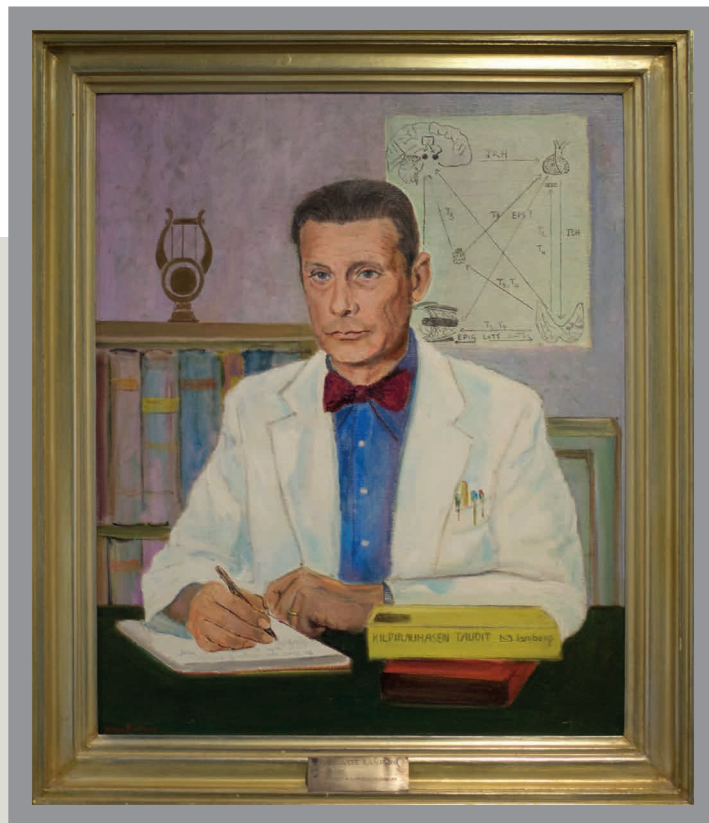




MINERVA FOUNDATION & MINERVA FOUNDATION INSTITUTE FOR MEDICAL RESEARCH



Scientific Report 2017



Front page image: A portrait of Professor Bror-Axel Lamberg
(March 1, 1924 – May 4, 2014), one of the founders of
Minerva Foundation and its Research Institute.
Painted by Håkan Brunberg.

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SUMMARY OF RESEARCH AND ACTIVITIES DURING THE YEAR 2017

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 Foundation Institute are to generate 1) a new knowledge base, 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 Minerva Foundation Institute through scientific approaches ranging from the use of cultured cells and genetically manipulated animal models to the investigation of human patients. The research undertaken in the groups of the Institute during 2017 is outlined in this report.

The 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 support of doctoral students, and the salaries of personnel. In 2017, external funds raised by the research groups covered 51% of the total Institute budget. It is of note that the amount of external, competitive research funds acquired by the groups has exceeded 1 M€ for the first time.

Research at the Institute thrived in 2017. The number and the quality of publications by the Minerva scientists showed an increasing trend: A total of 51 articles were published, 46 in international peer-reviewed journals, with a median impact factor of 4.97. In addition, three doctoral theses were finalized and defended during the year.

The study of lipid signaling and homeostasis in cardiovascular medicine was markedly strengthened as Docent Matti Jauhiainen, an acknowledged specialist in lipid and lipoprotein metabolism, joined the Institute in June 2017. To foster the exchange of scientific ideas and new collaborations, in 2017, the Institute organized five special seminars (listed on the right). Minerva Foundation's Medix Prize was delivered for the 30th time on September 18, and received quite remarkable publicity due to enhanced communication to the media (see p. 6). The Foundation's first Bror-Axel Lamberg prize was delivered on November 2, 2017, at the 70th Annual Meeting of the Finnish Endocrine Society (see p. 7). To promote cohesion between the groups working at the Institute, several internal recreational events were arranged: The Institute organized a summer excursion on June 16 and a Christmas party on December 1, while the personnel set up Easter and 1st of May celebrations. To conclude, the Institute thrived in 2017 both scientifically and financially, and proceeds into the New Year of 2018 with optimism and determination.

EVENTS AT MINERVA 2017

Seminars

MINERVA SEMINAR, BIOMEDICUM HELSINKI:

Tapani Viitala, Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki. *Real-time label-free monitoring of cell membrane interactions and cell responses*. March 3, 2017.

Rohit Loomba, Division of Gastroenterology, Department of Medicine, University of California, San Diego, USA. *Diagnosis and treatment of NASH*. March 15, 2017.

Harald Stenmark, Oslo University Hospital, Institute for Cancer Research, Department of Molecular Cell Biology, Oslo, Norway. *Protrudin and ER-endosome contact sites in endosome positioning*. September 4, 2017.

Nicholas Ktistakis, Babraham Institute, Cambridge, UK. *Selective and non-selective autophagy: the first 3 minutes*. September 6, 2017.

BIOMEDICUM HELSINKI SEMINAR

Frederic Meunier, Queensland Brain Institute, Clem Jones Centre for Ageing, Australia. *Nanoscale organization of the exocytic machinery in health and disease*. September 4, 2017

Prizes

30th ANNIVERSARY MEDIX PRIZE OF THE MINERVA FOUNDATION

AWARD CEREMONY AND LECTURE, BIOMEDICUM HELSINKI, SEPTEMBER 18, 2017:

Marko Salmi, Medical biochemistry and genetics, Institute of Biomedicine, University of Turku.

The winning article 2017:

Rantakari P, Jäppinen N, Lokka E, Morkkala E, Gerke H, Peuhu E, Ivaska J, Elima K, Auvinen K, Salmi M.

Fetal liver endothelium regulates the seeding of tissue-resident macrophages. Nature 2016; 538:392-396.

MINERVA FOUNDATION'S BROR-AXEL LAMBERG PRIZE IN ENDOCRINOLOGY, BIOMEDICUM HELSINKI, THE 70th ANNUAL MEETING OF THE FINNISH ENDOCRINE SOCIETY, NOVEMBER 2, 2017:

Jorma Toppari, Department of Biomedicine, University of Turku.

ADMINISTRATION

Doctoral Dissertations

Boris Vassilev: *Studies on proteins influencing cancer progression and regulating endocytic lipid trafficking.*

University of Helsinki, April 28, 2017. (Membrane biology)

Elina Isokuortti: *Non-alcoholic fatty liver disease – Studies on pathogenesis and diagnosis.* University of Helsinki, October 28, 2017. (Endocrinology)

Jenni Hyysalo: *Prevalence and Genetics of Non-Alcoholic Fatty Liver Disease.* University of Helsinki, December 16, 2017. (Endocrinology)

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, 2017. During this period, the board of trustees included the following persons:

Professor Caj Haglund, chair
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THE MINERVA FOUNDATION INSTITUTE FOR MEDICAL RESEARCH

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Carita Estlander-Kortman
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MEDIX PRIZE OF THE MINERVA FOUNDATION - 30TH ANNIVERSARY

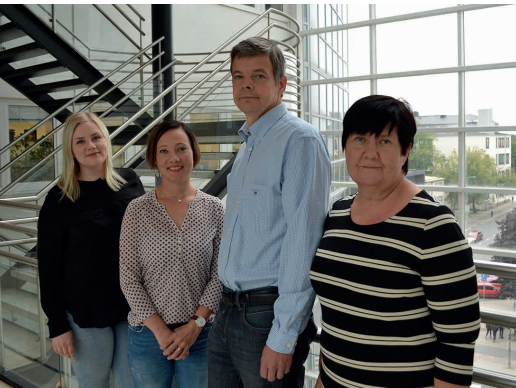


Photo on the left. The awarded research team works at the University of Turku. From left: Ph.D. student Norma Jäppinen, docent Kaisa Auvinen, professor Marko Salmi and docent Pia Rantakari. Courtesy of Martti Ahlström/Viestintätoimisto Verbi.

