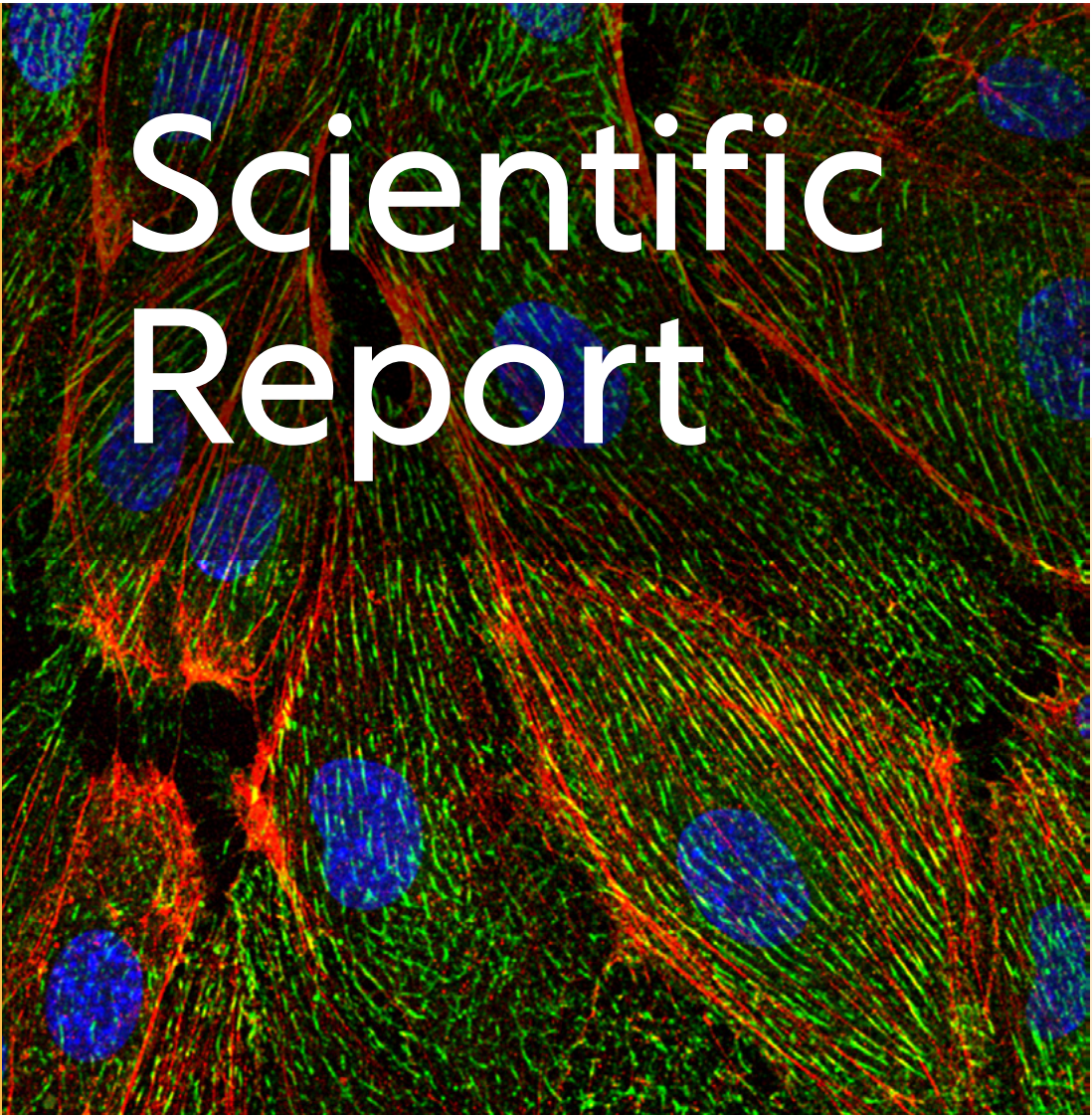




Minerva Foundation & Minerva Foundation Institute for Medical Research



Scientific Report

2022



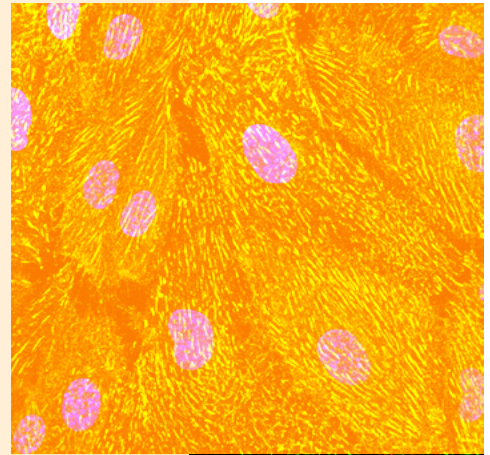
Front page Image. Human umbilical vein endothelial cells stained with DAPI (nucleus, blue), Alexa-594 phalloidin (actin filaments, red) and anti-integrin beta 1 (green). Courtesy of Amita Arora (Lipid Signaling and Homeostasis). See original image on page 24.

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

www.minervafoundation.fi
www.minervainstitute.fi

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Summary of research and activities in 2022

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 2022 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 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 €1 092 795 during 2022, covering 52% of the Institute's budget. During 2022, a total of 76 articles were published, 58 of which were original articles in international peer-reviewed journals. The median impact of all articles was 6.706. These are new records in the scientific productivity of the Institute. Moreover, M.Sc. Maria Ahonen Mehmeti, M.D. Mari Lahelma, and M.D. Rasmus Olander defended their doctoral theses in 2022.

During 2022, the renewal process of the Institute was continued. Docent Panu Luukkonen stepped in as head of the Fatty liver disease and diabetes group, starting in this post on March 1, 2022. Moreover, Docent Miina Ollikainen's group focusing on the epigenetics of common diseases joined the Institute on September 1, 2022.

On October 24–25, the Institute organized a scientific Minerva Foundation symposium, 'Mitochondria and Lipid Droplets' at the Hanasaari congress center. The hybrid meeting was of an extremely high quality, with presentations by global leaders in the field, and with a total of more than 150 participants.

To summarize: The Institute thrived in 2022 both scientifically and financially, continued its renewal process to reinforce work toward its strategic goals, and moves into 2023 with optimism and determination.

Events at Minerva 2022

Symposium

MINERVA FOUNDATION SYMPOSIUM

Mitochondria and Lipid Droplets
October 24 –25, Hanaholmen, Espoo, Finland

Read more on page 8–9.

Prizes and Grants

MEDIX PRIZE OF THE MINERVA FOUNDATION

Award Ceremony and Prize Lecture, September 12, 2022.

The winning article: Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. *Cell*. 2021; 184:1299–1313.

Authors: Casarotto PC, Giryck M, Fred SM, Kovaleva V, Moliner R, Enkavi G, Biojone C, Cannarozzo C, Sahu MP, Kaurinkoski K, Brunello CA, Steinzeig A, Winkel F, Patil S, Vestring S, Serchov T, Diniz CRAF, Laukkanen L, Cardon I, Antila H, Rog T, Piepponen TP, Bramham CR, Normann C, Lauri SE, Saarma M, Vattulainen I ja Castrén E.

Read more on page 6–7.

RALPH GRÄSBECK GRANT FOR RESEARCH IN LABORATORY MEDICINE

Docent Oscar Brück, M.D., Dr.Med.Sci.
Helsinki University Hospital
10.000 EUR

Read more on page 10–11.

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

From Selma and Maja-Lisa Selander's fund 23 grants were awarded 2022, in all 120.500 EUR.

The following theses were accepted at the University of Helsinki in 2022:

DOCTORAL THESES

Maria Ahonen Mehmeti. Mechanisms of adipocyte dysfunction in metabolic disease and cancer. December 9, 2022.

Sina Antony Kavalakatt. Urocortin 3 in obesity and type 2 diabetes. March 23, 2022.

Mari Lahelma. Lifestyle factors and lipid metabolism in non-alcoholic fatty liver disease, the metabolic syndrome, and atherosclerotic cardiovascular disease. December 16, 2022.

Rasmus FW Olander. Early cardiovascular morphology, function, and health following abnormal foetal growth. June 3, 2022.

MASTER'S THESES

Henrik Ahlstrand. Functional hypogonadism in type 2 diabetes and metabolic syndrome: the role of testosterone replacement therapy.

Melinda Tiderman. Esidiabeteksen eri muodot ja niiden merkitys terveydelle: kirjallisuuskatsaus.

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, 2022. During this period, the board of trustees included the following persons:

Board of Trustees

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The Minerva Foundation Institute for Medical Research

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Docent Matti Jauhiainen (January 1 – August 31)
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Docent Päivi Lakkisto
Professor Dan Lindholm
Docent Panu Luukkonen (from March 1)
Docent Miina Ollikainen (from September 1)
Docent Taisto Sarkola
Professor Ilkka Tikkanen
Professor Kid Törnquist
Professor Hannele Yki-Järvinen
M.Sc. Cia Olsson

Medix prize of the Minerva Foundation

New data on the modes of action of antidepressants

The Minerva Foundation's Medix Prize 2022 was awarded to a research group from the University of Helsinki. The research group produced new data on the modes of action of antidepressants. The research was published in the prestigious journal *Cell*.

Patients suffering from depression benefit from serotonin-increasing medications. This finding has resulted in a conclusion, commonly accepted for decades, that the primary cause of depression is a depletion in serotonin.

Antidepressants have been considered to influence the brain by means of serotonin or glutamate receptors. Receptors are protein molecules that bind neurotransmitters and medicinal agents. The findings of a research group of the University of Helsinki indicate that the matter is more complex than this. The research group is headed by MD **Eero Castrén**.

