



Minerva Foundation &
Minerva Foundation Institute
for Medical Research

Scientific Report

2021



Front page Image. Courtesy of Amita Arora (Lipid Signaling and Homeostasis). See original image on page 22.

Minerva Foundation
Minerva Foundation Institute for Medical Research
BIOMEDICUM Helsinki 2U
Tukholmankatu 8
00290 Helsinki
FINLAND

Tel. +358 2 941 25701

www.minervafoundation.fi
www.minervainstitute.fi

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Summary of research and activities in 2021

The 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. The Institute's focus areas are metabolic and cardiovascular diseases, non-alcoholic fatty liver disease, and neurodegenerative or 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, cell cultures, and genetically engineered animal models, to in vivo studies in human subjects. The research undertaken in the groups of the Institute during 2021 is outlined in this report.

The financial resources of the Minerva Foundation are directed at maintaining and further developing a research infrastructure that serves, in the most effective way possible, the work of the research groups. The groups are responsible for acquiring external funds to cover the costs of special reagents, the stipendium or salary support of students, and the salaries of other personnel. The external, competitive research funds acquired by the groups amounted to €830 000 during 2021, covering 51% of the Institute's budget. During the year 2021, a total of 60 articles were published, 41 of which were original articles in international peer-reviewed journals. The median impact of all articles was 5,53. Moreover, M.D. Kien Dang, M.Sc. Annika Koponen, and M.Sc. Kecheng Zhou, defended their doctoral theses in 2021.

During 2021, the renewal process of the Institute was continued. After the promotion of Docent Päivi Lakkisto as head of the *Cardiovascular research group* in 2020, two new groups were recruited in 2021. The group of Docent Daniel Gordin called *Cardiorenal diabetes*, joined Minerva in September 2021. Docent, Academy research fellow Miina Ollikainen (FIMM) was selected as a group leader. Her group will start at Minerva in September 2022. Moreover, the decision was made to promote Docent Panu Luukkonen to head of the *Fatty liver disease and diabetes group*, starting in this post upon his return from Yale University, US, in March 2022.

The global Covid-19 pandemic has continued in 2021, which has resulted in a number of safety measures at the Institute, including strict hygiene rules and limitations on numbers of personnel simultaneously present at the institute. However, the scientific productivity of Minerva has remained at a high level.

To summarize: Despite the continuing Covid-19 pandemic, the Institute thrived in 2021 both scientifically and financially, recruited new groups to reinforce work toward its strategic goals, and moves into 2022 with optimism and determination.

Events at Minerva 2021

Prizes and Grants

MEDIX PRIZE OF THE MINERVA FOUNDATION

Award Ceremony and Prize Lectures, webinar, September 20, 2021.

The winning article: Maternal Fecal Microbiota Transplantation in Cesarean-Born Infants Rapidly Restores Normal Gut Microbial Development: A Proof-of-Concept Study. *Cell*. 2020; 183:324–334.e5

Authors: Korpela K, Helve O, Kolho KL, Saisto T, Skogberg K, Dikareva E, Stefanovic V, Salonen A, Andersson S, de Vos WM.

Read more on page 6–7.

BROR-AXEL LAMBERG PRIZE IN ENDOCRINOLOGY

Professor Olle Kämpe, Department of Medicine (Solna), Karolinska Institutet, Sweden
Read more on page 8.

SELMA AND MAJA-LISA SELANDER'S FUND FOR RESEARCH IN ODONTOLOGY

From Selma and Maja-Lisa Selander's fund 17 grants were awarded 2021, in all 120.000 EUR.

The following theses were accepted at the University of Helsinki in 2021:

DOCTORAL THESES

Kien Dang. Diagnostic and prognostic role of expressed KRAS and BRAF mutation in MAPK/ERK-driven cancers. June 6, 2021. (Targeted Gene-Expression Analysis)

Annika Koponen. ORP2 - a lipid-binding protein controlling cellular cholesterol transport and signal transduction. April 1, 2021. (Lipid Signaling and Homeostasis)

Kecheng Zhou. Crosstalk between sphingolipid metabolism and nutrient signaling: Studies on LAPTM4B. March 4, 2021. (Membrane Biology)

MASTER'S THESES

Karin Cavonius. CNPY2 in neuronal endoplasmic reticulum stress signaling and Huntington's disease. (Associated group: Neuronal Signaling)

Jutta Joukio. The subcellular localization of myosin XVI in U2OS cells and its expression in the mouse brain. Accepted at the University of Turku. (Cellular Neuroscience)

Max Nurmi. Medfödda hjärtmissbildningars prenatala diagnoser, prognos och vårdplanering – Hur noggrann är informationen i förhållande till det postnatala skedet? (Cardiovascular Disease in the Young)

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, 2021. During this period, the board of trustees included the following persons:

Board of Trustees

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Professor Hannele Yki-Järvinen
M.Sc. Cia Olsson

Medix prize of the Minerva Foundation

Maternal fecal microbiota transplantation in caesarean-born infants restores normal gut microbial development

The Minerva Foundation's Medix Prize 2021, worth 20,000 EUR, was awarded to research groups from the University of Helsinki. The research groups are headed by Professor Willem M. de Vos and Professor Sture Andersson. The research groups demonstrated that intestinal microbiome of infants born by means of caesarean section can be restored using maternal faecal microbiota transplantation. This may support the normal development of the immune system of the infant. The research was published in the prestigious journal *Cell*.

Infants born by vaginal birth are colonised with maternal faecal microbes, which have an impact on the development of their immune systems for the rest of their lives. Caesarean section (CS) disturbs mother-to-neonate transmission, which means that the development of normal gut microbiome of the infant is prevented. This may compromise the infants' immune system and make them more susceptible to chronic illnesses.

"We tested whether the situation could be restored by means of faecal microbiota transplantation, which was performed on seven infants immediately after delivery.

The infants were given a diluted stool transplant from their own mothers delivered in the first human milk feeding," says Professor **Willem M. de Vos**.

The gut bacteria of the infants were monitored for three months. Their gut microbiota was compared to that of infants born by means of caesarean section but with no faecal microbiota transplantation as well as to that of infants born by vaginal delivery. The gut microbiota of infants with faecal transplants was rapidly restored to show significant similarity to that of infants born vaginally.



Professor Sture Andersson (left) and Professor Willem M. de Vos tell that results in this kind of research don't come fast. It took two years to do the actual research and about three years before that to mature the idea and prepare the study. It also took a year to publish the work in the journal *Cell*. Photographer: Juha Sarkkinen.



Members of the two research groups (from right): Willem M. de Vos, Evgenia Dikareva, Anne Salonen, Kirsi Skogberg, Katri Korpela, Kaija-Leena Kolho, Terhi Saisto, Otto Helve, Vedran Stefanovic, Sture Anderson. Photographer: Juha Sarkkinen.

“The Maternal Faecal Microbiota Transplantation (FMT) method is an efficient way to normalise the development of gut microbiota of CS-born infants. Thanks to the method, the risk of these infants having a serious illness at some point in their lives can be decreased,” Professor de Vos says.

According to Professor **Sture Andersson**, the FMT method may become a standard clinical procedure at some point, but several years of research will still be needed. The mechanism has now been described and the efficiency of the method has been proven. More research and methodological development work is still needed.

“Faecal transplantation sounds simple but it is not. We are talking about a couple of milligrams of maternal stool, which is not easy to measure. In addition, mothers must undergo extensive screening in order to ensure their good health and hence suitability for the method, because there is a risk of transmitting a serious illness from the mother to the infant. Therefore, screening must be thorough, and the method must be supported by a laboratory,” says Professor Andersson.

The research groups will continue their research in FMT. The follow-up of the seven infants participating

in the research will be extended. In addition, there is a new, more extensive blinded study with the goal of obtaining 60 participants. In this study, the CS-born infants will be administered either a maternal faecal transplant or a placebo. The gut microbiota and the development of the immune system of the infants will be followed up until the age of two.