Photo on the right. By the confocal microscope. From left: docent Kaisa Auvinen, Ph.D. student Norma Jäppinen, professor Marko Salmi and docent Pia Rantakari. Courtesy of Martti Ahlström/Viestintätoimisto Verbi.

In 2017 the “Finnish championship in biosciences,” Minerva Foundation’s Medix Prize, was awarded for the 30th time. The Medix Prize is donated by Medix Ltd. to the University of Helsinki for rewarding excellent Finnish scientific research from the field of biomedicine or clinical medicine and carried out as a whole or for most parts in Finland. The amount of the Medix Prize is 20 000 €. Minerva Foundation is the main owner of Medix Ltd.

The Medix Prize is awarded yearly for excellent Finnish research that has been published the previous year in an internationally reviewed scientific journal. The scientific evaluation of the candidate articles is carried out by a panel consisting of representatives from the universities of Helsinki, Turku, Tampere, Kuopio (Eastern Finland), and Oulu. The panel is nominated for a period of three years at a time.

The 2017 prize was awarded to a research team at the University of Turku, led by Professor Marko Salmi. The research article was published in *Nature* with the title “Fetal liver endothelium regulates the seeding of tissue-resident macrophages” (2016; 538:392–396). The awarded research group consists of professors Marko Salmi and Johanna Ivaska, docents Pia Rantakari, Kaisa Auvinen, and Kati Elima, researcher Heidi Gerke and PhD students Norma Jäppinen, Emmi Lokka, Elias Makkala, and Emilia Peuhu.

The award ceremony took place on Monday, September 18, 2017, at Biomedicum Helsinki. The chair of Minerva Foundation’s Scientific board, Professor Per-Henrik Groop, presented the Medix Prize, and the vice rector of Helsinki University, Professor Pertti Panula, delivered the prize to the winners.

A short description of the research:

The first molecular mechanism which controls the distribution of tissue-resident macrophages during development.

Macrophages belong to white blood cells and are essential for the immune system for fighting against infections. They also regulate the development, homeostasis, and repair of most tissues. Recent studies have shown that most macrophages have already distributed to the target organs during fetal development and use stem cell-like renewal mechanisms to survive through to adulthood.

The research team found that a blood vessel-specific gene, known as *Plvap*, was central for the normal distribution of tissue-resident macrophages in the body. Without the *Plvap* protein, the fetal liver-derived macrophages were practically missing from all organs. In contrast, the numbers and distribution of the earliest, yolk sac-derived macrophages and of the bone marrow-derived macrophages produced after birth were completely normal in the absence of the *Plvap* protein. Mechanistic studies showed that the *Plvap* protein bound molecules which guide the migration of macrophage precursors from the fetal liver stroma into the circulation.

The lack of fetal liver-derived macrophages was still having substantial effects on the macrophage-dependent functions during adulthood. For instance, the iron released normally from old red blood cells started to accumulate in the body. In addition, the development of the ductal system in the pubertal mammary gland was almost completely halted in the absence of *Plvap*.

This study, carried out entirely by Finnish researchers, opens up new avenues for studying the role of developmentally different macrophage subpopulations in the panoply of macrophage-dependent functions in the different tissues of the body. Moreover, it will pave the way for understanding macrophage trafficking between different tissues during fetal development.

MINERVA FOUNDATION'S BROR-AXEL LAMBERG PRIZE IN ENDOCRINOLOGY

The first Minerva Foundation's Bror-Axel Lamberg Prize in Endocrinology was awarded to Professor Jorma Toppari from the University of Turku. The award ceremony took place on Thursday, November 2, 2017, in Biomedicum Helsinki at the 70th Annual Meeting of the Finnish Endocrine Society. The chair of Minerva Foundation, Professor Caj Haglund, presented the prize.

The Bror-Axel Lamberg Prize in Endocrinology is a 10 000 € prize awarded every other year to a distinguished Finnish or Nordic scientist in the field of endocrinology. The Finnish Endocrine Society nominates three candidates for the prize, from whom Minerva Foundation selects the winner. The first prize, in 2017, was awarded to a Finnish scientist.

The winner of the first Bror-Axel Lamberg Prize, Jorma Toppari, is Professor of Physiology at the University of Turku and Chief Pediatric Physician at Turku University Hospital. He received his MD degree (Licentiate of Medicine) in 1983 and defended his doctoral thesis only three years later in 1986. Professor Toppari has docentships from both the University of Turku (in Anatomy) and University of Helsinki (in Pediatrics), and he has been appointed as an honorary professor of the University of Copenhagen and acted as a visiting professor at the University of Chile.

Before the Bror-Axel Lamberg Prize, Professor Toppari has been awarded the Unto Uotila award (Young Investigator Award) in 1993 and the Helena and Niilo Hallman award (Pediatric Research Award) in 1998. Professor Toppari has supervised nearly twenty doctoral theses and acted as an opponent for doctoral dissertations more than twenty times. He has also acted as editor-in-chief and a member of the editorial board for several international scientific journals.



The chair of Minerva Foundation, Professor Caj Haglund presented the prize.



Winner of the 2017 Bror-Axel Lamberg Prize in Endocrinology, Professor Jorma Toppari.

Professor Toppari's scientific bibliography includes more than 360 articles in refereed scientific journals and more than 100 other publications. At present, Professor Toppari and his research team are focusing on the early determinants of reproductive health.

Bror-Axel Lamberg (March 1, 1924 – May 4, 2014)

Bror-Axel Lamberg got his MD degree in 1949, after which his career continued in the Fourth Department of Internal Medicine at the University of Helsinki. Professor Johannes Wahlberg led Lamberg to study the thyroid-stimulating hypophysis hormone TSH. Lamberg was a pioneer in radioimmunoassays and he defended his doctoral thesis in 1953 on using radioactive phosphorus to measure TSH.

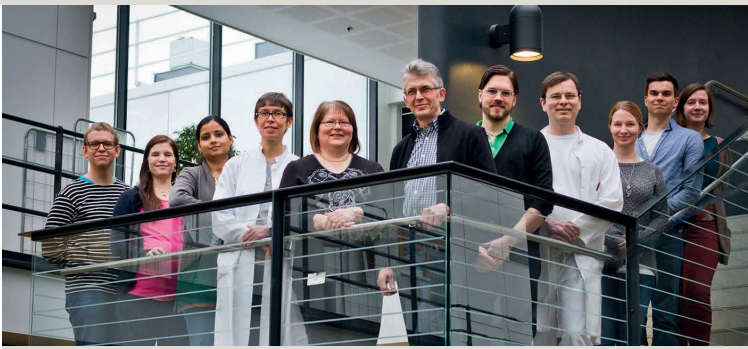
After his defense, Lamberg and his co-workers studied the lack of iodine in the Finnish population. His studies played an important part in having iodine added to common salt in Finland, which led to the eradication of endemic goiter. In 1971, Lamberg was appointed professor of endocrinology at the University of Helsinki. He performed his clinical work primarily at the HUS clinics in Meilahti.

Professor Bror-Axel Lamberg was awarded many prizes, including the Matti Äyräpää prize in 1979 and the J.W. Runeberg prize in 1985. During his active career, he acted as a chair and member of many societies and foundations. He was also granted honorary membership of several societies.

Professor Bror-Axel Lamberg was one of the founders of Minerva Foundation in 1959. The Foundation was formed to maintain the activity of Minerva Foundation Institute for Medical Research. His endocrinological research team was one of the first to start their research at the newly founded institution at a small hospital, Konkordia, in Helsinki. Professor Bror-Axel Lamberg was the first head of the Institute from 1959 to 1970.

Professor Lamberg was also one of the founders of the clinical service laboratory Medix Ltd. in 1964. From those days Medix has expanded and now consists of several companies offering clinical laboratory services, diagnostic bioreagents and rapid point-of-care tests. These companies are highly successful and offer crucial financial support to Minerva Foundation and Research Institute.