The article by the research group, published in the international journal *Cell*, demonstrates that antidepressants bind directly to TRKB neurotrophin receptors. The study questions the role of serotonin and glutamate receptors as the primary targets of antidepressants.

The research group was awarded with this year's Medix Prize, worth €20,000, for their work. According to

Dr Eero Castrén, his research group has worked in co-operation with the research groups of Professor **Ilpo Vattulainen** and Professor **Mart Saarma**.

"Their research groups have had a significant impact on the work of our research group, and the award will, thus, be divided between the researchers in the three groups," says MD Castrén.

According to Dr Castrén, although antidepressants bind to the TRKB receptor, their binding affinity is modest, yet therapeutically significant.

"A problem with antidepressants is that their clinical effects are delayed. It may take up to several weeks before their impacts are translated into clinical mood recovery. For this reason, our research group would like to find molecules, which would bind better to the TRKB receptor. Such findings would allow the development of new kinds of antidepressants with a faster effect," says Dr Eero Castrén.



Members Of the award-winning research group, from the left: Katja Kaurinkoski, Sulo Kolehmainen, Rafael Moliner, Eero Castrén, Seija Lågas and Cecilia Brunello. Photographer: Juha Sarkkinen.



The Finnish championship in biomedicine

The Medix Prize by the Minerva Foundation 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 35th time.

The Medix Prize is awarded by the University of Helsinki, and is donated to the university by the Minerva Foundation, which 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.



Photo above. The research group headed by MD, PhD Eero Castrén works at Biomedicum, Helsinki, Finland. From the left: Elias Jetsonen, Sulo Kolehmainen and Eero Castrén. Photographer: Juha Sarkkinen.

Photo below. Eero Castrén. Photographer: Juha Sarkkinen.

Minerva Foundation Symposium

Mitochondria and lipid droplets

Minerva Foundation organized on October 24-25 a hybrid symposium titled 'Mitochondria and Lipid Droplets'. These organelles play key roles in cellular energy and lipid metabolism, and their dysfunction is central in common metabolic diseases. The event took place at the Hanasaari congress center in Helsinki, and the program consisted of 14 invited presentations by global leading specialists in the field and top-level researchers from the Meilahti campus. The program of the symposium can be found at <https://minervafoundation.fi/2022/08/30/minerva-foundation-symposium-2022-3/>. The symposium was attended by slightly over 120 participants, of which approximately 50 participated on-site and 70 virtually.

The first two sessions on October 24 focused on mitochondrial nicotinamide adenine dinucleotide (NAD) metabolism and redox state, the role of mitochondrial dysfunction in epigenetic modification of nuclear chromatin, mitochondrial ketogenesis and pyruvate metabolism in non-alcoholic fatty liver disease (NAFLD), and a putative use of mitochondrial uncouplers in the treatment of NAFLD and cardiovascular diseases. Joseph Baur (University of Pennsylvania, Philadelphia, US) showed that

exogenous NAD supplementation can restore mitochondrial respiration, the NAD being taken up by cells by the transporter SLC25A51. Anu Wartiovaara (University of Helsinki) presented a pilot study with patients suffering from a mitochondrial myopathy, treated with niacin as a NAD booster, resulting in increased respiratory chain activity, muscle mass and strength and mitochondrial mass, accompanied by a reduction of liver fat content and visceral fat mass. Panu Luukkonen (Minerva



Photo. Top right: Anu Wartiovaara; From bottom left: Leigh Goedeke, Brian Finck, Marc Liesa Roig, Douglas Mashek, Miina Ollikainen and Brian Finck.



Photo. From left: Panu Luukkonen and Miina Ollikainen.

Institute) showed data suggesting that a skewed hepatic mitochondrial redox state characterizes a genetic form of NAFLD, while Miina Ollikainen (Minerva Institute) provided evidence that long-term treatment of obese subjects with nicotinamide riboside (NR) elevated the levels of NAD and its precursors in muscle coinciding with altered DNA methylation and decelerated biological aging. Peter Crawford (University of Minnesota, Minneapolis, US) reported on the role of ketogenesis and ketone bodies as mediators of integrative homeostasis, and Brian Finck (Washington University, St. Louis, US) on the mitochondrial pyruvate metabolism in NAFLD, targeting the gene encoding the mitochondrial pyruvate carrier, MPC. Finally, Leigh Goedeke (The Icahn School of Medicine at Mount Sinai, New York, US) presented fascinating results on the use of uncouplers as a potential therapy for NAFLD and cardiovascular diseases, based on work on mice and non-human primates.

On the second day of the symposium, the main emphasis was on lipid droplets (LD) and the mitochondria-LD association. After an initial talk by Karen Reue (University of California, LA, US) on X-chromosomal genes that escape X inactivation and their role in preadipocyte proliferation and lipid accumulation, Mike Henne (UT Southwestern Medical Center, Dallas, US) showed beau-

tiful data on metabolically distinct LD subpopulations. Sini Heinonen (University of Helsinki) reported on mitochondrial metabolism in adipose tissue in obesity and after weight loss, and Marc Liesa Roig (Molecular Biology Institute of Barcelona – Spanish National Research Council (IBMB-CSIC), Barcelona, Spain) on mitochondrial fission and heterogeneity in NAFLD or non-alcoholic steatohepatitis (NASH), suggesting that one could mitigate NASH by preventing the failure of mitochondria. In the final session, Orian Shirihai (UCLA, Los Angeles, US) presented fascinating work on characterizing the distinct peri-droplet and cytoplasmic mitochondrial populations and Douglas Mashek (University of Minnesota, Minneapolis, US) on the distinct metabolic activities of the peri-droplet and cytoplasmic LD. The symposium was closed by a talk by Heather Kay Hsu (Inipharma, Seattle, US), who introduced inhibition of HSD17B13 as a treatment for chronic liver disease.

To conclude, the excellent and topical presentations provided a unique view on current leading research on the two organelle systems that play central roles in metabolism. The symposium thus yielded new angles on the cellular and molecular mechanisms that could be targeted to alleviate the burden of common diseases.

Ralph Gräsbeck scholarship for research in laboratory medicine

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

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

The 2022 Ralph Gräsbeck Scholarship for Research in Laboratory Medicine is awarded to **Oscar Brück**, M.D., Dr.Med.Sci., Docent in Experimental Hematology, for the “*Cytomorphological digital twin*” project.

Oscar Brück leads the Hematoscope Lab at the Comprehensive Cancer Center, Department of Hematology and Center of Diagnostics, Helsinki University Hospital. Microscopic evaluation of May-Grünwald-Giemsa-stained cytological samples forms the cornerstone of the diagnostics and monitoring of blood cancers. His team is developing a computer vision-based diagnostic platform to digitize and automatically analyze cytological samples. Collectively, they have digitized the world's largest collection of MGG-stained clinical samples (n=40 000) and have initiated two international multicenter studies with partners from 5 countries.

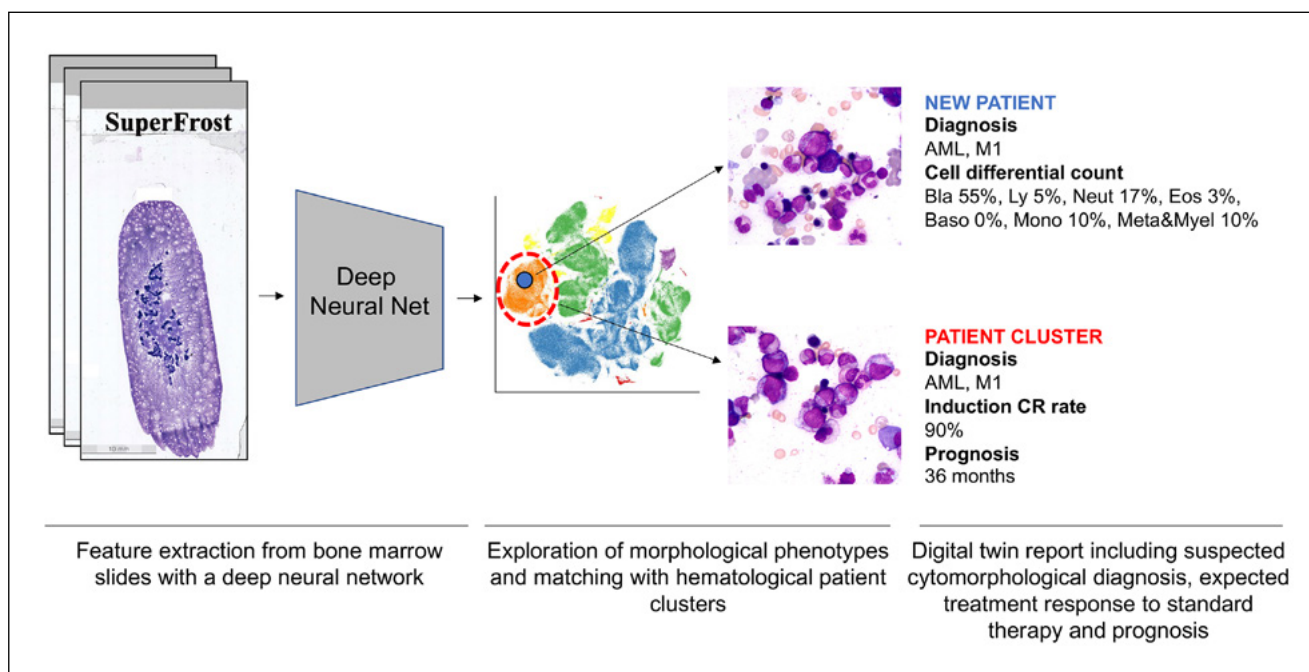
The Ralph Gräsbeck Scholarship was granted to Oscar Brück for developing a digital twin platform to accurately predict treatment response, complications and prognosis of new blood cancer patients by comparing their clinical, genetic and cytological profiles to all other patients. By identifying the most resembling twin patients, the algorithm can support or challenge clinical decisions. Clinical data and analytical infrastructures will



Docent Oscar Brück

be applied in the HUS Hematological Datalake, where Oscar Brück has been one of the key developers as part of the eCare-4-me project.

