courtesy of Siiri Luukkonen).

Theses completed in the group in 2018

The following doctoral theses were accepted at the University of Helsinki this year:

Susanna Lallukka: Non-alcoholic fatty liver disease: The role of insulin resistance, inflammation and the PNPLA3 I148M variant. January 13, 2018.

Panu Luukkonen: Heterogeneity of non-alcoholic fatty liver disease – Genetic and nutritional modulation of hepatic lipid metabolism. September 7, 2018.

Publications 2018

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Buzkova J, Nikkanen J, Ahola S, Hakonen AH, Sevastianova K, Hovinen T, **Yki-Järvinen H**, Pietiläinen KH, Lönnqvist T, Velagapudi V, Carroll CJ, Suomalainen A. Metabolomes of mitochondrial diseases and inclusion body myositis patients: treatment targets and biomarkers. *EMBO Mol Med*. 2018; 10(12).

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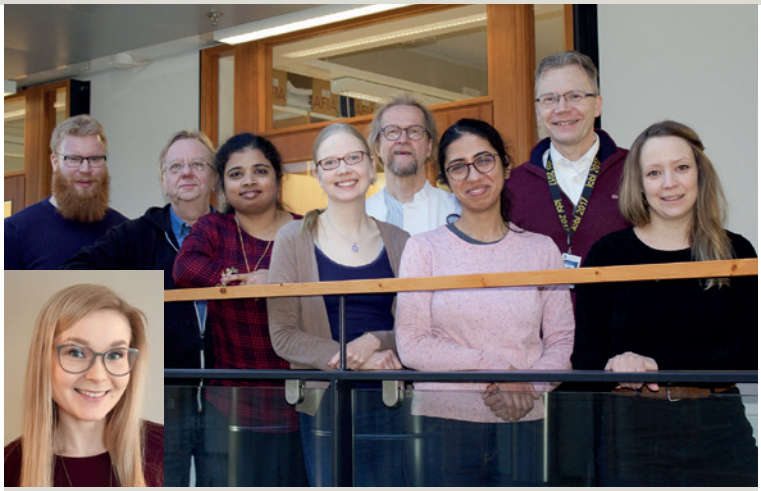
Yki-Järvinen H, **Luukkonen PK**. Diabetes, liver cancer and cirrhosis: What next? *Hepatology*. 2018; 68:1220-1222.



Group members

Vesa Olkkonen, Ph.D., Professor, Head
Matti Jauhiainen, Ph.D., Adjunct professor
P.A. Nidhina Haridas, Ph.D.
Amita Arora, Ph.D.
Henriikka Kentala, M.Sc., Ph.D. autumn 2018
Raghavendra Mysore, M.Sc., Ph.D. spring 2018
Hanna Ruhanen, M.Sc.
Annika Koponen, M.Sc.
Maria Ahonen, B.Sc.
Juuso Taskinen, B.Engin.
Jari Metso, M.Sc., Biochemistry technician
Eeva Jääskeläinen, Laboratory technician
Riikka Kosonen, M.Sc., Laboratory technician

External funding

The Academy of Finland
The Jane and Aatos Erkko Foundation
The Sigrid Jusélius Foundation
The Novo Nordisk Foundation
The Liv och Hälsa Foundation
The Paavo Nurmi Foundation
The Finnish Foundation for Cardiovascular Research
The Magnus Ehrnrooth Foundation

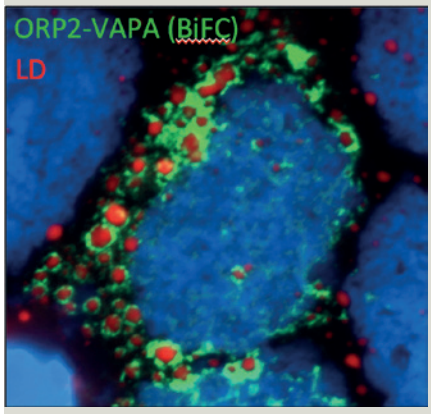


Figure. A HuH7 hepatoma cell expressing bimolecular fluorescence complementation (BiFC) constructs of ORP2 and its ER receptor VAPA. Lipid droplets (LD) are stained with Bodipy-C12 (red) and nuclei with DAPI (blue). ORP2-VAPA complexes located at ER domains encircling LDs are visualized as green fluorescence.

