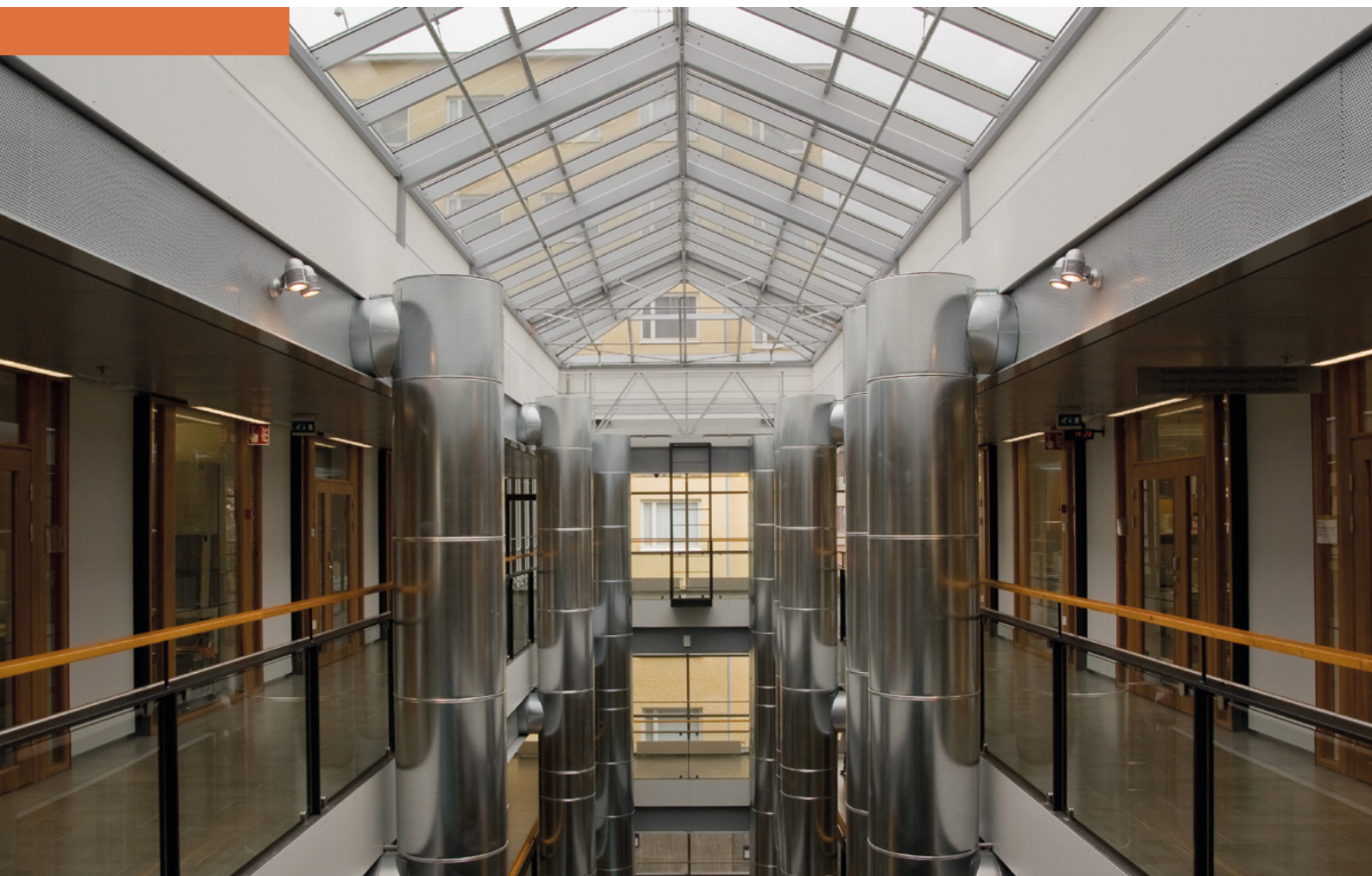




Scientific Report



Front page Image. Circos plot shows the chromosomal locations of 58 CpGs and trans-meQTLs with their methylation associated with pubertal development scale (PDS) or pubertal age (PA).
Courtesy of Markus K Youssef (Epigenomics of complex traits).

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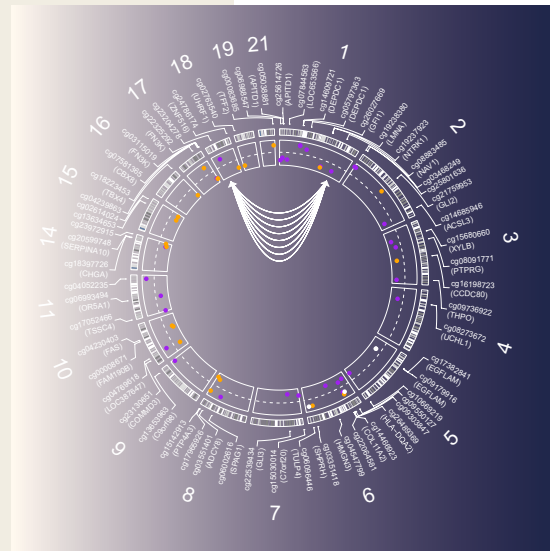
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www.minervainstitute.fi

Contents

- 4 Summary of research and activities in 2023
- 5 Administration
- 6 Medix prize of the Minerva Foundation
- 8 Bror-Axel Lamberg prize in endocrinology

Research groups

- 9 **Cardiorenal Diabetes**
Daniel Gordin, M.D., Dr.Med.Sci., Docent, Head
- 10 **Cardiovascular Disease in the Young**
Taisto Sarkola, M.D., Dr.Med.Sci., Docent, Head
- 12 **Cardiovascular Research**
Päivi Lakkisto, M.D., Dr.Med.Sci., Docent, Head
- 14 **Cellular Neuroscience**
Pirta Hotulainen, Ph.D., Docent, Head
- 16 **Epigenomics of Complex Traits**
Miina Ollikainen, Ph.D., Docent, Head
- 18 **Fatty Liver Disease and Diabetes**
Panu Luukkonen, M.D., Dr.Med.Sci., Docent, Head
- 20 **Lipid Signaling and Homeostasis**
Vesa Olkkonen, Ph.D., Professor, Head
- 22 **Membrane Biology**
Elina Ikonen, M.D., Dr.Med.Sci., Professor, Head
- 24 **Metabolism**
Heikki Koistinen, M.D., Dr.Med.Sci., Docent, Head
- 26 **Associated Group: Neuronal Signaling**
Dan Lindholm, M.D., Dr.Med.Sci., Professor, Head
- 28 **Publications**



Summary of research and activities in 2023

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 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 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 2023 is outlined in this report.

The financial resources of Minerva Foundation are directed at maintaining and further developing a research infrastructure that serves, in the most effective way possible, the work of the nine 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 €1 465 860 during 2023, which is the highest yet and covers more than 60% of the Institute's budget. During 2023, a total of 54 articles were published, 52 of which were original articles in international peer-reviewed journals. The median impact of all published articles was 6.1. Moreover, M.Sc. Selina Mäkinen, M.Sc. Pushpa Khanal and M.D. Juho Pirhonen defended their doctoral theses in 2023. In August, the institute hosted a special seminar by Prof. Martin Korte (Helmholtz Center for Infection Research, Germany), initiated a project aimed at renewing its visual impression and increasing its public visibility, and started preparations for an external evaluation of the institute taking place in the spring of 2024.

To summarize: The Institute thrived in 2023 both scientifically and financially, continued its work toward its strategic goals, and moves into 2024 with optimism and determination.

Events at Minerva 2023

Seminar

MINERVA SEMINAR
Biomedicum Helsinki, August 10, 2023

Professor MARTIN KORTE, Technische Universität Braunschweig, Germany.

Neurodegeneration and neuroinflammation: What the flu got to do with it.

Prizes and Grants

MEDIX PRIZE OF THE MINERVA FOUNDATION

Award Ceremony and Prize Lecture,
September 11, 2023

The winning article: Functional, metabolic and transcriptional maturation of human pancreatic islets derived from stem cells. *Nat Biotechnol.* 2022; 40:1042-1055.

Authors: Balboa D, Barsby T, Lithovius V, Saarimäki-Vire J, Omar-Hmeadi M, Dyachok O, Montaser H, Lund PE, Yang M, Ibrahim H, Näätänen A, Chandra V, Vihinen H, Jokitalo E, Kvist J, Ustinov J, Nieminen AI, Kuuluvainen E, Hietakangas V, Katajisto P, Lau J, Carlsson PO, Barg S, Tengholm A, Otonkoski T.

Read more on page 6–7.

BROR-AXEL LAMBERG PRIZE IN ENDOCRINOLOGY

Professor Pirjo Nuutila
Turku University Hospital and University of Turku

Read more on page 8.

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

From Selma and Maja-Lisa Selander's fund 21 grants were awarded 2023, in all 120.000 EUR.

The following theses were accepted at the University of Helsinki and University of Turku in 2023:

DOCTORAL THESES

Selina Mäkinen. Send in the signals: Studies on the mechanism of insulin resistance in human skeletal muscle. February 4, 2023.

Pushpa Khanal. Molecular regulation of the dendritic spine initiation. August 11, 2023.

Juho Pirhonen. Mechanisms of lipid deposition: Application of novel omics techniques, tissue imaging methods, and their synergistic deployment in lipid research. September 29, 2023.

MASTER'S THESES

Elizaveta Boiko. The role of PI4P in regulation of neuronal autophagy.

Mari Jokinen. An *in vitro* model of hepatic steatosis and lipotoxicity – a focus on mitochondrial dysfunction and redox state.

Ines Kumpulainen. Preeklampsins inverkan på barnets kroppsstorlek- och hjärtfunktion vid 11-årsåldern.

Sofia Saxen. Hur övervikt påverkar hjärtat hos kvinnor.

Joel Selänne. Hyponatremia päivystäjän päänsärkynä.

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, 2023. During this period, the board of trustees included the following persons:

Board of Trustees

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Professor Tom Böhling
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Professor Caj Haglund
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Docent Carina Wallgren-Pettersson

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The Minerva Foundation Institute for Medical Research

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Docent Panu Luukkonen
Docent Miina Ollikainen
Docent Taisto Sarkola
Professor Ilkka Tikkanen
Professor Kid Törnquist
Professor Hannele Yki-Järvinen
M.Sc. Cia Olsson

Medix prize of the Minerva Foundation – Towards cell therapy for diabetes

The Minerva Foundation's Medix Prize for 2023 was awarded to a research group from the University of Helsinki. The prize was awarded for a scientific article, published in the scientific journal *Nature Biotechnology*, on the development of stem cell therapy for the treatment of diabetes. The prize is worth €20,000.

In type 1 diabetes a person's body is unable to produce insulin. The condition is treated with insulin injections. For a long time, researchers have searched for ways to restore the body's ability to produce insulin to eliminate the need for injections.

Insulin-producing cells are located in pancreatic islets. Therefore, diabetes patients have undergone the transplantation of pancreatic islets from deceased organ donors. Research has revealed that this type of operation can restore a patient's ability to secrete insulin.

"In the best case, this method works quite well. However, few patients can be treated this way, because islets from one donor are usually not enough. Instead, the patient needs repeated transplants from two or three donors," explains Professor **Timo Otonkoski**, head of the award-winning research group.

There have been attempts to solve the problem with stem cells. Researchers have looked for methods to use them to generate pancreatic islets. These cells are known as pluripotent stem cells, which can be produced in unlimited quantities and are also used in many other medical studies. "Thus far, all pancreatic islets generated from stem cells have been immature and their insulin secretion poorly controlled," says Otonkoski.