Group Members

Ilkka Tikkanen, M.D., Dr.Med.Sci., Professor, Head
 Mika Laine, M.D., Dr.Med.Sci., Docent
 Päivi Lakkisto, M.D., Dr.Med.Sci., Docent
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 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 Finska Läkaresällskapet
 The Liv och Hälsa Foundation
 Research Funding of the Helsinki-Uusimaa Hospital District
 (state funding for university-level health research)

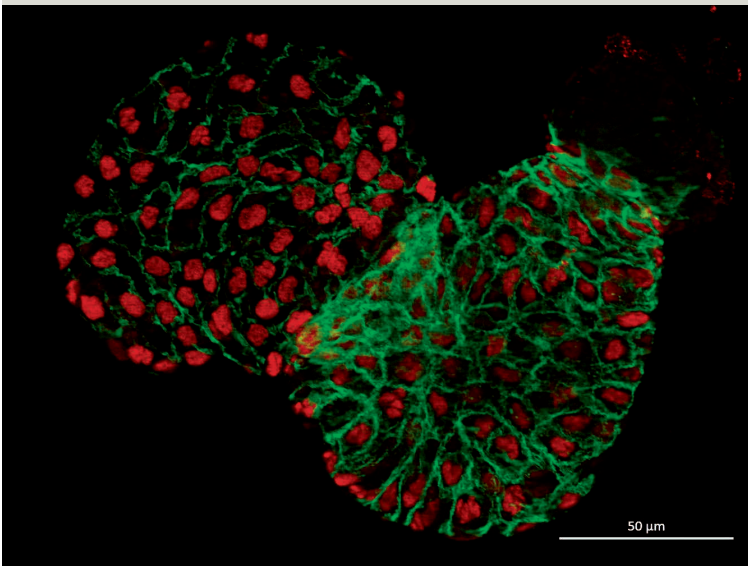


Figure. Immunostaining of zebrafish heart at 3 days post fertilization showing cell membranes (ZN-5, green) and nuclei (mef-2, red) (courtesy of Sanni Perttunen).

CARDIOVASCULAR RESEARCH

Main research activities

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

In these studies, a translational approach is applied, combining methods and findings of both basic science and clinical research in order to improve the evaluation and treatment of cardiovascular diseases.

The main projects worked on during 2017 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. In the rat myocardial infarction (MI) model, HO-1 and CO protect the heart against ischemic injury and enhance cardiac repair. Our recent findings have 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, notably miR-206, 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 development of heart failure after MI.

In collaboration with Adj. Prof. Hannele Laivuori, University of Helsinki (HU), we have studied the association of HO-1 gene (HMOX1) polymorphisms and risk of preeclampsia. The long allele of maternal microsatellite GTn repeat seems to predispose to a late-onset, less severe form of preeclampsia. Our recent findings showed 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 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, regeneration, and repair is needed.

Septins are small GTPases that are associated with actin and are important in the organization of cytoskeleton. In collaboration with Prof. Sanna Lehtonen, HU, we were able to show for the first time 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 diminishes the expression of retinaldehyde dehydrogenase 2 (*raldh2*), which catalyzes the synthesis of retinoic acid shown to modulate ischemic injury and stimulate cardiac regeneration.

Vezf1 encodes a nuclear protein containing six zinc finger motifs of the C2H2-type (krüppel-like) and a proline-rich transcriptional transactivation domain. In collaboration with Prof. Risto Kerkelä, University of Oulu, we investigated the role of *Vezf1* in regulating stress-induced cardiac hypertrophy and development of heart failure employing loss of function methods in embryonic zebrafish by using antisense oligomer molecules that block the translation or splicing of *Vezf1*. Our preliminary results demonstrate that *Vezf1* regulates the development of stress-induced cardiac hypertrophy by modulating β MHC 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. Based on initial RT-PCR array screening of experimental and clinical materials, followed by quantitative RT-PCR, several novel cardiovascular miRNAs of interest were identified. In collaboration with Adj Prof. Veli-Pekka Harjola, HUCH, and Dr. Yvan Devaux, Luxembourg Institute of Health, Luxembourg, we were able to show that high plasma

levels of miR-423-5p predict mortality in patients with acute cardiogenic shock.

Clinical hypertension

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

During the last year, 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.

Professor title

The President of the Republic of Finland conferred the title of professor on Ilkka Tikkanen, December 1, 2017.

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- Ukonen H, **Tikkanen I**. HFrEF: mitä uutta, mikä muuttunut mekanismeissa ja hoidossa. *Sydänääni.* 2017; 28:290-292.



Group members

Pirta Hotulainen, Ph.D., Docent, Head

Enni Bertling, Ph.D.

Rimante Minkeviciene, Ph.D.

Merja Joensuu, Ph.D. (2016–2018 at University of Queensland, Australia)

Amr Abou Elezz, M.Sc.

Iryna Hlushchenko, M.Sc.

Pushpa Khanal, M.Sc.

External funding

The Academy of Finland

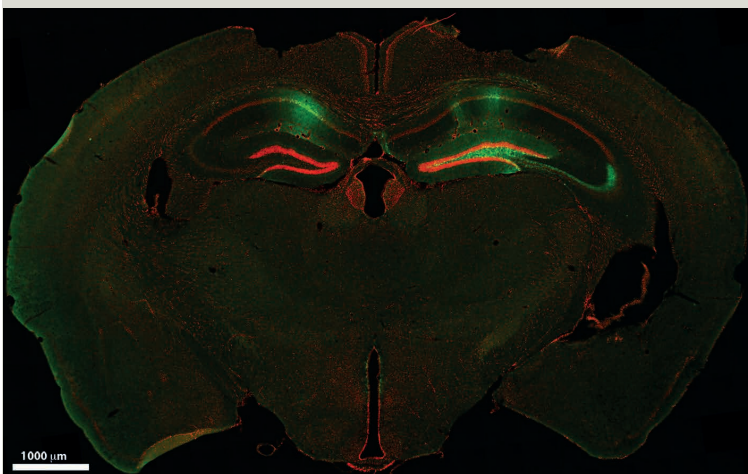
The Instrumentarium Foundation

The Liv och Hälsa Foundation

Päivikki and Sakari Sohlberg foundation

University of Helsinki Brain and Mind graduate school (Abou Elezz)

Alfred Kordelin foundation (Iryna Hlushchenko)



CELLULAR NEUROSCIENCE

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 reduce 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

Figure. Brain slice of one-year-old mouse. Subpopulation of hippocampal CA1 pyramidal neurons was visualized with GFP using lentiviral transduction (green). Nuclei are stained with DAPI, shown here in red (courtesy of Rimante Minkeviciene).

for normal brain function. Accordingly, both aberrant spine morphology 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).

During 2016, these studies were extended by the discovery of a novel actin regulatory mechanism in mammalian cells – actin tyrosine phosphorylation. We showed that actin is phosphorylated during neuronal development, when dendritic spines undergo rapid changes, as well as during synaptic plasticity, when dendritic spines need to quickly change their shape and size in order to “save” neuronal activity-induced changes to synaptic pathways (Bertling et al., 2016). The discovery of mammalian actin phosphorylation is important, as this will help us to understand the molecular basis of learning; how cells can change and store structural changes rapidly, in only a few minutes. The regulation of changes in the actin cytoskeleton during synaptic plasticity here discussed in detail in the review article “Dendritic spine actin dynamics in neuronal maturation and synaptic plasticity” (Hlushchenko et al., 2016). During 2017, we wrote two more reviews, one about actin regulation in spines and one about the actin binding proteins associated with autism spectrum disorder.

In our current projects, we are revealing the roles of the actin-regulating proteins Rif and gelsolin in neurons. We have continued studies with MIM with a broader behavioral test pattern. We have also started a project aiming to identify new initiating factors for dendritic spines. In addition, we are studying novel mechanisms to regulate the neuronal ac-

tin cytoskeleton (pH-dependent actin regulation). Furthermore, we are elucidating the effects of genetic mutations linked to autism spectrum disorder on dendritic spine density and morphology. Moreover, we are clarifying the special actin regulation underlying the structure of the axon initial segment. In addition, in 2016, we started a new project where 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 rescue the altered dendritic spine density and morphology in neurological diseases.