The Medix Prize by the Minerva Foundation is an important annual award for internationally high-level Finnish medical research. In year 2021 the Medix Prize will be awarded for the 34th time. The Medix Prize is awarded by the University of Helsinki, and is donated to the university by the Minerva Foundation.

The prize is awarded annually for excellent Finnish scientific research published as one article during the previous year. The research is to be in the fields of biomedicine or clinical medicine and performed fully or in its essential parts in Finland.

The awardee is selected by a committee consisting of representatives from the universities of Helsinki, Turku, Tampere, Eastern Finland and Oulu.

Minerva Foundation's Bror-Axel Lamberg Prize in endocrinology

The 2021 Bror-Axel Lamberg Prize in Endocrinology was awarded to Professor Olle Kämpe at the Department of Medicine (Solna), Karolinska Institutet, Sweden. The prize is 10 000 EUR and this was the third time the prize has been awarded. The award ceremony took place on Thursday, November 4, 2021, at the 74th Annual Meeting of the Finnish Endocrine Society. The chairman of the board of directors of the Minerva Foundation, Professor Caj Haglund, delivered the prize.

The Prize Committee explained their choice: "Professor Olle Kämpe has a record of accomplishment in endocrine research spanning three decades and covering studies from basic genetic studies to registry and epidemiology research. The red thread in his research has been autoimmune endocrine diseases.

Kämpe has described several autoantigens and autoantibodies in organ-specific autoimmune diseases. His research is characterized by broad and complementary methodological approaches, including the use of untraditional disease models to understand the pathogenesis of autoimmune diseases and his work has significantly improved the diagnosis, treatment, and follow-up of patients.

Kämpe has received numerous awards. In 2010 he was elected member of The Swedish Royal Academy of Science and in 2016 a member of the Nobel Assembly. He is currently a member of the Nobel Committee for Medicine or Physiology. He received the European Hormone Medal in 2020."

The Minerva Foundation's Bror-Axel Lamberg Prize in Endocrinology is a 10 000 EUR prize awarded every other year at the Annual Meeting of the Finnish Endocrine Society. It is awarded

to a Scandinavian scientist for innovative, high-quality research in the field of endocrinology. The Finnish Endocrine Society nominates three candidates for the prize, from whom the Minerva Foundation selects the winner. The first prize, in 2017, was presented to a Professor of Physiology Jorma Toppari from the University of Turku.



Professor Olle Kämpe

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



Bror-Axel Lamberg received 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 a 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 the 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 the Research Institute.

Research groups

A new group at Minerva 2021

Cardiorenal diabetes

Main research activities

Dr. Gordin was recently appointed faculty at Minerva. During the year, the research focus has been on a FinnDiane substudy aiming to improve knowledge on cerebrovascular disease in individuals with type 1 diabetes without any neurologic signs or symptoms. Dr. Jussi Inkeri investigated the association between blood glucose control and the cerebrovascular phenotype by MRI, observing no difference in those with and without small vessel disease. This surprising finding raised the question of which other metabolic disturbances may explain the varying cerebrovascular phenotype in these individuals to be the next step to investigate. Dr. Aleksi Tarkkonen compared early retinal disease by measuring retinal vessel diameter to the cerebrovascular phenotype in this cohort. Dr. Tarkkonen is now preparing a manuscript on the findings. Dr. Annina Tynjälä showed blood glucose variability to relate with arterial stiffness, a surrogate endpoint for CVD, in individuals with type 1 diabetes. A manuscript on the findings will be sent for review during the coming months. Dr. Rasmus Simonsen has been instrumental in setting up a renal lab within the FinnDiane neurovascular laboratory, enabling the renal phenotype to be deepened. A study on relative renal hypoxia in different patient groups at risk for kidney disease is ongoing. Preliminary results are expected during the first half of 2022.



Group members

Daniel Gordin, M.D., Dr.Med.Sci., Docent, Head
Rasmus Simonsen, M.D., Dr.Med.Sci.

Jussi Inkeri, M.D.

Aleksi Tarkkonen, M.D.

Anniina Tynjälä, M.D.

External funding

Academy of Finland

Medical Society of Finland

Medicinska Understödsföreningen Liv och Hälsa r.f.

Research Funding of the Helsinki-Uusimaa Hospital
District

Sigrid Jusélius Foundation

University of Helsinki

Wilhelm and Else Stockmann Foundation

Awards, honours and positions of trust

Docent Daniel Gordin: Board member of Finnish Hypertension Society; Board member of European Diabetic Nephropathy Study Group; Finska Läkaresällskapet's Prize 2021 (from Oy Medica Ab Prize Fond); Adjunct Faculty Joslin Diabetes Center, Harvard Medical School Boston MA.

Cardiovascular research in the young

Main research activities during 2021

During the year, the main research activities were in the project domains of fetal cardiovascular programming and prevention of cardiovascular disease. Study family visits were arranged in the Clinical Trial Unit at the Children's Hospital within the FINNCARE project (A lifestyle intervention for families with a history of pre-eclampsia – primary prevention of cardiovascular disease) during the spring and autumn despite the challenging Covid-19 pandemic times. Ph.D students Michelle Renlund and Anni Kivelä (collaboration with Tiina Jääskeläinen and Hannele Laivuori) worked actively on the FINNCARE project during the year. Furthermore, maternal and offspring cardiovascular morphology and function data from the RADIEL (Finnish Gestational Diabetes Prevention Study) 5-year-from-birth project was processed by Ph.D. student Linda Litwin, with one accepted manuscript reporting associations between maternal sub-clinical atherosclerosis and offspring arterial wall layer thickness and local stiffness. Ph.D. students Rasmus Olander and Linda Litwin finalized their theses during the year. During summer 2021, Sofia Saxen and Ines Kumpulainen worked on their Master's theses performed within the FINNCARE and SIVELU projects.

During the year, Max Nurmi finalized his Master's thesis related with accuracy of fetal cardiovascular assessments using ultrasound supervised by Taisto Sarkola.

Ph.D. student Essi Karikoski continued her work processing the data within the ORALPEDHEART study supervised by My Blomqvist and co-supervised by Taisto Sarkola.



Group members

Taisto Sarkola, M.D., Dr.Med.Sci., Docent, Head
My Blomqvist, D.D.S., Dr.Med.Sci.
Johnny Sundholm, M.D., Dr.Med.Sci.
Mari Ylinen, M.D., Dr.Med.Sci.
Linda Litwin, M.D.
Rasmus Olander, M.D.
Michelle Renlund, M.D.
Essi Karikoski, M.Sc.
Ines Kumpulainen, Medical student
Max Nurmi, Medical student
Sofia Saxen, Medical student
Maria Finne, M.Sc., Research coordinator

External funding

Foundation for Pediatric Research
Medical Society of Finland
Medicinska Understödsföreningen Liv och Hälsa r.f.
Sigrid Jusélius Foundation
Stiftelsen Dorothea Olivia, Karl Walter och
Jarl Walter Perkléns minne

A manuscript on the effect of motivational interview in adolescent type 1 diabetes to improve glycaemic control (NCT02637154; collaboration with Dr. Mari-Anne Pulkkinen) was published. The RCT study found no effect of motivational interviewing added to standard educational care to improve glycaemic control in adolescent type 1 diabetes.

A manuscript on the assessment of pericardial constriction and myocardial restriction with echocardiography in pediatric Mulibrey nanism was accepted for publication with Taisto Sarkola as first author. The study showed that echocardiography adds important information in the non-invasive cardiovascular pediatric Mulibrey nanism follow-up and could be used in pericardiectomy decision making.

The collaboration within the ADEF Helsinki (Alcohol/Drugs Exposure during Fetal life) consortium was continued, with Ph.D. student Niina-Maria Nissinen supervised by Anne Koponen.

During the year, postdoc Johnny Sundholm continued his part-time work on using very-high resolution ultrasound in the assessment of subclinical atherosclerosis in middle-aged women with obesity and gestational diabetes. Postdoc Mari Ylinen continued her work on a manuscript focusing on predictors of blood pressure and hypertension and related associations with left ventricular mass, following coarctation of the aorta repair.