His research group has done pioneering work in the development of stem cell therapy for diabetes. The award-winning article demonstrates that both structurally and functionally normal mature pancreatic islets can be generated from stem cells. Their insulin secretion is controlled in a normal manner, and they react to changes in sugar levels just as well as pancreatic islets from organ donors.

Otonkoski's research group worked in a laboratory setting and conducted tests on mice. Since the publication of the award-winning article, the first successful transplantations of islets produced from stem cells have been accomplished in the United States. Otonkoski believes that cell therapy will at some point become part of the clinical treatment of diabetes. It will be expensive, but since a significant part of the expenses incurred by the disease can be eliminated, even expensive can be cheap.

The model developed by the research group not only enables successful cell transplants, but also makes it possible to study the various ways diabetes is generated and how the disease can be treated and prevented. In the best-case scenario, it may even be possible to develop a drug that will prevent the development of diabetes.

Notable award in biomedicine

The Medix Prize is an important annual award for internationally high-level Finnish medical research. In a manner of speaking, it is the Finnish championship for biomedicine. This was the 36th time it has been awarded.

The Medix Prize is awarded by the University of Helsinki. The award sum is donated to the university by the Minerva Foundation. The foundation funds an institute for medical research at Biomedicum Helsinki.

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 winner is selected by a committee consisting of representatives from the universities of Helsinki, Turku, Tampere, Eastern Finland and Oulu, who are appointed for a period of three years.

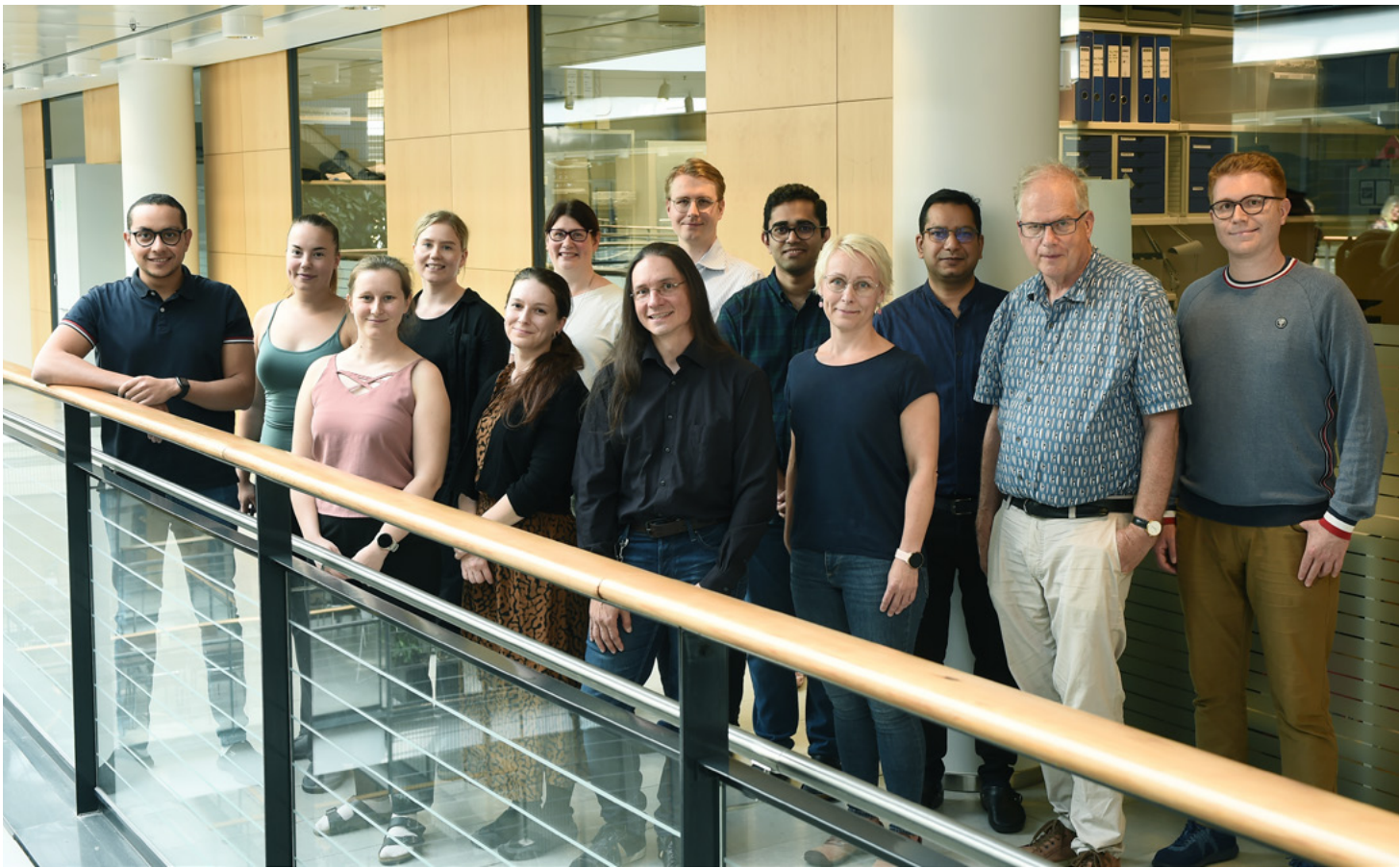


Photo above. The award-winning research group works in Biomedicum, Meilahti, Helsinki.

From left: Hossam Montaser, Martina Timonen, Eliisa Vähäkangas, Emma Ryhänen, Anna Ahmala, Jonna Saarimäki-Vire, Jouni Kvist, Väinö Lithovius, Sachin Muralidharan, Solja Eurola, Vikash Chandra, Timo Otonkoski, Diego Balboa. Tom Barsby is missing from the picture. Photographer: Juha Sarkkinen.



Professor Timo Otonkoski
Photographer: Juha Sarkkinen

Minerva Foundation's Bror-Axel Lamberg prize in endocrinology

Minerva Foundation's Bror-Axel Lamberg prize has been awarded to Professor **Pirjo Nuutila**.

At the Finnish Endocrine Society Endocrinology days on Nov 2, 2023, prof. Pirjo Nuutila was awarded the Minerva Foundation's Bror-Axel Lamberg prize, the prize sum being 10,000 €. The prize is awarded every other year to an exceptionally merited Scandinavian researcher in the field of endocrinology. This year the prize was awarded for the 4th time.

Pirjo Nuutila is professor of metabolic research at the National PET center functioning in the context of Turku University Hospital and the University of Turku research community. She also functions as chief physician of endocrinology at the Turku University Hospital. Prof. Nuutila is one of the most appreciated specialists of functional imaging in endocrinology. Her globally recognized studies have revealed new physiologic routes involved in insulin resistance and obesity as well as improved the diagnostic options available for the diagnostics of endocrine tumors. A special strength of Nuutila's are innovative imaging techniques employing positron emission tomography (PET) with radioactive tracer substances.

Prof. Nuutila is an active participant of the global scientific and endocrinology community. She is a long-standing member of the European Society of Endocrinologists (ESE) and has acted as chair of the Finnish Endocrine Society. She has presented her work as invited main lecturer in many conferences of ESE and other international conferences. Before the present award, her work has been recognized with a number of prestigious research awards, such as the Novo Nordisk Foundation Lecturer prize in 2022, the Ray A. Kroc prize in 2018, and the Steno medal in 2015.



Professor Pirjo Nuutila. Photographer Jyrki Mustonen.

Bror-Axel Lamberg (March 1, 1923 – 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.

Cardiorenal diabetes

Current Projects

Renal studies

During the year, we have initiated a study in rare kidney diseases (RKD). RKDs are a group of often genetic conditions with no targeted therapies. These are under-studied because of their rarity, thus inadequate sample sizes and statistical power. Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. We will study ADPKD in a large (>500,000) patient-enriched sample of the Finnish population (finngen.fi). The goal of this study is to improve understanding of ADPKD by assessing clinical and genetic tools, as well as systems biology. Tomas Visser has initiated his PhD studies as part of this project.

Renal diseases are major drivers of cardiovascular morbidity, early mortality, and poor quality of life. A thorough methodology including measurement of iohexol glomerular filtration rate (iGFR), effective renal plasma flow (ERPF), renal imaging by blood oxygenation level dependent (BOLD) magnetic resonance imaging (MRI) studies, and positron emission tomography/computed tomography (PET/CT), has been set up within the FinnDiane (finndiane.fi) study to investigate renal diseases. Rasmus Simonsen has been instrumental in setting up the lab. A drug study employing this methodology has started. Karoliina Ahtola is coordinating the study.

Cerebrovascular study in type 1 diabetes

Individuals who were part of this study underwent brain imaging (MRI), genetic (GWAS, WGS), metabolomic, cognitive, and retinal evaluations (Optical coherence tomography angiography, OCTA) as part of this FinnDiane sub-study. The patient investigations were finalized this year. The main finding so far is that one in four of these asymptomatic middle-aged individuals with T1D, showed signs of cerebral microbleeds. The final goal is to explore structural-functional associations between the brain, eye, and cognition. Jussi Inkeri, Iiris Kyläheiko, and Aleks Tarkkonen are preparing their PhDs as part of this study. Five manuscripts have been published thus far.



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

Group members

Rasmus Simonsen, M.D., Dr. Med. Sci.
Jussi Inkeri, M.D.
Aleksi Tarkkonen, M.D.
Iiris Kyläheiko, M.A.
Tomas Visser M.Bs.
Karoliina Ahtola, Research nurse

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
Wilhelm and Else Stockmann Foundation

Awards, honors and positions of trust 2023

Docent Daniel Gordin: President of the Finnish Society of Hypertension (until 2025).

Selected publications 2023

- Bouslama R, Dumont V, Lindfors S, Paavolainen L, Tienari J, Nisen H, Mirtti T, Saleem MA, **Gordin D**, Groop PH, Suetsugu S, Lehtonen S. Phosphorylation of PACSIN2 at S313 regulates podocyte architecture in coordination with N-WASP. *Cells*. 2023; 12:1487.
- Eriksson MI, Syreeni A, Sandholm N, Dahlström EH, **Gordin D**, Tatlisumak T, Putaala J, Groop PH, Martola J, Thorn LM; FinnDiane Study Group. Haptoglobin genotype and its relation to asymptomatic cerebral small-vessel disease in type 1 diabetes. *Acta Diabetol*. 2023; 60:749-756.
- Pauley ME, Vinovskis C, MacDonald A, Baca M, Pyle L, Wadwa RP, Fornoni A, Nadeau KJ, Pavkov M, Nelson RG, **Gordin D**, de Boer IH, Tommerdahl KL, Bjornstad P. Triglyceride content of lipoprotein subclasses and kidney hemodynamic function and injury in adolescents with type 1 diabetes. *J Diabetes Complications*. 2023; 37:108384.
- Tarkkonen A, Claesson TB, Eriksson MI, Forsblom C, Thorn LM, Summanen P, Groop PH, Putaala J, **Gordin D**, Martola J. Atrophy of the optic chiasm is associated with microvascular diabetic complications in type 1 diabetes. *Front Endocrinol (Lausanne)*. 2023; 14:1134530.
- Tynjälä A, Harjutsalo V, Jansson Sigfrids F, Groop PH, **Gordin D**; FinnDiane Study Group. Higher HbA_{1c} variability is associated with increased arterial stiffness in individuals with type 1 diabetes. *Cardiovasc Diabetol*. 2023; 22:47.