LIPID SIGNALING AND HOMEOSTASIS

Main research activities

In one of the major project entities, the group aims to elucidate how cells maintain the specific lipid compositions of their organelles and sense their internal lipid status to control vital cellular processes such as signal transduction, vesicle transport, motility, and proliferation. The concept of membrane contact sites (MCSs), zones of close contact between the limiting membranes of intracellular organelles, has in recent years moved into the focus of biomedical research. A major project in the group aims to unravel the function of OSBP-related proteins (ORPs) and other new MCS components, as well as their roles in diseases involving aberrant lipid transport or signaling.

In 2018, major activity in the group was directed at understanding the role of the ubiquitously expressed OSBP-related protein ORP2 in cellular energy metabolism and signaling. We employed gene-edited ORP2 knock-out hepatoma cells in order to comprehensively analyze the hepatocellular function of this protein. Our findings revealed crucial roles for functions of ORP2 in phosphoinositide-3-kinase (PI3K)/Akt signaling, glucose uptake, glycogen synthesis, glycolysis, and triglyceride metabolism, suggesting a novel role of the protein in bioenergetics and putatively in metabolic disease (Kentala et al., 2018). In a new branch of the project, we investigated the function of MCS components in endothelial cells (ECs), a cell type centrally involved in common diseases such as atherosclerosis and cancers. The data also demonstrate the function of ORP2 in Akt signaling in this cell type, as well as the roles of both ORP2 and another MCS component, Protrudin/ZFYVE27, in angiogenesis *in vitro*. In collaborative studies, we elucidated the function of ORP4L in phospholipase C regulation with Prof. D. Yan, Jinan University, Guangzhou, China (Pan et al., 2018). Moreover, we pinpointed a role for ORP5 and -8 in lipid transport from the ER to mitochondria with Dr. F. Giordano, I2BC, Gif-sur-Yvette, France (in preparation) and in the Ca^{2+} homeostasis in specific cell compartments with Prof. K. Törnquist, Minerva Institute and Åbo Akademi University (Pulli et al.,

2018). We further elucidated functions of ORP10, the phosphatase Sac1 and the four-phosphate-adaptor protein FAPP1 at ER-*trans*-Golgi contacts with Prof. M.A. De Matteis, TIGEM, Pozzuoli, Italy (Venditti et al., J. Cell. Biol., 2019, in press).

A second major activity in the group in 2018 focused on novel molecular machineries involved in the development of obesity and its comorbidities, insulin resistance (IR), type 2 diabetes, and atherosclerotic cardiovascular diseases (CVDs). We revealed that micro-RNA miR-107, previously associated with IR, inhibits CDK6 expression, differentiation and lipid storage in human adipocytes. Its elevated expression in adipocyte progenitors and adipocytes may dampen adipogenesis, and promote ectopic fatty acid accumulation and reduced glucose tolerance (Ahonen et al., 2018). We also focused on another miRNA associated with metabolic disease, miR-221-3p, and produced data suggesting that its expression in adipocytes may play an important role in the communication between cancer cells and adipocytes during tumor development (in preparation). Furthermore, study of the emerging cardiometabolic therapy target, Angiopoietin-like 3 (ANGPTL3) demonstrated key roles of this protein in both lipoprotein metabolism *in vivo* in human subjects (Tikkanen et al., Arterioscler. Throm. Vasc. Biol., 2019, in press) and in the intra-hepatocellular lipid metabolism (in preparation).

A third activity has been targeted to understanding the structure/function relationships of HDL in different pathophysiological conditions. We demonstrated that low expression of transcription factor USF1 is protective against atherosclerosis in mice and humans, improves the functionality of HDL particles, and boosts cholesterol efflux from macrophage foam cells (Ruuth et al., 2018). Our study carried out in familial hypercholesterolemia (FH) patients indicated that high LDL particle concentration is linked to dysfunctional HDL particles characterized by their altered remodeling and an impaired capacity to promote cholesterol removal from macrophages (Cedo et al., 2018). In addition, patients with abdominal aortic aneurysm (AAA) showed low levels of plasma apoA-I and preβ-HDL levels and impaired HDL-mediated cholesterol removal from macrophages, which could be mechanistically linked to AAA (Martinez-Lopez et al., 2018). Finally, we revealed in a rat model that proteolysis of apoA-I by chymase released from cardiac mast cells during ischemia impairs the ability of apoA-I to heal damaged endothelium in the ischemic myocardium (Kareinen et al., 2018).

Theses completed in the group in 2018

The following doctoral theses were accepted at the University of Helsinki this year:

Anna Tikka: Characterization of ANGPTL3 deficiency and molecular mechanisms of ANGPTL3 deficiency-induced hypolipodemia. January 19, 2018.