Thesis completed in the group in 2021

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

Max Nurmi. Medfödda hjärtmissbildningars prenatala diagnoser, prognos och vårdplanering – Hur noggrann är informationen i förhållande till det postnatala skedet?

Publications 2021

- Litwin L, **Sundholm JKM**, Meinilä J, Kulmala J, Tammelin TH, Rönö K, Koivusalo SB, Eriksson JG, **Sarkola T**. Ideal cardiovascular health and vascular phenotype associations in mothers with obesity and their six-year-old children. *Diabetes Metab Syndr Obes.* 2021; 14:3187-3197.
- Niemelä J, Ylänen K, Suominen A, Pushparajah K, Mathur S, **Sarkola T**, Jahnukainen K, Eerola A, Poutanen T, Vettenranta K, Ojala T. Cardiac function after cardiotoxic treatments for childhood cancer-left ventricular longitudinal strain in screening. *Front Cardiovasc Med.* 2021; 8:715953.
- Nissinen NM, Gissler M, **Sarkola T**, Kahila H, Autti-Rämö I, Koponen AM. Completed secondary education among youth with prenatal substance exposure: A longitudinal register-based matched cohort study. *J Adolesc.* 2021; 86:15-27.
- Tuomaala AK, Hero M, Tuomisto MT, Lähtenmäki M, Miettinen PJ, Laine T, Wehkalampi K, Kiiveri S, Ahonen P, Ojaniemi M, Kaunisto K, Tossavainen P, Lapatto R, **Sarkola T**, Pulkkinen MA. Motivational interviewing and glycemic control in adolescents with poorly controlled type 1 diabetes: A randomized controlled pilot trial. *Front Endocrinol (Lausanne).* 2021; 12:639507. eCollection 2021.

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 and in heart failure, to identify potential targets for cardiovascular medicines and novel biomarkers. 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 2021 are presented below.

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. The promoter region of HMOX1 contains a guanine–thymine (GT) microsatellite repeat. A long GTn repeat decreases HO-1 expression and is associated with cardiometabolic diseases and pre-eclampsia. 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 role of HO-1 and HO-1 gene polymorphisms in the development of cardiovascular and renal complications in type 1 diabetes.



Group members

Päivi Lakkisto, M.D., Dr.Med.Sci., Docent, Head

Ilkka Tikkanen, M.D., Dr.Med.Sci., Professor

Mika Laine, M.D., Dr.Med.Sci., Docent

Chunguang Wang, M.D., Dr.Med.Sci., Docent

Jere Paavola, M.D., Dr.Med.Sci.

Hong Wang, Ph.D.

Mikko Hänninen, M.D.

Karri Kalervo, M.D.

Tuomas Mäntylä, M.D.

Heli Segersvärd, 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

Aarne Koskelo Foundation

Finnish Cultural Foundation

Finnish Foundation for Cardiovascular Research

Finnish Foundation for Laboratory Medicine

Finnish Society of Clinical Chemistry

Finska Läkaresällskapet

Medicinska Understödsföreningen Liv och Hälsa r.f.

Research Funding of the Helsinki-Uusimaa Hospital District
(state funding for university-level health research)

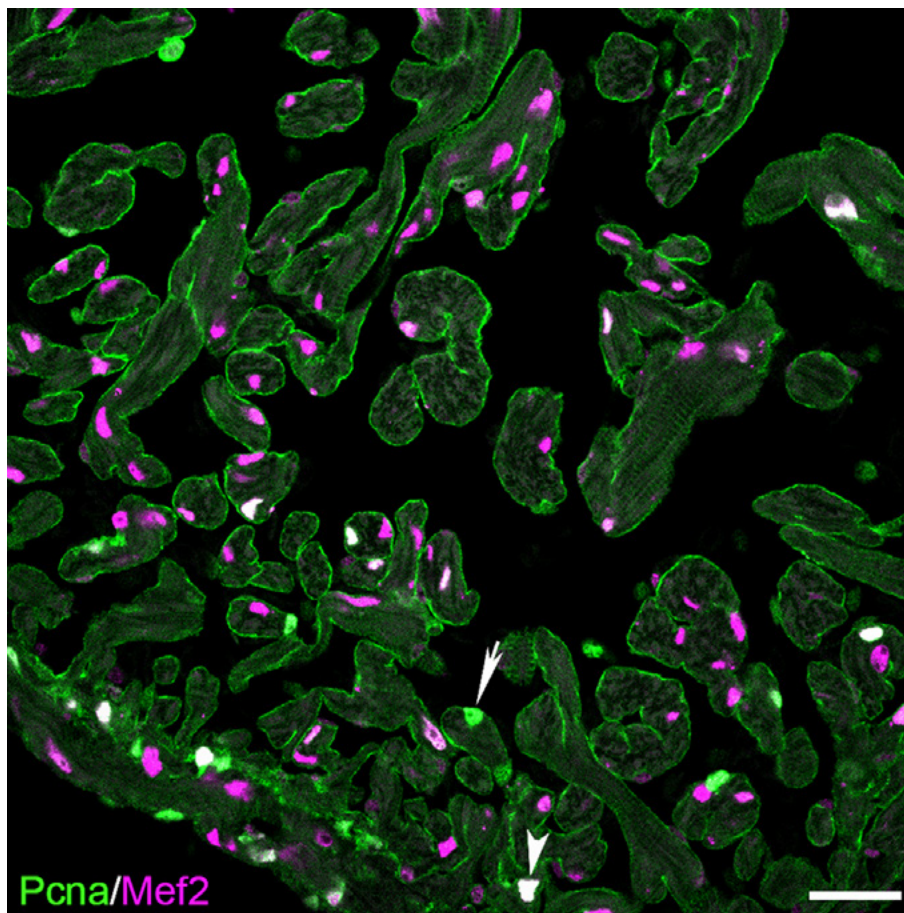


Figure. Immunohistochemical staining of Pcna (in green) and Mef2 (in magenta) in zebrafish ventricular sections. Arrow indicating Pcna+ non-cardiomyocytes. Arrowhead pointing Pcna+ cardiomyocytes (courtesy of Hong Wang).

New molecular mechanisms and biomarkers of cardiac injury and heart failure

The prognosis of chronic heart failure is still poor, despite optimal therapy with currently available cardiovascular drugs. Thus, deeper understanding of cellular and molecular mechanisms of heart failure and cardiac repair is needed to advance the discovery of novel drug target molecules and novel biomarkers for more personalized diagnostics and outcome prediction.

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, knockdown 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 2021.

In a new research project, we have used a multiomics approach to identify dysregulated signaling pathways and potential target molecules for new therapies in end-stage heart failure, in collaboration with prof. Juha Sinisalo. The most significant dysregulation was found in pathways regulating cardiac metabolism and muscle contraction. We identified alterations in the PKA/cAMP and PKG/cGMP signaling pathways, suggesting that they may play a major role in the progression of heart failure. In another study, we found increased expression of tankyrases in the failing human hearts and investigated their role as potential therapeutic targets. Tankyrase inhibition protected against cardiac dysfunction by regulating Wnt/ β -catenin signaling in a zebrafish isoproterenol-induced heart failure model.

MicroRNAs are short noncoding RNA molecules widely involved in the regulation of gene expression. Circulating miRNAs have emerged as potential diagnostic and prognostic biomarkers of cardiovascular disease. Cardiogenic shock (CS) is a severe state of inadequate systemic tissue perfusion due to low cardiac output, often resulting in multiorgan failure. In-hospital mortality is close to 40% even with current treatment. New biomarkers to stratify CS patients according to their risk and to optimize treatment are needed. In collaboration with Adj. Prof. Veli-Pekka Harjola, HUCH, and Dr. Yvan Devaux, the Luxembourg Institute of Health, Luxembourg we have identified several potential miRNA biomarker candidates using microarray profiling. We have shown that miR-21-5p, miR-320a-3p and miR-423-5p were independent predictors of 90-day all-cause mortality, indicating the potential of miRNAs as biomarkers for risk assessment in CS. Our studies on miRNAs in CS continued during 2021.