See also lab home page:

www.helsinki.fi/neurosci/hotulainenlab/

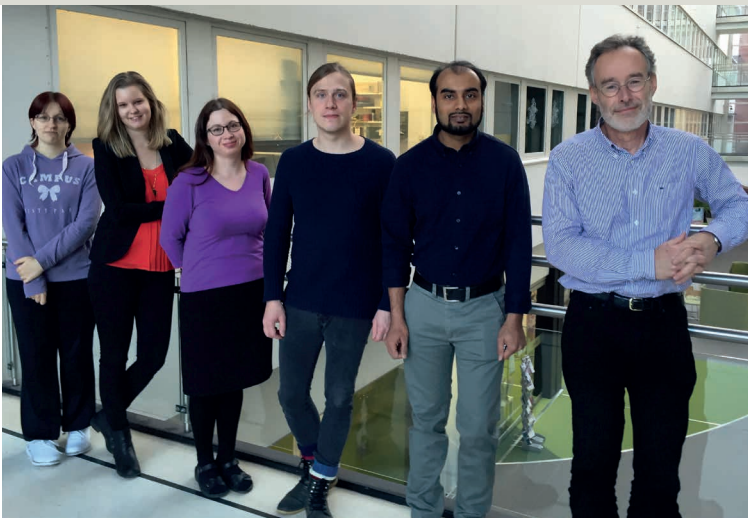
Publications 2017

Bertling E, Hotulainen P. New waves in dendritic spine actin cytoskeleton: From branches and bundles to rings, from actin binding proteins to post-translational modifications. *Mol Cell Neurosci.* 2017; 84:77-84.

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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, B.Sc.

Emilia Holm, B.Sc.

External funding

The Sigrid Juselius Foundation

The Liv och Hälsa Foundation

Svenska Kulturfonden

CELLULAR PHYSIOLOGY

Main research activities

Our research group investigates calcium and lipid signaling in cancer cells. Specifically, the group studies calcium and lipid signaling in thyroid and other human tumor-derived cancer cells. We are interested in understanding the importance of the canonical transient receptor potential (TRP) C-family of ion channels, as well as the actions of the sphingomyelin metabolite sphingosine 1-phosphate (S1P), on the regulation of thyroid cancer cell migration.

In a manuscript under revision we have shown that in anaplastic thyroid cancer cells, S1P potentially attenuates the expression and secretion of matrix metalloproteinases 2 and -9 (MMP2/9). This effect occurs through 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. Stimulating the cells with S1P also increases Rho activity, an important kinase in the regulation of at least MMP2 expression and activity. Thus, our results unveil a novel function for the S1P2 receptor in attenuating thyroid cancer cell invasion.

We are still continuing investigations of calcium signaling. Several proteins participate in regulating cellular calcium homeostasis, and we have been interested in the importance of the transient receptor potential (TRP) family of ion channels, especially the TRPC channels. These channels are present in normal, as well as cancerous cells, including human thyroid cancer cells, and potentially enhance the proliferation, migration, and invasion of cancer cells. Current on-going studies are aimed at investigating the importance of Orai channels and the stromal interacting molecules (STIM), in particular STIM-

1, on thyroid cancer cell physiology and how signaling through these channels differs from that observed for the TRPC channels. Orai1 and STIM-1 are of importance in regulating store-operated calcium entry, the calcium entry process activated when intracellular calcium stores are depleted due to agonist-induced signaling. Preliminary results suggest that similarities exist with TRPC-evoked signaling, but there are also some clear differences. A manuscript has now been compiled based on our results.

On-going work in our group also aims to understand compartmentalized calcium signaling in different types of cells. Since compartmentalized calcium 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. A manuscript is currently being prepared on the importance of sphingosine kinase-1 (SphK1), i.e. the kinase that phosphorylates sphingosine to S1P, in regulating compartmentalized calcium signals. A collaborative study with Prof. Vesa Olkkonen on the importance of oxysterol-binding protein related-protein 5 and 8 is also ready for submission.

Muhammad Yasir Asghar defended his Ph.D. thesis in September. The thesis, entitled *Sphingosine 1-phosphate receptor 2 and the TRPC1 ion channel as regulators of human thyroid cancer cell migration and proliferation* was accepted at Åbo Akademi University (Turku). Emilia Holm's Master's thesis entitled *Förändringar i proliferation, migration och proteinuttryck till följd av transfektion med TRPβ eller Runx2 i follikulära sköldkörtelcancerceller* was also accepted at Åbo Akademi University (Turku).

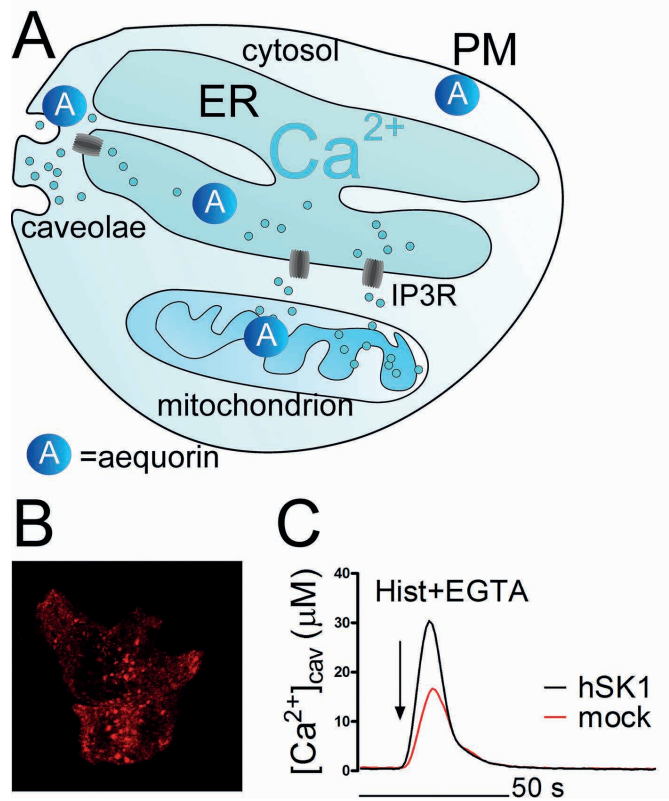


Figure. Different cellular organelles and compartments coordinate calcium (Ca^{2+}) signaling. A) A schematic representation of organelle-level Ca^{2+} signaling showing the specific intracellular localization of genetically engineered aequorin-based Ca^{2+} probes. Aequorins are utilized in our laboratory for Ca^{2+} measurements in the mitochondria, at the caveolae, at the plasma membrane (PM), in the endoplasmic reticulum (ER) and in the cytosol. Ca^{2+} is released from the ER during agonist-stimulation through the inositol-trisphosphate receptors (IP3R). The released Ca^{2+} is can for instance be taken up by the mitochondria to maintain the function of mitochondrial respiratory enzymes. At the caveolae, microdomains of high Ca^{2+} can be recorded due to the close apposition of caveolae and the ER. B) Representative confocal microscopy image showing the characteristic caveolin-1 enriched puncta in the plasma membrane. C) The caveolar Ca^{2+} microdomain is augmented by sphingosine kinase 1 (SK1) overexpression as compared to control cells (mock), modified from Pulli et al 2015.