Raghavendra Mysore: Novel molecular regulators of adipose tissue metabolism. May 18, 2018.

Henriikka Kentala: ORP2 – A sterol sensor controlling hepatocellular bioenergetics and actin cytoskeletal functions. August 18, 2018.

Selected publications 2018

Ahonen MA, **Haridas PAN**, **Mysore R**, Wabitsch M, Fischer-Posovszky P, **Olkkonen VM**. miR-107 inhibits CDK6 expression, differentiation, and lipid storage in human adipocytes. *Mol Cell Endocrinol*. 2019; 479:110-116. Epub 2018 Sep 24.

Cedó L, Plana N, **Metso J**, Lee-Rueckert M, Sanchez-Quesada JL, Kovanen PT, **Jauhiainen M**, Masana L, Escolà-Gil JC, Blanco-Vaca F. Altered HDL remodeling and functionality in familial hypercholesterolemia. *J Am Coll Cardiol*. 2018; 71:466-468.

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Kentala H, **Koponen A**, Vihinen H, **Pirhonen J**, Liebisch G, Pataj Z, **Kivelä A**, **Li S**, Karhinen L, **Jääskeläinen E**, Andrews R, Meriläinen L, Matysik S, **Ikonen E**, **Zhou Y**, Jokitalo E, **Olkkonen VM**. OSBP-related protein-2 (ORP2): a novel Akt effector that controls cellular energy metabolism. *Cell Mol Life Sci*. 2018; 75:4041-4057.

Koponen A, **Arora A**, **Takahashi K**, **Kentala H**, **Kivelä AM**, **Jääskeläinen E**, **Peränen J**, Somerharju P, **Ikonen E**, Viitala T, **Olkkonen VM**. ORP2 interacts with phosphoinositides and controls the subcellular distribution of cholesterol. *Biochimie*. 2018; 158:90-101.

Martínez-López D, Cedó L, **Metso J**, Burillo E, García-León A, Canyelles M, Lindholt JS, Torres-Fonseca M, Blanco-Colio LM, Vázquez J, Blanco-Vaca F, **Jauhiainen M**, Martín-Ventura JL, Escolà-Gil JC. Impared HDL (High-Density Lipoprotein) -Mediated Macrophage cholesterol efflux in patiens with abdominal aortic aneurysm – Brief report. *Arterioscler Thromb Vasc Biol*. 2018; 38:2750-2754.

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Pulli I, Lassila T, Pan G, Yan D, **Olkkonen VM**, **Törnquist K**. Oxysterol-binding protein related-proteins (ORPs) 5 and 8 regulate calcium signaling at specific cell compartments. *Cell Calcium*. 2018; 72:62-69.

Pan G, Cao X, Liu B, Li C, Li D, Zheng J, Lai C, **Olkkonen VM**, Zhong W, Yan D. OSBP-related protein 4L promotes phospholipase Cβ3 translocation from the nucleus to the plasma membrane in Jurkat T-cells. *J Biol Chem*. 2018; 293:17430-17441.

Ruuth M, Soronen J, Kaiharju E, Merikanto K, Perttilä J, **Metso J**, Lee-Rueckert M, Taskinen MR, Kovanen PT, Öörni K, **Olkkonen VM**, **Jauhiainen MS**, Laurila PP. USF1 deficiency alleviates inflammation, enhances cholesterol efflux and prevents cholesterol accumulation in macrophages. *Lipids Health Dis*. 2018;0 17:285.

MEMBRANE BIOLOGY

Group members

Elina Ikonen, M.D., Dr.Med.Sci., Academy Professor (Director), Head
Tomas Blom, Ph.D., Academy Research Fellow, Team Leader
Andrea Dichlberger, Ph.D. (team of T. Blom), Research Coordinator
Maarit Hölttä-Vuori, Ph.D.
Kristiina Kanerva, Ph.D.
Shiqian Li, Ph.D.
Johan Peränen, Ph.D.
Simon Pfisterer, Ph.D.
Veijo Salo, M.D.
Kecheng Zhou, M.Sc. (team of T. Blom)
Päivi Kleemola, Research assistant
Auli Nick, Dentistry student
Juho Pirhonen, Medical student
Lauri Vanharanta, Medical student
Anna Uro, Laboratory technician
Katharina Ven, TransMed student, Laboratory technician

International exchange students

Aura Partanen, Medical student, Karolinska University (3 months)
Samuel Kang, Dentistry student, Columbia University (team of T. Blom, 2 months)

External funding

The Academy of Finland: Centre of Excellence in Biomembrane Research,
Academy Professorship
The Sigrid Jusélius Foundation
Business Finland
University of Helsinki, Research Excellence and Infrastructure Funding (HiLIFE)

Main research activities

The group focuses on the molecular mechanisms of intracellular lipid transport and storage in mammalian cells as well as disturbances in these processes associated with human disease. Our research relates to the basic pathogenic mechanisms of lysosomal lipid storage diseases, non-alcoholic fatty liver disease, atherosclerosis, and lipodystrophies. In this context, we also develop novel techniques for lipid cell biology, including lipid imaging, analysis of rapid metabolic fluxes using lipid tracers, and manipulation of lipids in cells at improved temporal and spatial resolution.