During 2021, our group participated in the COST Action CA17129 Catalyzing transcriptomics research in cardiovascular disease (CardioRNA), in which Päivi Lakkisto served as a member of the Management Committee and as a co-leader of the Working Group: Best Practices and Experimental Standards.

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.

Publications 2021

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Cellular neuroscience

Main research activities

In order to understand how the brain works, it is fundamental to understand how different parts of neurons work and how changes in the structures of these units change the signal that the next neuron in the network receives. Neurons are unique cells, with highly polarized morphology and specialized domains. Dendrites receive incoming signals and bring electrical and biochemical signals to the soma. The axon extends from the soma and contains the axon initial segment (AIS) in the proximal region.

Our research uses the methods of cell biology (confocal and super-resolution imaging) but the impact lies in neuroscience. The overall common idea in our projects is to study how actin regulation affects neuronal functions. The ultimate goal of the group is the better understanding of the relationship of neuron structure and function. What happens if a neuron is built in an abnormal way? What is important and what is not? How do differences in the neuronal structures affect neuronal functions? This builds a bridge to neurological diseases. What cellular changes cause neurological disease symptoms?

Our research ranges from molecular studies up to the behavior of a living animal. Here, we describe our projects and aims starting from the single neuron level and finishing at the whole brain level.

Single neurons

The neuron itself is a mini-computer. It evaluates different signals and calculates, depending on the strength and number of the signals, whether the signal is taken forward. Appropriate organization of neuron subunits is needed for normal function.

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



Group members

Pirta Hotulainen, Ph.D., Docent, Head
Rimante Minkeviciene, Ph.D.
Jolanta Lundgren, Ph.D.
Pushpa Khanal, M.Sc.
David Micinski, M.Sc.
Jutta Joukio, M.Sc. student

External funding

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Medicinska Understödsföreningen Liv och Hälsa r.f.
Päivikki and Sakari Sohlberg Foundation
University of Helsinki Brain and Mind graduate school
(Pushpa Khanal)

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 dendritic spine morphology and density, as well as the length and location of AISs, is critical for normal brain function.

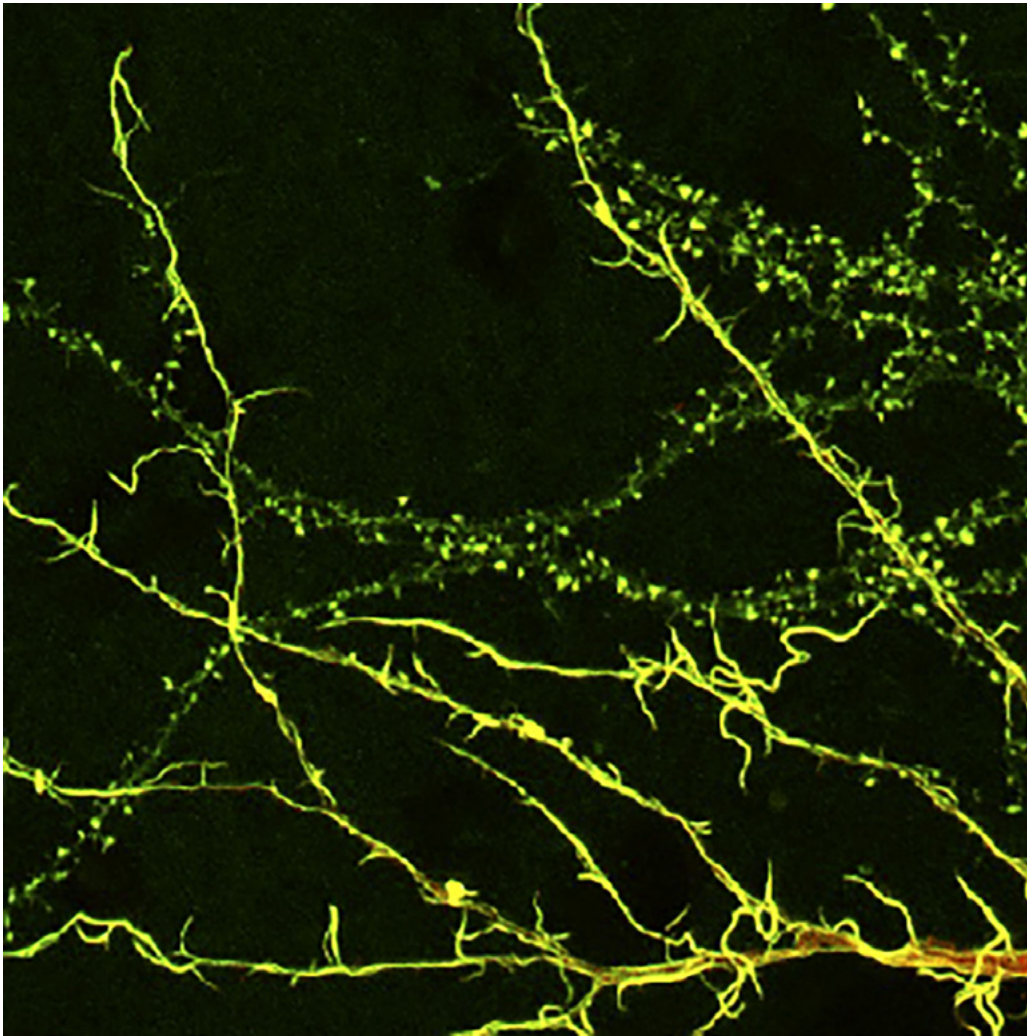


Figure. Cultured primary rat hippocampal neurons expressing either GFP-actin only (cell above) or GFP-actin with DsRed-CA7 (cell below). Comparison shows the strong phenotype induced by CA7 over-expression (courtesy of Pirta Hotulainen).

In psychiatric diseases, the number, strength, and selectivity of the contacts between neurons is often altered. For example, in autism spectrum disorder (ASD), there are too many weak connections and they are poorly selected. In schizophrenia, there is a loss of connections. The question is, what are the mechanisms underlying these defects in connections at the single neuron level? The possibilities seem to be alterations in dendritic spine initiation, dendrite branching, and axonal branching. The re-production of excitatory or inhibitory cells or their migration to their places in the brain, can also be altered. Too many cells or too many branches or too many spines all lead to overload of contacts and vice versa. Poor selectivity can be at least partially explained by altered spine/synapse stabilization mechanisms. Altered excitatory/inhibitory synapse balance is often associated with psychiatric diseases.

Our projects aim at clarifying how the excitation/ inhibition balance is regulated at the level of a single neuron. We started this with a small screening-type study, testing the effects of ASD mutations on five actin-binding proteins. We detected changes in both dendritic spines (excitation) and inhibitory synapses (Hlushchenko et al., 2018) but we could not conclude any common defect or clear mechanism that was regulating the excitation/inhibition balance. We are now continuing these studies by studying the role of myosin XVI in excitatory and inhibitory synapses. Myosin XVI is an interesting protein, as it is down-regulated in ASD and over-expressed in schizophrenia. We have already studied spine initiation by showing that MIM protein is a mechanism to initiate dendritic spines (Saarikangas et al., 2015). Now we are elucidating other mechanisms, particularly focusing on proteins initiating spines in an activity- dependent

manner. In 2021, we summarized the existing data on F-BAR domain containing proteins in the regulation of spine initiation (Khanal and Hotulainen, 2021). We have studied the spine stabilization mechanisms or mechanisms regulating synaptic plasticity with myosin IIb (Koskinen et al., 2014), actin phosphorylation (Bertling et al., 2016), and gelsolin (Hlushchenko et al., 2019). In 2021, we completed a long piece of collaborative work on how carbonic anhydrase 7, a protein regulating the pH of cells, regulates actin cytoskeleton and spine morphology in pyramidal neurons (Bertling, Blaesse, Seja et al., 2021).

In addition, we aim at a comprehensive understanding of how proteins are organized into AIS, focusing on the role of actin regulation. This branch of research was started by Amr Abouelezz, who defended his Ph.D. thesis at the beginning of 2020. The main article from the thesis was published in March 2020 (Abouelezz et al., 2020). David Micinski has continued these studies focusing on the mechanisms of actin polymerization in the AIS.

