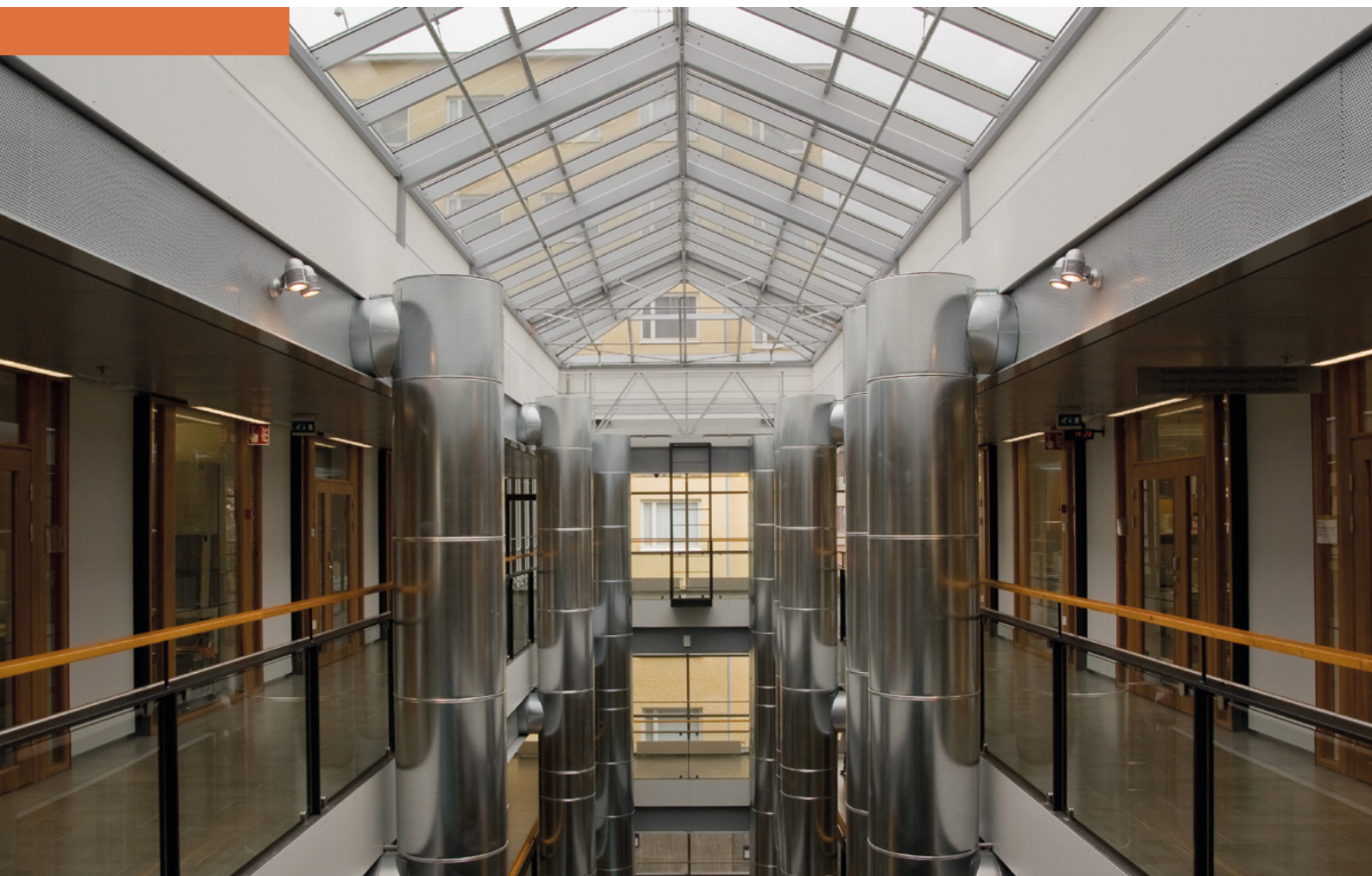




Minerva Foundation &
Minerva Foundation Institute
for Medical Research

Scientific Report





Front page Image: ER labelling of COS-7 cells (pseudo-colored).
Courtesy of Xin Zhou (Membrane biology).

Minerva Foundation
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BIOMEDICUM Helsinki 2U
Tukholmankatu 8
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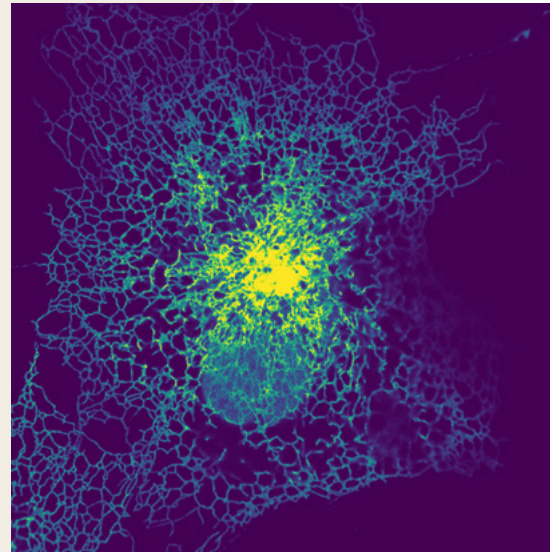
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Summary of research and activities in 2024

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, nonalcoholic 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 2024 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 €1 211 128 during 2024 and cover 55% of the Institute's budget. During 2024, a total of 68 articles were published, 55 of which were original articles in international peer-reviewed journals. The median impact of all the published articles was 5.5. Moreover, five students at the Institute, Suneeta Narumanchi, Michelle Renlund-Vikström, Taru Knuutinen, Juuso Taskinen, and Vignesh Srinivasan defended their doctoral theses in 2024. The Institute hosted three international special seminars (Prof. Dimitris Beis, Univ. of Ioannina, Greece; Prof. Peter Conlon, Beaumont Hospital, Dublin, Ireland; Dr. Veijo Salo, EMBL, Heidelberg, Germany).

During the spring of 2024, the Institute was subject to an external evaluation carried out by an international panel with five members. The results are being implemented to enhance the quality and effectiveness of the Institute's research. Furthermore, a project aimed at increasing the public visibility of the Institute was continued: New web pages for the Institute were published in January 2024, and during the year, special attention was focused on reporting significant events in the Institute's research groups on the web pages and as press releases. Major events included the awarding of the Novo Nordisk Foundation's prestigious Jacobaeus prize to a senior researcher at the Institute, professor Hannele Yki-Järvinen, and the nomination of a Minerva group leader, docent Heikki Koistinen, as professor of internal medicine at the Faculty of Medicine, University of Helsinki.

To summarize: The Institute thrived in 2024 both scientifically and financially, continued its work toward its strategic goals, and moves into 2025 with optimism and determination.

Events at Minerva 2024

Minerva Seminars

Biomedicum Helsinki

June 6, 2024

Associate professor

DIMITRIS BEIS

University of Ioannina, Greece

Zebrafish models of human disease

August 15, 2024

Professor

PETER CONLON

Beaumont Hospital, Dublin, Ireland

Inherited kidney disease and the Irish Kidney

Gene Project

August 22, 2024

Postdoctoral fellow

VEIJO SALO

EMBL, Heidelberg, Germany

Exploring organelle biogenesis with correlative

in situ cryo-electron tomography

Prizes and Grants

**MEDIX PRIZE OF THE MINERVA
FOUNDATION**

Award Ceremony and Prize Lecture,
October 7, 2024

The winning article: Single-cell functional genomics reveals determinants of sensitivity and resistance to natural killer cells in blood cancers. *Immunity*. 2023; 56:2816-2835.e13.

Authors: Dufva O, Gandolfi S, Huuhtanen J, Dashevsky O, Duàn H, Saeed K, Klievink J, Nygren P, Bouhlal J, Lahtela J, Näätänen A, Ghimire BR, Hannunen T, Ellonen P, Lähteenmäki H, Rumm P, Theodoropoulos J, Laajala E, Härkönen J, Pölönen P, Heinäniemi M, Hollmén M, Yamano S, Shirasaki R, Barbie DA, Roth JA, Romee R, Sheffer M, Lähdesmäki H, Lee DA, De Matos Simoes R, Kankainen M, Mitsiades CS, Mustjoki S.

Read more on page 6–8

RALPH GRÄSBECK GRANT FOR RESEARCH IN LABORATORY MEDICINE

Kim Daehong, PhD

University of Zurich, Switzerland

*Decoding the language of immune landscape on
the acute GvHD*

Read more on page 9.

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

From Selma and Maja-Lisa Selander's fund 22 grants were
awarded 2024, in all € 120 000.

The following theses were accepted at
the University of Helsinki, University of
Jyväskylä and Åbo Akademi University
in 2024:

DOCTORAL THESES

Anna Kankaanpää: Genetic and environmental influences
on biological ageing across different ages – Epigenetic
clocks as markers of biological ageing. April 19, 2024.

Essi Karikoski: Counselling to improve oral health
behavior in young children with major congenital heart
defects. January 19, 2024.