The group is broadly networked nationally and internationally, as reflected in our research activities. During 2018, we have published papers with collaborating research groups from Minerva Foundation Institute for Medical Research (Kentala et al., 2018; Koponen et al., 2018), the Academy of Finland Centre of Excellence in Biomembrane Research (Zhou et al., 2018), and the Institute for Molecular Medicine Finland (Hultsch et al., 2018), as well as with international collaborators (Sandhu et al., 2018; Kentala et al., 2018; Zhou et al., 2018). We have also published review articles summarizing recent progress in areas of interest, namely intracellular cholesterol transport and lipid droplet biogenesis (Ikonen, 2018; Ikonen and Salo, 2018). Below, two research highlights in 2018 are briefly discussed.

Aster proteins facilitate cholesterol transport from the plasma membrane to the endoplasmic reticulum

How cholesterol taken up by cells from high-density lipoproteins (HDL) is made available for modification or storage, has remained unknown. We described a family of endoplasmic reticulum (ER)-

resident cholesterol-binding proteins (called Aster proteins, a.k.a. GramD1 proteins) that localize at ER-plasma membrane contact sites upon cholesterol accumulation in the plasma membrane. The sterol-binding ASTER domain is structurally related to the START domain, and the N-terminal GRAM domain binds phosphatidylserine, mediating plasma membrane recruitment. Mice lacking Aster-B have defective adrenal steroidogenesis and cholesterol ester storage, due to an inability to transport cholesterol from the HDL receptor SR-B1 to the ER. Together, these findings uncover a nonvesicular pathway for plasma membrane-ER cholesterol transport in mammals (Sandhu et al., 2018).

Ceramide binding mechanism of a lysosomal membrane protein identified

Late endosomal organelles are key sites for the generation of ceramide, a bioactive sphingolipid that regulates cell stress. We have earlier identified a lysosomal transmembrane protein LAPTM4B facilitating ceramide export from these organelles (Blom T et al., Nat Chem Biol 2015; 11:799). We have now discovered in atomistic detail the ceramide interaction site of LAPTM4B and elucidated its functional importance in lysosomal nutrient signaling. The third transmembrane domain of LAPTM4B contains preferred ceramide contact points, and the adjacent intramembrane acidic residue is critical for regulating ceramide-induced conformational changes of this domain. This, in turn, regulates the interaction between LAPTM4B and an amino acid transporter, controlling mTORC signaling. We postulate that this may be a general mechanism by which transmembrane proteins sense and respond to ceramide: membrane-embedded acidic residues next to a sphingolipid-binding motif confer structural flexibility that can be regulated by sphingolipids (Zhou et al., 2018).

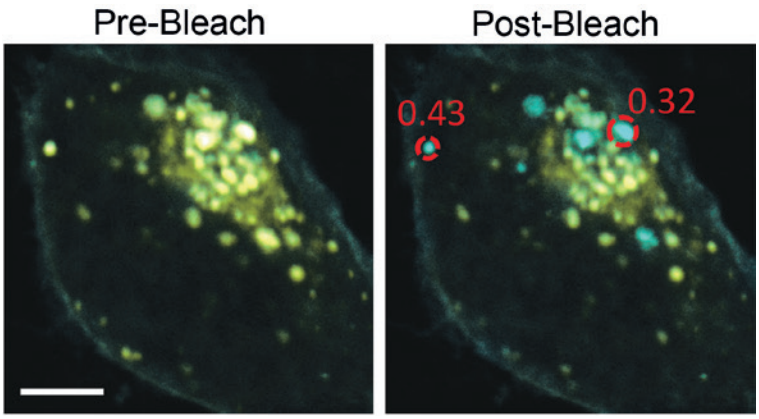

Figure. A HuH7 hepatoma cell expressing bimolecular fluorescence complementation (BiFC) constructs of ORP2 and its ER receptor VAPA. Lipid droplets (LD) are stained with Bodipy-C12 (red) and nuclei with DAPI (blue). ORP2-VAPA complexes located at ER domains encircling LDs are visualized as green fluorescence.