Neuronal networks

The brain consists of different neuron types and other cells. Neurons are connected to each other, forming a network of cells capable of computing various signals. We have become interested in the olfactory bulb as an example circuit for the following reasons: 1) Altered sense of smell is associated with neurological diseases, 2) The olfactory bulb is a small and apparently simple circuit, 3) Myosin XVI, a protein associated with various psychiatric diseases, is highly expressed in the olfactory bulb. We are currently studying the effects of myosin XVI knock-out for cells contributing to the olfactory circuit.

The brain

At the level of the brain, our main question is, how does the brain control behavior and especially, how do defects in brain anatomy affect behavior? At the level of the brain, we have mainly studied the role of MIM in development, controlling behavior, and aging (Saarikangas et al., 2015; Minkeviciene et al., 2019).

Awards, honours and positions of trust

Docent Pirta Hotulainen: Chair of Brain Research Society of Finland; Vice Chair of FENS-Kavli network; Member of national long covid group (Health ministry).

Thesis completed in the group in 2021

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

Jutta Joukio. The subcellular localization of myosin XVI in U2OS cells and its expression in the mouse brain.

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Fatty liver disease and diabetes

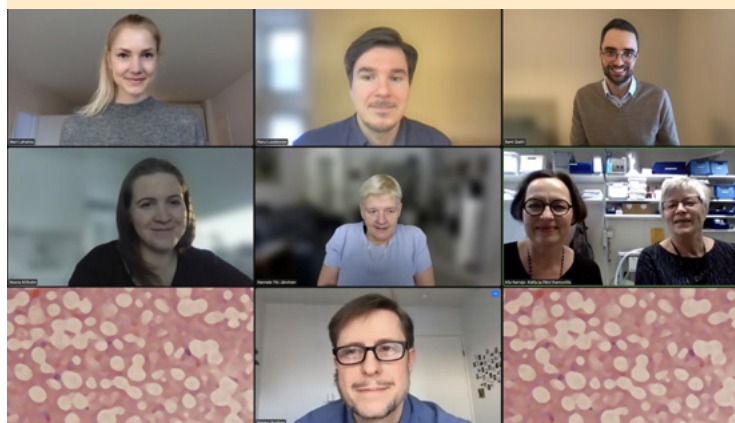
Main research activities

We have continued mechanistic in vivo and in vitro studies addressing the mechanisms underlying subtypes of NAFLD in humans caused by the common genetic risk variants in PNPLA3 and MBOAT7 and the protective effects of variants in HSD17B13 and MARC1. Regarding the PNPLA3 I148M variant, we have shown, contrary to previous studies suggesting this protein is exclusively expressed in the liver, that PNPLA3 is most abundantly expressed in adipose tissue in humans and that it changes adipose tissue composition in a potentially healthy polyunsaturated direction. Consistent with the beneficial effects of this gene variant on the risk of metabolic disease, it abolishes insulin resistance-induced atherogenic changes in plasma lipids and lipoproteins.

Regarding the protective variant in HSD17B13, we found carriers of this variant to have higher concentrations of polyunsaturated phosphatidylcholines in the human liver than noncarriers. This hepatic lipid profile is remarkably similar to that in carriers of another recently discovered protective variant in MARC1. These data, together with mechanistic studies in animals, suggest that hepatic phosphatidylcholines might play an important role in the progression of NAFLD.

We have set up an in vivo stable isotope methodology to measure intrahepatic lipid fluxes (work by Docent Panu Luukkonen, currently a post-doctoral fellow at the Yale School of Medicine) in subtypes of NAFLD.

We are a partner in the EU H2020: Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) project (<https://litmus-project.eu/>). LITMUS is a project aiming at developing better biochemical and imaging tests for diagnosing various stages of NAFLD (total funding €45 million).



Group members

Hannele Yki-Järvinen, M.D., Dr.Med.Sci., F.R.C.P.,
Professor, Head
Panu Luukkonen, M.D., Dr.Med.Sci., Docent
Kimmo Porthan, M.D., Dr.Med.Sci., Docent
Susanna Lallukka, M.D., Dr.Med.Sci.
Noora Ahlholm, M.D.
Mari Lahelma, M.D.
Sami Qadri, M.D.
Sanja Sädevirta, M.D.
P.A. Nidhina Haridas, Ph.D.
You Zhou, Ph.D.
Anni Poikola, Medical student
Aila Karioja-Kallio, Laboratory technician,
Research nurse
Päivi Ihamuotila, Laboratory technician, Research nurse

External funding

Academy of Finland
EU H2020: Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS), 2017–2022 (project 777377)
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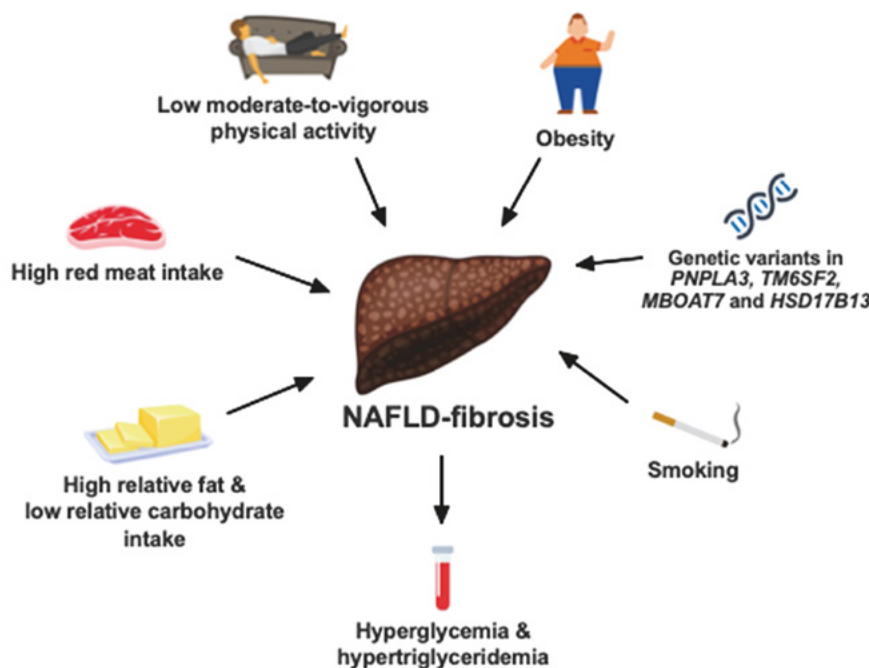


Figure. An overview of factors predisposing to non-alcoholic fatty liver disease (NAFLD) (courtesy of Mari Lahelma).

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Lipid signaling and homeostasis

Main research activities

One of the interests of the unit is membrane contact sites (MCS), zones of close contact between the limiting membranes of intracellular organelles. In 2021, major activity in the group was directed at understanding the role of the endoplasmic reticulum (ER)-late endosome MCS protein Protrudin/ZFYVE27, in endothelial cell (EC) functions. The protein was found to play a crucial role in angiogenesis both *in vitro* and *in vivo*, the underlying mechanism being pinpointed at the regulation of mTOR(+) endosome positioning in the EC and the activity of focal adhesion kinase crucial for cell motility (Arora et al., manuscript in revision). The other activity focused on MCS function in EC addressed the global effects of pharmacologic inhibition of OSBP, a cholesterol-PI4P exchanger at ER-*trans*-Golgi MCS. Lipidomic and transcriptomic as well as imaging and biochemical analyses of the inhibitor treated cells revealed major effects on EC cholesterol, sphingolipid, and glycerophospholipid homeostasis as well as on the gene expression of ER stress-related pathways, likely reflecting cholesterol accumulation in the ER (Taskinen et al., manuscript submitted).