Dr. Brück has authored over 30 publications in international peer-reviewed journals such as *Cancer Discovery*, *Blood Cancer Discovery*, *Cancer Cell*, and *Leukemia* and has supervised three Master's theses in engineering. He has previously received the Biomedicum Helsinki Foundation Prize (2020), American Society of Hematology Outstanding abstract award (2017), Ensio Hyvärinen Award (2017), and Vihtori ja Tutta Pentti Award (2013).



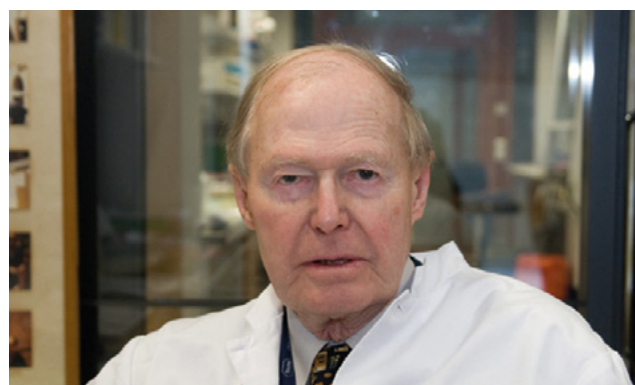
Ralph Gräsbeck (July 6, 1930 – January 22, 2016)

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 (now Yhtyneet Medix Laboratoriot) 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.

A new group at Minerva 2022

Epigenomics of complex traits

Main research activities

Docent Miina Ollikainen was appointed as a group leader at Minerva in September 2022. Our group studies the role of genetics and the environment in epigenetic processes, and how these processes relate to the development of common diseases and complex traits. We utilize trait-discordant and -concordant twin pairs from the Finnish Twin Cohort Study, which enable the dissection of the effects of genes and the environment in the observed epigenetic-trait associations. Our group aims to produce reliable trait biomarkers, and potential risk predictors and intervention targets for common diseases.

Since joining Minerva, the research work of the group has focused on the identification of DNA methylation patterns associated with mitochondrial function in obesity, and with breast cancer, and in assessing the role of adolescence lifestyle and parental investment in biological aging and mortality.

Obesity and mitochondrial function

We are studying the dynamics of nuclear methylome and mitochondrial biogenesis in obesity to identify potential future obesity prevention and therapy targets. We have previously shown that obesity is linked to mitochondrial dysfunction and epigenetic alterations. Therefore M.Sc. Aino Heikkinen wanted to determine by studying BMI-discordant monozygotic twins if mitochondria boosting with nicotine amide riboside (NR) would affect the cell's methylation capacity and thereby the methylation of nuclear DNA. NR modulated the epigenetic control of gene expression in muscle and adipose tissue in both co-twins. However, NR did not ameliorate adiposity or metabolic health. This study was done in collaboration with Professors Kirsi Pietiläinen and Eija Pirinen, and it has been accepted for publication in Science Advances.

Aging and lifestyle

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.

M.Sc. Mikaela Hukkanen is currently assessing if lifelong reproductive investment results in an accelerated aging rate by investigating the effects of reproduction. M.Sc. Kankaanpää has shown that an un-



Group members

Miina Ollikainen, Ph.D., Docent, Head
Hannes Bode, M.Sc.
Aino Heikkinen, M.Sc.
Mikaela Hukkanen, M.Sc.
Anna Kankaanpää, M.Sc.
Mia Urjansson, Research nurse

External funding

Academy of Finland
EU H2020 MSCA-ITN-ETN (Hannes Bode)
NIH/NIDA (National Institutes of Health/National Institute on Drug Abuse, USA)
Sigrid Jusélius Foundation
University of Helsinki, Doctoral Programme in Population Health (Aino Heikkinen)

healthy lifestyle in adolescence is associated with accelerated aging in adulthood. As physical activity behavior clustered with other health-related lifestyles (smoking, excess energy intake, alcohol use), M.Sc. Kankaanpää has carried on to study whether epigenetic aging mediates the association between long-term physical activity patterns and all-cause mortality.

Breast cancer

M.Sc. Hannes Bode is funded by the EU CANCERPREV PhD program, where we are working toward an understanding of how breast and skin cancer can be prevented. M.Sc. Bode contributes to this aim by assessing genetics, DNA methylation, and environmental and behavioral risk factors individually and jointly as risk factors for breast cancer.

Awards, honors, and positions of trust

Docent Miina Ollikainen: Board member of the Doctoral Program in Population Health, University of Helsinki; Steering group member of the Finnish Twin Cohort Study, University of Helsinki; Scientific advisory board member of Tobacco-free Finland 2030 network; Editorial board member of Epigenomes, Clinical Epigenetics, Frontiers in Epigenomics and Epigenetics journals.

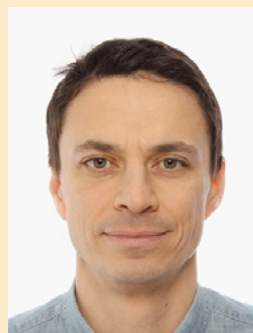
Cardiorenal diabetes

Main research activities

Current Projects

During the year, the research focus has been on a FinnDiane substudy aiming to improve knowledge on cerebrovascular disease in individuals with type 1 diabetes without any neurological signs or symptoms. The goal of this collaborative longitudinal study is to characterize and find risk factors for cerebrovascular disease in individuals with type 1 diabetes (T1D) by performing brain imaging and neuro-psychological testing.

The following progress has been achieved within the study during 2022. Dr. Jussi Inkeri investigated the association between blood glucose control and the cerebrovascular phenotype by MRI, observing no difference in those with and without small vessel disease. This surprising finding raised the question of which other metabolic disturbances may explain the varying cerebrovascular phenotype in these individuals as the next step to investigate. Dr. Aleks Tarkkonen compared early retinal disease by measuring retinal vessel diameter of the cerebrovascular phenotype in this cohort. He is currently learning a new methodology, optical coherence tomography angiography (OCTA), an in-depth analysis of the retinal vasculature. Iris Kyläheiko, a neuropsychologist, has joined the group, working on cognitive capacity within the study. Dr. Rasmus Simonsen has been instrumental in setting up a renal lab within the FinnDiane neurovascular laboratory. A study on relative renal hypoxia in different patient groups at risk for kidney disease is ongoing. Further, Karoliina Ahtola has been the research nurse of our group for a year now. The group is part of a recently founded international nephrology task force within the FinnGen consortium. The aim is to detect genetic defects explaining rare kidney diseases.



Group members

Daniel Gordin, M.D., Dr.Med.Sci., Docent, Head
Rasmus Simonsen, M.D., Dr.Med.Sci.
Jussi Inkeri, M.D.
Aleksi Tarkkonen, M.D.
Iiris Kyläheiko, M.Sc.
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
University of Helsinki
Wilhelm and Else Stockmann Foundation

Awards, honours and positions of trust

M.D. Aleks Tarkkonen: Abstract Prize, European Society of Hypertension Annual Meeting 2022.

Publications 2022

- Gordin D**, Bjornstad P, van Raalte DH. Lipids in CKD: What do we actually know? *Atherosclerosis*. 2022; 350:97-99.
- Inkeri J, Adeshara K, Harjutsalo V, Forsblom C, Liebkind R, Tatlisumak T, Thorn LM, Groop PH, Shams S, Martola J, Putaala J, **Gordin D**; FinnDiane Study Group. Glycemic control is not related to cerebral small vessel disease in neurologically asymptomatic individuals with type 1 diabetes. *Acta Diabetol*. 2022; 59:481-490.
- Kostiainen I, Karppinen N, Simonen P, Rosengård-Bärlund M, Lindén R, Tarkkanen M, **Gordin D**, Rapola J, Schalin-Jäntti C, Matikainen N. Arterial function, biomarkers, carcinoid syndrome and carcinoid heart disease in patients with small intestinal neuroendocrine tumours. *Endocrine*. 2022; 77:177-187.
- Wadén J, **Gordin D**, Lappalainen K, Venermo M, **Tikkanen I**. Renovascular Hypertension, Diagnosis and Care (Renovaskulaarisen hypertension diagnostiikka ja hoito). *Duodecim*. 2022; 138:1703-9.

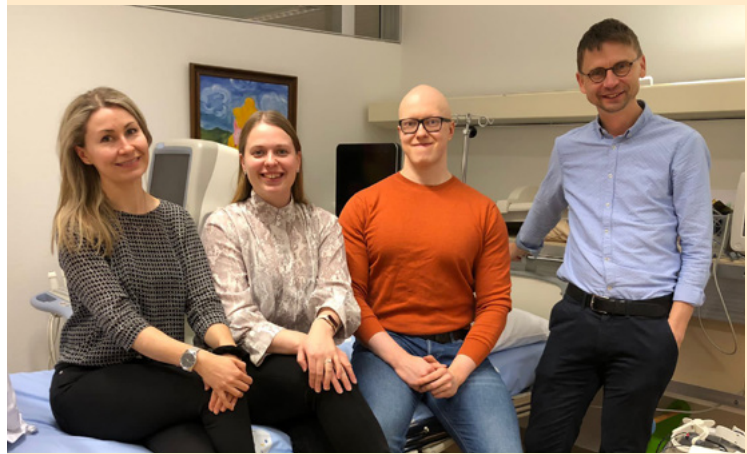
Cardiovascular research in the young

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 visits were arranged in the Clinical Trial Unit at the Children's Hospital within the FINNCARE project (A lifestyle intervention for families with a history of pre-eclampsia – primary prevention of cardiovascular disease) during 2022 despite the challenging Covid-19 pandemic times. All visits were successfully coordinated and managed by Maria Finne and Juho Suomi. Ph.D students Michelle Renlund and Anni Kivelä (collaboration with Tiina Jääskeläinen and Hannele Laivuori) worked actively within the project during the year. A PhD student mini seminar was arranged together with the Daniel Gordin -group in spring 2022. The FINNCARE protocol was published in early 2022 with Taisto Sarkola as last author. Research visits within the FINNCARE randomized clinical trial section will be completed by summer 2023.