Suneeta Narumanchi: Septin7b and let-7c modulate
cardiac function and regeneration in zebrafish. June 5,
2024.

Michelle Renlund-Vikström: Cardiovascular health in
preadolescent children following in-utero exposure to pre-
eclampsia. June 7, 2024.

Taru Knuutinen: The importance of calcium channels in
thyroid cancer. September 27, 2024.

Juuso Taskinen: The role of endoplasmic reticulum
membrane contact sites in human endothelial cells.
October 4, 2024.

Vignesh Srinivasan: Novel roles of the protein
deubiquitinase USP14 in proteostasis regulation and cell
stress responses. October 11, 2024.

MASTER'S THESES

Teodóra Faragó: Smoking status classification based on
EPIC methylation array data.

Erika Saari. The role of the peroxisomal plasmalogen
biosynthesis pathway in cholesterol homeostasis.

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 to December 31, 2024.

During this period, the following persons served as
trustees:

Board of Trustees

Professor Caj Haglund, chair

M.Sc. (Econ. & Bus. Adm.) Kim Karhu, vice chair

Professor Patrik Finne

Professor Per-Henrik Groop

M.Sc. (Econ. & Bus. Adm.) Peter Immonen

Scientific Committee

Professor Per-Henrik Groop, chair

Professor Tom Böhlting

Professor Patrik Finne

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Docent Suvi Silén

Docent Carina Wallgren-Pettersson

Financial Committee

M.Sc. (Econ. & Bus. Adm.) Kim Karhu, chair

M.Sc. (Econ. & Bus. Adm.) Peter Immonen

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Professor Caj Haglund

Agent for Minerva Foundation

M.Sc. (Econ. & Bus. Adm.) Patrik Lerche

The Minerva Foundation Institute for Medical Research

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Professor Vesa Olkkonen, chair

Docent Daniel Gordin

Docent Pirta Hotulainen

Professor Elina Ikonen

Professor Heikki Koistinen

Docent Päivi Lakkisto

Professor Dan Lindholm

Docent Panu Luukkonen

Docent Miina Ollikainen

Docent Taisto Sarkola

M.Sc. Cia Olsson

Medix prize of the Minerva Foundation – Killer cells to combat blood cancers

Natural killer (NK) cells circulate in the body, scan cancerous cells, detect and destroy them. Some cancer cells, however, are able to escape NK cells. This escape mechanism has, until now, been unknown. A research group from the University of Helsinki has studied and identified these mechanisms in their research on blood cancers. The findings allow the development of new cancer treatments.

The article on the findings of the research group has been awarded this year's Medix prize. The article was published in the prestigious international journal *Immunity*. The prize is worth € 20 000.

The international research group is headed by lead researcher, Professor of Translational Hematology **Satu Mustjoki** from the Faculty of Medicine at the University of Helsinki and the Comprehensive Cancer Centre of Helsinki University Hospital. The main authors of the article were Postdoctoral Researchers **Olli Dufva** and **Sara Gandolfi**.

Genetic scissors in operation

Today, some blood cancers can be treated by means of immunotherapy, in which the T cells of the patient's immune system are activated to recognise and attack cancer cells. CAR T-cell therapy, for example, has changed the treatment models for certain blood cancers, such as leukaemias and cancers of the lymphoid tissue.

According to Professor Satu Mustjoki, these therapies are not effective in all patients with blood cancer. They can in fact have very severe side effects. Solutions are therefore being sought from amongst other cell types of the immune system.

The use of NK cells does not entail similar side effects. Natural killer cells are already being experimented on in patients in clinical trials. However, up until now we have not known the underlying mechanism of how certain cancer cells manage to evade killer cell activity and how this evasion could be circumvented.

"Our research included genome-scale functional genomic screens using the genetic scissors technology. This means that we deleted the genes of blood cancer cells one by one and studied how the silencing and reactivation of the expression of each gene impacted on the killer cell's ability to destroy cancer cells," Professor Mustjoki says.

Using this method, the research group was able to identify new mechanisms for NK cell mediated cancer cell killing. They also discovered with single-cell sequencing method that different blood cancer cell types activate NK cells in different ways and therefore have varying sensitivity to natural killer cells.

According to Professor Mustjoki, the results of the research will help to develop new, better and individualised therapies for blood cancers.



Head of the research team and lead researcher, Professor Satu Mustjoki. Photographer Juha Sarkkinen.



Photo above. Members of Professor Satu Mustjoki's research team. Photographer Juha Sarkkinen.

Photo below. The main authors of the awarded article Postdoctoral fellow Olli Dufva and Postdoctoral researcher Sara Gandolfi examining leukaemia cells by microscope at the cell culture laboratory. Photographer Juha Sarkkinen.



Chairman of the Board of the Minerva Foundation, Professor Caj Haglund, head of the research team and lead researcher Professor Satu Mustjoki, Postdoctoral researcher Sara Gandolfi and Vice-Rector for Research, Doctoral Education and Sustainability at University of Helsinki, Professor Anne Portaankorva. Photographer Juha Sarkkinen.

Donated by the Minerva Foundation, awarded by the University of Helsinki

The Medix Prize is an important annual award for internationally high-level Finnish medical research. The Medix Prize is, in a manner of speaking, the Finnish championship for biomedicine. This year's Medix Prize was awarded for the 37th time.

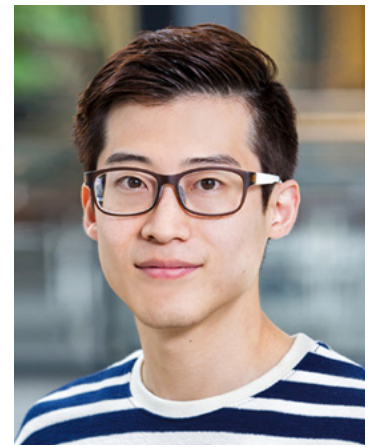
The Medix Prize is awarded by the University of Helsinki, and it is donated to the university by the Minerva Foundation. Minerva Foundation funds the Minerva Foundation Institute for Medical Research at Biomedicum Helsinki.

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 awardee 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.

Ralph Gräsbeck Grant for Research in Laboratory Medicine

The 2024 Ralph Gräsbeck Grant for Research in Laboratory Medicine has been awarded to PhD **Daehong Kim** at the University of Zurich, Institute of Experimental Immunology, Switzerland. The Ralph Gräsbeck scholarship was granted to Kim for his research *“Decoding the Language of Immune Landscape on the Acute GvHD.”*



Postdoctoral researcher Daehong Kim.

This year's Ralph Gräsbeck grant will support pioneering research aimed at unraveling the complexities of acute graft-versus-host disease (aGvHD) following allogeneic hematopoietic stem cell transplants (allo-HSCT).

Allo-HSCT remains the only curative option for various hematological cancers, yet aGvHD presents a major challenge, with a mortality rate of up to 70% within seven months of onset. Despite its severity, there are currently no effective treatments for aGvHD. The project seeks to address this critical gap by exploring the intricate relationship between genetic variants and immune system dysfunction in aGvHD.

Leveraging high-dimensional single-cell cytometry, the applicant has initiated a systemic characterization of immune cells in preclinical models of aGvHD. The study will investigate how genetic risk variants, identified through genetic array systems and associated with autoimmune GvHD, correlate with deep immune phenotypes in aGvHD

patients. Utilizing advanced computational tools, multiplexed tissue imaging, and single-cell spectral flow cytometry, the research aims to reveal functional associations of these genetic mutations.

The outcomes of this research will provide invaluable insights into the pathogenesis of aGvHD and could pave the way for novel therapeutic targets, ultimately guiding the development of disease-modifying treatments. This project represents a significant stride toward improving patient outcomes and understanding the immune mechanisms underlying aGvHD.

The Ralph Gräsbeck Grant is awarded every other year for a scientist who has defended his/her doctoral thesis during the past seven years in the field of laboratory medicine and continued innovative and high-quality research in the same field. The amount of the grant is € 10 000 and this is the fourth time the grant is awarded.

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

Ralph Gräsbeck achieved his M.D. degree in 1952 at the remarkably young age of 22. His career continued in the Fourth Department of Internal Medicine at the University of Helsinki, where he was inspired by his chief and mentor, Professor Bertel von Bonsdorff, to study the physiology and pathophysiology of vitamin B12. This led to his M.D. thesis in 1956, in which he described the presence and vitamin B12 transporting function of 'intrinsic factor' in human gastric juice.

As a researcher, Ralph Gräsbeck is probably most famous for the discovery and analysis of Imerslund-Gräsbeck syndrome, which is part of the Finnish disease heritage. He made various observations with his colleagues about the metabolism of vitamin B12 – also called cobalamin – and its disorders. He also took part in the investigation of tapeworm-induced anemia. Moreover, he introduced the concept of reference value, which replaced the illogical concept of normal value.

In the 1950s, Gräsbeck worked as a biochemistry researcher at Johns Hopkins University, Baltimore, USA, and the Medical Nobel Institute (part of the Karolinska

Institute) in Stockholm. Gräsbeck was appointed lecturer (docent) in clinical chemistry at the University of Helsinki in 1959. He was head physician of the central laboratory at Maria Hospital from 1960 to 1990.