A second major activity in the group in 2021 focused on the dysregulation of adipocyte metabolism under conditions of insulin resistance, more specifically the function of the insulin-regulated thyroid hormone responsive protein (THRSP). The THRSP mRNA is during euglycemic, hyperinsulinemic clamp strongly induced in white adipose tissue, the response being dampened in insulin resistant subjects. Moreover, THRSP expression correlated positively with the M-value. In cultured SGBS adipocytes knock-down of THRSP resulted in mitochondrial dysfunction and a disturbance of the sphingolipid metabolism (Ahonen et al., submitted), indicating how its reduced expression in insulin-resistant adipose tissue may contribute to metabolic disease.



Group members

Vesa Olkkonen, Ph.D., Professor, Head
Kid Törnquist, Ph.D., Professor
Matti Jauhiainen, Ph.D., Docent
Amita Arora, Ph.D.
Muhammad Yasir Asghar, Ph.D.
P.A. Nidhina Haridas, Ph.D.
Dan Pham Duc, Ph.D.
Annika Koponen, M.Sc., Ph.D. spring 2021
Maria Ahonen, M.Sc.
Vaishali Chaurasiya, M.Sc.
Taru Lassila, M.Sc.
Meghana Nagaraj, M.Sc.
Ilari Pulli, M.Sc.
Juuso Taskinen, B.Engin., M.Sc.
Riikka Kosonen, M.Sc., Laboratory technician

External funding

Academy of Finland
Diabetes Wellness Finland
Finnish Foundation for Cardiovascular Research
Jane and Aatos Erkko Foundation
Magnus Ehrnrooth Foundation
Medicinska Understödsföreningen Liv och Hälsa r.f.
Sigrid Jusélius Foundation

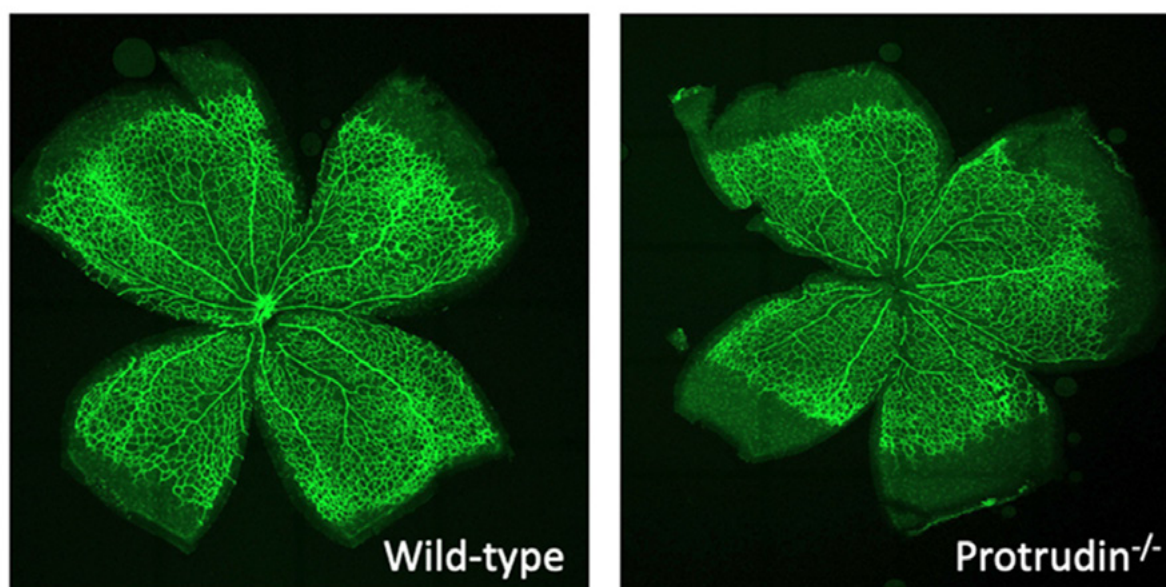


Figure. Retardation of the progression of retinal vasculature in Protrudin $-/-$ mouse pups. Isolectin B4 staining of the retinas of 7-day old animals; a representative image is shown (courtesy of Amita Arora).

We are actively continuing collaborative work to understand the role of lipoproteins and their regulatory factors in cardiometabolic derangements. Cholesterol loading converged the colony-stimulating-factor (CSF)-dependent expression of key genes related to macrophage cholesterol balance and inflammation. These findings suggest that transformation of CSF-polarized macrophages into foam cells may reduce their atheroinflammatory potential in atherogenesis (Lappalainen et al., 2021). The functional status of lipoprotein particles contributes to atherogenesis. We demonstrated that children with familial hypercholesterolemia (FH) displayed increased atherogenicity of LDL and disrupted HDL function, thus further adding to our understanding of the cardiovascular risk in FH children (Christensen et al., 2021). Regarding HDL we showed that *Streptococcus pneumoniae* pneumolysin (PLY) and neuraminidase A (NanA) impair HDL function by causing chemical and structural modifications of HDL particles. The results suggest that accumulation of these modified HDL particles in the arterial intima may present a trigger for complement activation and inflammatory response, and thereby promote atherogenic disease progression (Syed et al., 2021). As a novel methodological approach, we recently generated coronary artery disease HDL-targeted, single-chain recombinant antibodies and now demonstrate that they show promise in improving diagnosis and prediction of future cardiac events (Negi et al, 2021).

Our investigations regarding the importance of stromal interacting molecule 1 (STIM1) in thyroid cancer were recently published (Asghar et al. 2021). Our results indicated that STIM1 could be a putative target for thyroid cancer therapy, as STIM1 was overexpressed in all forms of human thyroid cancer samples investigated. Furthermore, knock-down of STIM1 potentially blocked both proliferation and invasion of thyroid cancer cells in vitro, and attenuated thyroid cancer cell growth in a zebra fish model. Investigations on the importance of calcium signalling in the expression of thyroid-specific proteins in thyroid cancer cell lines have also continued. In addition, together with Dan Lindholm, we have started a project addressing the role of autophagy in thyroid cancer cells.

Thesis completed in the group in 2021

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

Annika Koponen. ORP2 - a lipid-binding protein controlling cellular cholesterol transport and signal transduction. April 1, 2021.

Awards, honours and positions of trust

Prof. Vesa Olkkonen: The Lääkäri ja Kongressi (Doctor & Congress) prize of the The Finnish Fair Foundation for organising in Helsinki the European Atherosclerosis Conference 2021 (EAS 2021) on May 30-June 2, 2021.



Prof. Katriina Aalto-Setälä, Prof. Vesa Olkkonen and Prof. Marja-Riitta Taskinen were awarded the Lääkäri ja Kongressi (Doctor & Congress) prize of The Finnish Fair Foundation for organising in Helsinki the highly successful European Atherosclerosis Conference 2021 (EAS 2021) with >2400 registered participants, on May 30-June 2, 2021.

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Membrane biology

Main research activities

Our group focuses on understanding how major membrane lipids are transported between cell compartments, how dynamic storage of lipids in lysosomes and lipid droplets is controlled, and how defects in these processes can give rise to human diseases. To this aim, we also develop novel techniques for lipid cell biological analyses, such as novel lipid imaging techniques, detection of rapid metabolic fluxes of lipids, and acute manipulation of proteins controlling lipid distribution in cells and tissues.

In 2021, Ph.D. student Kecheng Zhou defended his thesis on the ceramide-interacting late endosomal protein LAPT4B in a virtual dissertation. In July, the group's long-standing work was recognized by the European Biophysical Society Avanti Polar Lipids Award to Elina Ikonen, in recognition of the most important European scientific contributions in understanding the biophysics of lipids. Our group also started as a partner in a new European Research Training Network EndoConnect (H2020-MCSA-ITN) which held a successful on-site kick-off meeting in Groningen in November.