Cardiovascular research in the young

Main research activities

During the year, the main research activities were in the project domains of fetal cardiovascular programming and prevention of cardiovascular disease. Study family follow-up 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; NCT04676295) until April 2023 (please see follow-up completion dinner photograph with the Sarkola-Laivuori groups together). All visits were successfully coordinated and managed by Maria Finne and Juho Suomi. PhD students Michelle Renlund and Anni Kivelä (collaboration with Tiina Jääskeläinen and Hannele Laivuori) worked actively within the project during the year. PhD student mini seminars were arranged with the Daniel Gordin group in January and June 2023. Renlund presented her research data as an abstract at AEPC2023 (Dublin) and NPCM2023 (Helsinki), and Kivelä presented her research data as an abstract at NPCM2023 (Helsinki). The Nordic Pediatric Cardiology meeting (NPCM2023) including 120 participants from Nordic and Baltic countries on September 13–15, 2023 at Hanaholmen (Espoo) was arranged and hosted by Taisto Sarkola in collaboration with the Finnish Cardiac Society.

Three articles from FINNCARE with PhD student Michelle Renlund-Vikström as first author were published. The first article showed that pre-eclampsia exposed children develop an increased systolic and pulse pressure profile, as well as increased arterial stiffness at mean 11 years. The elevated blood pressure in pre-eclampsia-exposed children was related to maternal gestational blood pressure and child prematurity, whereas arterial stiffness was determined by child characteristics at follow-up. The alterations in blood pressure were pronounced in early-onset pre-eclampsia-exposed children. The second article showed that the peripheral artery media thickness of pre-eclampsia-exposed children was no different from that of non-exposed children but is positively associated with blood pressure. Adiposity was related to local carotid artery stiffness. No relationship with adventitial thickness was, however, found. And there were also no relationships between arterial



Taisto Sarkola
M.D., Dr.Med.Sci., Docent, Head

Group members

My Blomqvist, D.D.S., Dr.Med.Sci.
Mari Ylinen, M.D., Dr.Med.Sci.
Linda Litwin, M.D., Dr.Med.Sci.
Essi Karikoski, M.Sc.
Michelle Renlund-Vikström, M.D.
Laura Biskop, Medical student
Karita Hyvönen, Medical student
Ines Kumpulainen, Medical student
Sofia Saxén, Medical student
Maria Finne, M.Sc., Research coordinator
Juho Suomi, M.Sc., Research coordinator

External funding

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

wall layer structure or stiffness and maternal gestational or child perinatal factors. The third article showed that heart rate variability in pre-eclampsia-exposed children is not altered pre-puberty, and elevated SBP following pre-eclampsia exposure is not related to heart rate variability. Child adiposity could, however, be related to decreased cardiac vagal tone. Taken together, these adverse associations in arterial health may reflect the early progression of cardiovascular disease in pre-eclampsia-exposed children.

During 2023, the medical students Laura Biskop and Karita Hyvönen started working on their Master's theses within the FINNCARE projects. Ines Kumpulainen and Sofia Saxén completed their work on their Master's theses, supervised by Taisto Sarkola.

Furthermore, the relationship between data on child cardiovascular morphology and function and physical activity from the RADIEL (Finnish Gestational Diabetes Prevention Study) 5-year-from-birth project was processed by Linda Litwin with one article showing that in young at-risk children, moderate-to-vigorous physical activity is associated with cardiovascular remodeling (increased left ventricular mass and increased arterial media thickness), partly in a sex-dependent way, likely representing physiological adaptation. However, children's sedentary time showed no association with cardiovascular health in early childhood.

PhD student Essi Karikoski continued her work processing the data within the ORALPEDHEART study (NCT03329170) supervised by My Blomqvist and co-supervised by Taisto Sarkola. Two articles were published showing 1) Children with major congenital heart disease experience poorer oral health behavior in comparison with children with no known systemic conditions during early childhood, and 2) Children with major congenital heart disease are at risk for poor oral health behavior that could be improved with early and repeat oral health promotion parental counseling by phone by a dental hygienist. During the year PhD student Essi Karikoski finalized her doctoral thesis with the defense scheduled for January 2024.

The collaboration within the ADEF Helsinki (Alcohol/Drugs Exposure during Fetal life) consortium was continued with PhD student Niina-Maria Nissinen Thesis defense October 13, 2023 at Tampere University with important co-author supervision provided by Taisto Sarkola. One published article with Niina-Maria Nissinen as first author showed that receipt of long-term financial social assistance among youth with prenatal substance exposure likely reflects maternal substance abuse linked with maternal financial situation and care instability in childhood. In addition, one article with Anne M. Koponen as first author showed a strong association between adverse childhood experiences and neurodevelopmental disorders in youth following prenatal substance exposure.

Photo from FINNCARE follow-up completion dinner on March 24th, 2023: Michelle Renlund, Taisto Sarkola, Maria Finne, Tiina Jääskeläinen, Juho Suomi, Hannele Laivuori, Anni Kivelä, and Eija Kortelainen.

Thesis completed in the group in 2023

The following Master's theses were accepted at the University of Helsinki this year:

Ines Kumpulainen: Preeklampsins inverkan på barnets kroppsstorlek- och hjärtfunktion vid 11-årsåldern.

Sofia Saxen: Hur övervikt påverkar hjärtat hos kvinnor.

Publications 2023

Karikoski E, **Sarkola T**, Blomqvist M. Early counselling to improve oral health behavior in children with major congenital heart defects - a randomized controlled trial. *Caries Res.* 2023; 57:563-574.

Koponen AM, Nissinen NM, Gissler M, Autti-Rämö I, Kahila H, **Sarkola T**. Adverse childhood experiences and neurodevelopmental disorders among youth with and without prenatal substance exposure: A longitudinal matched register-based cohort study. *Nordisk Alkohol Nark.* 2023; 40:176-198.

Litwin L, **Sundholm JKM**, Olander RFW, Meinilä J, Kulmala J, Tammelin TH, Rönö K, Koivusalo SB, Eriksson JG, **Sarkola T**. Associations between sedentary time, physical activity, and cardiovascular health in 6-year-old children born to mothers with increased cardiometabolic risk. *Pediatr Exerc Sci.* 2023 Dec 28:1-9. doi: 10.1123/pes.2023-0058. Online ahead of print.

Nissinen NM, Rangmar J, Autti-Rämö I, Gissler M, Kahila H, Raitasalo K, **Sarkola T**. Financial difficulties in youth prenatally exposed to substances: A longitudinal register-based cohort study. *Drugs: Education, Prevention & Policy.* 2023; doi.org/10.1080/09687637.2023.2176285

Renlund MA, Jääskeläinen TJ, Kivelä ASE, Heinonen ST, Laivuori HM, **Sarkola TA**. Blood pressure, arterial stiffness, and cardiovascular risk profiles in 8-12-year-old children following preeclampsia (FINNCARE-study). *J Hypertens.* 2023; 41:1429-1437.

Renlund M, Jääskeläinen T, Kivelä A, Heinonen S, Laivuori H, **Sarkola T**. Determinants of vascular structure and function in at-risk children born to mothers managed for pre-eclampsia (FINNCARE study). *Front Cardiovasc Med.* 2023; 10:1264921.



Cardiovascular research

Main research activities

Our research group studies the molecular mechanisms of cardiac injury, repair, and regeneration in myocardial infarction and heart failure, to identify potential targets for cardiovascular medicines and novel biomarkers. We are particularly interested in the role of non-coding RNAs in the development and progression of heart failure. In our 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 2023 are presented below.

New molecular mechanisms and biomarkers of cardiac injury and heart failure

Heart failure is a significant cause of morbidity and mortality. The prognosis of heart failure remains poor, despite optimal therapy with currently available cardiovascular drugs. A better understanding of cellular and molecular mechanisms of heart failure is needed to advance the development of novel treatments and diagnostic tools for heart failure.

We have previously used a multiomics approach to identify dysregulated signaling pathways and potential target molecules for new therapies in ischemic heart failure, in collaboration with Prof. Juha Sinisalo. The most significant dysregulation was found in pathways regulating cardiac metabolism, muscle contraction, and cardiac fibrosis. We identified alterations in natriuretic peptides and the PKA/cAMP and PKG/cGMP signaling pathways, suggesting that they may play a major role in the progression of heart failure. During 2023, we have continued this project by investigating how non-coding RNAs regulate these key molecules and pathways and thus the development and progression of heart failure. In these studies, we use cardiac cell cultures and zebrafish heart failure models.

MicroRNAs (miRNAs) are short noncoding RNA molecules that play an important role in the pathogenesis of heart failure. In addition, circulating miRNAs have emerged as potential diagnostic and prognostic biomarkers of cardiovascular disease. Cardiogenic shock (CS) is the most severe form of acute heart 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. We have shown earlier in collaboration with Adj. Prof. Veli-Pekka Harjola, that miR-21-5p, miR-320a-3p, and miR-423-5p were independent predictors of 90-day mortality,



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

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Mika Laine, M.D., Dr.Med.Sci., Docent
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Ian Hägerström, Medical student
Katariina Immonen, B.Sc., Laboratory technician
Sanni Perttunen, B.Sc., Laboratory technician

External funding

Aarne Koskelo 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.
Paulo Foundation
Research Funding of the Helsinki-Uusimaa Hospital District (state funding for university-level health research)
Päivikki and Sakari Sohlberg Foundation

indicating the potential of miRNAs as biomarkers for risk assessment in CS. Our studies on novel miRNA biomarkers in CS continued during 2023. We are also investigating the origin and function of circulating miRNAs to better understand the significance of measured miRNA levels in disease pathophysiology.

During 2023, 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.

Molecular mechanisms of cardiac regeneration

We use zebrafish models to study molecular mechanisms of heart failure. Unlike humans, zebrafish are capable of fully regenerating their heart and restoring cardiac function following injury, making them an excellent model for investigating factors regulating the development and recovery of HF. During 2023, we have been working on zebrafish transcriptomics data to identify noncoding RNAs that regulate cardiac regeneration after injury.

Septins are small GTPases that are associated with actin and are important in the organization of the cytoskeleton. We have shown earlier 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. Our studies elucidating the role of septins in cardiac recovery and regeneration after myocardial injury continued during 2023.

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, and the Folkhälsan Institute of Genetics, to study the role of HO-1 and *HMOX1* gene polymorphisms in the development of cardiovascular and renal complications in type 1 diabetes.

In addition, we have generated HO-1 knockout zebrafish line using CRISPR/Cas9 technology. During 2023, we have studied the effects of HO-1 knockout on cardiac function and cardiac response to stress in zebrafish.

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 2023

Kurra V, Eräranta A, Paavonen T, Honkanen T, Myllymäki J, Riutta A, **Tikkanen I**, **Lakkisto P**, Mustonen J, Pörsti I. Moderate hyperuricaemia ameliorated kidney damage in a low-renin model of experimental renal insufficiency. *Basic Clin Pharmacol Toxicol.* 2023; 132:21-32.