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

Ralph Gräsbeck was one of the founders of Minerva Foundation and Minerva Foundation Institute for Medical Research in 1959. He played a key role in the founding of the Medix clinical laboratory in 1964 and of the company Medix Biochemica in 1985. Gräsbeck was the director of the Institute from 1971 to 1993 and an active researcher at Minerva almost until his death. The Institute's research focuses on medically important maladies, such as diabetes, neurological disorders, cancer, and cardiovascular diseases.

Research groups

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. IgA Nephropathy (IgAN) in turn, has the highest prevalence of primary glomerulonephritis. We will study these diseases in a large (>550,000) patient-enriched sample of the Finnish population (finngen.fi). The goal of this study is to improve understanding of ADPKD and IgAN by assessing clinical and genetic tools, as well as systems biology. Tomas Visser and Matti Sentürk have initiated their Ph.D. thesis 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 Ph.D. thesis as part of this study.



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.

Matti Sentürk M.Bs.

Tomas Visser M.Bs.

Karoliina Ahtola, Research nurse

External funding

Academy of Finland

Medical Society of Finland (Finska Läkaresällskapet)

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

Docent Daniel Gordin: president of the Finnish Society of Hypertension

Selected publications 2024

Adeshara K, et al. Protein glycation products associate with progression of kidney disease and incident cardiovascular events in individuals with type 1 diabetes. *Cardiovasc Diabetol.* 2024; 23:235.

Adeshara K, et al. Altered oxidant and antioxidant levels are associated with vascular stiffness and diabetic kidney disease in type 1 diabetes after exposure to acute and chronic hyperglycemia. *Cardiovasc Diabetol* 2024; 23:350.

Gordin D, et al. A sham-controlled randomised pilot trial on baroreflex activation therapy in patients with resistant hypertension: What will the future hold? *Blood Press.* 2024; 33:2417887.

Gordin E, et al. A clinical study on urinary clusterin and Cystatin B in dogs with spontaneous acute kidney injury. *Vet Sci.* 2024; 11:200.

Inkeri J, et al. No correlation between carotid intima-media thickness and long-term glycemic control in individuals with type 1 diabetes. *Acta Diabetol.* 2024; 61:441-449. *Equal contribution.

Kostiainen I, et al. Value of repeat 5-HIAA measurements as a predictor of carcinoid heart disease: A prospective 5-year follow-up study in patients with small intestinal neuroendocrine tumors. *Cancers (Basel).* 2024; 16:3896.

Simonsen JR, et al. Sham-controlled randomized pilot trial on baroreflex activation therapy in resistant hypertension. *Hypertension.* 2024; 81:e91-e93.

Tarkkonen A, et al. Retinal artery to vein ratio is associated with cerebral microbleeds in individuals with type 1 diabetes. *J Hypertens.* 2024; 42:1039-1047.

van Raalte DH, et al. Combination therapy for kidney disease in people with diabetes mellitus. *Nat Rev Nephrol.* 2024; 20:433-446.

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. The FINNCARE project (A lifestyle intervention for families with a history of pre-eclampsia – primary prevention of cardiovascular disease; NCT04676295) study visits were completed in 2023 and the project is now in the data analysis and manuscript writing phase.

Two articles from FINNCARE with PhD student Michelle Renlund-Vikström as first author have been published. The first article showed that heart rate variability in pre-eclampsia exposed children is not altered in prepuberty, and elevated systolic blood pressure following pre-eclampsia exposure is not related to heart rate variability. Child adiposity could, however, be related to decreased cardiac vagal tone. The second article showed that preadolescent pre-eclampsia exposed children display a more globular-shaped right ventricle with higher longitudinal systolic displacement, as well as mildly altered diastolic indices, with the alterations being pronounced in early-onset pre-eclampsia. Lean body mass and adiposity are independently related to left ventricular mass and left atrial volume, and systolic blood pressure with left ventricular mass in both pre-eclampsia exposed and non-exposed children. These unfavorable associations indicate remodeling of the cardiac structure in young children also being reflected in mild functional changes in pre-eclampsia exposed children. Taken together, these adverse associations in arterial health may reflect the early progression of cardiovascular disease in pre-eclampsia exposed children. In June 2024, M.D. Michelle Renlund-Vikström (supervised by Taisto Sarkola) defended her Ph.D. thesis, which was approved with honors at the Medical Faculty at the University of Helsinki. Medical students Laura Biskop and Laura Hytönen continued working on their Master's theses within the FINNCARE project. During the year, M.D. Anna Savolainen started as a new Ph.D. student in the FINNCARE project. A Ph.D. student mini seminar was arranged with the Daniel Gordin group in April 2024 at Minerva.



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

Group members

My Blomqvist, D.D.S., Dr.Med.Sci.
Essi Karikoski, M.Sc., Ph.D. in spring 2024
Michelle Renlund-Vikström, M.D., Dr.Med.Sci. in summer 2024
Mari Ylinen, M.D., Dr.Med.Sci.
Anna Savolainen, M.D.
Laura Biskop, Medical student
Karita Hyvönen, Medical student
Maria Finne, M.Sc., Research coordinator

External funding

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

Essi Karikoski defended her Ph.D. thesis in January 2024 within the ORALPEDHEART study (NCT03329170), supervised by My Blomqvist and co-supervised by Taisto Sarkola. Both Essi Karikoski and My Blomqvist continued their work within the projects in the autumn of 2024.

Within the ADEF Helsinki (Alcohol/Drugs Exposure during Fetal life) consortium collaboration, one article was published showing that hospital care for injury and poisoning is more common in youth with prenatal drug exposure and is largely explained by the related postnatal child and maternal factors. The study suggests that long-term support to families with maternal substance abuse problems could prevent injury and poisoning in the vulnerable child population.

In May 2024, Taisto Sarkola started as chair of the European society AEPC Fetal Cardiology working group council for a three-year period (2024–2027). In September 2024, Taisto Sarkola started as Editor of the ISUOG journal *Ultrasound in Obstetrics and Gynecology* (impact factor 6.1) for a three-year period (9/2024–8/2027) covering fetal cardiology.

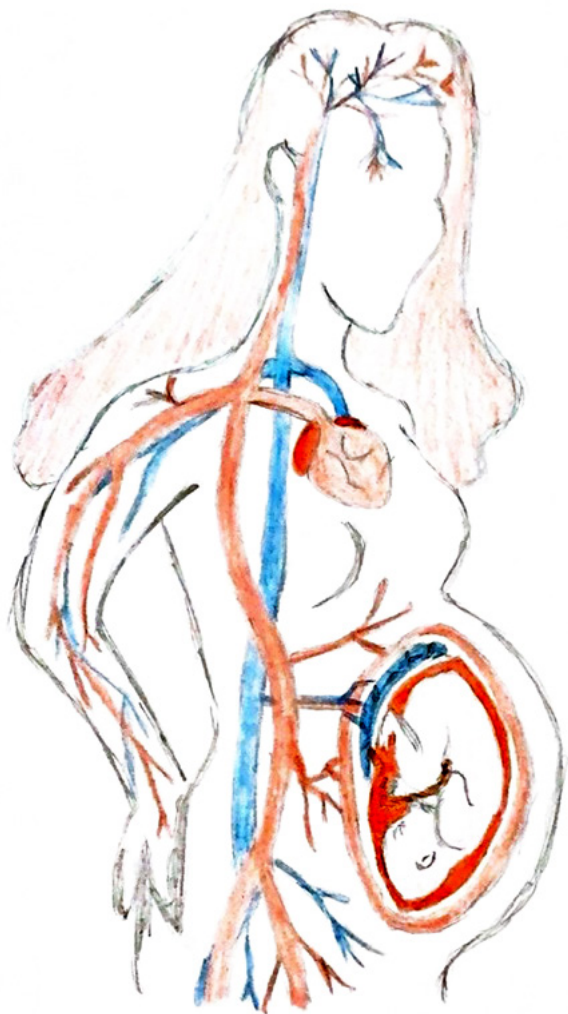


Figure. Front cover from Michelle Renlund-Vikström Dr.Med.Sci -Thesis "Cardiovascular health in preadolescent children following in-utero exposure to pre-eclampsia", defence June 7, 2024. Doctoral dissertation was approved with honors by the University of Helsinki Faculty of Medicine.

<https://helda.helsinki.fi/server/api/core/bitstreams/cb71e552-7c9c-45d6-bd41-135acd780bb7/content>

Awards, honors, and positions of trust

Docent Taisto Sarkola: Ultrasound in Obstetrics and Gynecology, Editor (fetal cardiology) 9/2024–8/2027; Pre-examiner of two PhD thesis at the Medical Faculty in Lund/Sweden (Dr Katrin Fricke and Dr Michael J Lewis) and one PhD thesis at the Medical Faculty in Tampere/Finland (Dr Asta Uusitalo); Positions of trust in the following organizations: AEPC/Fetal Cardiology working group council chair 2024–2027 Finnish Medical Ultrasound Society, member of the board 2020–Gyllenberg foundation, member of the board 2023–Scandiatransplant pediatric heart and lung group member 2020–

Theses completed in the group in 2024

The following doctoral thesis supervised by Taisto Sarkola (student not affiliated to Minerva) was accepted at the University of Helsinki this year:

Essi Karikoski: Counselling to improve oral health behavior in young children with major congenital heart defects. January 19, 2024.