Group members

Hannele Yki-Järvinen, M.D., Dr.Med.Sci., F.R.C.P, Professor, Head
 P.A. Nidhina Haridas, Ph.D.
 You Zhou, Ph.D. (bioinformatics analyses)
 Jenni Hyysalo, M.D., Dr.Med.Sci. autumn 2017
 Elina Isokuortti, M.D., Dr.Med.Sci. autumn 2017
 Susanna Lallukka, M.D.
 Panu Luukkonen, M.D.
 Sanja Sädevirta, M.D.
 Laura Ahtiainen, Medical student
 Mari Lahelma, Medical student
 Iida Tuokkola, Medical student
 Markus Kallio, Medical student
 Antti Hakkarainen, M.Sc. Technician
 Anne Salo, Laboratory technician, Research nurse
 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 2017, we have continued to study the heterogeneity of non-alcoholic fatty liver disease (NAFLD). This is because comparison of ‘Metabolic NAFLD’ and NAFLD due to common genetic variants in PNPLA3 and TM6SF2 allows the dissection of mechanisms underlying insulin resistance in the human liver from that attributed to steatosis alone. Panu Luukkonen published an article on the effects of the TM6SF2 E167K variant on hepatic lipid metabolism. Unlike common ‘Obese/Metabolic’ NAFLD, NAFLD due to the E167K variant in TM6SF2 is characterized by a lack of hypertriglyceridemia and a lower risk of cardiovascular disease. In animals, a similar phenotype results from a deficiency of phosphatidylcholines (PCs), a major family of membrane lipids. By combining lipidomics and transcriptomics analyses of the human liver samples with *in vitro* experiments in TM6SF2 silenced HuH7 cells in studied performed by the group of Vesa Olkkonen, it was shown that the human liver in carriers of the TM6SF2 E167K variant is characterized by a deficiency of polyunsaturated PCs. *In vitro* and *ex vivo* data demonstrated impaired incorporation of polyunsaturated fatty acids into complex lipids, which could contribute to a deficiency of polyunsaturated PCs. These data highlight the importance of polyunsaturated fatty acid metabolism in liver NAFLD.

We have also studied whether cardiovascular risk factors differ between different types of NAFLD. Susanna Lallukka showed that coagulation factor activities and production from the liver are increased in ‘Metabolic NAFLD’. In contrast, subjects with increased liver fat content due to the PNPLA3 I148M variant do not have increased activity of coagulation factors as 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. In addition, she determined that baseline liver fat content predicts NAFLD and advanced fibrosis after an 11-year period more accurately than metabolic measurements.

Elina Isokuortti defended her thesis, the last article from which studied the utility of a surrogate measure of insulin resistance, HOMA-IR, to diag-

nose NAFLD and whether this marker is influenced by the type of NAFLD. She showed in a population-based study and using patients whose liver fat content has been accurately measured using proton magnetic resonance spectroscopy that a HOMA-IR greater than 2.0 accurately predicts both 'Metabolic NAFLD' and 'PNPLA3 NAFLD.' However, inter-laboratory variation in fasting insulin measurements and therefore HOMA-IR is considerable.

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 test for liver disease 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 Programme.

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

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



Figure. Three Doctors of Medical Sciences. From left: Susanna Lallukka (January 2018), Jenni Hyysalo (October 2017) and Elina Isokuortti (December 2017).

Honors

The article by Panu Luukkonen "Hepatic ceramides dissociate steatosis and insulin resistance in patients with non-alcoholic fatty liver disease" (*J Hepatol.* 2016; 64:1167-75) was awarded a trophy by the Web of Science as it was amongst the top 1% most cited articles in the field of clinical research in the world.

Professor Yki-Järvinen was elevated to First Class Knight of the White Rose of Finland by President Sauli Niinistö Dec 2017.

Thesis completed in the group in 2017

The following doctoral thesis was accepted at the University of Helsinki this year:

Elina Isokuortti: Non-alcoholic fatty liver disease – Studies on pathogenesis and diagnosis. October 28, 2017.

Jenni Hyysalo: Prevalence and genetics of non-alcoholic fatty liver disease. December 16, 2017.

Publications 2017

Isokuortti E, Zhou Y, Peltonen M, Bugianesi E, Clement K, Bonnefont-Rousselot D, Lacorte JM, Gastaldelli A, Schuppan D, Schattenberg JM, Hakkarainen A, Lundbom N, Jousilahti P, Männistö S, Keinänen-Kiukaanniemi S, Saltevo J, Anstee QM, **Yki-Järvinen H.** Use of HOMA-IR to diagnose non-alcoholic fatty liver disease: a population-based and inter-laboratory study. *Diabetologia.* 2017; 60:1873-1882.

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Lallukka S, Sädevirta S, Kallio MT, Luukkonen PK, Zhou Y, Hakkarainen A, Lundbom N, Orho-Melander M, **Yki-Järvinen H.** Predictors of liver fat and stiffness in non-alcoholic fatty liver disease (NAFLD) - an 11-year prospective study. *Sci Rep.* 2017; 7:14561.

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Muniandy M, Heinonen S, **Yki-Järvinen H,** Hakkarainen A, Lundbom J, Lundbom N, Kaprio J, Rissanen A, Ollikainen M, Pietiläinen KH. Gene expression profile of subcutaneous adipose tissue in BMI-discordant monozygotic twin pairs unravels molecular and clinical changes associated with sub-types of obesity. *Int J Obes (Lond).* 2017; 41:1176-1184.

Parks E, **Yki-Järvinen H,** Hawkins M. Out of the frying pan: dietary saturated fat influences nonalcoholic fatty liver disease. *J Clin Invest.* 2017; 127:454-456.



Group members

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 P.A. Nidhina Haridas, Ph.D.
 Annukka Kivelä, Ph.D.
 Henriikka Kentala, M.Sc.
 Raghavendra Mysore, M.Sc.
 Hanna Ruhanen, M.Sc.
 Annika Koponen, M.Sc.
 Maria Ahonen, B.Sc.
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 Eeva Jääskeläinen, Laboratory technician
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External funding

The Academy of Finland
 The Diabetes Research Foundation
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 The Liv och Hälsa Foundation
 The Magnus Ehrnrooth Foundation
 The Novo Nordisk Foundation
 The Sigrid Jusélius Foundation
 Jane and Aatos Erkko Foundation

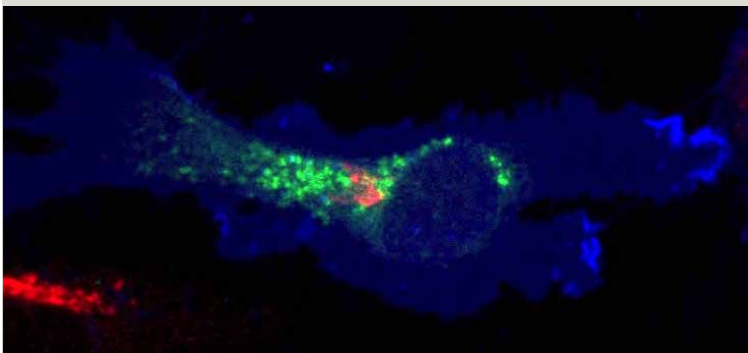


Figure. A human umbilical vein endothelial cell (HUVEC) transfected with ORP2-GFP (green), a fluorescent probe for PI(4,5)P2 (blue), and stained for the Golgi apparatus marker GM130 (red) (courtesy of Annukka Kivelä).

LIPID SIGNALING AND HOMEOSTASIS

Main research activities

One of the main aims of 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. A novel concept, that 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. MCSs provide high capacity and specificity platforms for the inter-organelle transport of small molecules such as lipids, Ca^{2+} and other signals. A major project in the group aims to unravel the function of OSBP-related proteins and other new MCS components, as well as their roles in diseases involving aberrant lipid transport or signaling.

In 2017, major activity in the group was directed at understanding the role of MCSs in cell signaling, viability, motility, and proliferation. We employed CRISPR-Cas9-mediated gene editing to knock out ORP2 in human hepatoma cells in order to comprehensively analyze its hepatic function. Our findings revealed crucial roles of ORP2 in actin cytoskeletal regulation, cell adhesion, migration, and proliferation (Kentala et al., 2017). A parallel study (Kentala et al., submitted) identifies intimate links of the ORP2 knock-out phenotypes with 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. In another 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. Collaborative studies addressed the role of POLR1A and ORP11 in a rare, severe neurodegenerative disease (Kara et al., 2017) and identified OSBP as a molecular target of the anti-enteroviral compound TTP-8307 (Albulescu et al., 2017).