In 2021, we made major steps forward in understanding how LDL cholesterol is transported out of late endosomal/lysosomal compartments into the plasma membrane. We discovered that in migrating cells, this route uses recycling endosomes as an intermediate station and that lipid transfer from lysosomes to recycling endosomes primes the activity of focal adhesion kinase, a key regulator of cell adhesions (Takahashi et al., 2021). Our previous collaboration with the Olkkonen group (Koponen et al., 2020) had led us to postulate that the oxysterol-binding protein homolog ORP2 may play a role in this lipid transfer process. By using a novel strategy developed in our lab to acutely deplete endogenous cellular proteins (Li et al., 2019), we showed that upon acute ORP2 removal from LDL-loaded cells, cholesterol transfer from late to recycling endosomes was indeed impaired. The counter-transport of the phosphoinositide lipid PI(4,5)₂ from recycling to late endosomes was also attenuated. These lipid transfer processes could be rescued by lipid transfer com-



Group members

Elina Ikonen, M.D., Dr.Med.Sci., Professor (Director), Head
Maarit Hölttä-Vuori, Ph.D., University lecturer
Kristiina Kanerva, Ph.D.
Shiqian Li, Ph.D.
Viola Nähse, Ph.D.
Miesje van der Stoel, Ph.D.
Xin Zhou, Ph.D.
Heljä Lång, M.D.
Juho Pirhonen, M.D.
Lauri Vanharanta, M.D.
Annabel Goudriaan, M.Sc.
Abel Szkalitsity, M.Sc.
Kecheng Zhou, M.Sc., Ph.D. spring 2021
Päivi Kleemola, Research assistant
Tiina Pohjankoski, Research assistant
Anna Uro, Laboratory technician

External funding

Academy of Finland
EU MCSA EndoConnect network
Jane and Aatos Erkkö Foundation
Leducq Foundation for Cardiovascular Research
Sigrid Jusélius Foundation
University of Helsinki, Research Excellence and Infrastructure Funding (HiLIFE)

petent but not incompetent ORP2. Together, these data argue that ORP2 facilitates bidirectional lipid movement at membrane contacts between late and recycling endosomes (reviewed in Olkkonen and Ikonen, 2021; for a broader view of cholesterol trafficking circuits via interconnected lipid fluxes, please see Zhou and Ikonen, 2021).

We also advanced our understanding of how nascent lipid droplets form in the endoplasmic reticulum (ER) membrane and how triacylglycerols are deposited into lipid droplets (reviewed by Thiam and Ikonen, 2021). Specifically, we showed that the integral ER membrane protein seipin, originally identified as a protein mutated in the most severe human lipodystrophy, can trap triacylglycerols in the ER bilayer (Prasanna et al., 2021). This facilitates the nanoscale phase-separation of triglycerides in the membrane to form a lens-like structure that can function as a seed for lipid droplet generation. We also identified critical amino acid residues in the seipin hydrophobic helices that are critical for the triglyceride sequestering function of seipin.

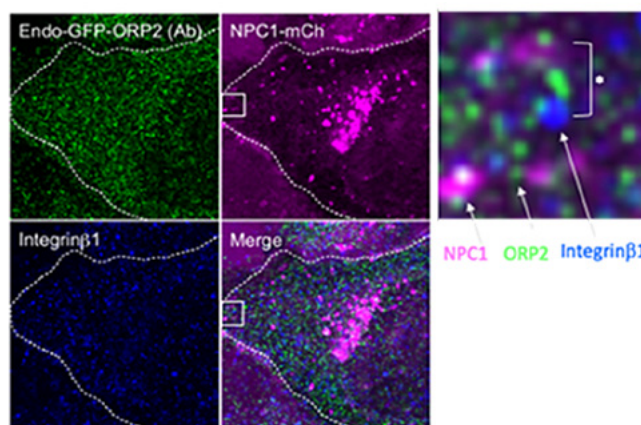


Figure. Endogenous ORP2 localization in human A431 cells loaded with LDL for 4 h. Punctate ORP2 structures associate with both NPC1 containing late endosomal organelles and integrinβ1 containing recycling endosomes at the cell periphery. Occasionally ORP2 dots appear to bridge these organelles (asterisk) (courtesy of Kohta Takahashi, see Takahashi et al., *EMBO J* 2021 for details).

Thesis completed in the group in 2021

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

Kecheng Zhou. Crosstalk between sphingolipid metabolism and nutrient signaling: Studies on LPTM4B. March 4, 2021.

Awards, honours and positions of trust

Prof. Elina Ikonen: European Biophysical Society (EBSA) – Avanti Polar Lipids Award 2021.

Publications 2021

Dichlberger A, Zhou K, Bäck N, Nyholm T, Backman A, Mattjus P, Ikonen E, Blom T. LPTM4B controls the sphingolipid and ether lipid signature of small extracellular vesicles. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2021; 1866:158855.

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Olkkonen VM, Ikonen E. Cholesterol transport in the late endocytic pathway: Roles of ORP family proteins. *J Steroid Biochem Mol Biol*. 2021; 216:106040.

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Prasanna X, **Salo VT, Li S, Ven K, Vihinen H, Jokitalo E, Vattulainen I, Ikonen E.** Seipin traps triacylglycerols to facilitate their nanoscale clustering in the endoplasmic reticulum membrane. *PLoS Biol*. 2021; 19:e3000998.

Takahashi K, Kanerva K, Vanharanta L, Almeida-Souza L, Lietha D, Olkkonen VM, Ikonen E. ORP2 couples LDL-cholesterol transport to FAK activation by endosomal cholesterol/PI(4,5)P₂ exchange. *EMBO J*. 2021; 14:e106871.

Thiam AR, **Ikonen E.** Lipid droplet nucleation. *Trends Cell Biol*. 2021; 31:108-118.

Zhang X, McDonald JG, Aryal B, Canfrán-Duque A, Goldberg EL, Araldi E, Ding W, Fan Y, Thompson BM, Singh AK, Li Q, Tellides G, Ordovás-Montanes J, García Milian R, Dixit VD, **Ikonen E**, Suárez Y, Fernández-Hernando C. Desmosterol suppresses macrophage inflammasome activation and protects against vascular inflammation and atherosclerosis. *Proc Natl Acad Sci U S A*. 2021; 118:e2107682118.

Metabolism

Main research activities

We study the molecular mechanisms of insulin resistance, especially in human skeletal muscle. To this end, we have obtained skeletal muscle biopsies from 148 clinically characterized men covering all glucose tolerance phenotypes: normal, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes (T2D). We have analyzed skeletal muscle proteomes using a data-independent acquisition (DIA) method, a sequential window acquisition of all theoretical mass spectra (SWATH-MS) proteomics technique. The analysis of 148 skeletal muscle proteomes has revealed a downregulation in several proteins involved in mitochondrial electron transport or respiratory chain complex assembly already in prediabetic IFG and IGT muscles, with most profound decreases in T2D muscle. In addition, phospho-proteomic analysis has revealed changes in phosphorylation of several signaling pathways in prediabetic and T2D muscles. These data highlight impaired mitochondrial energy metabolism in the transition from prediabetes into T2D (Öhman et al., 2021).

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 FUSION, we study the genetic architecture of T2D and related traits. As part of a research collaboration, in which the FUSION study also participated, a large multi-ancestry, genome-wide genetic discovery meta-analysis of lipid levels was performed. Increasing diversity of the study population led to improvements in fine-mapping functional variants and the portability of polygenic prediction (Graham et al., 2021).

In another collaborative project, the role of neuropeptide urocortin 3 (UCN3) in adipose tissue function was investigated. The overexpression of UCN3 in 3T3-L1 adipocytes increased glucose uptake and ameliorated markers of cellular stress response and inflammation (Kavalakatt et al., 2021).



Group members

Heikki Koistinen, M.D., Dr.Med.Sci., Docent, Head
Selina Mäkinen, M.Sc.
Leena Kinnunen, Phil. kand.