The following doctoral thesis (student affiliated to Minerva) was accepted at the University in Helsinki this year:

Michelle Renlund-Vikström: Cardiovascular health in preadolescent children following in-utero exposure to pre-eclampsia. June 7, 2024.

Publications 2024

Koponen AM, Gissler M, Nissinen NM, Autti-Rämö I, Kahila H, **Sarkola T.** Cumulative risk factors for injuries and poisoning requiring hospital care in youth with prenatal substance exposure: A longitudinal controlled cohort study. *Nordisk Alkohol Nark.* 2024; 41:156–174.

Koponen AM, Nissinen NM, Gissler M, Autti-Rämö I, Kahila H, **Sarkola T.** Sikiöaikana päihteille altistuneet lapset aikuisuuden kynnyksellä – Yhteenveto ADEF Helsinki –tutkimusprojektin tuloksista. *Sosiaalilääketieteellinen aikakauslehti.* 2024; 61:323–335.

Renlund M, Tulppo MP, Kivelä A, Laivuori H, Heinonen S, Jääskeläinen T, **Sarkola T.** Preeclampsia-exposed children's heart rate variability 8–12 yr after index pregnancy: FINNCARE study. *Am J Physiol Heart Circ Physiol.* 2024; 326:H74–H81.

Renlund-Vikström M, Jääskeläinen TJ, Kivelä A, Heinonen S, Laivuori H, **Sarkola T.** Cardiac structure and function in 8- to 12-year-old children following in-utero exposure to preeclampsia (FINNCARE Study). *J Am Heart Assoc.* 2024; 13:e034494.

Sarkola T, Lipsanen-Nyman M, Jalanko H, Jokinen E. Vascular structure and stiffness in pediatric Mulibrey nanism using ultra-high frequency ultrasound. *Veins and Lymphatics.* 2023; 12:11826.

Cardiovascular research

Main research activities

Our 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 noncoding RNAs in the development and progression of heart failure. The main projects worked on during 2024 are presented below.

New molecular mechanisms and biomarkers of 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 the 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 2024, we have continued this project by investigating how specific long noncoding RNAs and microRNAs (miRNAs) regulate these key molecules and pathways, and thus the development and progression of heart failure. In these functional studies, we use human cardiac cell cultures and zebrafish heart failure models.

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, with in-hospital mortality 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 Prof. Lina Badimon, we have shown that elevated plasma miR-619-5p predicts the development of cardiogenic shock and mortality



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

Group members

Ilkka Tikkanen, M.D., Dr.Med.Sci., Professor
Mika Laine, M.D., Dr.Med.Sci., Docent
Chunguang Wang, M.D., Dr.Med.Sci., Docent
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Suneeta Narumanchi, M.Sc., Ph.D. in spring 2024
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External funding

Aarne Koskelo Foundation
Finnish Foundation for Cardiovascular Research
Finnish Foundation for Laboratory Medicine
Finnish Society of Clinical Chemistry
Medical Society of Finland (Finska Läkaresällskapet)
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Paulo Foundation
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Päivikki and Sakari Sohlberg Foundation

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

During 2024, our group participated in the COST Action AtheroNET (CA21153), the Network for implementing multiomic approaches in atherosclerotic cardiovascular disease prevention and research, in which Päivi Lakkisto served as a member of the management committee.

Molecular mechanisms of cardiac regeneration

We use zebrafish models to study the molecular mechanisms of heart failure. Unlike humans, zebrafish are capable of fully regenerating their hearts and restoring cardiac function following injury, making them an excellent model for investigating factors that regulate the development and recovery of heart failure. During 2024, we have been working on zebrafish transcriptomics data to identify and validate the functions of noncoding RNAs that regulate cardiac regeneration after injury.

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 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 an HO-1 knockout zebrafish line using CRISPR/Cas9 technology. We observed that *hmx1a* deficiency leads to cardiac fibrosis and dysfunction, as well as impaired cardiac response to stress. According to our results, HMOX1 homeostasis is essential for maintaining cardiac function, and targeting the HMOX1 pathway is a potential novel strategy for cardiac therapeutics.

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.

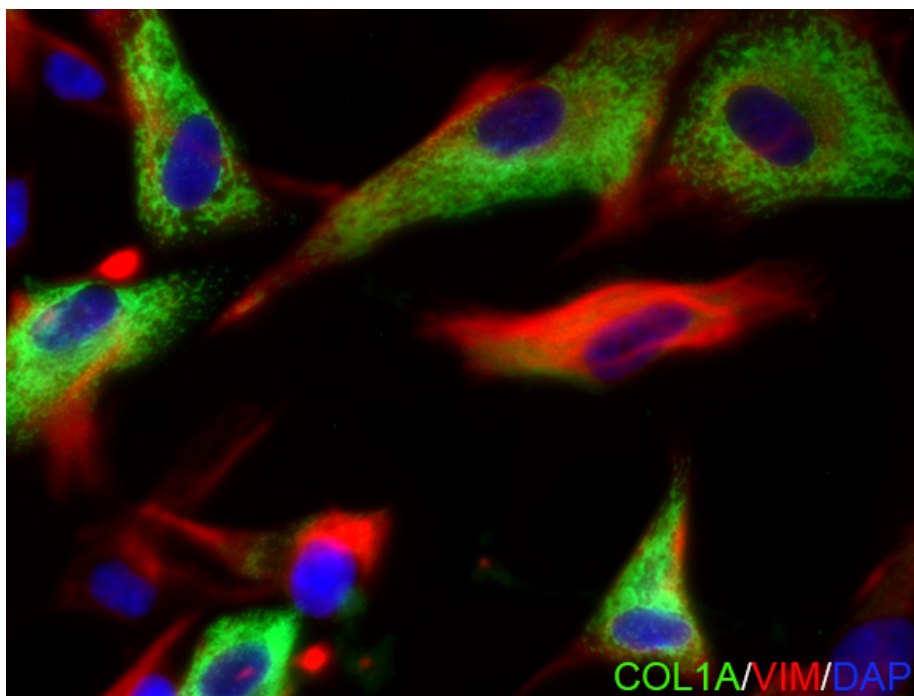


Figure. Immunostaining of human primary cardiac fibroblasts for Vimentin and Collagen 1A. COL1A, Collagen 1A; VIM, Vimentin; DAPI, 4',6-diamidino-2-phenylindole (courtesy of Hong Wang).

Thesis completed in the group in 2024

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

Suneeta Narumanchi: Septin7b and let-7c modulate cardiac function and regeneration in zebrafish. June 5, 2024.

Publications 2024

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Cellular neuroscience

Main research activities

The main focus areas of the cellular neuroscience group have been brain development, learning, and structural plasticity. This year, we started a new project which elucidates long-term effects of transient, peripheral inflammation on the brain. In this project, we are interested to know what the long-term consequences of the peripheral inflammation for learning and memory are and which cells in the brain contribute to these changes.

The group has had a specific interest in two neuronal structures: dendritic spines and the 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 the 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 the structure of the AIS. Research in recent years has elucidated the mechanisms of actin cytoskeleton regulation in dendritic spines and the AIS, in health and disease. Methodologically, the group ranges from molecules to animal behavior, and our strengths lie in microscopy techniques.

Regulation of dendritic spine initiation

Spine initiation factors are proteins, which interact with the plasma membrane and actin cytoskeleton in order to push out the first protrusion from the neuronal dendrite. Spine initiation is the first step in spine morphogenesis and 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 the changes in neural networks in health and disease.

So far, we have identified two spine initiation factors (MIM (Saarikangas et al., 2015) and Gas7 (Khanal et al., 2023)) and the Soderling lab has identified 1 (srGAP3 (Carlson et al., 2011)). This year, Aqsa Jabeen continued the work started by Pushpa Khanal to characterize the expression pattern and function of a close MIM-homologue called ABBA.



Pirta Hotulainen, Ph.D., Docent, Head

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David Micinski, M.Sc.
Emilia Toissalo, M.Sc.
Jaan Korpikoski, M.Sc.

External funding

Medicinska Understödsföreningen Liv och Hälsa r.f.
Sigrid Jusélius Foundation
University of Helsinki, Doctoral Education Pilot (Jaan Korpikoski)

While we are starting to understand the molecular mechanism of how initiation factors push the first protrusion out (Khanal and Hotulainen, 2021), we still have poor understanding on how spine initiation factors are regulated. To clarify the possible signaling cascade from neuron activation to increased spine density, we have been testing how neuron activity and compounds such as BDNF affect spine initiation factor expression using organotypic rat hippocampal brain slices. One possibility for regulating spine initiation factor expression is regulation via micro-RNAs. So far, we have identified one miRNA which down-regulates the expression of Gas7 and MIM.