Publications 2018

Hultsch S, Kankainen M, Paavolainen L, Kovanen RM, **Ikonen E**, Kangaspeska S, Pietiäinen V, Kallioniemi O. Association of tamoxifen resistance and lipid reprogramming in breast cancer. *BMC Cancer*. 2018; 18:850.

Ikonen E. Mechanisms of cellular cholesterol compartmentalization: recent insights. *Curr Opin Cell Biol*. 2018; 53:77-83.

Kentala H, **Koponen A**, Vihinen H, **Pirhonen J**, Liebisch G, Pataj Z, **Kivelä A**, **Li S**, Karhinen L, **Jääskeläinen E**, Andrews R, Meriläinen L, Matysik S, **Ikonen E**, **Zhou Y**, Jokitalo E, **Olkkonen VM**. OSBP-related protein-2 (ORP2): a novel Akt effector that controls cellular energy metabolism. *Cell Mol Life Sci*. 2018; 75:4041-4057.

Koponen A, **Arora A**, **Takahashi K**, **Kentala H**, **Kivelä AM**, **Jääskeläinen E**, **Peränen J**, Somerharju P, **Ikonen E**, Viitala T, **Olkkonen VM**. ORP2 interacts with phosphoinositides and controls the subcellular distribution of cholesterol. *Biochimie*. 2018; 158:90-101.

Sandhu J, **Li S**, Fairall L, **Pfisterer SG**, Gurnett JE, Xiao X, Weston TA, Vashi D, Ferrari A, Orozco JL, Hartman CL, Strugatsky D, Lee SD, He C, Hong C, Jiang H, Bentolila LA, Gatta AT, Levine TP, Ferng A, Lee R, Ford DA, Young SG, **Ikonen E***, Schwabe JWR*, Tontonoz P*. Aster proteins facilitate nonvesicular plasma membrane to er cholesterol transport in mammalian cells. *Cell*. 2018; 175:514-529. *co-last authors

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Zhou K, **Dichlberger A**, Martinez-Seara H, Nyholm, TKM, **Li S**, Ah Kim Y, Vattulainen I, **Ikonen E**, **Blom T**. A ceramide-regulated element in the late endosomal protein LAPTM4B controls amino acid transporter interaction. *ACS Cent Sci*. 2018; 4:548-558.

METABOLISM

Group members

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Selina Mäkinen, M.Sc.
Petro Kyrylenko, Medical bachelor

External funding

Research Funding of Helsinki-Uusimaa Hospital District
(state funding for university-level health research)
Liv och Hälsa
Finska Läkaresällskapet
Finnish Diabetes Research Foundation
Diabetes Wellness Sverige (grant no 598-174)
Laboratoriolääketieteen edistämissäätiö

Main research activities

We study the molecular mechanisms of insulin resistance in human skeletal muscle, using primary human muscle cells as a research model. Moreover, we collaborate closely with the FUSION study (Finland-United States Investigation of NIDDM Genetics, head principal investigator (PI) Prof. Michael Boehnke, University of Michigan, Ann Arbor, USA), with the head of the group, Docent Heikki Koistinen being one of the FUSION PIs.

In a collaborative research effort, novel endocrine effectors contributing to inter-tissue crosstalk were identified using a bioinformatics-based approach. Adipose expressed lipocalin-5 and its human ortholog lipocalin-6, were shown to regulate mitochondrial function in skeletal muscle cells, while NOTUM, a factor secreted by liver, was shown to promote browning of white adipose tissue (Seldin et al., 2018).

As part of the FUSION Tissue Study, we have obtained skeletal muscle biopsies from well-characterized individuals covering all stages of glucose tolerance (normal, impaired fasting glucose, impaired glucose tolerance, as well as newly diagnosed type 2 diabetes), and have performed mRNA sequencing to obtain complete skeletal muscle transcriptome (Scott et al. 2016). By using allele-specific expression, we have investigated cis-acting genotype-environment interactions in this dataset. We have identified ten potential environmental response expression quantitative trait loci across clinical traits such as gender, systolic blood pressure, and LDL-cholesterol concentration (Taylor et al. 2018).

In a large research collaboration, in which the FUSION study also participated, coding variant data was collected for more than 80 000 type 2 diabetes cases and more than 300 000 controls. Forty coding variant association signals were found. Only five of the signals were related to low-frequency variants and their effect sizes were small. When the associated variants were fine-mapped in their regional context, only 16 signals were shown to have evidence for causality, and 13 signals were identified to be false leads (Mahajan et al., 2018).