Ph.D. student Rasmus Olander defended his thesis in June 2022 within the SIVELU project. Two articles from the PhD thesis were published during the year. One article showed that arterial dimensions in childhood are associated with current anthropometrics, especially lean body mass and sex, explaining differences in arterial layer thickness. No signs of fetal programming of cardiovascular risk or arterial health in early childhood were, however, found. The other article showed that cardiac morphology is predicted by lean body mass during childhood, even in the setting of abnormal fetal growth. The results were consistent with a limited effect of fetal programming on cardiac dimensions during childhood. Minor changes in diastolic function were present in children born both small and large for gestational age, however, the clinical significance of these changes at this stage was likely to be small during early childhood.

Furthermore, maternal and offspring cardiovascular morphology and function data from the RADIEL (Finnish Gestational Diabetes Prevention Study) 5-year-from-birth project was processed by Ph.D. student Linda Litwin with



Group members

Taisto Sarkola, M.D., Dr.Med.Sci., Docent, Head
 My Blomqvist, D.D.S., Dr.Med.Sci.
 Johnny Sundholm, M.D., Dr.Med.Sci.
 Mari Ylinen, M.D., Dr.Med.Sci.
 Linda Litwin, M.D., Dr.Med.Sci. in 2022
 (Medical University of Silesia, Katowice, Poland)
 Rasmus Olander, M.D., Dr.Med.Sci. in 2022
 Michelle Renlund, M.D.
 Essi Karikoski, M.Sc.
 Ines Kumpulainen, Medical student
 Max Nurmi, 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

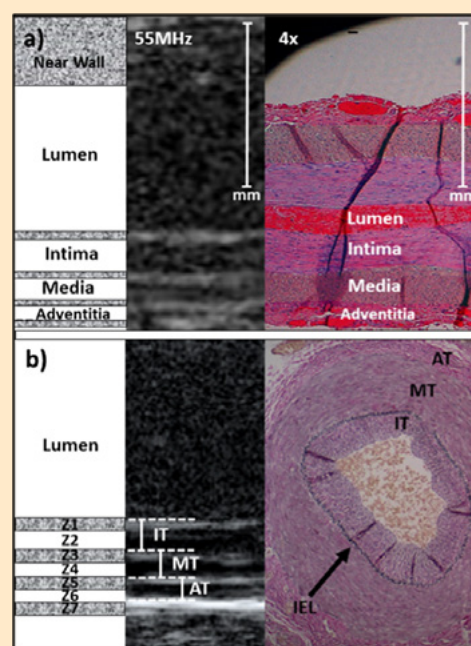


Figure. Schematic, 55MHz UHF-derived image, and corresponding histology of temporal arteries with evident intimal thickening. Leading edge borders are shown. IT – Intima; MT – Media; AT – Adventitia; IEL – Internal elastic laminae. Modified from Sundholm et.al. 2019, figure previously published in Sundholm J. Non-invasive vascular structure and pathology using very-high resolution ultrasound (Thesis) <https://helda.helsinki.fi/bitstream/handle/10138/305377/NON-INVA.pdf?sequence=1&isAllowed=y>

the completion of her PhD thesis and its defense in September 2022. One additional manuscript following her thesis on the relationship of physical activity to cardiovascular health parameters during early childhood is still in progress.

During the year, postdoc Johnny Sundholm's article was published showing within the RADIEL project that obese early middle-aged women have increased arterial intima-media thickness and brachial artery adventitia thickness compared to non-obese counterparts. Furthermore, the association between BMI and intima-media thickness is partly mediated through blood pressure levels.

During the year, Max Nurmi finalized his first article related to the accuracy of fetal cardiovascular assessments using ultrasound, supervised by Taisto Sarkola. The study showed fetal congenital heart disease diagnosis and counseling to be accurate and reliable overall between 2010-2020 at the New Children's Hospital (Helsinki University Hospital), and elaborated specific areas of uncertainty in clinical fetal cardiology practice that may be important to consider in fetal CHD evaluation and counseling provided in mid-gestation.

Ines Kumpulainen and Sofia Saxén continued their work on their Master's theses, supervised by Taisto Sarkola.

Ph.D. student Essi Karikoski continued her work processing the data within the ORALPEDHEART study supervised by My Blomqvist and co-supervised by Taisto Sarkola. One article was published showing that parents of children with congenital heart disease perceived an oral health promotion intervention as important and feasible to implement in daily life in children with systemic diseases overall. Further studies on the timing of first contact with families and the use of additional Web-based support are needed.

A manuscript on liver aspects in pediatric Mulibrey nanism was published with Taisto Sarkola as co-author. The study showed that echocardiography adds important information in non-invasive cardiovascular pediatric Mulibrey nanism follow-up and could be used in pericardiectomy decision-making.

The collaboration within the ADEF Helsinki (Alcohol/Drugs Exposure during Fetal life) consortium continued, with Ph.D. student Niina-Maria Nissinen supervised partly by Taisto Sarkola. One article was published that showed mood and neurotic disorders to be more common following prenatal exposure to substances and interlinked with significant adversities in the postnatal caregiving environment and out-of-home care.

Postdoc Mari Ylinen's article within the retrospective Coarctation of the aorta project was published, showing higher systolic blood pressure and hypertension in repaired coarctation of aorta to be related to increasing age at first procedure and arm-leg gradient at follow-up. Transverse arch and isthmus diameters at follow-up were inversely related to blood pressure.

Thesis completed in the group in 2022

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

Rasmus FW Olander. Early cardiovascular morphology, function, and health following abnormal foetal growth. June 3, 2022.

Publications 2022

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Karikoski E, Junttila K, Järvinen M, **Sarkola T,** Blomqvist M. Parental perceptions and experiences of an oral health care promotion intervention for children with congenital heart defects. *Int J Qual Stud Health Well-being.* 2022; 17:2070968.

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Olander RFW, Sundholm JKM, Suonsyrjä S, Sarkola T. Arterial health during early childhood following abnormal fetal growth. *BMC Pediatr.* 2022; 22:40.

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Sundholm JK, Litwin L, Rönö K, Koivusalo SB, Eriksson JG, **Sarkola T.** Ultra-high frequency ultrasound delineated changes in carotid and muscular artery intima-media and adventitia thickness in obese early middle-aged women. *Diab Vasc Dis Res.* 2022; 19:14791641221094321.

Ylinen MK, Pihkala JI, Salminen JT, **Sarkola T.** Predictors of blood pressure and hypertension long-term after treatment of isolated coarctation of the aorta in children-A population-based study. *Interact Cardiovasc Thorac Surg.* 2022; 35:ivac212.

Cardiovascular research

Main research activities

Our research group studies the molecular mechanisms of cardiac injury and repair after myocardial infarction and in heart failure, to identify potential targets for cardiovascular medicines and novel biomarkers. In these studies, a translational approach is applied, combining methods and findings from both basic science and clinical research in order to improve the evaluation and treatment of cardiovascular diseases. The main projects worked on during 2022 are presented below.

Role of heme oxygenase-1 (HO-1) in cardiovascular diseases

HO-1 and its reaction products, carbon monoxide (CO), biliverdin, and bilirubin, have a variety of cardiovascular protective properties. The promoter region of HMOX1 contains a guanine–thymine (GT) microsatellite repeat. A long GTn repeat decreases HO-1 expression and is associated with cardiometabolic diseases and pre-eclampsia. We continued the collaboration with Prof. Per-Henrik Groop and the FinnDiane Study Group, HU, Helsinki University Hospital (HUCH), and the Folkhälsan Institute of Genetics, to study the role of HO-1 and HO-1 gene polymorphisms in the development of cardiovascular and renal complications in type 1 diabetes.

New molecular mechanisms and biomarkers of cardiac injury and heart failure

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

Figure. Zebrafish echocardiographic imaging. Left panel: Longitudinal axis image of adult heart. V, ventricle outlined in red. Right panel: Pulsed-wave Doppler interrogation of atrioventricular inflow. E, early diastolic wave; A, atrial systolic wave. Courtesy of Hong Wang.

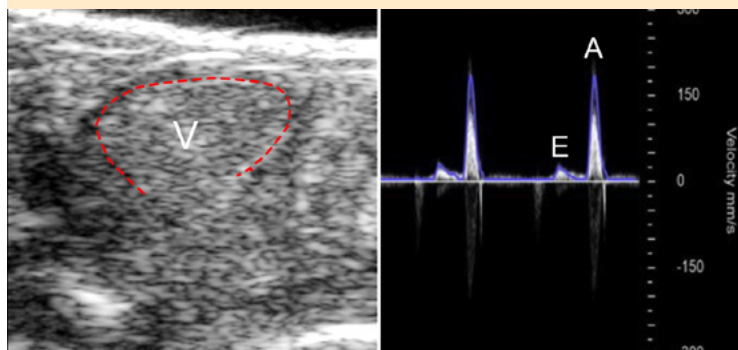


Group members

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

External funding

Aarne Koskelo Foundation
Finnish Cultural Foundation
Finnish Foundation for Cardiovascular Research
Finnish Foundation for Laboratory Medicine
Finnish Society of Clinical Chemistry
Medical Society of Finland
Medicinska Understödsföreningen Liv och Hälsa r.f.
Research Funding of the Helsinki-Uusimaa Hospital District
(state funding for university-level health research)



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 2022.