A second major activity in the group in 2017 focused on novel molecular machineries involved in the development of obesity, insulin resistance, type 2 diabetes, and atherosclerotic cardiovascular diseases (CVDs). We discovered that Angiopoietin-like 8 (ANGPTL8), a protein strongly induced by insulin, acts to inhibit intracellular lipolysis in adipocytes (Mysore et al., 2017a), and is regulated by miR-221-3p, a micro-RNA species implicated in obesity and type 2 diabetes (Mysore et al., 2017b). A study of the *TM6SF2* gene, a variant of which predisposes to fatty liver and steatohepatitis, revealed that its depletion in hepatoma cells results in a reduction of polyunsaturated fatty acids, especially arachidonic acid, in membrane phospholipids (Ruhanen et al., 2017). This provides a plausible explanation for the reduction of very-low-density lipoprotein secretion and cardioprotection in the variant carriers.

In a study using samples from the FINRISK and Health 2000 surveys, the serum concentration of ANGPTL3, a functional partner of ANGPTL8 and regulator of lipoprotein lipase activity, correlated positively with age, phospholipid transfer protein (PLTP), and cholesteryl ester transfer protein (CETP) activities, but not with lipid or life style attributes. Interestingly, subjects who carried known *ANGPTL3* sequence variants had abnormally high total cholesterol (TC) and LDL cholesterol concentrations. Exome sequencing yielded five new *ANGPTL3* variant carriers who also had abnormally high TC (Tikka et al., 2017). Thus, we could not identify Finnish *ANGPTL3* variants with a hypolipidemic effect as reported e.g. in Italy.

Diabetes and fatty liver have been associated with low levels of high-density lipoprotein (HDL) cholesterol, and thus could impair macrophage-specific reverse cholesterol transport (m-RCT), whereby peripheral cholesterol is transported to the liver for excretion. The Liver X receptor (LXR) plays a critical role in m-RCT. We demonstrated that downregulation of the LXR axis impairs cholesterol transfer from macrophages to feces in db/db mice, while the induction of the LXR axis partly restores the m-RCT by elevating the liver and small intestine expressions of the LXR targets Abcg5/g8 (Errico et al., 2017). The on-going HDL projects include specific antibody production by using a phage display-based approach to establish a test for the detection of pro-atherogenic, non-functional HDL subspecies and to explore their potential in the risk assessment and monitoring of atherosclerotic coronary artery disease (CAD).

Position of trust

Professor Vesa Olkkonen was elected chair of the Finnish Atherosclerosis Society in March 2017.

Publications 2017

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- Mysore R**, Liebisch G, **Zhou Y**, **Olkkonen VM**, **Nidhina Haridas PA**. Angiopoietin-like 8 (Angptl8) controls adipocyte lipolysis and phospholipid composition. *Chem Phys Lipids.* 2017a; 207(Pt B):246-252.
- Mysore R**, Ortega FJ, Latorre J, **Ahonen M**, Savolainen-Peltonen H, Fischer-Posovszky P, Wabitsch M, **Olkkonen VM**, Fernández-Real JM, **Nidhina Haridas PA**. MicroRNA-221-3p regulates Angiopoietin-like 8 (ANGPTL8) expression in adipocytes. *J Clin Endocrinol Metab.* 2017b; 102:4001-4012.
- Ruhanen H**, **Nidhina Haridas PA**, Eskelinen EL, Eriksson O, **Olkkonen VM**, Käkälä R. Depletion of *TM6SF2* disturbs membrane lipid composition and dynamics in HuH7 hepatoma cells. *Biochim Biophys Acta.* 2017; 1862:676-685.
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Group members

Elina Ikonen, M.D. Dr.Med.Sci., Academy Professor (Director), Head
 Tomas Blom, Ph.D., Academy Research Fellow, Team Leader
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 Andrea Dichlberger, Ph.D. (team of T. Blom)
 Maarit Hölttä-Vuori, Ph.D.
 Kristiina Kanerva, Ph.D.
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 Shiqian Li, Ph.D.
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 Johan Peränen, Ph.D.
 Simon Pfisterer, Ph.D.
 Veijo Salo, M.D.
 Juho Pirhonen, Medical student
 Lauri Vanharanta, Medical student
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External funding

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

MEMBRANE BIOLOGY

Main research activities

The group investigates the molecular mechanisms of intracellular lipid storage in mammalian cells as well as disturbances in these processes associated with human diseases. In this context, we develop novel techniques for lipid cell biology, including micro/nano-scopic imaging of lipids and manipulating lipids in cells at improved temporal and spatial resolution. Below, some of the research highlights during 2017 are discussed.

Lipid droplets (LDs) are the main lipid storage organelles in cells, present in virtually all cell types. Research in this area has gained momentum because LDs represent the cellular hallmark in pathological conditions related to obesity: they serve as dynamic storage sites of triacylglycerols, cholesteryl esters, and other lipophilic compounds, and as an important buffer against lipotoxicity. LDs are generated as outgrowths of the endoplasmic reticulum (ER) and as demonstrated by our recent findings, retain functional contacts with the ER (Salo et al., 2016). In adipocytes and under steatotic conditions, LDs enlarge upon homotypic clustering and fusion with each other. In non-adipocytic cells, this is balanced by LD dissociation mechanisms that have remained poorly understood.

In LD proteomics, we identified several components of the actin cytoskeleton as LD-associated proteins. In particular, we found the abundant actin-binding protein myosin IIa to concentrate around LDs in focal points, at sites where LDs dissociate from each other (Pfisterer et al., 2017). These sites were formed by the activity of the actin-nucleating factor formin-like 1, also present on the surface of LDs. Remarkably, in cells depleted of non-muscle myosin IIa, LD dissociations were less prevalent and LDs became enlarged, storing elevated amounts of

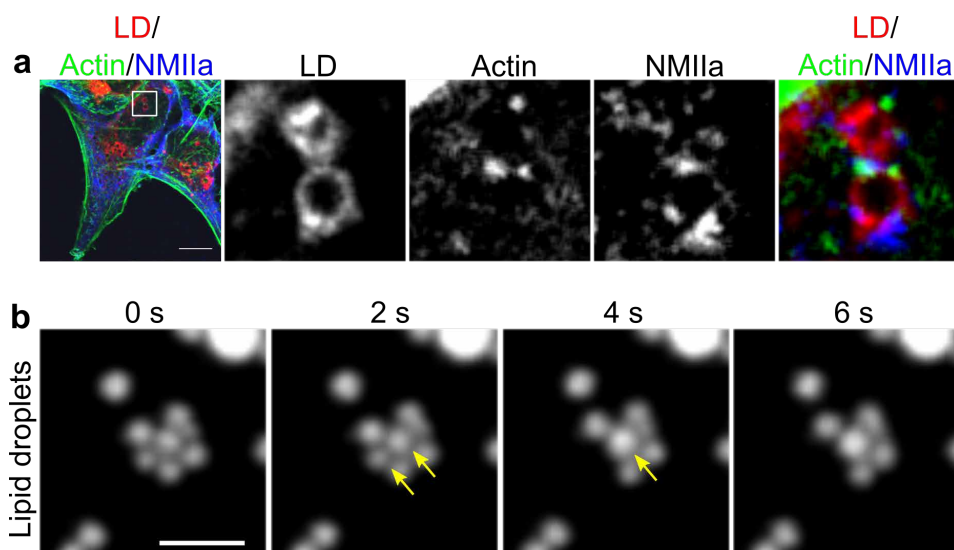


Figure. a) Localization of actin and non-muscle myosin IIa (NMIIa) at lipid droplet contact sites. U2OS cells expressing the lipid droplet marker protein Cherry-HPOS were treated with oleic acid, fixed and stained for NMIIa and actin (Phalloidin). Scale 10 μ m. b) Visualization of lipid droplet fusion. U2OS cells were treated with oleic acid to induce lipid droplet formation and blebbistatin to inhibit NMIIa activity. Lipid droplets were stained with LipidTOX green and subjected to live cell microscopy. Scale 2 μ m. Courtesy of Simon Pfisterer.

triglycerides. Moreover, in cells from patients harboring mutations in non-muscle myosin IIa, the accumulation of lipids in LDs was enhanced. Our results therefore suggest that non-muscle myosin IIa regulates the dissociation of LDs, and that myosin IIa dysfunction contributes to lipid imbalance in humans (Pfisterer et al., 2017). On-going research is directed to further dissecting the mechanisms of lipid droplet formation and dynamic turnover.