Regulation of axon initial segment plasticity

While dendritic spines have been the major focus of this group, two PhD students in the group have studied actin regulation in the axon initial segment (AIS). This segment contains a high density of ion channels, and with these ion channels it controls the initiation of action potentials. The first AIS study showed that actin filaments are crucial for the maintenance of the high order of AIS proteins (Abouelezz et al., 2020).

The AIS is also capable of large-scale relocation in an activity-dependent manner. This represents a form of homeostatic plasticity in which neurons regulate their own excitability by changing the size and/or position of the AIS. While AIS plasticity is important for proper functionality of AIS-containing neurons, the cellular and molecular mechanisms of AIS plasticity are poorly understood. David Micinski, who continued the AIS work in the group after Amr Abouelezz, analyzed changes in the AIS actin cytoskeleton during AIS plasticity using structured illumination microscopy (SIM) imaging (Micinski and Hotulainen, 2024). In this study, we showed that the number of longitudinal actin fibers increased transiently 3 hours after plasticity induction. We further showed that actin polymerization, especially formin-mediated actin polymerization, is required for AIS plasticity and the formation of longitudinal actin fibers. These results indicate that active re-organization of the actin cytoskeleton is required for proper AIS plasticity. Two of Micinski's especially beautiful and high-quality SIM images were used as examples of SIM images in a review describing the super-resolution imaging of the neuronal cytoskeleton (Butler-Hallisey and Leterrier, 2024) (Figure).

Establishing a timeline for cellular changes in the central nervous system during and after transient peripheral inflammation

Inflammation is a process characterized by the activation of immune and non-immune cells that protect the host from pathogens or tissue injuries. While it is relatively clear that the presence of peripheral inflammation, either

acute or chronic, affects the brain (Tan et al., 2023), it is unclear whether resolved inflammation leaves lasting effects on the brain. It is known that virus infections, often causing severe inflammatory events, as well as severe sepsis, increase the risk of developing neurological disorders (Benros et al., 2011; Guerra et al., 2012; Benros et al., 2013; Levine et al., 2023). Thus, we hypothesized that severe inflammation leaves lasting effects on the brain that persist even after the visible symptoms of inflammation have subsided.

Currently, the duration of these effects and the specific changes in the brain are poorly known. Furthermore, it is unknown how these changes are maintained over time and whether they can be mitigated. Addressing these gaps in knowledge is critical for understanding how peripheral inflammation influences the brain. To explore these questions, we have established a rheumatoid arthritis (RA) mouse model called the collagen antibody-induced arthritis (CAIA) model. We will evaluate changes using behavioral analyses, imaging, cytokine measurements, and electrophysiology.

Awards, honors, and positions of trust

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

Publications 2024

Micinski D, Hotulainen P. Actin polymerization and longitudinal actin fibers in axon initial segment plasticity. *Front Mol Neurosci*. 2024; 17:1376997.

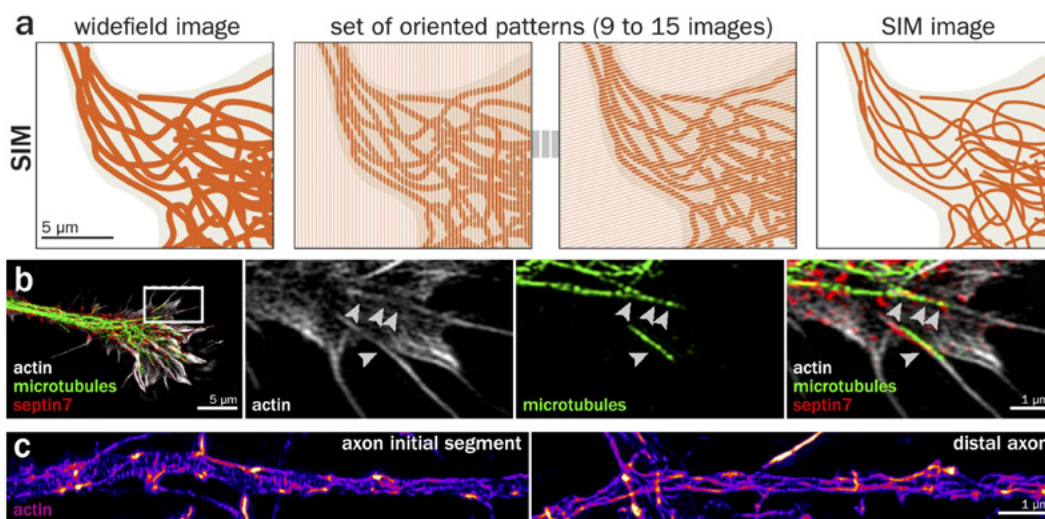


Figure: Structured illumination microscopy (SIM) of the neuronal cytoskeleton.

a) Principle of SIM: the labeled sample (microtubules in a neuron, left) is illuminated with a series of fringe patterns, varying the orientation and the phases (9–15 images total, middle). After processing, a two-fold improvement in image resolution is obtained (right). b) Growth cone of a cultured neuron fixed and stained for actin (gray), microtubules (green), and septin7 (red), imaged by 3D SIM. Right images are zooms of the box highlighted on the left image. Arrowheads point to a septin-positive bundle between actin filaments and microtubules. Adapted from Nakos et al., PNAS 2022. c) AIS (left) and distal axon (right) of cultured neurons fixed and stained for actin using phalloidin, imaged by 3D SIM. The periodic actin rings are clearly visible along the AIS but are more difficult to discern along the distal axon due to the presence of numerous longitudinal actin filaments. Adapted from Micinski and Hotulainen, 2024.

Figure reused from Butler-Hallisey, C., Leterrier, C. Super-resolution imaging of the neuronal cytoskeleton. *npj Imaging* 2, 50 (2024). <https://doi.org/10.1038/s44303-024-00054-y>

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 human diseases and traits. During 2024, we have continued our research linking mitochondrial biogenesis and epigenetics to obesity, and studies on 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. Further, we have explored the potential of multi-omics analyses in complex human traits.

We have previously demonstrated that epigenetic, transcriptomic and metabolomic profiling can identify unhealthy obesity. To further address obesity-related health risks, we studied DNA methylation in the development of type 2 diabetes (T2D) and its complications, and showed that DNA methylation may be useful marker for risk of T2D complications (Christiansen et al., EBioMed 2024). We continued to investigate the effect of metabolic syndrome (MetS) and its components on aging, and demonstrate that MetS is associated with accelerated aging, independent of physical activity, smoking, or alcohol consumption (Föhr et al., IJO 2024). However, the effect of genetics in the associations is rather strong.

Alterations in mitochondrial metabolism in obesity may indicate disrupted communication between mitochondria and nucleus, crucial for adapting to changing metabolic demands. Epigenetic modifications may influence the intricate interplay between these two. PhD student Aino Heikkinen has identified DNA methylation sites associated with mitochondrial biogenesis and investigated whether these methylation sites are linked to body composition, clinical biomarkers, physical activity, and biological aging, and explored the potential causal relationships. Her findings indicate that alterations in mitochondrial biogenesis precede obesity, and especially that mitochondrial biogenesis, insulin sensitivity, and certain body fat measures are causal to *SH3BP4* methylation and expression (Heikkinen et al., medRxiv 2024).

Postdoctoral researcher Tianyu Zhu has leveraged our multi-omics twin data to investigate the epigenetic and physiological mechanisms that may mediate polygenic risk for obesity and associated health risk as part of her newly funded project, entitled "Revolutionizing Obesity Risk Prediction: A Twin-based Evolutionary Approach". In collaboration with Group Kaprio, University of Helsinki, we have contributed to two rather technical studies involving multi-omics analyses in relation to cardiovascular traits. The first study provides a platform for researchers to evaluate how the choice of omics, ML classifiers, and dimension reduction can influence the quality of CVD risk factor predictions (Drouard et al., BMC Med Inform Decis Mak 2024). In the second study, we demonstrate how social behavior and especially sub-



Miina Ollikainen, Ph.D., Docent, Head

Group members

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Anna Kankaanpää, M.Sc.,
Ph.D. in spring 2024
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Volter Lukander, M.Sc.
Annika Oppenbeck, M.Sc.
Mia Urjansson, Research nurse

External funding

Sigrid Jusélius Foundation
Medicinska Understödsföreningen Liv
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EU H2020 MSCA-ITN-ETN
NIH/NIDA (National Institutes of
Health/National Institute on Drug
Abuse, USA)
The Cancer Foundation
The Emil Aaltonen Foundation
Yrjö Jahnsson Foundation
HiLIFE Joint Postdoc Funds
University of Helsinki Funds
University of Helsinki, Doctoral
Program in Population Health
University of Helsinki, Doctoral
Education Pilot in Precision Cancer
Medicine (iCANDOC)

stance use are connected to the internal and external exposomes, while controlling for familial confounders (Drouard et al., Sci Rep 2024).

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. These 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 accepted for publication in Eur J Epidemiol (Kankaanpää et al., 2025).