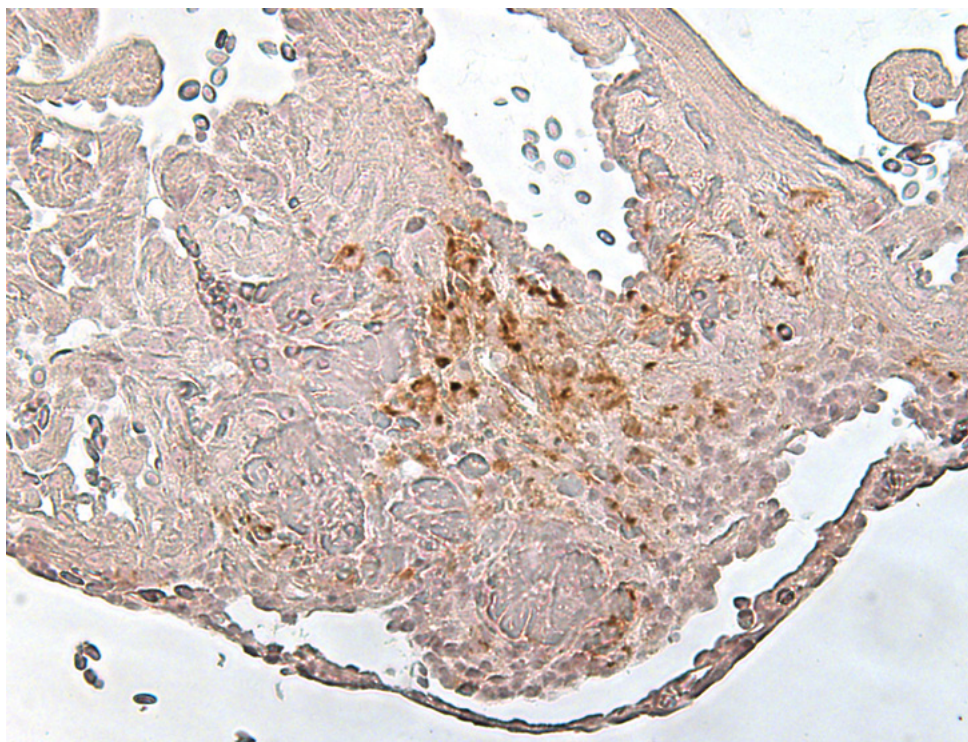


Figure. Zebrafish heart 2 weeks after cryoinjury (myocardial infarction) showing increased collagen I (brown staining) in the injury area. Courtesy of Hong Wang.

Cellular neuroscience

Main research activities

The main focus areas of the cellular neuroscience group are brain development, learning, and structural plasticity as well as neuropathic pain. The group has had a specific interest in two neuronal structures: dendritic spine and axon initial segment (AIS). The AIS is a specialized compartment that separates the axonal and somatodendritic components. Dendritic spines are small protrusions along dendrites, and excitatory synapses are located in dendritic spines. Precise control of dendritic spine morphology and density as well as the length and location of AIS are critical for normal brain function. Accordingly, both aberrant spine morphology and non-functional AIS are linked to many neurological diseases. The actin cytoskeleton is a structural element underlying the appropriate morphology of dendritic spines and structure of the AIS. Research in recent years has elucidated the mechanisms of actin cytoskeleton regulation in dendritic spines and AIS, in health and disease. Methodologically the group ranges from molecules to animal behavior, and our strengths lie in microscopy techniques.

Spine initiation factors are proteins which interact with the plasma membrane and actin cytoskeleton to push out the first protrusion from the neuronal dendrite. Spine initiation is the first step in spine morphogenesis and it is thus important when neurons control how many new spines should form and where. Spine formation is linked to various neuronal functions including learning. Therefore, understanding the mechanisms and regulation of spine initiation is necessary to understand the mechanisms underlying changes in neural networks in health and disease.

Up until 2023, we had identified one spine initiation factor called MIM (Saarikangas et al., 2015), and the Soderling lab had identified srGAP3 (Carlson et al., 2011). In 2023, we published the identification of the third spine initiation factor called Gas7 (Khanal et al., 2023). Gas7 was interesting because it used a different molecular mechanism to push the first protrusion out than MIM and srGAP3. The known spine initiation factors MIM and srGAP3 curve the plasmamembrane with their I- and iF-BAR domains to induce proto-protrusions which help to initiate filopodium growth. Gas7 F-BAR domain does not curve the membrane in vitro, but it creates flat



Pirta Hotulainen, Ph.D., Docent, Head

Group members

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Pushpa Khanal, M.Sc., Ph.D. in fall 2023
David Micinski, M.Sc.
Emilia Toissalo, M.Sc.

External funding

Medicinska Understödsföreningen Liv och Hälsa r.f.
Sigrid Jusélius Foundation
University of Helsinki (Pushpa Khanal)

scaffolds under the plasma membrane. However, Gas7 engages actin polymerization effectively to push the proto-protrusion out from the membrane. The most exciting finding, however, was that Gas7 localization, and thus spine initiation, is regulated by neuronal activity. This is exciting because this is the first time that a direct mechanism for how neuron activity can enhance spine formation has been shown.

Specific information is stored in the specific group of neurons and especially in the connections of these neurons. The group of neurons that store specific information together is called an engram. Allocation of neurons to an engram depends on their activity and in a simplified view, active neurons connect to each other and then later get activated together. Based on these ideas, it is expected that neuronal activation would enhance the formation of connections between active neurons. However, before the Gas7-study, we did not know how neuronal activity could be translated to new connections. Forming a new, stable connection starts by reaching out to other neurons; in other words, by initiating new spines.

Gas7 and SrGAP3 have relatively broad expression throughout the mouse's life. In contrast, the expression of MIM drops after early development in all other brain regions except the Purkinje cells in the cerebellum. During early development, the spine density increases quickly. It might be that during development the spines are added randomly to generate a preliminary neuronal network which can then be defined later in life. MIM could serve as an early spine initiation factor, which produces spines efficiently all over the dendrites. After early development, spine initiation could be shifted to activity-based spine initiation, and this could be driven by Gas7 (See Figure). The exact location of a new spine might not be crucial. Instead, it might be sufficient to increase the probability of initiating new spines to wire the firing neurons together.

After publishing her results in *eNeuro*, Pushpa Khanal defended her thesis in August 2023. In November 2023 she started her postdoctoral training at the Scott Soderling Laboratory at Duke University (USA).

Awards, honors, and positions of trust

Docent Pirta Hotulainen: Chair of Brain Research Society of Finland; Chair of FENS-Kavli Alumni network.

Thesis completed in the group in 2023

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

Pushpa Khanal: Molecular regulation of the dendritic spine initiation. August 11, 2023.

The following Master's thesis supervised by P. Hotulainen and V. Olkkonen was accepted at the University of Helsinki this year:

Elizaveta Boiko. The role of PI4P in regulation of neuronal autophagy.

Publications 2023

Khanal P, Boskovic Z, Lahti L, Ghimire A, Minkeviciene R, Opazo P, Hotulainen P. Gas7 is a novel dendritic spine initiation factor. *eNeuro*. 2023; 10:ENEURO.0344-22.2023.

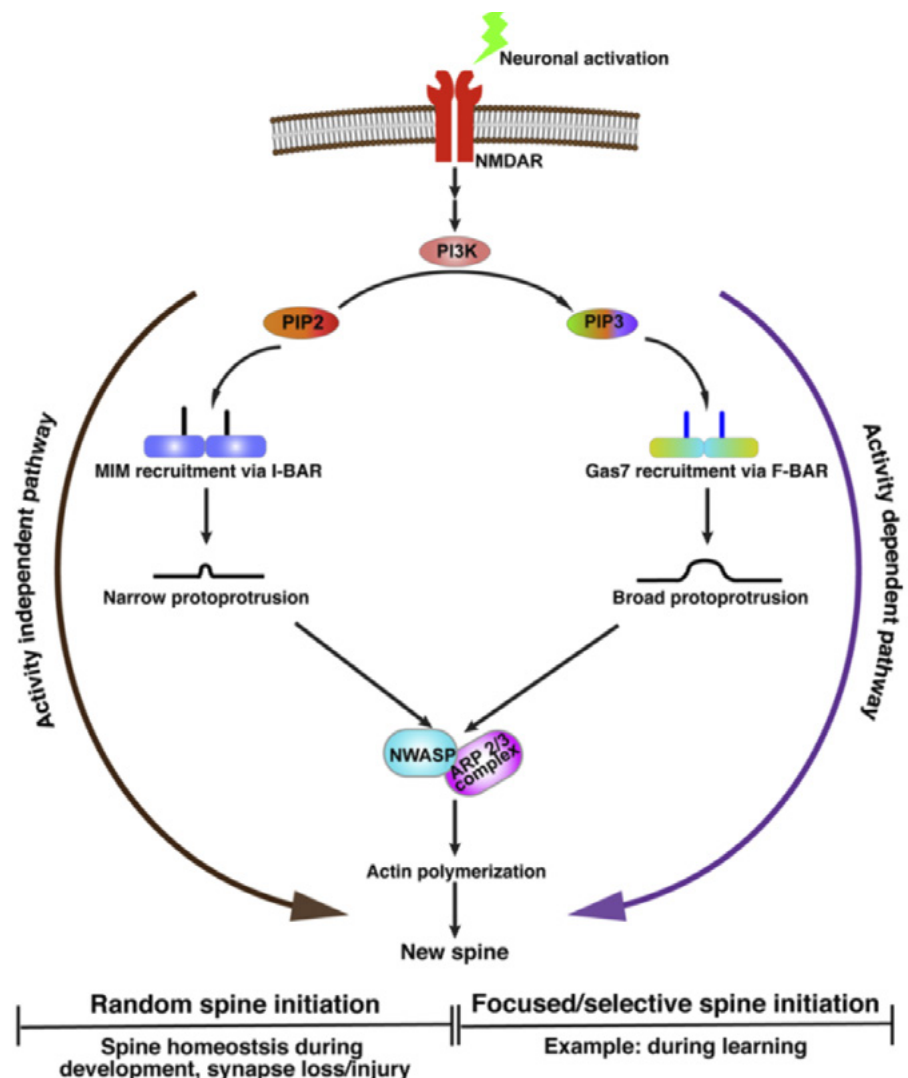


Figure. Hypothetical model illustrating two different modes of dendritic spine initiation. The activity-independent pathway might be more important to maintain spine homeostasis, for instance during development or synapse loss/injury, whereas the activity-dependent pathway might be especially important when there is a need to induce spines at a specific time in a specific location; for example, during learning. From Pushpa Khanal's PhD thesis.

Epigenomics of complex traits

Main research activities

We study epigenetics as one of the mechanisms for the environment to act on genome function in relation to complex diseases and traits. We also study epigenetics as a biomarker for health-related behaviors and biological aging. We use the Finnish Twin Cohort Study participants and apply various twin study designs, which enable ruling out confounding factors shared by the co-twins, dissecting the effects of genes and environment in the observed associations, and to infer causality. In addition to aiming at increasing our understanding of complex human diseases and traits, we aim to produce reliable trait biomarkers, risk predictors, and potential intervention targets for common diseases.

During 2023, the research work of the group has focused on mitochondrial biogenesis and epigenetics in obesity, and in assessing the roles of genes and environment in the associations between obesity-related traits and lifestyles and biological aging. In addition, we have worked toward understanding the risk factors for breast cancer, and cannabis use-related epigenetics as part of our international collaboration networks.

Obesity and mitochondrial function

We are interested in mitochondrial dysfunction in obesity, as our (and others') previous studies have shown a clear link between these two. We studied the potential of nicotinamide riboside (NR) in improving obesity-associated mitochondrial dysfunction in metabolically active tissues of BMI discordant MZ twin pairs supplemented with NR. We showed that although NR improved NAD⁺ metabolism, muscle mitochondrial number, myoblast differentiation, and gut microbiota composition, it did not improve metabolic health. NR also showed a capacity to modulate epigenetic control of gene expression and mitochondrial biogenesis (Lapatto et al., 2023). This study was done in collaboration with Professors Kirsi Pietiläinen and Eija Pirinen.

As part of her PhD studies, MSc Aino Heikkinen has been investigating the complex interactions between mitochondrial biogenesis, DNA methylation and obesity-related clinical outcomes. Her studies highlight specific changes in adipose tissue DNA methylation and gene expression that are influenced by mitochondrial biogenesis, and certain obesity-related measures.

Obesity and lifestyle-related aging

We are studying biological aging and how various lifestyles and risk factors affect the rate of biological aging, with the ultimate aim to pinpoint targets for action. In these projects, we use epigenetic clocks, which are the most promising predictors of biological aging.