In an effort to establish novel tools for manipulating cholesterol in the cellular milieu, we have engineered the major bacterially produced cholesterol metabolizing enzyme, cholesterol oxidase. This enzyme is commonly used as a tool to reduce cellular cholesterol content. We have earlier shown that the produced cholestenone reduces membrane order and is released from cells more avidly than cholesterol (Neuvonen et al., 2014). We have now developed a regulatable fragment complementation system for cholesterol oxidase. The enzyme was split into two moieties that can be reconstituted into a functional enzyme in a rapamycin sensitive manner (Chernov et al., 2017). In a split fluorescent protein (split GFP-COase), the oxidation activity correlated with the fluorescence level. The process is reversible upon rapamycin removal, the split GFP-COase fluorescence is lost and cellular cholesterol levels return to normal (Chernov et al., 2017). Thus, this system provides a new tool for manipulating cholesterol in mammalian cells.

Thesis completed in the group in 2017

The following doctoral thesis was accepted at the University of Helsinki this year:

Boris Vassilev: Studies on proteins influencing cancer progression and regulating endocytic lipid trafficking. April 28, 2017.

Publications 2017

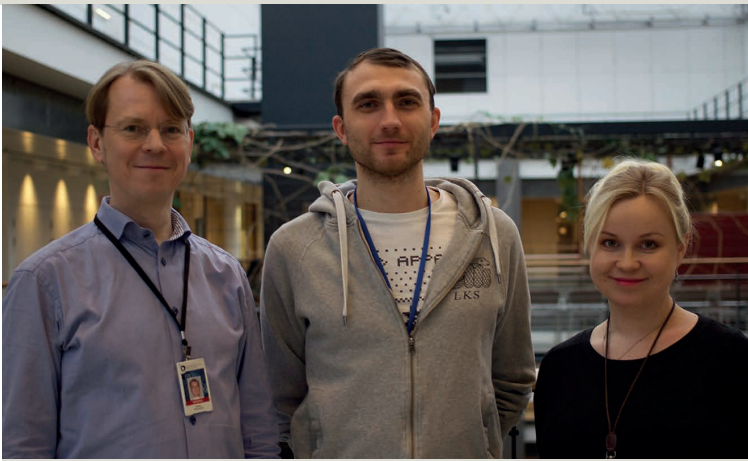
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Research Funding of Helsinki-Uusimaa Hospital District
 (state funding for university-level health research)
 Liv och Hälsa
 Finska Läkaresällskapet
 Jalmari and Rauha Ahokas Foundation
 Finnish Diabetes Research Foundation

METABOLISM

Main research activities

In 2017, the research activity of the group continued with its primary focus on the regulation of glucose metabolism in human skeletal muscle, using primary human muscle cells as a research model.

As saturated fatty acids are implicated in the development of insulin resistance, and unsaturated fatty acids may have a protective effect on metabolism, we tested whether insulin resistance induced by saturated fatty acid palmitate can be ameliorated by concomitant exposure to unsaturated fatty acid oleate. We found that exposure of primary human myotubes to palmitate impaired insulin signaling at the level of Akt-Ser473, AS160, and GSK-3 β , and induced phosphorylation of the ER stress signaling target PERK and stress kinase JNK 54 kDa isoform. These effects on intracellular signaling were virtually abolished by concomitant exposure of palmitate-treated myotubes to oleate. Exposure to palmitate, oleate or their combination reduced insulin-stimulated glucose uptake. This was associated with increased mitochondrial ROS production in palmitate-treated myotubes co-incubated with oleate, and was alleviated by antioxidants (Mäkinen et al., 2017).

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.

Large collaborative efforts, in which the FUSION study has also participated, have revealed novel data on genetic variation that contributes to T2D, plasma lipid levels, lean body mass and obesity (e.g. Jason et al., 2017; Liu et al., 2017; Zillikens et al., 2017; Scott et al., 2017; Graff et al., 2017; Justice et al., 2017).

In particular, a missense variant of *AKT2* has been identified in a large international collaboration, which also included subjects from the FU-

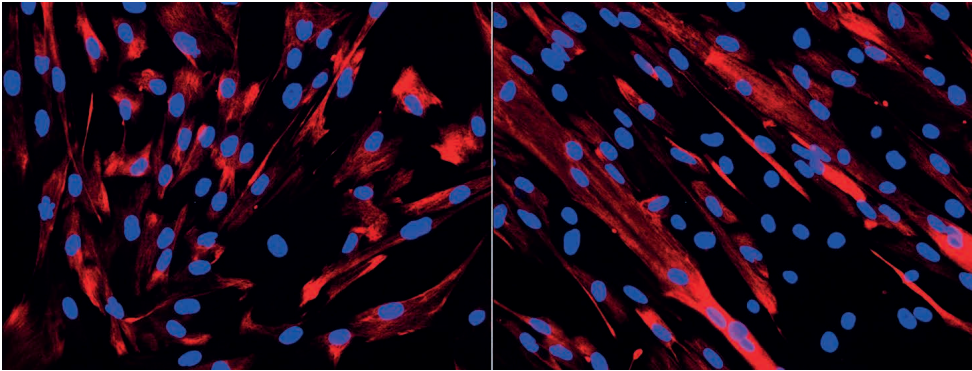


Figure. Primary human myoblasts (left panel) and differentiated primary human myotubes (right panel), stained with anti-desmin antibody (red colour) (courtesy of Selina Mäkinen).

SION and METSIM (Metabolic Syndrome in Men study, PI Prof. Markku Laakso) cohorts. *AKT2* is an important effector in the insulin signal transduction pathway, and this *AKT2* variant is specific to Finns and very rare in non-Finnish Europeans. It is associated with higher fasting insulin concentrations and predisposes people to T2D (Manning et al., 2017).

Since the population-based METSIM cohort contains several carriers of this variant, we have started a collaboration with Prof. M. Laakso, University of Eastern Finland, and Prof. Pirjo Nuutila, Turku PET Center, to study the role of this signaling variant in the pathogenesis of insulin resistance. Nondiabetic carriers and non-carriers for this variant were identified in the METSIM study. These subjects were called back for a positron emission tomography (PET) study with [¹⁸F]-fluorodeoxyglucose during euglycemic hyperinsulinemia. This in vivo determination of tissue specific glucose uptake revealed that p.P50T/*AKT2* carriers had an increased rate of endogenous glucose production and reduced whole body glucose uptake. Moreover, glucose uptake in skeletal muscle, liver, brown adipose, and bone marrow was reduced in carriers. Interestingly, brain glucose uptake was increased in variant carriers (Latva-Rasku et al., **Epub ahead of print**).

Given the particular relevance of *AKT2* in glucose metabolism in skeletal muscle, we have created primary muscle cell cultures from carriers of the *AKT2* variant and wild type controls for detailed *in vitro* studies that are currently on-going at Minerva. These data will complement the *in vivo* investigations and provide further mechanistic evidence of the pathophysiological significance of the Finnish *AKT2* variant.

Thesis completed in the group in 2017:

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

Cynthia Moed-Ring: Endoplasmic reticulum stress as an underlying factor of insulin resistance and type 2 diabetes mellitus. June 2017.

Publications 2017

Graff M et al. Genome-wide physical activity interactions in adiposity - A meta-analysis of 200,452 adults. *PLoS Genet.* 2017; 13:e1006528.

Jason F et al. Sequence data and association statistics from 12,940 type 2 diabetes cases and controls. *Sci Data.* 2017; 4:170179.

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Liu DJ et al. Exome-wide association study of plasma lipids in >300,000 individuals. *Nat Genet.* 2017; 49:1758-1766.