We have used a multiomics approach to identify dysregulated signaling pathways and potential target molecules for new therapies in end-stage heart failure, in collaboration with prof. Juha Sinisalo (Wang C et al., 2022). The most significant dysregulation was found in pathways regulating cardiac metabolism and muscle contraction. We identified alterations in the PKA/cAMP and PKG/cGMP signaling pathways, suggesting that they may play a major role in the progression of heart failure. In another study, we found increased expression of tankyrases in failing human hearts and investigated their role as potential therapeutic targets (Wang H et al., 2022). Tankyrase inhibition protected against cardiac dysfunction by regulating Wnt/ β -catenin signaling in a zebrafish isoproterenol-induced heart failure model. The translational potential of this finding is high, as tankyrase inhibitors are already in clinical trials for various diseases.

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 a severe state of inadequate systemic tissue perfusion due to low cardiac output, often resulting in multiorgan failure. In-hospital mortality is close to 40% even with current treatment. New biomarkers to stratify CS patients according to their risk and to optimize treatment are needed. We have shown earlier in collaboration with Adj. Prof. Veli-Pekka Harjola, HUCH, and Dr. Yvan Devaux, the Luxembourg Institute of Health, that miR-21-5p, miR-320a-3p, and miR-423-5p were independent predictors of 90-day all-cause mortality, indicating the potential of miRNAs as biomarkers for risk assessment in CS. Our studies on miRNA biomarkers in CS continued during 2022. We are also investigating the role of miRNAs in the development and progression of heart failure using experimental models.

During 2022, 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. We have contributed to the writing of two recently published guidelines by CardioRNA COST action (De Gonzalo-Calvo et al., 2022; Lakkisto et al., 2022). The purpose of the guidelines is to improve the reproducibility and standardization of RNA quantification and thus facilitate the incorporation of RNA biomarkers into clinical practice in the future.

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.

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Cellular neuroscience

Main research activities

To understand how the brain works, it is fundamental to understand how neurons and different parts of neurons work. Neurons are unique cells, with highly polarized morphology and specialized domains. Dendrites receive incoming signals and bring electrical and biochemical signals to the soma. The axon extends from the soma and contains the axon initial segment (AIS) in the proximal region.

Our research uses the methods of cell biology (confocal and super-resolution imaging), but the impact lies in neuroscience. The overall common idea in our projects is to study how the actin cytoskeleton affects neuronal functions. The ultimate goal of the group is the better understanding of the relationship of neuron structure and function. What happens if a neuron is built in an abnormal way? How do differences in the neuronal structures affect neuronal functions? This builds a bridge to neurological diseases. What cellular changes cause neurological disease symptoms?

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

Neurons

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

The axon initial segment (AIS) is the site of action potential initiation. At same time, the AIS serves as a barrier between dendrites and axons, by sorting vesicles and proteins to the axon or somatodendritic compartment. The majority of excitatory synapses in the central nervous system exist on small bulbous structures on dendrites known as dendritic spines. The dendrites



Group members

Pirta Hotulainen, Ph.D., Docent, Head,
The Sigrid Jusélius senior researcher
Aqsa Jabeen, M.Sc.
Pushpa Khanal, M.Sc.
David Micinski, M.Sc.
Emilia Toissalo, M.Sc.
Elizaveta Boiko, B.Sc. (shared student with Vesa Olkkonen)
Alexei Kramm, B.Sc., Summer student

External funding

Medicinska Understödsföreningen Liv och Hälsa r.f.
Sigrid Jusélius Foundation
University of Helsinki Brain and Mind graduate school
(Pushpa Khanal and David Micinski)

of a single neuron can contain hundreds to thousands of spines. During learning, new spines will appear. At the same time, other spines and synapses will be removed. Thus, dendritic spines can be considered 'memory units' or 'stuff that memories are made of.' Through adding or removing, or strengthening or weakening, these units, the brain modulates its function. By reorganizing synaptic pathways, new skills are stored in the brain. Precise control of dendritic spine morphology and density, as well as the length and location of AISs, is critical for normal brain function.

In psychiatric diseases, the number, strength, and selectivity of the contacts between neurons is often altered. For example, in autism spectrum disorder (ASD), there are too many weak connections and they are poorly selected. In schizophrenia, there is a loss of connections. The question is, what are the mechanisms underlying these defects in connections at the single neuron level? This is not an easy question as many steps in brain development or later in adulthood plasticity can go wrong. There can be problems in producing different cell types in the beginning of brain development. When neurons have formed, dendrites or axons may grow and branch wrong. When dendrites are on place, there can be abnormal dendritic spine formation or stabilization.

Most of our projects are fundamental research where we elucidate molecular mechanisms underlying neuronal functions. We have characterized molecular mechanisms for different steps of dendritic spine morphogenesis. We have also studied how neuronal activity affects regulation of the actin cytoskeleton. Currently we are interested in proteins initiating spines in a neuron activity-dependent manner. We are also investigating different ways to regulate spine initiation factors, and a new line of research is focusing on miRNA-regulation.

In addition, we aim at a comprehensive understanding of how proteins are organized into AIS, focusing on the role of actin regulation. This branch of research was started by Amr Abouelezz, who defended his Ph.D. thesis at the beginning of 2020. David Micinski has continued these studies, focusing on the mechanisms of actin polymerization in the AIS. In 2022, David and Amr described the super-resolution imaging methodology used in AIS studies in Micinski et al. (2022).

The brain

At the level of the brain, our main question is, how does the brain control behavior and, especially, how do defects in neurons affect behavior? At the level of the brain, we have mainly studied the role of spine initiation factor MIM in development, controlling behavior, and aging (Saarikangas et al., 2015; Minkeviciene et al., 2019). Currently we are elucidating the role of ASD- and schizophrenia-linked myosin XVI in the brain.

Awards, honors, and positions of trust

Docent Pirta Hotulainen: Chair of Brain Research Society of Finland; Vice Chair of the FENS-Kavli network; Member of national long Covid group (Health Ministry); listed among 100 Health Influencers in Finland 2022 (Mediuutiset).

Publications 2022

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Micinski D, Lahti L, Abouelezz A. Measuring Properties of the Membrane Periodic Skeleton of the Axon Initial Segment using 3D-Structured Illumination Microscopy (3D-SIM). *J Vis Exp.* 2022; 180.

Health ministry national long covid expert group (**P. Hotulainen**) (In Finnish): Pitkäkestoinen COVID-19 –STM:n nimittämän asiantuntijaryhmän konsensuslausuma 7.1.2022. https://api.hankeikkuna.fi/asiakirjat/241a9421-540f-41ee-bd23-68713de7a527/766c5113-ab91-43d8-a041-d491a45c06ed/YHTEENVETO_20221222120933.pdf

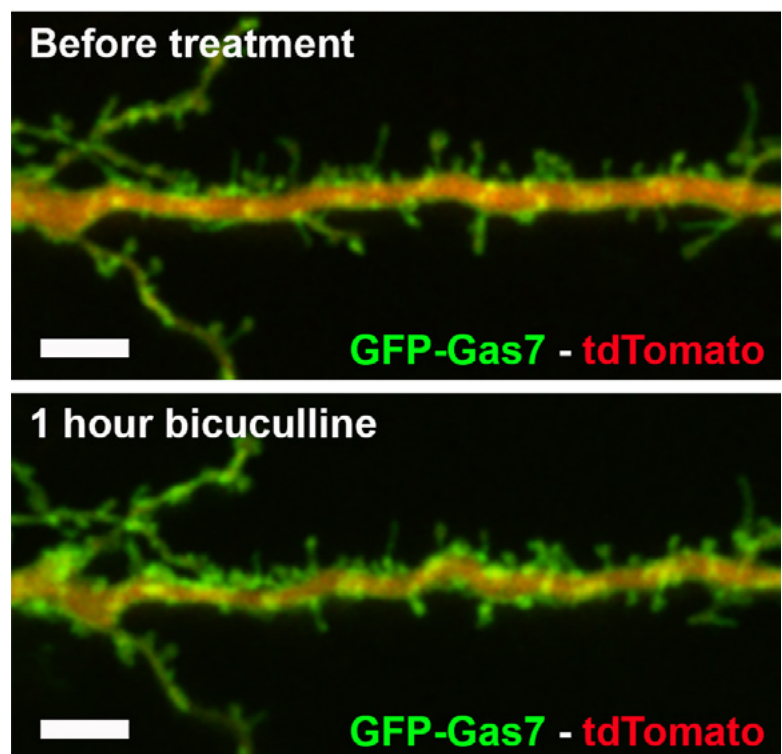


Figure. Gas7-protein clusters upon neuron activation. Dendrite of GFP-Gas7 (green) and tdTomato (red) expressing hippocampal pyramidal neuron in DIV12 organotypic slice. Dendrite was imaged before treatment and 1 hour after bicuculline treatment. Bicuculline inhibits inhibitory neurons and this inhibition activates excitatory neurons. Gas7 clusters upon bicuculline treatment. Experiment and picture: Pirta Hotulainen/Zoran Boskovic.