AKT2 is an important effector in the insulin signal transduction pathway, and it is necessary for insulin action on glucose uptake and glycogen synthesis in human skeletal muscle cells (Bouzakri et al., 2006). We have identified a Finnish-specific partial loss-of-function mutation in *AKT2*. This variant increases risk for type 2 diabetes and is associated with fasting hyperinsulinemia (Manning et al., 2017). In collaboration with Prof. M. Laakso, University of Eastern Finland, and Prof. Pirjo Nuutila, Turku PET Center, we have studied the effect of this signaling variant on insulin sensitivity *in vivo*. In vivo determination of tissue specific glucose uptake by FDG-PET technique revealed that p.P50T/*AKT2* carriers had reduced insulin-stimulated glucose uptake in skeletal muscle, liver, brown adipose, and bone marrow (Latva-Rasku et al., 2018). Given the particular relevance of *AKT2* in glucose metabolism in skeletal muscle, we have created primary muscle cell cultures from carriers of the Finnish *AKT2* variant and wild type controls for detailed *in vitro* studies that are currently ongoing at Minerva.

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NEURONAL SIGNALING

Group members

Dan Lindholm, M.D., Dr.Med.Sci., Professor, Head
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Congyu Jin, Ph.D.
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Vignesh Srinivasan, M.Sc.
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Jane Narvik, B.Sc.
Taavi Vanaveski, B.Sc.
Laura Failla, Neuroscience M.Sc. student
Roosa Saarreharju, Neuroscience M.Sc. student
Kristiina Söderholm, Laboratory technician

External funding

The Academy of Finland
The Finska Läkaresällskapet
The Liv och Hälsa Foundation
The Magnus Ehrnrooth Foundation
EU H2020-MSCA-RISE project, SZ_TEST

Main research activities

We study trophic factors in neurodegenerative diseases, such as Huntington's (HD) and Parkinson's disease (PD). We focus on PGC1/PPARγ signaling in neurons and on mitochondria, as well as on the roles of endoplasmic reticulum (ER) stress and protein degradation pathways, including the ubiquitin proteasome and autophagy systems. We employ various biochemical, proteomic, molecular biology, and cell biology methods for our studies, such as primary neuron cultures, and genetically modified mice. The majority of the group is housed in Medium, Faculty of Medicine of the University of Helsinki, and the group is actively engaged in research at Minerva. During 2018, the group worked on three main areas of research.

1. PPARγ/PGC-1α signaling in GABAergic neurons, and use of Helsinki biobank samples

Peroxisome proliferator activated receptor-gamma (PPARγ) is a nuclear receptor involved in the control of cell metabolism and inflammation in different tissues. Drugs acting on PPARγ are used for the treatment of human metabolic disorders, such as type 2 diabetes, but they may also have beneficial effects in brain disorders (Patrone et al., 2014). We have previously studied transgenic mice with overexpression of PGC-1α, a transcriptional coactivator for PPARγ, in neurons (Mudo et al., 2012; Mäkelä et al., 2016). Transcriptome and proteomic analyses showed an increase in specific GABA-A receptors in the PGC-1α transgenic mice that was confirmed by stimulation of the PPARγ receptors using specific ligands (unpublished). During the last year we have studied the effects of the increased GABA-A receptors on the biochemical and neurophysiological properties, as well as on the behavior of the transgenic mice (unpublished). Dysfunctional GABAergic signaling is a consistent finding in neuropsychi-

atric diseases including schizophrenia (SZ). We will hence crossbreed our transgenic mice with those carrying risk genes for SZ in order to reveal possible novel therapies for the disorder. Along with this, we are employing a novel method to detect antibody profiles in biological material (Sadam et al., 2018), by analyzing serum samples of SZ patients obtained from the Helsinki Biobank. This project is an EU-funded collaboration called SZ_ TEST Horizon2010 to facilitate early molecular diagnostics and novel treatments of SZ.

2. Canopy-2 is a novel trophic factor for neurons

Endoplasmic Reticulum (ER) stress is part of many human disorders, including neurodegenerative diseases (Lindholm et al., 2017). We have studied the function of Usp14 in ER stress in HD (Srinivasan, MSc thesis, 2018) as well as the role of the ER-linked saposin-like Canopy-2 (CNPY-2) previously shown to affect metabolic signaling in various cell types (Do et al., 2012). We observed that CNPY-2 targets ER stress and can protect neuronal cells including mutant huntingtin-expressing striatal cells against cell stress (unpublished). We are currently studying this further, focusing on the mechanisms by which CNPY2 affords neuroprotection and on the analysis of CNPY2 gene deleted (knock-out, KO) mice that recently became available (unpublished).