Miina Ollikainen, Ph.D., Docent, Head

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Tianyu Zhu, Ph.D.
Hannes Bode, M.Sc.
Aino Heikkinen, M.Sc.
Mikaela Hukkanen, M.Sc.
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Mia Urjansson, Research nurse

External funding

Academy of Finland
NIH/NIDA (National Institutes of Health/National Institute on Drug Abuse, USA)
Sigrid Jusélius Foundation
Medicinska Understödsföreningen Liv och Hälsa r.f.
EU H2020 MSCA-ITN-ETN
The Cancer Foundation (Hannes Bode)
University of Helsinki, Doctoral Program in Population Health (Aino Heikkinen)
The Emil Aaltonen Foundation (Mikaela Hukkanen)

Obesity is a heritable complex phenotype that can increase the risk of age-related outcomes. It had been suggested that obesity is associated with accelerated aging, and we showed for the first time that BMI associates with age acceleration, independent of genetic effects, and perhaps in part due to insulin resistance (Lundgren et al., 2022). We continued to investigate the effect of metabolic syndrome (MetS) and its components on aging. MetS has been associated with premature aging, but whether this association is driven by genetics or lifestyle factors had remained unclear. The results of our recent study suggest that MetS is associated with accelerated aging, independent of physical activity, smoking, or alcohol consumption (Föhr et al., 2023). However, the effect of genetics in the associations is rather strong.

It is known that aging is associated with a loss of muscle mass and function, leading to adverse outcomes such as frailty and increased mortality risk. Exercise training has been proposed as one of the most efficient ways to promote healthy aging. However, the mechanisms by which physical activity delays the age-related decline in skeletal muscle are not fully understood. We studied the effects of aerobic fitness, exercise training, and inactivity on DNA methylome and transcriptome in muscle tissue in a large-scale international collaboration. We demonstrated that exercise training targets many age-related transcripts and DNA methylation loci to main-

tain younger methylome and transcriptome profiles, specifically in genes related to muscle structure, metabolism, and mitochondrial function (Voisin et al., 2023).

As part of her PhD studies, MSc Anna Kankaanpää investigated if individuals with differences in their long-term leisure time physical activity (LTPA) patterns also differ for their biological aging rate and mortality, and if DNA methylation mediates the favorable associations between long-term LTPA and mortality. Furthermore, she evaluated the influence of potential reverse causality and finally explored whether the associations between long-term LTPA and mortality are independent of genetic and environmental effects shared by twins in a pair. Although biological aging was accelerated in sedentary and highly active classes, the thorough analyses suggest that rather than LTPA per se reducing the risk of mortality, being active may be an indicator of a healthy phenotype and lifestyle, which co-occur with lower mortality risk. This work has been published as a preprint (Kankaanpää et al., 2023).

CANCERPREV

As part of the CANCERPREV MSCA-ITN-ETN, we have investigated night shift work as an environmental risk factor for breast cancer, and observed that women with night shift work had a 1.58-fold higher risk of breast cancer compared with women who worked daytime only. We further demonstrated that night work may be associated with breast cancer risk independent of shared environmental and genetic factors (Schernhammer et al., 2023). We also studied the epigenetics of puberty and its timing, as this is one of the known risk factors for breast cancer. This study highlights the role of genetics and the unique environment in pubertal timing and development and provide evidence for DNA methylation being a putative mechanistic link between genotypes and puberty, as well as puberty-related diseases such as breast cancer (Sehovic et al., 2023). In addition, as part of his PhD studies, MSc Hannes Bode investigated the role of DNA methylation in breast cancer risk and showed that most of the observed associations between DNA methylation and future breast cancer diagnosis remained after controlling for genetic factors, pointing to the importance of environmental risk factors (Bode et al., preprint 2023).

Cannabis epigenetics

We have actively contributed to Cannabis epigenetics consortia work, and we published a meta-analysis paper on DNA methylation changes associated with lifetime cannabis use independent of cigarette smoking (Fang et al., 2023).

Figure. We studied if the effect of nicotinamide riboside (NR) supplementation can be seen as methylation alterations in genes involved in NAD⁺ biosynthesis, mitochondrial biogenesis, protein quality control and fatty acid oxidation, OXPHOS and satellite cell identity. We performed differential methylation analysis and identified DNA methylation changes upon NR in almost 30% of the investigated CpG sites. Most of the CpG sites became hypomethylated (Lapatto et al 2023).

Awards, honors, and positions of trust

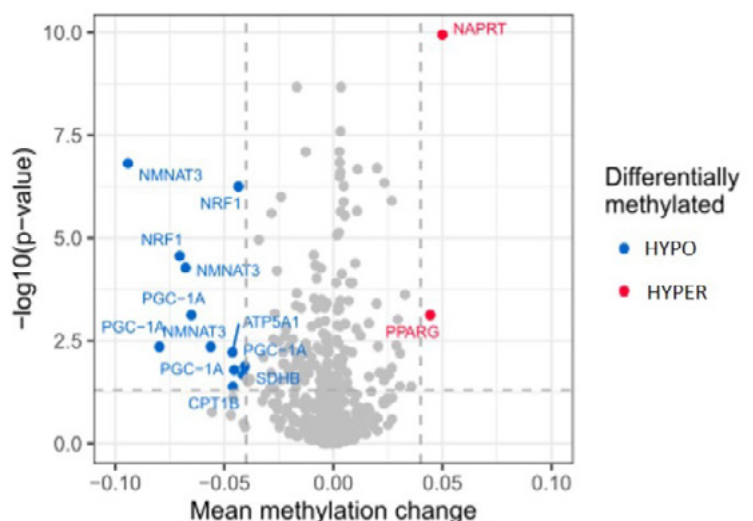
M.Sc. Mikaela Hukkanen: Best Presentation award at the DocPop workshop, University of Helsinki, November 2023.

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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 common genetic variants that modify the risk of NAFLD in humans.

The *PNPLA3* I148M variant at rs738409 is the strongest genetic risk factor for all stages of fatty liver disease. In collaboration with the Shulman Lab at Yale University, we used state-of-the-art stable isotope techniques to demonstrate that this variant has a marked effect on hepatic metabolism *in vivo* in humans. After an overnight fast, the *PNPLA3* variant carriers had higher plasma beta-hydroxybutyrate concentrations and lower hepatic *de novo* lipogenesis (DNL) compared to non-carriers. After a mixed meal, fatty acids were partitioned more toward ketogenesis in carriers, which was associated with a more reduced hepatic mitochondrial redox state. During a ketogenic diet, carriers had increased rates of intrahepatic lipolysis, increased beta-hydroxybutyrate concentrations, and decreased rates of hepatic mitochondrial citrate cycle flux. Taken together, our results demonstrate that the *PNPLA3* I148M variant induces hepatic mitochondrial dysfunction leading to reduced DNL and channeling of carbons to ketogenesis. These findings have implications for precision medicine approaches in the treatment of NAFLD, and also for understanding why the *PNPLA3* variant predisposes to progressive liver disease.

We have also demonstrated that the protection against liver fibrosis conferred by the loss-of-function variant (rs72613567-A) at *HSD17B13* and by *Hsd17b13* knockdown in mice is associated with decreased hepatic pyrimidine catabolism at the level of dihydropyrimidine dehydrogenase. This finding was validated by showing that a pharmacological inhibition of pyrimidine catabolism by a dihydropyrimidine dehydrogenase inhibitor phenocopies the *HSD17B13*-mediated protection against liver fibrosis. Together, our results suggest hepatic pyrimidine catabolism as a novel therapeutic target in NAFLD.

We have also developed and validated multiple new clinical scores to improve the detection of liver disease in both the general population and patients.

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).



Panu Luukkonen
M.D., Dr.Med.Sci., Docent, Head

Group members

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External funding

Academy of Finland
EU H2020 Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS), 2017-2023 (project 777377)
Finnish Medical Foundation
Emil Aaltonen Foundation
Instrumentarium Science Foundation
Novo Nordisk Foundation
Orion Research Foundation
Research Funding of Helsinki- Uusimaa Hospital District (state funding for university-level health research)
Sigrid Jusélius Foundation

Thesis completed in the group in 2023

The following Master's thesis was accepted at the University of Turku in 2023:

Mari Jokinen. An *in vitro* model of hepatic steatosis and lipotoxicity – a focus on mitochondrial dysfunction and redox state.

Publications 2023

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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 2023, we investigated the role of endoplasmic reticulum (ER) MCS in endothelial cell (EC) functions. These MCS were disrupted by knocking down the ER MCS organizing components VAPA/B, followed by lipidome and transcriptome analyses as well as various functional assays. ER MCS depletion led to multifaceted outcomes, which include suggested elevated ER free cholesterol content and ER stress, alterations in lipid metabolism, ER-Golgi function, and vesicle transport, as well as a reduction in angiogenesis in vitro. The knock-down also induced an inflammatory response, consistent with upregulation of markers of early atherogenesis (Taskinen et al., 2023). To conclude, ER MCS mediated by VAPA/B play a crucial role in maintaining cholesterol traffic and sustain normal endothelial functions. In another branch of the project, we initiated a study on the functions of another MCS component, the lipid transporter Nir2/PITPNM1 in primary EC.

A new major project in the group investigates molecular defects in the communication between adipocytes and endothelial cells in obese adipose tissue. We set up and optimized a methodology for isolating the two cell types from human visceral fat biopsies and for EC-adipocyte co-culture. In a proof-of-principle article, we reported the method development and demonstrated reciprocal communication between the two cell types in a transfilter setting (Chaurasiya et al., 2023). Moreover, we initiated omics analyses of EC and adipocytes isolated from obese and normal weight human subjects, in order to identify obesity-associated molecular fingerprints.

In a PhD study focusing on a protein called GOLM1/GP73, a novel biomarker for cancers and liver diseases, we carried out functional analysis of the protein in hepatocytes and cholangiocytes. The results demonstrated impacts of GOLM1 overexpression or knock-down on multiple cellular functions including lipid homeostasis, immune and inflammatory responses, intracellular transport, DNA synthesis, and cell proliferation. Our observations bring up the interesting possibility of employing GOLM1 as a new therapy target for diseases of the liver.

Kid Törnquist: We continued with our research on novel signaling pathways in thyroid cancer cells. In collaboration with Prof. Dan Lindholm, we have shown that USP14, a deubiquitinating enzyme involved in protein degradation, participates in the regulation of both proliferation and migration of thyroid cancer cells (Srinivasan et al., 2023). The studies further revealed that inhibiting



Vesa Olkkonen, Ph.D., Professor, Head

Group members

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Sanni Perttunen, B.Sc. Laboratory technician

External funding

Academy of Finland
Sigrid Jusélius Foundation
Jane and Aatos Erkko Foundation
Medicinska Understödsföreningen Liv och Hälsa r.f.
Diabetes Research Foundation
Finnish Foundation for Cardiovascular Research
Finnish Society of Sciences and Letters
Päivikki and Sakari Sohlberg Foundation
Magnus Ehrnrooth Foundation

USP14 enhanced proteasome activity and autophagy flux in thyroid cancer cells.

Matti Jauhiainen: In ongoing collaborative research, we aim to understand the role of lipoproteins and their regulatory factors in cardiometabolic diseases. We studied whether HDL2 and HDL3, the major HDL subclasses, modulate the energy metabolism of skeletal muscle cells. Mouse and human skeletal muscle myotubes were used to investigate the influences of human HDL2 and HDL3 on glucose and fatty uptake and oxidation. The results demonstrated that HDL enhances fatty acid oxidation in human myotubes but improves anaerobic metabolism in mouse myotubes, supporting the role of HDL as a circulating modulator of energy metabolism (Lund et al., 2023).