Fatty liver disease and diabetes

Main research activities

We have continued mechanistic in vivo and in vitro studies addressing the mechanisms underlying subtypes of NAFLD in humans caused by metabolic dysfunction ('Metabolic NAFLD'), and by common genetic risk-modifying variants in PNPLA3, TM6SF2, MBOAT7, HSD17B13 and MARC1 ('Genetic NAFLD').

We have recently shown that the pathogenesis of NAFLD in these two subtypes is strikingly different. 'Metabolic NAFLD' is characterized by hyperinsulinemia, hepatic oversupply of substrates (glucose, amino acids, fatty acids), increased hepatic *de novo* lipogenesis and adipose tissue insulin resistance. In contrast, 'Genetic NAFLD' is not characterized by any substrate excess but by increased hepatic mitochondrial redox state and inhibition of hepatic pathways dependent on tricarboxylic acid activity, such as *de novo* lipogenesis.

The amount of fibrosis in the liver is the key prognostic factor in NAFLD. To this end, we have recently demonstrated that first-degree relatives of individuals with NAFLD with advanced fibrosis have a significant, 12-fold increased risk of advanced fibrosis as compared to those without a family history of advanced NAFLD. Our results, which were confirmed in an independent cohort in the US, suggest that routine screening for the first-degree relatives of patients with advanced fibrosis is warranted.

We have also developed 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).



Group members

Hannele Yki-Järvinen, M.D., Dr.Med. Sci., F.R.C.P, Professor, Head (January 1 – February 28)
Panu Luukkonen, M.D., Dr.Med.Sci. Docent, Head (from March 1)
Kimmo Porthan, M.D., Dr.Med.Sci., Docent
Laura Granö, M.D., Dr.Med.Sci
Mari Lahelma, M.D., Dr.Med.Sci. in 2022
Noora Ahlholm, M.D.
Sami Qadri, M.D.
Sanja Sädevirta, M.D.
P.A. Nidhina Haridas, Ph.D.
You Zhou, Ph.D.
Juho Asteljoki, B.Sci.
Mari Jokinen, B.Sci.
Anni Poikola, Medical student
Aila Karioja-Kallio, Laboratory technician, Research nurse
Päivi Ihmuotila, Laboratory technician, Research nurse

External funding

Academy of Finland
EU H2020 Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS), 2017–2023 (project 777377)
Finnish Medical 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

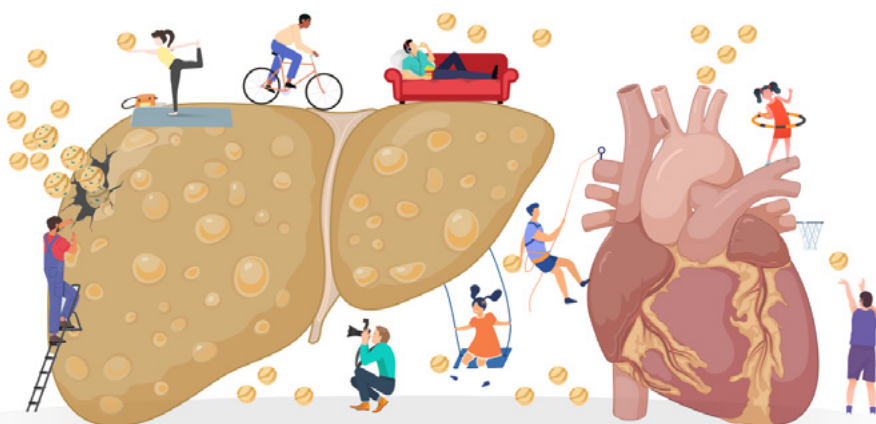


Figure. Lifestyle factors modifying cardiometabolic health. Courtesy of Mari Lahelma. Created with BioRender.com and Freepik.com.

Thesis completed in the group in 2022

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

Mari Lahelma. Lifestyle factors and lipid metabolism in non-alcoholic fatty liver disease, the metabolic syndrome, and atherosclerotic cardiovascular disease. December 16, 2022.

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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 2022, the major activity in the group was directed at understanding the role of the endoplasmic reticulum (ER)-late endosome MCS protein Protrudin/ZFYVE27, in endothelial cell (EC) functions. The protein was found to play a crucial role in angiogenesis both *in vitro* and *in vivo*, the underlying mechanism being pinpointed at the activity of focal adhesion kinase crucial for cell motility (Arora et al., 2022). The other activity focused on MCS function in EC addressed the global effects of pharmacological inhibition of OSBP, a cholesterol-PI4P exchanger at ER-*trans*-Golgi MCS. Lipidomic and transcriptomic as well as imaging and biochemical analyses of the inhibitor treated cells revealed major effects on EC cholesterol, sphingolipid, and glycerophospholipid homeostasis as well as on the gene expression of ER stress-related pathways, likely reflecting cholesterol accumulation in the ER (Taskinen et al., 2022). In further collaborative studies on MCS, we have contributed to functional analyses of ORP4L, which mediates phosphatidylinositol 4-phosphate transport from the Golgi to the plasma membrane in leukemia cells (Zhong et al., 2022), as well as ORP5 and -8, which mediate phosphatidylserine transport from the ER to mitochondria (Monteiro-Cardoso et al., 2022).

A second important activity in the group in 2022 focused on the dysregulation of adipocyte metabolism under conditions of insulin resistance; more specifically the function of the insulin-regulated thyroid hormone responsive protein (THRSP). The THRSP mRNA is during euglycemic, hyperinsulinemic clamp strongly induced in



Group members

Vesa Olkkonen, Ph.D., Professor, Head
 Kid Törnquist, Ph.D., Professor
 Matti Jauhiainen, Ph.D., Adjunct professor
 Amita Arora, Ph.D.
 Muhammad Yasir Asghar, Ph.D.
 Dan Pham Duc, Ph.D.
 P.A. Nidhina Haridas, Ph.D.
 Zdrune Polianskyte-Prause, Ph.D.
 Maria Ahonen Mehmeti, M.Sc., Ph.D. in 2022
 Vaishali Chaurasiya, M.Sc.
 Taru Knuutinen, M.Sc.
 Meghana Nagaraj, M.Sc.
 Ilari Pulli, M.Sc.
 Juuso Taskinen, B.Engin., M.Sc.
 Elizaveta Boiko, B.Sc. (shared student with Pirta Hotulainen)
 Ida Hilska, B.Sc.
 Riikka Kosonen, M.Sc., Laboratory technician
 Sanni Perttunen, B.Sc. Laboratory technician

External funding

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

white adipose tissue, the response being dampened in insulin-resistant subjects. In cultured SGBS adipocytes, knock-down of THRSP resulted in mitochondrial dysfunction and a disturbance of sphingolipid metabolism, indicating how its reduced expression in insulin-resistant adipose tissue may contribute to metabolic disease (Ahonen et al., 2022). In 2022, we launched a new major project to investigate molecular defects in the communication between adipocytes and endothelial cells in obese white adipose tissue. During the year, we have set up and optimized a methodology for isolation of the two cell types from human visceral adipose biopsies and started collection of cell material from patients operated on at Jorvi Hospital.

In a Ph.D. 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 hepatocellular carcinoma cells. The results demonstrated impacts of GOLM1 knock-down on lipid homeostasis, mitochondrial function, Golgi apparatus integrity and cell proliferation (Nagaraj et al., 2022). Our observations suggest that GOLM1 could be employed as a new therapy target for diseases of the liver.

In ongoing collaborative research we aim to understand the role of lipoproteins and their regulatory factors in cardiometabolic diseases but also in cancer. Previous research identified lipid metabolic pathways to be highly enriched in pancreatic ductal adenocarcinoma (PDAC) cells. We have demonstrated that HDL-mediated efficient cholesterol removal from cancer cells results in PDAC cell growth reduction and induction of apoptosis *in vitro*. This effect is driven by an HDL particle composition-dependent interaction with SR-B1 and ABCA1 on cancer cells. AAV-mediated overexpression of APOA1 and rHDL injections decreased PDAC tumor development *in vivo*. We conclude that efficient, HDL-mediated cellular cholesterol depletion represents an interesting strategy to interfere with the aggressive growth of PDAC (Oberle et al., 2022).

Neutrophil proteinase 3 (PR3) is a multifunctional neutral serine protease involved in the regulation of pro-inflammatory processes, but its potential causal roles in the lipid-driven responses in atherosclerosis have remained unexplored. Atherosclerotic lesions but not normal

intima contained PR3. Cultured human monocyte-derived macrophages avidly ingested the PR3-modified LDL particles and were converted into foam cells. Incubation of HDL particles with PR3 led to proteolysis of their major apolipoproteins (apoA-I, apoA-II, and apoE) and impaired their ability to promote cholesterol efflux from macrophage foam cells. Thus, by proteolytically modifying LDL and HDL particles, PR3 may promote cholesterol accumulation both extra- and intracellularly in atherosclerotic lesions (Nguyen et al., 2022).

In our efforts to develop novel HDL analytical methods for clinical use, time-resolved fluorescence (TRF) based direct two-site apoA-I immunoassays were established using recombinant apoA-I antibodies generated against HDL particles from plasma of patients with coronary artery disease (CAD). We evaluated the clinical performance among patients with suspected obstructive CAD. The direct two-site apoA-I assay showed a similar prediction of atherosclerosis as the Framingham Risk Score (FRS). Assays targeting heterogeneity in HDL's main apolipoprotein, apoA-I, could provide a potential approach to improve the identification of patients at risk of developing CAD (Negi et al., 2022).