3. p75NTR in control of lipid metabolism and gene expression

p75NTR is a receptor for neurotrophins, including the nerve growth factor (NGF) and pro-NGF, and is expressed in both the brain and peripheral tissues. We have described a signaling pathway for p75NTR in the regulation of cholesterol and lipid uptake in cells (Pham et al., 2016). This pathway is based upon activation of the transcription factor, Sterol regulator element binding protein-2 (SREBP2), with an increase in low-density lipoprotein receptors (LDLRs). The expression of the neurotrophins was also elevated in mouse models of fatty liver. During the last year, we have studied the p75NTR signaling pathway in more detail, and noted that caspase-2 plays a crucial role in SREBP and LDLR regulation. Gene profiling using RNAseq further revealed a network of lipid genes that are altered in p75NTR KO mice compared with controls (Pham et al., submitted). The serum levels of cholesterol and triglycerides were also substantially reduced in the p75NTR KO (unpublished), showing a physiological role of p75NTR in dyslipidemias that may be of clinical significance. In addition, p75NTR KO revealed distinct changes in gene expression in the brain that warrant further studies.

Thesis completed in the group in 2018

The following Master's thesis was accepted at the University of Helsinki this year:

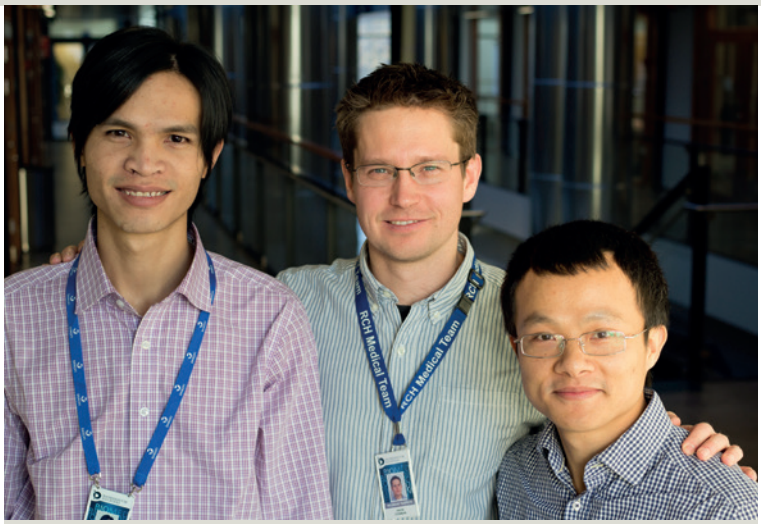
Vignesh Srinivasan: The proteasome associated deubiquitinating enzyme, USP14 and its novel interacting partners HSC70 & XBP1u are downregulated in a cellular model of Huntington´s disease.

Publications 2018

Calza G, Nyberg E, Mäkinen M, Soliymani R, Cascone A, **Lindholm D**, Barborini E, Baumann M, Lalowski M, Eriksson O. Lactate-induced glucose output is unchanged by metformin at a therapeutic concentration - A mass spectrometry imaging study of the perfused rat liver. *Front Pharmacol.* 2018; 9:141. eCollection 2018.

Sadam H, Pihlak A, Kivil A, Pihelgas S, Jaago M, Adler P, Vilo J, Vapalahti O, Neuman T, **Lindholm D**, Partinen M, Vaheri A, Palm K. Prostaglandin D2 receptor DP1 antibodies predict vaccine-induced and spontaneous narcolepsy type 1: Large-scale study of antibody profiling. *EBioMedicine.* 2018; 29:47-59.

TARGETED GENE-EXPRESSION ANALYSIS



Group members
Jakob Stenman, M.D., Dr.Med.Sci., Docent, Head
Ho Huu Tho, M.D., Dr.Med.Sci.
Kien Dang, M.D.

External funding
Wilhelm och Else Stockmanns Foundation
Finska Läkaresällskapet

Main research activities

The aim of the research group is to develop novel diagnostic assays based on PCR and Next Generation Sequencing. Technical development is focused on applications where there are specific difficulties in utilizing conventional PCR, as well as on improvements in sequencing pre-amplification.