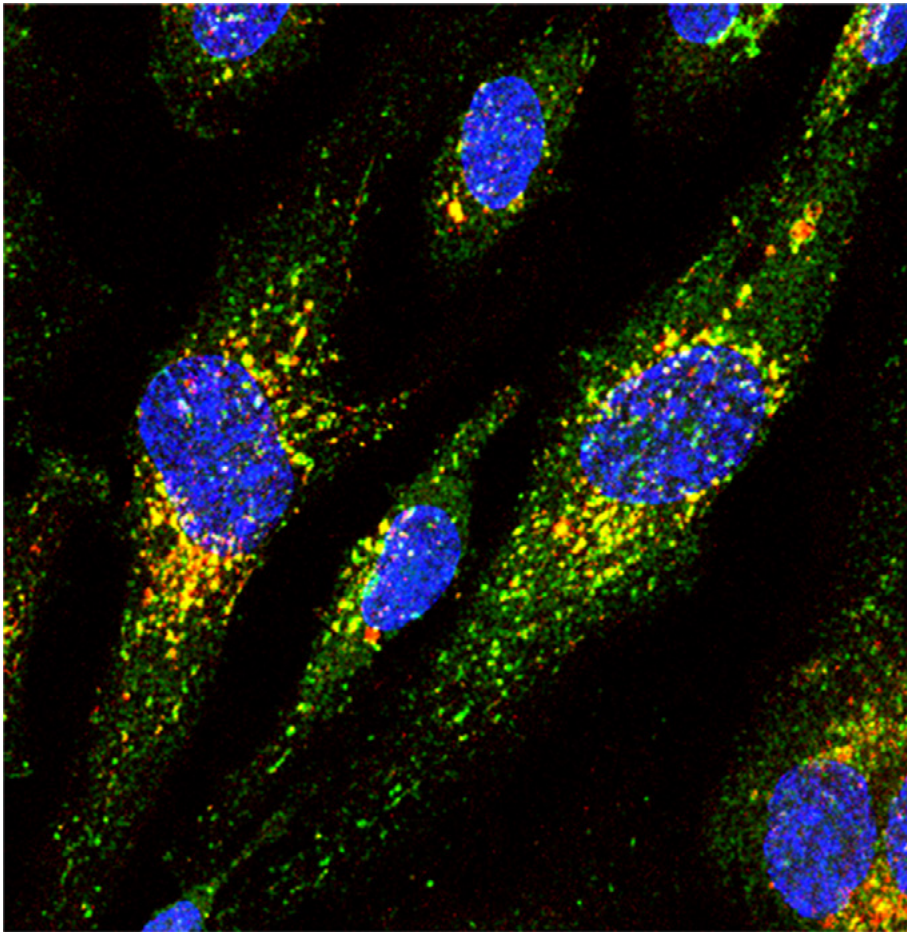


Figure. Human umbilical vein endothelial cells stained for the lysosomal marker Lamp1 (red) and mechanistic target of rapamycin (mTOR, green). Nuclei are visualized with DAPI. Courtesy of Dr. Amita Aurora.

Publications 2023

- Chaurasiya V, Pham DD, Harju J, Juuti A, Penttilä A, Emmagouni SKG, Nguyen VD, Zhang B, Perttunen S, Keskitalo S, Zhou Y, Pietiläinen KH, Haridas PAN, Olkkonen VM.** Human visceral adipose tissue microvascular endothelial cell isolation and establishment of co-culture with white adipocytes to analyze cell-cell communication. *Exp Cell Res.* 2023; 433:113819.
- Chen H, Lu C, Tan Y, Weber-Boyvat M, Zheng J, Xu M, Xiao J, Liu S, Tang Z, Lai C, Li M, **Olkkonen VM, Yan D, Zhong W.** Oculocerebrorenal syndrome of Lowe (OCRL) controls leukemic T-cell survival by preventing excessive PI(4,5)P₂ hydrolysis in the plasma membrane. *J Biol Chem.* 2023; 299:104812.
- Ikonen E, Olkkonen VM.** Intracellular cholesterol trafficking. *Cold Spring Harb Perspect Biol.* 2023; 15:a041404.
- Lund J, Lähteenmäki E, Eklund T, Bakke HG, Thoresen GH, Pirinen E, **Jauhiainen M, Rustan AC, Lehti M.** Human HDL subclasses modulate energy metabolism in skeletal muscle cells. *J Lipid Res.* 2023; 65:100481.
- Mäkinen S, Datta N, Rangarajan S, Nguyen Y, Olkkonen VM, Latva-Rasku A, Nuutila P, Laakso M, Koistinen HA.** Finnish-specific AKT2 gene variant leads to impaired insulin signalling in myotubes. *J Mol Endocrinol.* 2023; 70:e210285.
- Pihlström S, Richardt S, Määttä K, Pekkinen M, **Olkkonen VM, Mäkitie O, Mäkitie RE.** SGMS2 in primary osteoporosis with facial nerve palsy. *Front Endocrinol (Lausanne).* 2023; 14:1224318.

Srinivasan V, Asghar MY, Zafar S, Törnquist K, Lindholm D. Proliferation and migration of ML1 follicular thyroid cancer cells are inhibited by IU1 targeting USP14: role of proteasome and autophagy flux. *Front Cell Dev Biol.* 2023; 11:1234204. eCollection 2023.

Taskinen JH, Ruhanen H, Matysik S, Käkälä R, Olkkonen VM. Systemwide effects of ER-intracellular membrane contact site disturbance in primary endothelial cells. *J Steroid Biochem Mol Biol.* 2023; 232:106349.

Thesis completed in the group in 2023

The following Master's thesis supervised by P. Hotulainen and V. Olkkonen was accepted at the University of Helsinki this year:

Elizaveta Boiko. The role of PI4P in regulation of neuronal autophagy.

Membrane biology

Main research activities

Our group focuses on studying how major membrane lipids are transported in human cells, how the dynamic storage and mobilization of lipids dictates organelle communication and cellular metabolism, and how defects in these processes give rise to human diseases. To this end, we also develop new methods for lipid cell biology, including imaging techniques, biochemical detection of rapid lipid metabolic fluxes, and acute manipulation of proteins controlling lipid distribution in cells and tissues.

During 2023, we achieved major improvements in the auxin-inducible degron (AID) technology that was originally reported by us in Li et al. (2019) and applied in our earlier studies (e.g. Salo et al., 2019; Takahashi et al., 2021). In short, this method allows efficient auxin-inducible depletion of endogenous human transmembrane, cytoplasmic, and nuclear proteins within ~1 h. It is particularly powerful for analyzing the functions of essential cellular proteins whose constitutive loss-of-function is lethal, and for proteins whose loss-of-function results in complex compensatory phenotypes, as is often the case for proteins involved in lipid transport and metabolism. However, the generation of human AID cell lines requires the introduction of several genetic engineering steps and has therefore remained challenging. We have now developed a streamlined procedure in which AID cell lines can be generated in a single step with high homozygous degron-tagging efficiency. This is not only applicable for several human cancer cell lines, but also for human embryonic stem cells (hESCs). Moreover, we established efficient differentiation of such engineered hESCs and rapid removal of a broad spectrum of target proteins from differentiated neurons. This provides the first demonstration that AID can efficiently remove endogenous proteins from differentiated human cells (Li et al., 2023).

We have also continued studies on the mechanism of lipid droplet (LD) biogenesis in the endoplasmic reticulum (ER). A key protein regulating this process is the oligomeric integral ER protein seipin. Defective function of seipin causes the most severe characterized human lipodystrophy. We have earlier elucidated how this protein controls the formation of triacylglycerol (TAG)-rich LDs (e.g. Salo et al., 2019, Santinho et al., 2020, Prasanna et al., 2021, Thiam and Ikonen, 2021). We have now dissected how the other main neutral lipid component of LDs, cholesteryl esters (CEs), are packaged into LDs in the ER. Biophysical studies revealed that CEs condense in the bilayer and nucleate droplets when the CE/



Elina Ikonen
M.D., Dr.Med.Sci., Professor (Director), Head

Group members

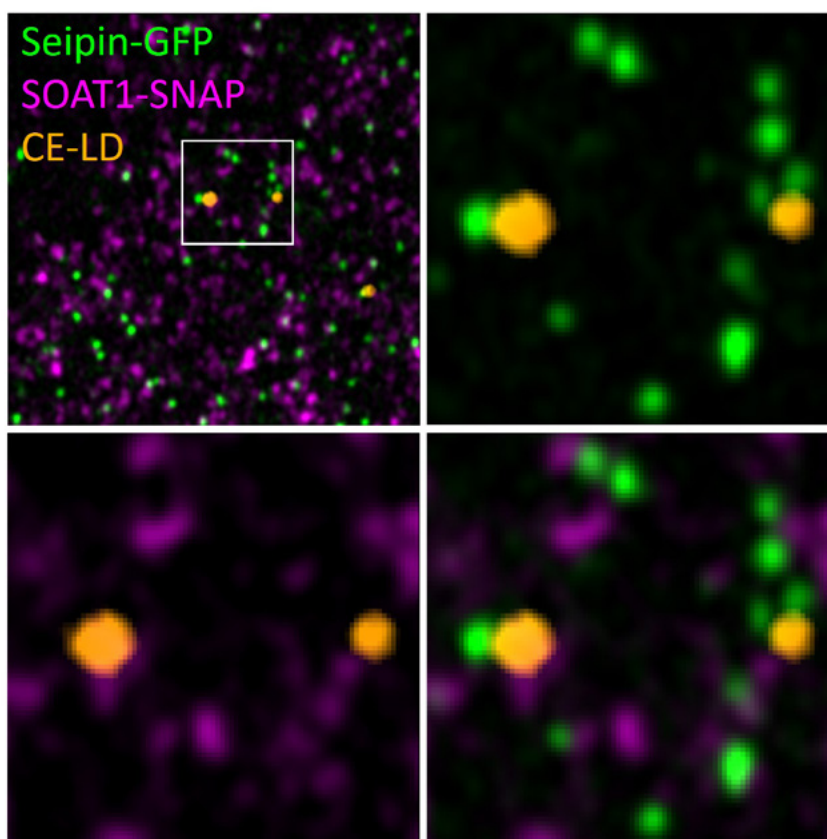
Maarit Hölttä, Ph.D., University lecturer
Kristiina Kanerva, Ph.D.
Viola Nähse, Ph.D.
Miesje van der Stoel, Ph.D.
Xin Zhou, Ph.D.
Haoran Li, M.Sc.
Heljä Lång, M.D.
Juho Pirhonen, M.D.
Ábel Szkalitsity, M.Sc.
Lauri Vanharanta, M.D.
Csaba Vörös, M.Sc., Technical assistant
Päivi Kleemola, Research assistant
Markus Konttinen, Research assistant
Erika Saari, Research assistant
Anna Uro, Laboratory technician

External funding

Academy of Finland
EU MCSA ITN EndoConnect
EU MCSA Postdoctoral fellowship PIP-AID
Jane and Aatos Erkkö Foundation
Leducq Foundation for Cardiovascular Research
University of Helsinki, DPBM and ILS doctoral programs
University of Helsinki, Research Excellence and Infrastructure Funding (HiLIFE)

phospholipid ratio reaches over 10-15%. Interestingly, this concentration is reduced in the presence of TAGs in the membrane that thereby facilitate CE nucleation. Accordingly, blocking TAG synthesis inhibits, and boosting TAG synthesis stimulates, cellular CE LD nucleation. In cells, CE LDs emerged at seipin defined sites, similarly as for TAG LDs. This appears to be due to the propensity of seipin to lower the initial TAG concentration required to generate TAG “seeds,” which then catalyze the nucleation of CE LDs (Dumesnil et al., 2023).