As part of his PhD studies, MSc Hannes Bode investigated the role of DNA methylation in breast cancer (BC) risk and showed that most of the observed associations between DNA methylation and future BC diagnosis remain independent of genetic factors, and point to the importance of environmental risks (Bode et al., Clin Epig 2024). Hannes continued to investigate stressful life events as an environmental BC risk, and showed that women exposed to over 10 stressful life events exhibit an almost two-fold increase in risk of BC (Azzi and Bode et al., medRxiv 2024).

Awards, honors, and positions of trust

Docent Miina Ollikainen: Co-Director of Doctoral Program in Population Health, University of Helsinki.

Theses completed in the group in 2024

The following doctoral thesis supervised by Miina Ollikainen (student not affiliated to Minerva) was accepted at the University of Jyväskylä this year:

Anna Kankaanpää. Genetic and environmental influences on biological ageing across different ages – Epigenetic clocks as markers of biological ageing. April 19, 2024.

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

Teodóra Faragó: Smoking status classification based on EPIC methylation array data.

Publications 2024

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Fatty liver disease and diabetes

Main research activities

We have continued mechanistic in vivo and in vitro studies addressing the heterogeneity of metabolic dysfunction-associated steatotic liver disease (MASLD, previously known as non-alcoholic fatty liver disease, NAFLD), with a special focus on the mechanisms underlying common risk-modifying genetic variants in humans.

In addition, we have developed and validated new clinical scores and biomarkers to improve the early detection of liver disease in both the general population and patients. Our group has also contributed to national and international clinical practice guidelines on the diagnosis and treatment of MASLD.

As a new original line of research, we are pursuing elucidating the role of hepatic mitochondrial reductive stress (i.e. an increased ratio of reduced and oxidized nicotinamide adenine dinucleotide; [NADH]/[NAD⁺]) in the pathogenesis of MASLD. We have previously shown that common genetic risk factors of MASLD increase this stress. In addition to genetic risk factors, we hypothesize that increased hepatic mitochondrial reductive stress is a feature of other risk factors of MASLD, such as excessive metabolism of fatty acids and alcohol in the liver. Conversely, we postulate that amelioration of hepatic mitochondrial reductive stress is an underrecognized characteristic of many of the currently available MASLD therapies. Ultimately, our goal is to identify novel therapeutic approaches for MASLD.

We are a partner in the EU H2020: Liver Investigation: Testing Marker Utility in Steatohepatitis. 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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Aila Karioja-Kallio, Laboratory technician, Research nurse
Päivi Ihmuotila, Laboratory technician, Research nurse

External funding

Academy of Finland
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
University of Helsinki
Wilhelm and Else Stockmann's Foundation

Awards, honors, and positions of trust

Docent Panu Luukkonen: Rising Star Award 2024 by the *United European Gastroenterology*; Associate Editor of the *Journal of Hepatology*.

Professor Hannele Yki-Järvinen: Jacobaeus Award 2024 by the Novo Nordisk Foundation; Organizer, Keystone Symposium, *Metabolic Dysfunction Associated Steatohepatitis and therapeutic approaches*, Feb 23-26, 2025, Fairmont Banff Springs, Banff, AB, Canada; EASD/EASL/EASO member of the guideline writing group: EASL-EASD-EASO Clinical Practice Guidelines for the management of *Non-alcoholic Fatty Liver Disease*.

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Photo. M.Sc. Mari Jokinen investigating mitochondrial localization in liver cells using fluorescence microscopy. Photographer Juha Sarkkinen.

Lipid signaling and homeostasis

Main research activities

A major project in the group investigates molecular defects in the adipocytes and endothelial cells (EC) of obese white adipose tissue. After setting up a methodology for isolating the two cell types from human visceral fat biopsies and for EC-adipocyte co-culture in 2023, we now carried out omics profiling of mature adipocytes (MeA) and EC isolated from obese (BMI>30) and lean (BMI<25) donors, and combined the adipocyte data with similar data of our collaborators from (1) fat biopsies of subjects after and before bariatric surgery-induced weight loss and (2) primary human adipocytes incubated with a conditioned medium of type 1 macrophages (MCM). The data suggest that the inflammatory activation of adipocytes is a major driver of white adipose tissue dysfunction in obesity. The omics data reveal aspects of mitochondrial dysfunction, dysregulation of lipid metabolism and vesicular trafficking in obese adipocytes. The adipose EC proteomics suggests that the obese EC become increasingly quiescent and launch a response to maintain the cellular redox balance. The first publication from the results is being assembled. This project is run as a collaboration with the unit of Prof. José Manuel Fernández-Real and Dr. Francisco Ortega at the IDIBGI Institute, Girona, Spain.

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 human cholangiocytes, which express the protein at high levels. The results of an interactome and functional study identified a number of putative GOLM1 interacting partners involved in essential cellular regimes such as mitochondrial and Golgi functions, ribonucleoprotein biogenesis, cell cycle, and basement membrane organization. GOLM1 silencing resulted in impaired mitochondrial function, reduced mitochondrial and P-body markers, increased apoptosis, and reduced cell adhesion, suggesting crucial roles of GOLM1 in maintaining normal cholangiocyte function and metabolism. The protein could thus be employed as a new therapy target for diseases of the liver (Nagaraj et al., manuscript submitted).

One of the long-standing interests of the unit is membrane contact sites (MCS), zones of close contact between the limiting membranes of intracellular organelles. In 2024, we investigated the role of a MCS component, the previously poorly known OSBP family member ORP7, in endothelial cell (EC) functions. Inhibition of ORP7 was shown to result in an increase in gene expression related to lipid metabolism and



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Group members

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Vaishali Chaurasiya, M.Sc.
Taru Knuutinen, M.Sc., Ph.D. in fall 2024
Meghana Nagaraj, M.Sc.
Juuso Taskinen, B.Engin., M.Sc., Ph.D. in fall 2024
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External funding

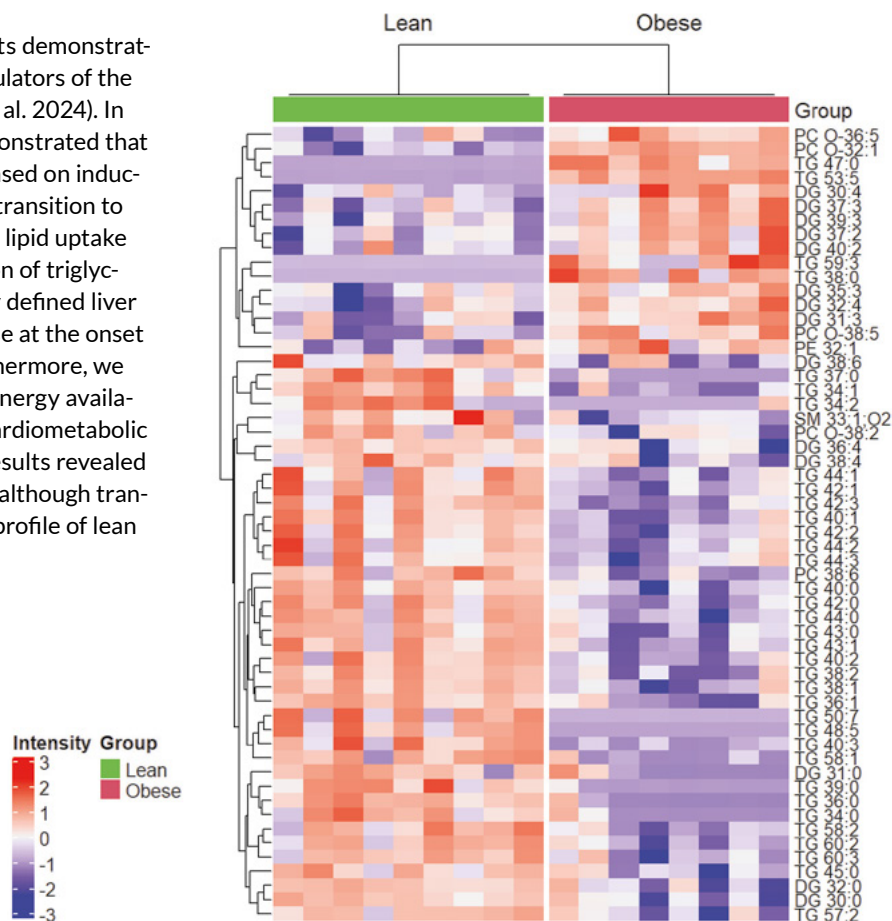
Academy of Finland
Sigrid Jusélius Foundation
Jane and Aatos Erkko Foundation
Medicinska Understödsföreningen Liv och Hälsa r.f.
Diabetes Research Foundation
Finnish Society of Sciences and Letters
Yrjö Jahnesson Foundation
Magnus Ehrnrooth Foundation

inflammation, while genes associated with cell cycle and cell division were downregulated. Lipidomic analysis revealed a number of changes, many of which involved cholesteryl esters and triglycerides. Along with reduced lipid stores, ABCG1-mediated cholesterol efflux and angiogenesis decreased. Moreover, interactomics revealed an interaction of ORP7 with AKT1, a central metabolic regulator (Taskinen et al., 2024). The results highlight functions of ORP7 as a new regulator in EC lipid metabolism, inflammation, and cell cycle.