We have developed a novel technique (ExBPRT) for the ultra-sensitive detection of expressed mutations (Ho et al., 2015). The ExBPRT technique has recently been granted US and European patents. Applying this technique, we have studied FFPE tissue samples from a large cohort of colorectal cancer (CRC) patients and shown that expression of the BRAF V600E mutation in colorectal carcinoma, which is known to confer a poor prognosis, correlates with a low SPINK1 expression level. Further, *in vitro* experiments showed that treatment with MEK-inhibitor Trametinib led to increased SPINK1 secretion in BRAF V600E-positive cells. These findings suggest that Trametinib treatment, which inhibits both MEK1 and MEK2, might be effective in the BRAF V600E-positive/SPINK1-low subpopulation of patients with CRC, for whom no effective treatment is currently available (Räsänen et al., Mol Oncol, epub ahead of print). We have further studied the expression of mutant KRAS in this cohort and found a strong correlation with prognosis, which cannot be seen when mutations are detected in DNA, but is in agreement with previous reports that have shown a strong correlation between the tissue expression of ras protein p21 and prognosis (manuscript in preparation).

In collaboration with our previous PhD student, Dr. Tho Ho, now head of the Biomedical & Pharmaceutical Applied Research Center at the Department of Genomics, Vietnam Military Medical University (VMMU), our main focus is now on developing liquid biopsy assays based on ExBPRT for monitoring the response to treatment and defining targets for individualized treatments in different malignant conditions.

TELOMERE RESEARCH

Group members

Frej Fyhrquist, M.D., Dr.Med.Sci., Professor emeritus
Outi Saijonmaa, Ph.D., Docent
Anders Eriksson-Palojärvi, D.V.M.

External funding

The Finska Läkaresällskapet

Main research activities

We have been studying leukocyte telomere length (LTL) using Southern blot in more than 7 000 subjects. We have reported significant associations of LTL with gender, age, smoking, alcohol consumption, physical activity, body mass index, progression of albuminuric nephropathy in type 1 diabetes, and insertion/deletion (I/D) polymorphism in the converting enzyme (ACE) gene.

In cooperation with Prof. Ilkka Pörsti, University of Tampere, we measured LTL in 522 healthy Finnish subjects participating in a study on hemodynamics. The results show the well-known relation of LTL to age and gender, but no association of heart rate with LTL. The results will be published in 2019.

A study focusing on telomeres and cardiovascular health in the young was started in 2012 in collaboration with Prof. Antti Jula (Institute of Health and Welfare, Turku), as a sub-study of STRIP (Sepelvaltimotaudin Riskitekijöiden Interventio Projekti). The study comprised >500 subjects each in the intervention and control groups, with follow-up covering early childhood to maturity. This longitudinal study has been on-going during 2013–2018. The results suggest that a healthy life style intervention is associated with slower telomere attrition compared with controls. To be published 2019.

To recognize genetic associations of hydrochlorothiazide-induced change in serum uric acid (SUA) concentration, a genome-wide association study on hydrochlorothiazide-induced change in SUA was conducted in 214 Finnish men from the GENRES study (cooperation with Professor Kimmo Kontula, University of Helsinki). Replication analyses were performed in 465 Finns from the LIFE study. In GENRES, we identified 31 loci associated with hydrochlorothiazide-induced change in SUA at $p < 5 \times 10\text{-}5$. rs1002976 near VEGFC associated with the change in GENRES and in LIFE. Moreover, rs950569 near BRINP3 was associated with the change in SUA in GENRES and LIFE. The analysis of previously reported SNPs and candidate genes provided some proof for PADI4 and ABCC4. We report genetic markers that may predict the increase in SUA concentration during thiazide treatment. Published in 2018.

Publications 2018

Ala-Mutka EM, Rimpelä JM, **Fyhrquist F**, Kontula KK, Hiltunen TP. Effect of hydrochlorothiazide on serum uric acid concentration: a genome-wide association study. *Pharmacogenomics*. 2018; 19:517-527.

PUBLICATIONS 2018

ORIGINAL ARTICLES

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2. Ala-Mutka EM, Rimpelä JM, **Fyhrquist F**, Kontula KK, Hiltunen TP. Effect of hydrochlorothiazide on serum uric acid concentration: a genome-wide association study. *Pharmacogenomics*. 2018; 19:517-527.
3. **Asghar MY**, Kemppainen K, Lassila T, **Törnquist K**. Sphingosine 1-phosphate attenuates MMP2 and MMP9 in human anaplastic thyroid cancer C643 cells: Importance of S1P2. *PLoS One*. 2018; 13:e0196992. eCollection 2018.
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