Figure. Localization of endogenous seipin and SOAT1 in cholesterol loaded cells. Human A431 cells were fluorescently tagged at the endogenous gene loci encoding the integral endoplasmic reticulum (ER) membrane proteins sterol-O acyltransferase 1 (SOAT1) and seipin. SOAT1 is the enzyme catalyzing cholesterol esterification and seipin is a key protein controlling the biogenesis of cholesteryl ester -rich lipid droplets (CE LDs) (Dumesnil et al., 2023). The cells were acutely loaded with methyl-beta-cyclodextrin complexed cholesterol, inducing cholesterol esterification and the formation of CE LDs. CE LDs are associated with seipin complexes at ER-LD contacts (arrowheads) while SOAT1 oligomers are not enriched at CE LD contacts. Courtesy of Lauri Vanharanta.



Awards, honors, and positions of trust

Professor Elina Ikonen: Vice-Dean of Research at the Faculty of Medicine, University of Helsinki in 2023; Member of the Scientific Advisory Committee of the European Molecular Biology Laboratory starting 2023.

Ph.D. Xin Zhou: Poster Prize, EMBO Workshop Membrane shaping and remodeling by proteins, November 2023, Kunming, China.

Thesis completed in the group in 2023

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

Juho Pirhonen. Mechanisms of lipid deposition: application of novel omics techniques, tissue imaging methods, and their synergistic deployment in lipid research. September 29, 2023

Publications 2023

Dumesnil C, **Vanharanta L**, Prasanna X, Omrane M, Carpentier M, Bhaskar A, Enkavi G, **Salo VT**, Vattulainen I, **Ikonen E**, Thiam AR. Cholesterol esters form supercooled lipid droplets whose nucleation is facilitated by triacylglycerols. *Nat Commun.* 2023; 14:915.

Ikonen E, Olkkonen VM. Intracellular cholesterol trafficking. *Cold Spring Harb Perspect Biol.* 2023; 15:a041404.

Nähse V, Raiborg C, Tan KW, Mørk S, Torgersen ML, Wenzel EM, Nager M, Salo VT, Johansen T, **Ikonen E**, Schink KO, Stenmark H. ATPase activity of DFCP1 controls selective autophagy. *Nat Commun.* 2023; 14:4051.

Preprint

Li S, Wang Y, **van der Stoep M**, Zhou X, Madhusudan S, **Kanerva K**, Ngyen VD, Eskici N, **Olkkonen VM**, Zhou Y, Raivio T, and **Ikonen E**. One-step generation of auxin-inducible degron cells with high-efficiency homozygous tagging. <https://www.biorxiv.org/content/10.1101/2023.03.26.534268v1>.

Metabolism

Main research activities

We are interested in the regulation of metabolism and especially in the molecular mechanisms regulating insulin action in human skeletal muscle. As a main research model, we are using primary muscle cell cultures, established from muscle biopsies obtained from clinically carefully characterized volunteers. We analyze mechanisms predisposing and leading to insulin resistance and seek novel ways to improve insulin action. We have a variety of in vitro methods to study cell metabolism at our disposal.

Finland-United States Investigation of NIDDM Genetics (FUSION) is an international multi-organizational collaborative project, the main goal of which is to identify genetic risk factors that predispose to T2D and related intermediate traits. We collaborate closely with the FUSION study, with the head of the group, Docent Heikki Koistinen being one of the FUSION PIs.

As part of FUSION, we have participated in large collaborative effort to study the genetic background of postprandial insulin resistance and we have identified 9 candidate genes associated with insulin-stimulated glucose disposal (Williamson et al., 2023).

As part of the ongoing genetic analyses of the FUSION and METSIM (Metabolic Syndrome in Men) studies, we have identified a missense variant p.P50T/AKT2, which is specific to Finns (MAF = ~1%) and very rare in non-Finnish Europeans. This variant of insulin signaling target AKT2 is associated with higher fasting insulin concentrations and predisposes to type 2 diabetes (T2D). We have established an internationally unique and the largest collection of primary muscle cell cultures from carriers of the Finnish p.P50T/AKT2 variant, and we have demonstrated a large-scale impairment in insulin signaling in myotubes from variant carriers (Mäkinen et al., 2023).

In a collaboration with the Dasman Diabetes Institute, analysis of whole exome sequencing data revealed *SLC17A1*, *SLC17A3*, *TATDN2* and *TMEM131L* as novel candidate genes in familial type 1 diabetes in Kuwait (Hedda et al., 2023).



Heikki Koistinen
M.D., Dr.Med.Sci., Docent, Head

Group members

Sreesha Sree, Ph.D.
Selina Mäkinen, Ph.D.
Leena Kinnunen, Ph.C.
Henric Kultalahti, M.B.

External funding

Finnish Cultural Foundation
Jalmari and Rauha Ahokas Foundation
Liv och Hälsa
Medical Society of Finland
Research Funding of Helsinki-Uusimaa Hospital District
(state funding for university-level health research)

Awards, honors, and positions of trust

Docent Heikki Koistinen: Svante Stenman prize 2023, Finska Läkaresällskapet (Medical Society of Finland) "som belöning för en framgångsrik och uppskattad gärning inom den svenskspråkiga medicinska undervisningen – for successful and valued medical teaching in Swedish language"; Vice-member of the Collegium of University of Helsinki; Member of the board of the Finnish Diabetes Research Society; Member of the Finnish JUFO panel (Publication Forum, Federation of Finnish Learned Societies), panel of Clinical Medicine.

Thesis completed in the group in 2023

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

Selina Mäkinen. Send in the signals: Studies on the mechanism of insulin resistance in human skeletal muscle. February 4, 2023.

The following Master's thesis supervised by Dr Koistinen (student not affiliated to Minerva) was accepted at the University of Helsinki this year:

Joel Selänne. Hyponatremia päivystäjän päänsärkynä (Hyponatremia as a headache for an ER-doctor).

Publications 2023

Hebbbar P, Nizam R, John SE, Antony D, Dashti M, Channanath A, Shaltout A, Al-Khandari H, **Koistinen HA**, Tuomilehto J, Alsmadi O, Thanaraj TA, Al-Mulla F. Linkage analysis using whole exome sequencing data implicates SLC17A1, SLC17A3, TATDN2 and TMEM131L in type 1 diabetes in Kuwaiti families. *Sci Rep*. 2023; 13:14978.

Li JH, Brenner LN, Kaur V, Figueroa K, Schroeder P, Huerta-Chagoya A; MAGIC Investigators (**Koistinen HA**); Diabetes Prevention Program (DPP) Research Group; Udler MS, Leong A, Mercader JM, Florez JC. Genome-wide association analysis identifies ancestry-specific genetic variation associated with acute response to metformin and glipizide in SUGAR-MGH. *Diabetologia*. 2023; 66:1260-1272.

Mäkinen S, Datta N, Rangarajan S, Nguyen Y, Olkkonen VM, Latva-Rasku A, Nuutila P, Laakso M, Koistinen HA. Finnish-specific AKT2 gene variant leads to impaired insulin signalling in myotubes. *J Mol Endocrinol*. 2023; 70:e210285.

Williamson A, Norris DM, Yin X, Broadaway KA, Moxley AH, Vadlamudi S, Wilson EP, Jackson AU, Ahuja V, Andersen MK, Arzumanyan Z, Bonnycastle LL, Bornstein SR, Bretschneider MP, Buchanan TA, Chang YC, Chuang LM, Chung RH, Clausen TD, Damm P, Delgado GE, de Mello VD, Dupuis J, Dwivedi OP, Erdos MR, Silva LF, Frayling TM, Gieger C, Goodarzi MO, Guo X, Gustafsson S, Hakaste L, Hammar U, Hatem G, Herrmann S, Højlund K, Horn K, Hsueh WA, Hung YJ, Hwu CM, Jonsson A, Kårhús LL, Kleber ME, Kovacs P, Lakka TA, Lauzon M, Lee IT, Lindgren CM, Lindström J, Linneberg A, Liu CT, Luan J, Aly DM, Mathiesen E, Moissl AP, Morris AP, Narisu N, Perakakis N, Peters A, Prasad RB, Rodionov RN, Roll K, Rundsten CF, Sarnowski C, Savonen K, Scholz M, Sharma S, Stinson SE, Suleman S, Tan J, Taylor KD, Uusitupa M, Vistisen D, Witte DR, Walther R, Wu P, Xiang AH, Zethelius B; Meta-Analysis of Glucose and Insulin-related Traits Consortium (MAGIC); Ahlqvist E, Bergman RN, Chen YI, Collins FS, Fall T, Florez JC, Fritsche A, Grallert H, Groop L, Hansen T, **Koistinen HA**, Komulainen P, Laakso M, Lind L, Loeffler M, März W, Meigs JB, Raffel LJ, Rauramaa R, Rotter JI, Schwarz PEH, Stumvoll M, Sundström J, Tönjes... Genome-wide association study and functional characterization identifies candidate genes for insulin-stimulated glucose uptake. *Nat Genet*. 2023; 55:973-983.

Preprints

Brotman SM, El-Sayed Moustafa JS, Guan L, Broadaway KA, Wang D, Jackson AU, Welch R, Currin KW, Tomlinson M, Vadlamudi S, Stringham HM, Roberts AL, Lakka TA, Oravilahti A, Silva LF, Narisu N, Erdos MR, Yan T, Bonnycastle LL, Raulerson CK, Raza Y, Yan X, Parker SCJ, Kuusisto J, Pajukanta P, Tuomilehto J, Collins FS, Boehnke M, Love MI, **Koistinen HA**, Laakso M, Mohlke KL, Small KS, Scott LJ. Adipose tissue eQTL meta-analysis reveals the contribution of allelic heterogeneity to gene expression regulation and cardiometabolic traits. *bioRxiv*. 2023 Oct 27:2023.10.26.563798. doi: 10.1101/2023.10.26.563798.

Varshney A, Manickam N, Orchard P, Tovar A, Zhang Z, Feng F, Erdos MR, Narisu N, Ventresca C, Nishino K, Rai V, Stringham HM, Jackson AU, Tamsen T, Gao C, Yang M, Koues OI, Welch JD, Burant CF, Williams LK, Jenkinson C, DeFronzo RA, Norton L, Saramies J, Lakka TA, Laakso M, Tuomilehto J, Mohlke KL, Kitzman JO, **Koistinen HA**, Liu J, Boehnke M, Collins FS, Scott LJ, Parker SCJ. Population-scale skeletal muscle single-nucleus multi-omic profiling reveals extensive context specific genetic regulation. *bioRxiv*. 2023 Dec 15:2023.12.15.571696. doi: 10.1101/2023.12.15.571696.

Associated group:

Neuronal signaling

Main research activities

We study trophic factors in neurodegenerative diseases with a 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 2023, we worked on three main areas of research.

USP14 and protein ubiquitination in neurodegenerative disorders and in cancer cells

Disturbances in protein homeostasis are associated with several human diseases, including cancer and neurodegenerative disorders (Lindholm et al., 2017; Ajoalabady et al., 2022). The deubiquitinating enzyme USP14 (Ubiquitin Specific Protease 14) is associated with the proteasome and is a major player in the control of proteostasis by influencing levels of protein ubiquitination and the activity of the proteasome (Srinivasan et al., 2020). USP14 is widely expressed in the brain and in neurons and has been linked to nerve cell signaling and neurological disorders. We previously observed that USP14 plays a role in clearing of mutant Htt protein aggregates by also binding to the ER protein, IRE1 α (Hyrskyluoto et al., 2014). We then showed that USP14 also plays a role in autophagy regulation in neuronal cells by affecting the autophagy flux and the autophagy-associated protein LC3B (Srinivasan et al., 2020). To reveal the protein targets and further biological roles of USP14, we deleted USP14 in neuroblastoma cells using CRISPR/Cas9 and discovered novel functions of USP14 in the regulation of mitochondria, oxidative stress and lysosomes (Srinivasan et al., Manuscript under review). Using quantitative mass spectrometry, we also noted that USP14 can undergo posttranslational phosphorylation in cells, and the significance of this will be studied more in the coming year.