Matti Jauhiainen (collaborative studies): We investigated the potential of PCSK9 antibodies (evolocumab or alirocumab) to bring back cholesterol efflux from macrophages in patients with heterozygous familial hypercholesterolemia (heFH) and further to enhance the macrophage-specific reverse cholesterol transport

(RCT) pathway in a mouse model. The results demonstrated that PCSK9 inhibitors act as positive regulators of the RCT pathway in heFH patients (DiNunzio et al. 2024). In another collaborative investigation, we demonstrated that the liver responds to a dyslipidemic insult based on inducible models of FH and APOB tracing. A fast transition to atherogenic APOB lipoprotein levels caused lipid uptake by Kupffer cells (KCs) and rapid accumulation of triglycerides and cholesterol in the liver. The study defined liver KCs as key mediators of the hepatic response at the onset of atherosclerosis (Borràs et al., 2024). Furthermore, we investigated the associations between low energy availability (LEA), body composition, and serum cardiometabolic profile in 23 athletes and 21 controls. The results revealed that loss of fat and LEA may have beneficial although transient effects on the serum cardiometabolic profile of lean individuals (Jouhki et al., 2024).

Figure. Heatmap of lipids present at different relative concentrations in adipocytes isolated from omental fat biopsies of lean and obese subjects undergoing cholecystectomy. The columns represent individual subjects, each row represents a lipid species, and the colours represent the relative concentrations of lipids. Red denotes a high and blue a low concentration. Lipid species with similar abundance patterns are grouped together in clusters on the left.



Theses completed in the group in 2024

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

Taru Knuutinen: The importance of calcium channels in thyroid cancer. September 27, 2024.

Juuso Taskinen: The role of endoplasmic reticulum membrane contact sites in human endothelial cells. October 4, 2024.

Publications 2024

Borràs C, Canyelles M, Girona J, Ibarretxe D, Santos D, Revilla G, Llorente-Cortes V, Rotllan N, Kovanen PT, **Jauhiainen M**, Lee-Rueckert M, Masana L, Arrieta F, Martínez-Botas J, Gómez-Coronado D, Ribalta J, Tondo M, Blanco-Vaca F, Escolà-Gil JC. PCSK9 antibodies treatment specifically enhances the macrophage-specific reverse cholesterol transport pathway in heterozygous Familial Hypercholesterolemia. *JACC Basic Transl Sci*. 2024; 9:1195-1210.

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Li S, Wang Y, van der Stoep M, Zhou X, Madhusudan S, Kanerva K, Nguyen VD, Eskici N, **Olkkonen VM**, Zhou Y, Raivio T, and **Ikonen E**. HiHo-AID2: boosting homozygous knock-in efficiency enables robust generation of human auxin-inducible degron cells. *Genome Biol*. 2024; 25:58.

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Taskinen J, Holopainen M, Ruhanen H, van der Stoep M, Kälälä R, **Ikonen E**, Keskitalo S, Varjosalo M, **Olkkonen VM**. Functional omics of ORP7 in primary endothelial cells. *BMC Biology*. 2024; 22:292.

Membrane biology

Main research activities

During 2024, we have reported on an improved method that enables rapid, auxin-inducible degradation (AID) of a protein of interest from mammalian cells, including differentiated human cells (Li et al., 2024). This system is particularly useful for revealing the primary functions of essential cellular proteins, whose loss of function is lethal or results in complex compensatory phenotypes with reduced viability. This is often the case for proteins that control key steps of lipid transport and metabolism and that represent major focus areas of our research.

Suppressor of actin 1 (Sac1) is a highly conserved lipid phosphatase from yeast and plants to humans. Its knock-out causes preimplantation lethality in mice, and we identified a strong negative selection against *SACML1* gene loss-of-function variants in human populations (Zhou and van der Stoel et al., bioRxiv 2024). We therefore employed the AID system to unravel the immediate consequences of removing this vital protein. We identified Golgi V-ATPase as a critical effector of Sac1 controlled trans-Golgi network (TGN) membrane cholesterol and PI(4)P composition. Our studies reveal that Golgi deacidification ensuing from Sac1 degradation disrupts the structural and functional integrity of the organelle, leading to Golgi fragmentation and defects in cargo secretion and terminal glycosylation. Acute removal of Sac1 from differentiated human trophoblasts compromises the glycosylation and secretion of human chorionic gonadotropin, a hormone critical for the implantation of the embryo. These mechanisms help to explain the intolerance for loss of Sac1 function during mammalian development.

We have also employed the AID system in several collaborative studies, for example, to dissect the role of the endoplasmic reticulum (ER) stress sensor inositol-requiring enzyme 1 α (IRE1 α) in mediating the hypertrophy of cardiomyocytes (Li et al., 2024) and the role of the ER microprotein adipogenin in facilitating adipose tissue expansion (Li et al., bioRxiv 2024).

We are a partner in the EU MCSA Innovative Training Network EndoConnect and in the Leducq Foundation "Cellular and systemic cholesterol transport in physiology and disease" Transatlantic Network of Excellence.



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

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External funding

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

Awards, honors, and positions of trust

Professor Elina Ikonen: Member of the Scientific Advisory Committee of the European Molecular Biology Laboratory (EMBL).

Thesis completed in the group in 2024

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

Erika Saari. The role of the peroxisomal plasmalogen biosynthesis pathway in cholesterol homeostasis.

Publications 2024

Li C, Li S, Zhang G, Li Q, Song W, Wang X, Cook JA, van der Stoel M, Wright BW, Altamirano F, Niewold EL, Han J, Kimble G, Zhang P, Luo X, Urta H, May HI, Ferdous A, Sun XN, Deng Y, Ikonen E, Hetz C, Kaufman RJ, Zhang K, Gillette TG, Scherer PE, Hill JA, Chen J, Wang ZV. IRE1 α mediates the hypertrophic growth of cardiomyocytes through facilitating the formation of initiation complex to promote the translation of TOP-motif transcripts. *Circulation*. 2024; 150: 1010-1029.

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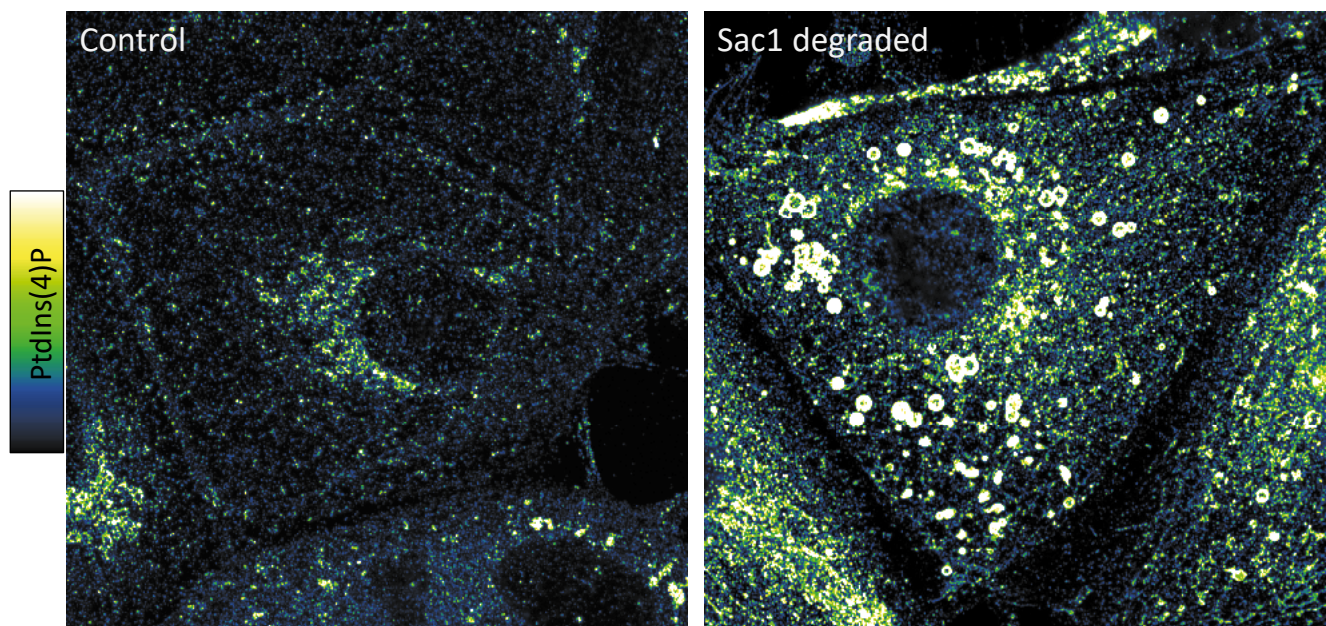


Figure. Phosphatidylinositol-4-phosphate (PI4P) accumulates in human trophoblasts where PI(4)P-phosphatase Sac1 was removed for 4 h using auxin-inducible degradation. Courtesy of Dr. Xin Zhou.