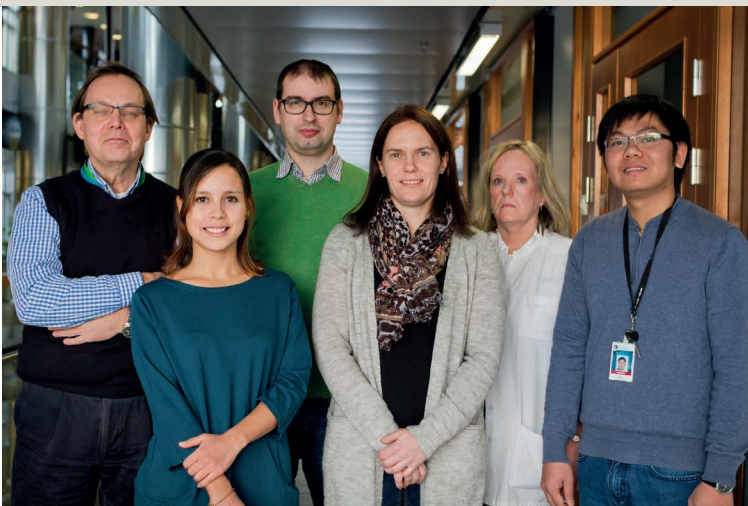
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Zillikens MC et al. Large meta-analysis of genome-wide association studies identifies five loci for lean body mass. *Nat Commun.* 2017; 8(1):80.



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NEURONAL SIGNALING

Main research activities

We study trophic factors in neurodegenerative diseases, such as Huntington's (HD) and Parkinson's disease (PD). We focus on PGC1/PPAR γ 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, and their alterations in neurological diseases. We employ various biochemical, proteomic, molecular biology, and cell biology methods for our studies, including neuronal 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 2017, the group worked on three main areas of research.

1. PPAR γ and PGC-1 α signaling in neuroprotection and in GABAergic neurons.

Peroxisome proliferator activated receptor-gamma (PPAR γ) is a nuclear receptor involved in the control of cell metabolism and inflammation in different tissues. Drugs acting on PPAR γ are used for the treatment of human metabolic disorders, such as type-2 diabetes. However these drugs can also have beneficial effects in various brain disorders (Patrone et al., 2014) but the mechanisms are not fully understood. We have generated transgenic mice with overexpression of PGC-1 α , a transcriptional coactivator for PPAR γ , in neurons and showed that these animals exhibit neuroprotection against MPTP, a neurotoxin for midbrain dopamine neurons (Mudo et al., 2012), and against kainic acid-induced degeneration of the hippocampal neurons (Mäkelä et al., 2016). Using quantitative proteomics and gene expression analyses, we observed increases in the levels of mitochondrial as well as other proteins in the PGC-1 α overexpression mice. PGC-1 α is normally expressed abundantly in parvalbumin-positive

interneurons in the brain, and we studied these neurons in more detail, observing changes in specific GABA receptors in our PGC-1 α mice (unpublished). We are currently investigating whether interneurons and GABAergic neurotransmission are altered in the PGC-1 α mice and whether this is related to stimulation of PPAR γ receptors. Dysfunctional GABAergic signaling is a consistent finding in neurodevelopmental diseases. We will therefore also investigate PGC1/PPAR γ signaling in neurodevelopment and in models of schizophrenia (SZ). This latter is part of the EU-funded consortium SZ_TEST Horizon2010 to facilitate early molecular diagnostics and novel treatments of SZ.

2. Neurotrophic factors and ER stress in neurodegeneration

ER stress is part of many human disorders, including neurodegenerative diseases, metabolic disorders, atherosclerosis, and cancer (Lindholm et al., 2017). We have shown previously that there is an activation of ER stress, and particularly the inositol-requiring enzyme 1 α (IRE1 α) signaling pathway in HD (Hyrskyluoto et al., 2014). Major efforts have been made to understand its physiology and to find ways to interfere with the stress signaling using drugs or other compounds. We hypothesized that ER stress signaling can be regulated in neurons by neurotrophic factors and compounds acting on IRE1 α and other signals. In this context, we have studied the ER-linked saposin-like Canopy (CNPY) family of proteins that play a role in cell and metabolic signaling in various cell types (Do et al., 2012). We have cloned CNPY2 and recently observed that this factor can target ER stress and protect neuronal cells against cell stress, including mutant huntingtin expressing striatal cells (unpublished). We are currently studying this observation further and how CNPY2 can act by intracellular or extracellular mechanisms to provide neuroprotection and counteract ER stress.

3. p75NTR in control of cell lipid metabolism and gene expression

p75NTR is a receptor for neurotrophins, including the nerve growth factor (NGF) and pro-NGF, and is expressed both in the brain and in peripheral tissues. We have recently 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) following caspase-3 cleavage by p75NTR stimulations, and leading to increases in low-density lipoprotein receptors (LDLRs). In a mouse model of fatty liver, the expression levels of NGF and pro-NGF were increased together with LDLR expression, suggesting a physiological role of p75NTR in dyslipidemias. We have now investigated the pathway downstream of p75NTR in more detail, and noted that caspase-2 after phosphorylation by the kinase p38MAPK plays a crucial role in SREBP and LDLR regulation. Gene profiling using RNA-seq further revealed a network of lipid and metabolic genes that are altered in p75NTR gene deleted livers compared with controls (Pham et al., submitted). There are also distinct changes in gene expression in the brains of p75NTR KO mice that we will be the objectives of our studies in the future.

Publications 2017

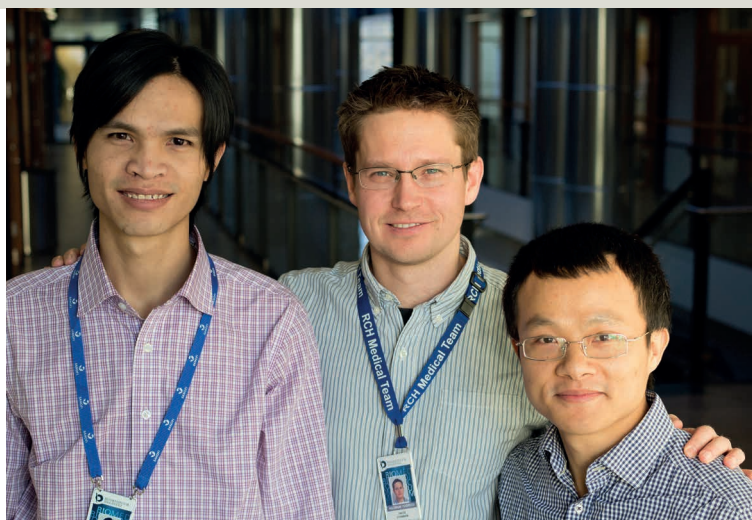
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TARGETED GENE- EXPRESSION ANALYSIS

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).



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Kien Dang, M.D.

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Finska Läkaresällskapet

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.

Publications 2017

Dang KX, Ho T, Sistonen S, Koivusalo A, Pakarinen M, Rintala R, Stenman UH, Orpana A, **Stenman J**. No tissue expression of KRAS or BRAF mutations in 61 adult patients treated for esophageal atresia in early childhood. *Eur J Pediatr Surg*. 2017; Sep 5. [Epub ahead of print]
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Anders Eriksson-Palojärvi, D.V.M.

External funding

The Finska Läkaresällskapet

TELOMERE RESEARCH

Main research activities

Our team has studied leukocyte telomere length (LTL) in more than 7 000 subjects. We have reported significant associations of LTL with e.g. 1) gender, 2) age, 3) smoking, 4) alcohol consumption, 5) physical activity, 6) body mass index, 7) progression of albuminuric nephropathy in type 1 diabetes, and 8) insertion/deletion (I/D) polymorphism DD of the angiotensin-I converting enzyme (ACE) gene. Results 7) and 8) represent novel observations.

During 2015-2017, in cooperation with Prof. Ilkka Pörsti, University of Tampere, we measured LTL in 522 healthy Finnish subjects participating in a study on hemodynamics. The preliminary results show the known relation of LTL to age and gender, but no association of heart rate, or a number of other variables, with LTL. The results will be published in 2018.

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 2013–2016. The results suggest that a healthy life style intervention is associated with slower telomere attrition compared with controls. To be published 2018.

Publications 2017

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Original article

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