We have continued with our research on the significance of calcium signaling in thyroid cancer cells. We have shown that the expression of two important thyroid transcription factors, thyroid hormone receptor beta 1 (TR β 1), and Runx-related transcription factor 2 (Runx2), are regulated by calcium signaling (Asghar et al., 2022). Blocking calcium entry in thyroid cancer cells increased the protein level of TR β 1, whereas that of Runx2 was downregulated. We also showed the expression of the TR β 1 protein is downregulated in human thyroid cancer tissues and cell lines compared with the normal thyroid tissues and a primary cell line, whilst that of Runx2 is upregulated. Overexpression of TR β 1 in thyroid cancer cells attenuated proliferation and invasion, and increased the expression of the thyroid-specific proteins thyroglobulin, thyroperoxidase, and thyroid transcription factor-1. Furthermore, together with Prof. Dan Lindholm we have continued a project related to the role of autophagy in thyroid cancer cells.

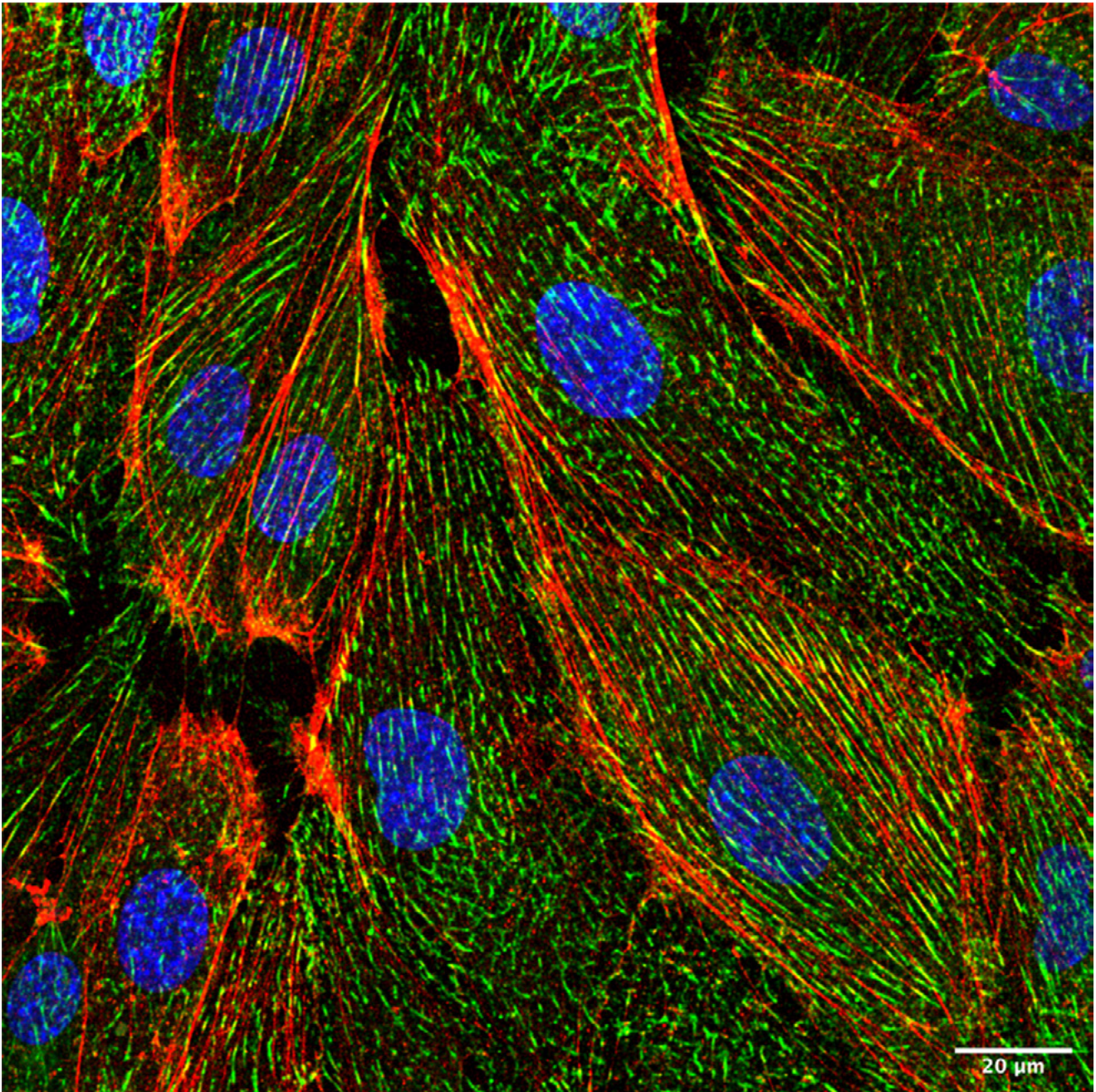


Figure. Human umbilical vein endothelial cells stained with DAPI (nucleus, blue), Alexa-594 phalloidin (actin filaments, red) and anti-integrin beta 1 (green). Courtesy of Amita Arora.

Thesis completed in the group in 2022

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

Maria Ahonen Mehmeti. Mechanisms of adipocyte dysfunction in metabolic disease and cancer. December 9, 2022.

Publications 2022

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Membrane biology

Main research activities

Our group focuses on studying how major membrane lipids are transported in mammalian cells, how the dynamic storage and mobilization of lipids dictates organelle communication and cellular metabolism, and how defects in these processes can give rise to human diseases. To this aim, we also develop techniques 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 2022, we reported on the crosstalk between endoplasmic reticulum (ER), lipid droplets, and mitochondria during adipogenesis and mitophagy; we established an automated imaging platform for profiling lipid storage in primary human leukocytes; and we revealed early lipid metabolic changes in human pancreatic cancer.

A key protein regulating the formation of the cellular lipid storage sites, lipid droplets, from the ER is seipin. Loss-of-function mutations in this protein lead to the most severe characterized human lipodystrophy, and we have earlier elucidated how this protein controls lipid droplet biogenesis (e.g. Salo et al., 2019; Prasanna et al., 2021). We have now shown that seipin can also localize to ER membranes that form contacts with mitochondria and that seipin plays a role in mitochondrial calcium import and metabolism needed for adipogenesis (Combot et al., 2022). We have also discovered unexpected synergies between lipid metabolism and mitophagy, i.e. autophagic degradation of mitochondria, by revealing that DGAT1-dependent lipid droplet biogenesis regulates the progression of mitophagy *in vivo* (Long et al., 2022).

We established an imaging platform for quantifying lipid uptake, storage, and mobilization from human leukocytes from a few milliliters of blood and demonstrated as a proof-of-principle how this may be used to assess the efficacy of cholesterol-lowering medication (Pfisterer et al., 2022). Commercialization of a new personalized diagnostic test for scrutinizing optimal cholesterol medication is in progress by our previous group member, Simon Pfisterer.



Group members

Elina Ikonen, M.D., Dr.Med.Sci., Professor (Director), Head
Maarit Hölttä, Ph.D., University lecturer
Kristiina Kanerva, Ph.D.
Shiqian Li, Ph.D.
Heljä Lång, M.D.
Viola Nähse, Ph.D.
Juho Pirhonen, M.D.
Miesje van der Stoel, Ph.D.
Lauri Vanharanta, M.D.
Xin Zhou, Ph.D.
Haoran Li, M.Sc.
Ábel Szkalitsity, M.Sc.
Päivi Kleemola, Research assistant
Bibi Hannikainen, 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
Sigrid Jusélius Foundation
University of Helsinki, DPBM and ILS doctoral programs
University of Helsinki, Research Excellence and Infrastructure Funding (HiLIFE)

In collaboration with investigators from the Helsinki University Central Hospital, Lund University, and Biological Research Center in Szeged, we discovered that in clinically operable pancreatic cancer, regions distant from the malignant areas that appear histologically normal display alterations in lipid transport and metabolism (Pirhonen et al., 2022). These changes are prognostic for survival and may be pharmacologically targeted. We validated these initial findings made with 14 patients in 51 additional patients from two cohorts.