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 for studying cell metabolism at our disposal.

Hypoxia-inducible transcription factors (HIFs) regulate adaptive cellular responses to low oxygen concentrations. Under normoxia, HIFs are targeted for degradation by hypoxia-inducible factor prolyl 4-hydroxylase enzymes (HIF-P4Hs). Inhibition of HIF-P4Hs leads to stabilization of HIFs and activation of the HIF-response pathway. As there is evidence from preclinical models suggesting that HIF-P4H inhibitors could be utilized to treat metabolic disorders associated with insulin resistance, we tested if roxadustat, a HIF-P4H inhibitor approved for treatment of renal anemia, affects glucose metabolism in primary human myotubes. Muscle cell cultures were established from donors with normal glucose tolerance as well as with type 2 diabetes. Exposure of primary human myotubes to roxadustat led to stabilization of the nuclear HIF1 protein and transcriptional activation of the HIF-response. Moreover, exposure of primary myotubes to roxadustat led to a metabolic shift: a reduction in mitochondrial oxygen consumption and an increase in glycolytic rate was observed regardless of diabetes status. While roxadustat did not affect basal glucose uptake or glycogen synthesis, co-incubation with roxadustat enhanced insulin-stimulated glycogen synthesis in myotubes from donors with type 2 diabetes. Thus, roxadustat affects glucose metabolism in primary human myotubes and may improve insulin action on glycogen synthesis in type 2 diabetes (Mäkinen et al., 2024).

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, professor Heikki Koistinen being one of the FUSION PIs.

As part of FUSION, we have participated in a large collaborative effort to study the genetic background of obesity. Using a case-control approach, we found that people homozygous for a loss-of-function genetic variant in the small integral membrane protein 1 (SMIM1) gene had excess body weight, dyslipidemia and reduced resting energy expenditure (Stefanucci et al., 2024).



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Leena Kinnunen, Ph.C.
Henric Kultalahti, M.B.

External funding

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

In a collaboration with the Dasman Diabetes Institute, we found that both sucrose-free soybean oil-based and sucrose-free cocoa butter-based high-fat diets induced gut dysbiosis in mice and led to steatosis, hepatic inflammation, and impaired glucose homeostasis (Jacob et al., 2024; Kochumon et al., 2024). We identified that hsa-miR-320a-3p and its key targets are dysregulated in type 1 diabetes (Nizam et al., 2024). We found that sclerostin, osteoprotegerin, receptor activator of nuclear factor kappa-B ligand, and glycoprotein non-metastatic melanoma protein B concentrations were increased in people with T2D, highlighting dysregulation in bone remodeling markers in type 2 diabetes (Alramah et al., 2024; Cherian et al., 2024).

In a collaboration with investigators from the Department of Obstetrics and Gynecology, South Karelia Central Hospital, University of Helsinki and Helsinki University Hospital, we performed untargeted metabolomic profiling of fasting serum samples in early pregnancy and identified distinct metabolomic features in different gestational diabetes (GDM) subtypes. These data suggest alterations in maternal lipid metabolism in early-pregnancy, especially in overweight women with early-onset GDM (Masalin et al., 2024).



Photographer Juha Sarkkinen

Awards, honors, and positions of trust

Professor Heikki Koistinen: Vice-member of the Collegium of University of Helsinki, 2022-2026; Member of the Finnish JUFO-panel (Publication Forum; forum to classify publications channels and created by the Finnish scientific community to support the quality assessment of academic research, Federation of Finnish Learned Societies); Panel of Clinical Medicine, 2022-2024; Member of the scientific committee and reviewer of grant applications of the Finnish Diabetes Research Foundation 2024 onwards; Member of the board of the Finnish Society of Internal Medicine 2024 onwards.

Publications 2024

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J, Al-Mulla F, Ahmad R. Soybean oil-based HFD induces gut dysbiosis that leads to steatosis, hepatic inflammation and insulin resistance in mice. *Front Microbiol*. 2024; 15:1407258.

Kochumon S, Malik MZ, Sindhu S, Arefanian H, Jacob T, Bahman F, Nizam R, Hasan A, Thomas R, Al-Rashed F, Shenouda S, Wilson A, Albeloushi S, Almansour N, Alhamar G, Al Madhoun A, Alzaid F, Thanaraj TA, **Koistinen HA**, Tuomilehto J, Al-Mulla F, Ahmad R. Gut dysbiosis shaped by cocoa butter-based sucrose-free HFD leads to steatohepatitis, and insulin resistance in mice. *Nutrients*. 2024; 16:1929.

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Stefanucci L, Moslemi C, Tomé AR, Virtue S, Bidault G, Gleadall NS, Watson LPE, Kwa JE, Burden F, Farrow S; DBDS Genetic Consortium; Chen J; MAGIC (**Koistinen HA**); Vösa U, Burling K, Walker L, Ord J, Barker P, Warner J, Fray A, Renhstrom K, Ashford SE, Piper J, Biggs G, Erber WN, Hoffman GJ, Schoenmakers N, Erikstrup C, Rienck K, Dziegiel MH, Ullum H, Azzu V, Vacca M, Aparicio HJ, Hui Q, Cho K, Sun YV, Wilson PW, Bayraktar OA, Vidal-Puig A, Ostrowski SR, Astle WJ, Olsson ML, Storry JR, Pedersen OB, Ouwehand WH, Chatterjee K, Vuckovic D, Frontini M. SMIM1 absence is associated with reduced energy expenditure and excess weight. *Med*. 2024; 5:1083-1095.e6.

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 2024, we worked on two main areas of research.

USP14 and altered protein ubiquitination in human SHSY5Y dopaminergic cells

Disturbances in protein homeostasis are associated with several human diseases, including cancer and neurodegenerative disorders (Lindholm et al., 2017). 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). We previously observed that USP14 plays a role in clearing of mutant Htt protein aggregates by binding to the ER protein, IRE1 α (Hyrskyluoto et al., 2014). We have now deleted USP14 in cells using CRISPR/Cas9 and discovered novel functions of USP14 in the regulation of mitochondria, oxidative stress and lysosomes in human SHSY5Y dopaminergic cells (Srinivasan et al., PhD thesis 2024). We identified α -synuclein (α -syn) as one of the targets that was up-regulated in the absence of USP14 likely due to reduced degradation by proteasomes (Srinivasan et al, preprint). Hence, USP14 is a promising factor to consider in order to target α -syn in dopaminergic neurons and in Parkinson's disease.



Dan Lindholm

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

Group members

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Nisa Pitafi, B.Sc.
Pyy Aunola, Medical student
Urho Kere, Medical student

External funding

Finnish Society of Sciences and Letters
Magnus Ehrnrooth Foundation
Medical Society of Finland (Finska Läkaresällskapet)
Medicinska Understödsföreningen Liv och Hälsa r.f.

ER stress and effects of CNPY2 in models of Huntington's disease and in thyroid cancer

ER stress is associated with the pathophysiology of neurodegenerative diseases (Lindholm et al., 2017). Emerging data show that ER stress signals can be mitigated in cells the action of different proteins and substances. We have previously cloned canopy 2 (CNPY2), an ER-resident protein found in different tissues including the brain. Using immunochemistry, we observed that CNPY2 is expressed in striatal and cortical neurons in vivo in the neuronal circuitry regulating body movements. CNPY2 was further altered in these neurons in the N171-82Q mice as a model of Huntington's disease (HD) (Scordino et al, 2024)). We then noted that overexpression of CNPY2 is protective against ER stress in neuronal cell cultures, whilst its down-regulation rendered cells more prone to stress-mediated degeneration. The precise physiological roles of CNPY2 in neurons and in brain diseases are currently under investigations using gene-deleted mice. Along with this, we have recently cloned a novel variant of the protein named CNPY2-X, arising from alternative splicing and with a different intracellular location in cells that will require more investigations.

In collaboration with Professor Kid Törnquist, we have further studied the role of CNPY2 in thyroid cells. Compared with control thyroid tissue CNPY2 was up-regulated in thyroid cancer cells. Silencing of CNPY2 by siRNA reduced the cell proliferation as well as migration of the thyroid tumor cells (Asghar et al, manuscript). Hence, CNPY2 is a novel survival factor for thyroid tumors and the mechanisms involved are under investigation.

Awards, honors, and positions of trust

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

Thesis completed in the group in 2024

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

Vignesh Srinivasan: Novel roles of the protein deubiquitinase USP14 in proteostasis regulation and cell stress responses. October 11, 2024.

Publications 2024

Scordino M, Stepanova P, Srinivasan V, Pham DD, Eriksson O, Lalowski M, Mudò G, Di Liberto V, Korhonen L, Voutilainen MH, Lindholm D. CNPY2 protects against ER stress and is expressed by corticostriatal neurons together with CTIP2 in a mouse model of Huntington's disease. *Front Mol Neurosci.* 2024; 17:1473058.

Preprint

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Original articles

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