External funding

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Medical Society of Finland
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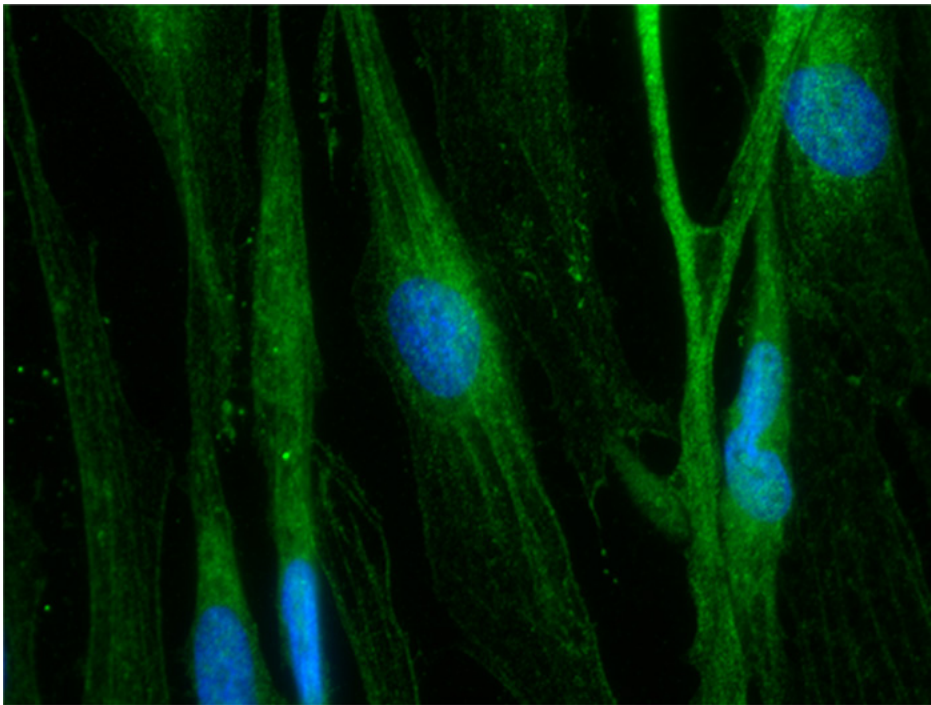


Figure. Permeabilized primary human skeletal muscle cells stained with GLUT4 antibody (green). Nuclear staining with DAPI (blue) (courtesy of Selina Mäkinen).

Awards, honours and positions of trust

Docent Heikki Koistinen: Chair of the board of the Finnish Diabetes Research Society.

Publications 2021

- Chen J et al., Meta-Analysis of Glucose and Insulin-related Traits Consortium (MAGIC). The trans-ancestral genomic architecture of glycemic traits. *Nat Genet.* 2021; 53:840-860.
- Goodrich JK et al., Determinants of penetrance and variable expressivity in monogenic metabolic conditions across 77,184 exomes. *Nat Commun.* 2021; 12:3505.
- Graham SE et al., The power of genetic diversity in genome-wide association studies of lipids. *Nature.* 2021; 600:675-679.
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- Öhman T, Teppo J, **Datta N**, **Mäkinen S**, Varjosalo M, **Koistinen HA.** Skeletal muscle proteomes reveal downregulation of mitochondrial proteins in transition from prediabetes into type 2 diabetes. *iScience.* 2021; 24:102712.

Associated group:

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 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 2021, we worked on three main areas of research.

USP14 in neuronal autophagy and in cell models of HD

Protein homeostasis (proteostasis) is known to be dysfunctional in several human diseases. In neurodegenerative disorders such as HD, there is an accumulation of mutant or misfolded proteins impairing cell functions and viability.

USP14 is a deubiquitinating enzyme associated with the proteasome and important for protein degradation. We noted that inhibition of proteasome activity reduced the amount of bound USP14, and furthermore proteomic analyses identified the chaperone, HSC70, and the autophagy regulator, GABARAP as binding partners for USP14 outside the proteasome. Mutagenesis of USP14 resulted in a W58A-USP14 mutant that did not bind to the proteasome and can be used a tool for further studies (Srinivasan et al., 2019). Using quantitative mass spectrometry, we could show that USP14 undergoes posttranslational modifications (PTMs) in human neuroblastoma cells. The functional significance of these PTMs for the



Group members

Dan Lindholm, M.D., Dr.Med.Sci., Professor, Head
Ove Eriksson, Ph.D., Docent
Karin Cavanaugh, M.Sc.
Vignesh Srinivasan, M.Sc.
Jimi Kuusipalo, B.Sc.
Kristiina Söderholm, Laboratory technician

External funding

EU H2020-MSCA-RISE project, SZ_TEST
Finnish Society of Sciences and Letters
Magnus Ehrnrooth Foundation
Medical Society of Finland
Medicinska Understödsföreningen Liv och Hälsa r.f.

physiology of USP14 in neurons and in models of HD is currently under investigation.

We are also currently studying the role of USP14 and its inhibition in tumour cells using a thyroid cancer cell model in collaboration with Prof Kid Törnquist and Dr Yasir Asghar at Minerva.

Neurotrophic factors in cell and in vivo models of HD

Endoplasmic reticulum (ER) stress is linked to the pathophysiology of neurodegenerative diseases including HD (Lindholm et al., 2017). Cerebral dopamine neurotrophic factor (CDNF) is a protein with a unique mechanism of action, mitigating ER stress as demonstrated in models of PD (Voutilainen et al., 2015). We noted that CDNF also has a protective role in striatal neurons against neurotoxin quinolinic acid by reducing ER stress (Stepanova et al., 2020). In collaboration with Dr. Voutilainen's group, we have studied CDNF further in the the N171-82Q transgenic model of HD (Stepanova et al., under submission). Along with this we are studying Canopy 2 (CNPY2), which is an ER resident protein that we have cloned before. CNPY2 can influence ER stress and may itself act as an initiator of the unfolded protein response, as shown in liver cells. We have evidence that overexpression of CNPY2 is neuroprotective whilst its downregulation renders neurons more prone to ER stress-mediated cell degeneration. We further observed that CNPY2 is increased in striatal neurons expressing 109Q-containing mutant huntingtin protein (manuscript under preparation). The mechanisms and functions of CNPY2 in HD and other brain diseases will be studied further using different models including gene knock-out mice.

3. PGC-1 α signaling enhances GABAergic transmission in mouse brain

Peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α) is a master regulator of mitochondria biogenesis and cell stress with a role in metabolic and degenerative diseases. Using transcriptome and proteomic analyses we recently showed an increase in specific GABA-A receptors in PGC-1 α transgenic mice resulting in an increased anxiety-like behavior (Vanaveski et al., 2021). Dysfunctional GABAergic signaling is a consistent finding in neuropsychiatric diseases including schizophrenia (SZ). Within an EU-funded collaboration called SZ_TEST, we have analyzed serum samples of SZ patients obtained from the Helsinki Biobank and Tartu University (manuscript under preparation).

Thesis completed in the group in 2021

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

Karin Cavonius. CNPY2 in neuronal endoplasmic reticulum stress signaling and Huntington's disease.

Publications 2021

Törnquist K, Asghar MY, Srinivasan V, Korhonen L, Lindholm D.

Sphingolipids as modulators of SARS-CoV-2 infection. *Front Cell Dev Biol.* 2021; 9:689854.

Vanaveski T, Molchanova S, Pham DD, Schäfer A, Pajanoja C, Narvik J, Srinivasan V, Urb M, Koivisto M, Vasar E, Timmusk T, Minkeviciene R, Eriksson O, Lalowski M, Taira T, Korhonen L, Voikar V, Lindholm D. PGC-1 α signaling increases GABA(A) receptor subunit $\alpha 2$ expression, GABAergic neurotransmission, and anxiety-like behavior in mice. *Front Mol Neurosci.* 2021; 14:588230.

Publications 2021

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3. **Asghar MY, Lassila T**, Paatero I, Nguyen VD, Kronqvist P, Zhang J, Slita A, Löf C, Zhou Y, Rosenholm J, **Törnquist K**. Stromal interaction molecule 1 (STIM1) knock down attenuates invasion and proliferation and enhances the expression of thyroid-specific proteins in human follicular thyroid cancer cells. *Cell Mol Life Sci*. 2021; 78:5827-5846.
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Minerva Foundation
Minerva Foundation Institute for Medical Research
BIOMEDICUM Helsinki 2U
Tukholmankatu 8
00290 Helsinki
FINLAND

Tel. +358 2 941 25701

www.minervafoundation.fi
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