In collaboration with Professor Kid Törnquist and Dr Yasir Asghar at Minerva, we have further studied the role of USP14 and its inhibition in tumor cells using thyroid cancer cells as a model. The first manuscript has been recently published (Srinivasan et al., 2023). We then noted that the thyroid cancers express different types of galectins, proteins involved in inflammation



Dan Lindholm, M.D., Dr.Med.Sci., Professor, Head

Group members

Dan Lindholm, M.D., Dr.Med.Sci., Professor, Head
Ove Eriksson, Ph.D., Docent
Elise Seynaeve, M.Sc.
Miriana Scordino M.Sc.
Vignesh Srinivasan, M.Sc.
Chiara Valencia M.Sc.
Urho Kere, Medical student

External funding

Finnish Society of Sciences and Letters
Magnus Ehrnrooth Foundation
Medical Society of Finland
Medicinska Understödsföreningen Liv och Hälsa r.f.
University of Helsinki, Doctoral Program in Biomedicine (DPBM)

and immune responses (Manuscript in preparation), and these will be studied further in collaboration with colleagues at Palermo University in Italy.

Neurotrophic factors in models of neurodegenerative diseases

ER stress is linked to the pathophysiology of neurodegenerative diseases including Huntington's disease (HD) (Lindholm et al., 2017) and, as recently also shown, Alzheimer's disease (Ajoalabady et al., 2022). Cerebral dopamine neurotrophic factor (CDNF) is a protein with a unique mechanism of action, mitigating ER stress, as demonstrated in models of Parkinson's disease (Voutilainen et al., 2015), and recently also in Amyotrophic Lateral Sclerosis (De Lorenzo et al., 2023). In collaboration, we have shown that CDNF has a protective role in striatal neurons against neurotoxin quinolinic acid by reducing ER stress (Stepanova et al., 2020), as well as in a genetic model for HD, the N171-82Q mice (Stepanova et al., 2023).

Alongside this, we are studying Canopy 2 (CNPY2), which is an ER-resident protein that we have cloned before. We have observed that overexpression of CNPY2 is neuroprotective, whilst its downregulation

renders neurons more prone to ER stress-mediated cell degeneration. CNPY2 is further expressed in striatal and cortical neurons in vivo in the neuronal circuitry regulating body movements and is altered in N171-82Q mice as a model of HD (manuscript under preparation). The regulation and mechanisms of action of CNPY2 in neurons are currently under investigation using different in vitro models as well as gene knock-out mice.

Altered immune response in acute neuropsychiatric patients

In an EU-funded collaboration with the University of Tartu, University of Linköping and Tallinn Technical University we have analyzed the immune response in blood samples of acute psychosis patients to reveal possible novel biomarkers for the disease. Data obtained using the multiplex proximity extension assay technique revealed significant changes in some pro-inflammatory cytokines in the blood of acute psychosis patients compared with controls. The levels of EN-RAGE were increased in the patients in particular, suggesting a role of blood neutrophils in the early stage of the disease. These results were recently published (Korhonen et al., 2023) followed by an invitation to write a review on the work behind the paper on the matter (Lindholm, 2023). We are currently collecting additional samples to study the role of EN-RAGE in acute psychosis and other neuropsychiatric disorders.

Awards, honors, and positions of trust

Professor Dan Lindholm: Chair of Biological Section in the Finnish Society of Sciences and Letters.

Publications 2023

- De Lorenzo F, Lüningschrör P, Nam J, Beckett L, Pilotto F, Galli E, Lindholm P, Rüdert von Collenberg C, Tii Mungwa S, Jablonka S, Kauder J, Thau-Habermann N, Petri S, Lindholm D, Saxena S, Sendtner M, Saarma M, Voutilainen MH. CDNF rescues motor neurons in models of amyotrophic lateral sclerosis by targeting endoplasmic reticulum stress. *Brain*. 2023; 146:3783-3799.
- Korhonen L, Paul ER, Wählén K, Haring L, Vasar E, Vaheri A, Lindholm D. Multivariate analyses of immune markers reveal increases in plasma EN-RAGE in first-episode psychosis patients. *Transl Psychiatry*. 2023; 13:326.
- Reigada D, Maza RM, Muñoz-Galdeano T, Barreda-Manso MA, Soto A, Lindholm D, Navarro-Ruiz R, Nieto-Díaz M. Overexpression of the X-linked inhibitor of apoptosis protein (XIAP) in neurons improves cell survival and the functional outcome after traumatic spinal cord injury. *Int J Mol Sci*. 2023; 24:2791.
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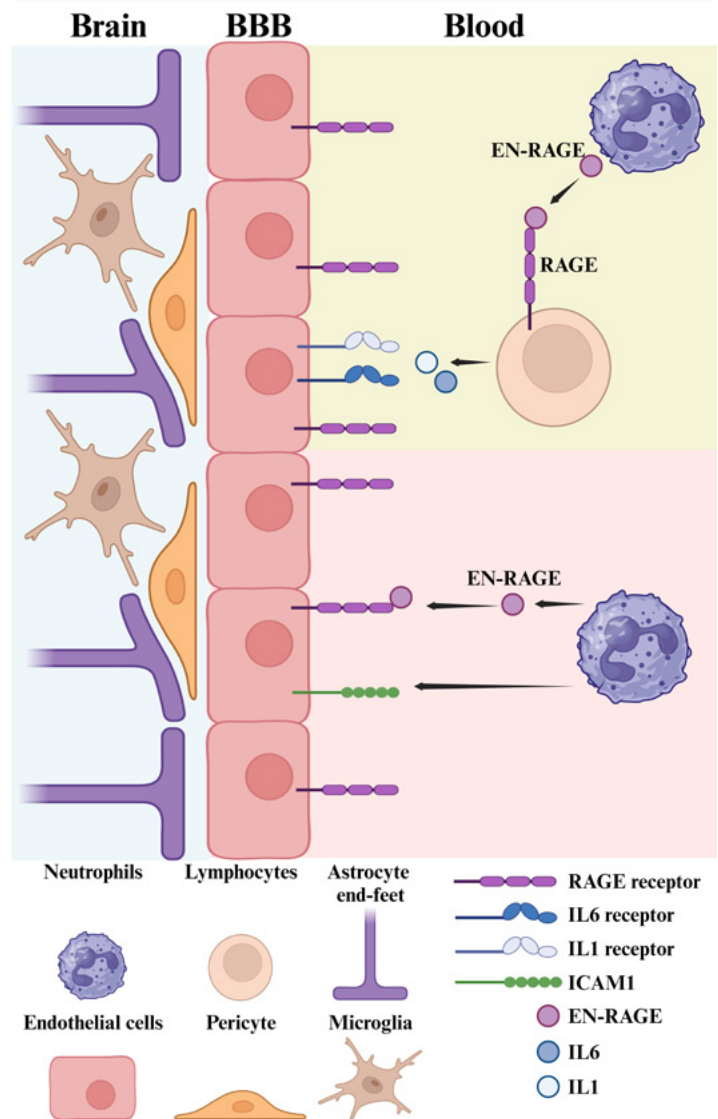


Figure. Graphical abstract of the publication by Korhonen et al in Translation Psychiatry.

EN-RAGE is produced by neutrophils and acts on adjacent lymphocytes via its receptor RAGE. This causes an increase cytokines such as IL-6 and IL-1 that act on the blood-brain barrier (BBB). Endothelial cells respond to EN-RAGE by increases in adhesion molecules like ICAM-1 that leads to an enhanced recruitment of neutrophils and their transmigration into brain tissue contributing to cell responses in acute psychosis.

The figure is a courtesy by Dr. Vignesh Srinivasan.

Publications 2023

Original articles

1. Bouslama R, Dumont V, Lindfors S, Paavolainen L, Tienari J, Nisen H, Mirtti T, Saleem MA, **Gordin D**, Groop PH, Suetsugu S, Lehtonen S. Phosphorylation of PACSIN2 at S313 regulates podocyte architecture in coordination with N-WASP. *Cells*. 2023; 12:1487.
2. Canivet CM, Zheng MH, **Qadri S**, Vonghia L, Chuah KH, Costentin C, George J, Armandi A, Adams LA, Lange NF, Blanchet O, Moal V, Younes R, Roux M, Chan WK, Sturm N, Eslam M, Bugianesi E, Wang Z, Dufour JF, Francque S, **Yki-Järvinen H**, Zheng KI, Boursier J. Validation of the blood test MACK-3 for the noninvasive diagnosis of fibrotic NASH: an international study with 1,924 patients. *Clin Gastroenterol Hepatol*. 2023; 21:3097-3106.e10.
3. **Chaurasiya V**, **Pham DD**, Harju J, Juuti A, Penttilä A, **Emmagouni SKG**, Nguyen VD, Zhang B, **Perttunen S**, Keskitalo S, Zhou Y, Pietiläinen KH, **Haridas PAN**, **Oikkonen VM**. Human visceral adipose tissue microvascular endothelial cell isolation and establishment of co-culture with white adipocytes to analyze cell-cell communication. *Exp Cell Res*. 2023; 433:113819.
4. Chen H, Lu C, Tan Y, Weber-Boyyat M, Zheng J, Xu M, Xiao J, Liu S, Tang Z, Lai C, Li M, **Oikkonen VM**, Yan D, Zhong W. Oculocerebrorenal syndrome of Lowe (OCRL) controls leukemic T-cell survival by preventing excessive PI(4,5)P₂ hydrolysis in the plasma membrane. *J Biol Chem*. 2023; 299:104812.
5. Coassolo L, Liu T, Jung Y, Taylor NP, Zhao M, Charville GW, Nissen SB, **Yki-Järvinen H**, Altman RB, Svensson KJ. Mapping transcriptional heterogeneity and metabolic networks in fatty livers at single-cell resolution. *iScience*. 2022; 26:105802.
6. De Lorenzo F, Lüningschrör P, Nam J, Beckett L, Pilotto F, Galli E, Lindholm P, Rüdert von Collenberg C, Tii Mungwa S, Jablonka S, Kauder J, Thau-Habermann N, Petri S, **Lindholm D**, Saxena S, Sendtner M, Saarma M, Voutilainen MH. CDNF rescues motor neurons in models of amyotrophic lateral sclerosis by targeting endoplasmic reticulum stress. *Brain*. 2023; 146:3783-3799.
7. Dumesnil C, **Vanharanta L**, Prasanna X, Omrane M, Carpentier M, Bhapkar A, Enkavi G, **Salo VT**, Vattulainen I, **Ikonen E**, Thiam AR. Cholesterol esters form supercooled lipid droplets whose nucleation is facilitated by triacylglycerols. *Nat Commun*. 2023; 14:915.
8. Eriksson MI, Syreeni A, Sandholm N, Dahlström EH, **Gordin D**, Tatlisumak T, Putaala J, Groop PH, Martola J, Thorn LM; FinnDiane Study Group. Haptoglobin genotype and its relation to asymptomatic cerebral small-vessel disease in type 1 diabetes. *Acta Diabetol*. 2023; 60:749-756.
9. Föhr T, Waller K, Viljanen A, Rantanen T, Kaprio J, **Ollikainen M**, and Sillanpää E. Mortality associations with DNA methylation-based biological aging and physical functioning measures across a 20-year follow-up period. *J Gerontol A Biol Sci Med Sci*. 2023; 78:1489-1496.
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