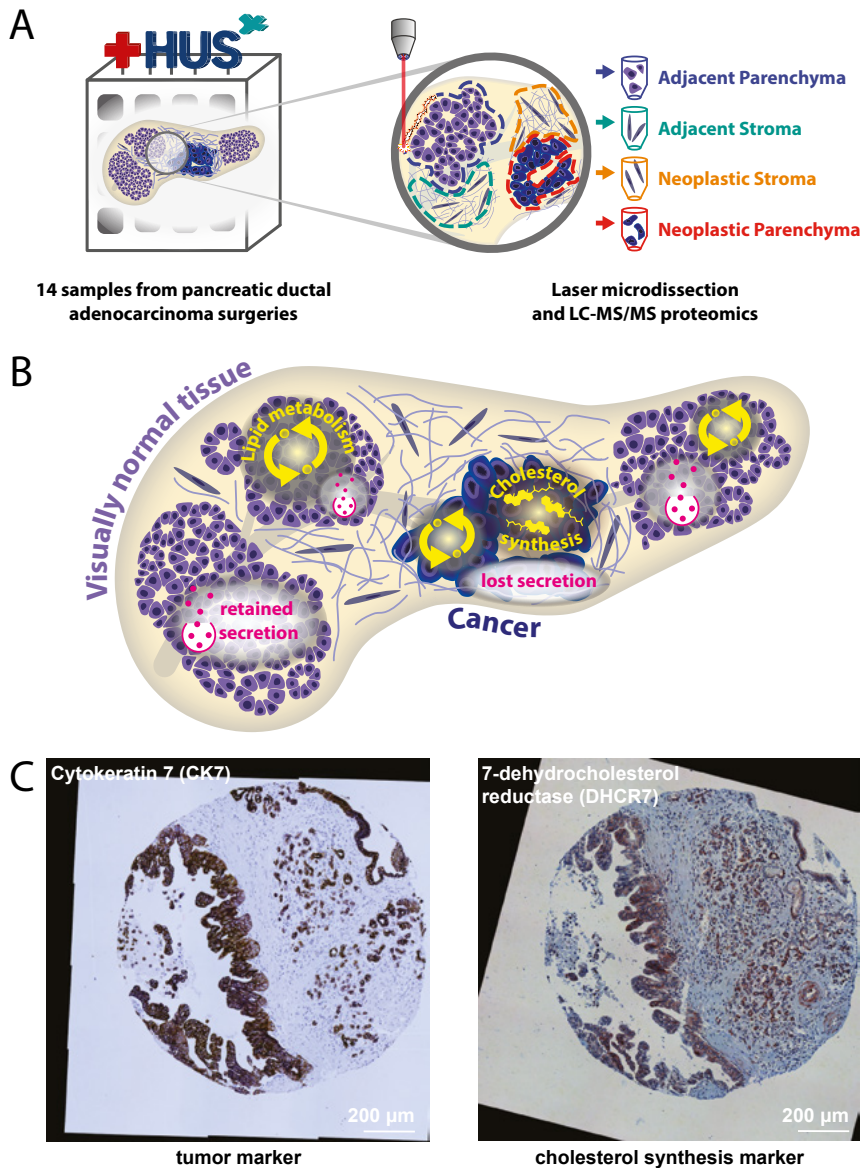


Figure. Lipid metabolic reprogramming in pancreatic cancer. A. Study design, B. Key findings, C. Exemplary immunohistochemical stainings of tumor microarrays (courtesy of Abel Szkalitsity, see Pirhonen et al. Cancer Res 2022 for details).

Awards, honors, and positions of trust

Prof. Elina Ikonen: Vice-Dean of Research at the Faculty of Medicine, University of Helsinki in May 2022; Member of Academia Europaea in June 2022.

Publications 2022

Combot Y, **Salo VT**, Chadeuf G, **Höltkä M**, **Ven K**, Pulli I, Ducheix S, Pecqueur C, Renoult O, Lak B, **Li S**, Karhinen L, Belevich I, Le May C, Rieusset J, Le Lay S, Croyal M, Tayeb KS, Vihinen H, Jokitalo E, **Törnquist K**, Vigouroux C, Cariou B, Magré J, Larhlimi A, **Ikonen E***, Prieur X*. Seipin localizes at endoplasmic-reticulum-mitochondria contact sites to control mitochondrial calcium import and metabolism in adipocytes. *Cell Rep.* 2022; 38:110213. *co-corresponding authors

Long M, Sanchez-Martinez A, Longo M, Suomi F, Stenlund H, Johansson AI, Ehsan H, **Salo VT**, Montava-Garriga L, Naddafi S, **Ikonen E**, Ganley IG, Whitworth AJ, McWilliams TG.

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Pfisterer SG, **Brock I**, **Kanerva K**, Hlushchenko I, Paavolainen L, Ripatti P, Islam MM, Kytälä A, Di Taranto MD, Scotto di Frega A, Fortunato G, Kuusisto J, Horvath P, Ripatti S, Laakso M, **Ikonen E**. Multiparametric platform for profiling lipid trafficking in human leukocytes. *Cell Rep Methods.* 2022; 2:100166.

Pirhonen J, **Szkalitsity A**, Hagström J, Kim Y, Migh E, Kovacs M, Höltkä M, Peränen J, Seppänen J, Haglund C, Gil J, Rezeli M, Malm J, Horvath P, Marko-Varga Gy, Puolakkainen P, and **Ikonen E**. Lipid metabolic reprogramming extends beyond histological tumor demarcations in human operable pancreatic cancer. *Cancer Res.* 2022; 82: 3932.

Pirhonen J, **Szkalitsity A**, Hagström J, Kim Y, Migh E, Kovacs M, Höltkä M, Peränen J, Seppänen H, Haglund K, Gil J, Rezeli M, Malm J, Horvath P, Marko-Varga G, Puolakkainen P, and **Ikonen E**. Rasva-aineenvaihdunnan muutos ulottuu histopatologisesti normaaleille alueille leikatuissa haimasyövissä. *Duodecim.* 2022; 22: 2041.

Metabolism

Main research activities

Our research group is interested in the regulation of metabolism and especially in the molecular mechanisms that lead to the development of insulin resistance in human skeletal muscle. As a research model, we are using primary muscle cell cultures that have been established from muscle biopsies obtained from clinically carefully characterized volunteers. As part of the ongoing genetic analyses of the FUSION (Finland-United States Investigation of NIDDM Genetics) 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. We have continued our work to characterize the action of insulin on glucose metabolism and intracellular signaling events in myotubes from p.P50T/AKT2 variant carriers.

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 (head principal investigator (PI) Prof. Michael Boehnke, University of Michigan, Ann Arbor, USA), with the head of the group, Docent Heikki Koistinen, being one of the FUSION PIs. As part of FUSION, we have participated in large collaborative efforts that have revealed novel genetic associations and mechanisms that impact blood lipid concentrations (Hindy et al., 2022; Kanoni et al., 2022; Ramdas et al., 2022), and have described a comprehensive map of genomic regions that contain most of the common variants that affect height (Yengo et al., 2022). We have found that people with adverse cardiometabolic phenotype have lower expression of angiotensin I converting enzyme 2 (ACE2) in subcutaneous adipose tissue (El-Sayed Moustafa et al., 2022).

Urocortin neuropeptides play a role in regulating energy homeostasis, and low-grade inflammation is a risk factor for development of metabolic syndrome. In collaborative projects, we have observed alterations in plasma concentrations of urocortin neuropeptides as well as alterations in the expression of urocortin neu-



Group members

Heikki Koistinen, M.D., Dr.Med.Sci., Docent, Head
Sreesha Sree, Ph.D.
Selina Mäkinen, M.Sc.
Leena Kinnunen, Ph.C.

External funding

Finnish Cultural Foundation
Medical Society of Finland
Research Funding of Helsinki-Uusimaa Hospital District
(state funding for university-level health research)

ropeptide mRNAs in peripheral blood mononuclear cells in samples obtained from overweight children (Kavalakatt et al., *Nutrients* 2022 and *Obesity* 2022). We also observed increased concentrations of IL-23 mRNA in subcutaneous adipose tissue samples from people with increased LDL-cholesterol concentration (Kochumon et al., 2022a), and found an association between adipose tissue expression of steroid receptor RNA activator and Toll-like receptors and interferon regulatory factors in people with obesity and/or type 2 diabetes (Kochumon et al., 2022b).

Awards, honors, and positions of trust

Docent Heikki Koistinen: Chair of the Board of the Finnish Diabetes Research Society; Vice-member of the collegium of University of Helsinki; Årets svenskspråkiga lärarbragd 2022, Medicinarklubben Thorax (an annual prize for teachers' deeds awarded by the Swedish-speaking medical students' organization Thorax at the University of Helsinki).

Thesis completed in the group in 2022

The following Master's theses supervised by Dr. Koistinen (students not affiliated to Minerva) were accepted at the University of Helsinki this year:

Henrik Ahlstrand. Functional hypogonadism in type 2 diabetes and metabolic syndrome: the role of testosterone replacement therapy.

Melinda Tiderman. Esidiabeteksen eri muodot ja niiden merkitys terveydelle: kirjallisuuskatsaus.

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

Sina Antony Kavalakatt. Urocortin 3 in obesity and type 2 diabetes. March 23, 2022.

Publications 2022

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- Selänne J, **Koistinen H**. Hyponatremia päivystäjän päänsärkynä. *Duodecim*. 2022; 138:2003-10.
- Yengo L et al., A saturated map of common genetic variants associated with human height. *Nature*. 2022; 610:704-712.

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 2022, we worked on three main areas of research.

Role of USP14 and its phosphorylation in protein degradation in neurons

USP14 is a deubiquitinating enzyme associated with the proteasome and important for protein degradation. We previously noted that inhibition of proteasome activity reduced the amount of bound USP14, and identified the chaperone, HSC70, and the autophagy regulator, GABARAP, as binding partners for USP14. Using quantitative mass spectrometry, we observed that USP14 can undergo posttranslational modifications (PTMs) such as phosphorylation in human neuroblastoma cells. During the last year, we have studied the functional significance of the phosphorylation of specific serine residues protein in Usp14 for its activity in neuron cells including primary neurons isolated from rodent brains (manuscript).

In collaboration with Prof Kid Törnquist and Dr Yasir Asghar at Minerva, we have further studied the role of USP14 and its inhibition in tumor cells using a thyroid cancer cell model (manuscript in preparation)

Group members

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

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Neurotrophic factors in models of Huntington's disease

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 (Ajovalaby 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 PD (Voutilainen et al., 2015). CDNF also has a protective role in striatal neurons against neurotoxin quinolinic acid by reducing ER stress (Stepanova et al., 2020). We have now studied CDNF further in a genetic model for HD, the N171-82Q mice (manuscript re-submitted). 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 altered in striatal neurons expressing 109Q-containing mutant huntingtin protein (manuscript under preparation). The mechanisms of action of CNPY2 are currently under investigation using different cell models as well as gene knock-out mice.

Altered antibody immune response in human diseases including neuropsychiatric disorders

We have participated in an EU-funded collaboration, SZ_TEST, to study antibody immune responses in human diseases using a novel next-generation phage display method, mimotope-variation analysis (MVA). Using MVA, the consortium identified a reduced antibody response to a peptide antigen found in the poliovirus sequence in patients with major cardiac events including heart infarction (Pupina et al., 2022). MVA also proved instrumental in studying antibody responses against SARS-CoV-2 spike protein in different individuals (Jaago et al., 2022). Current studies are focused on the analysis of serum samples and immune reactivity in control and schizophrenia patients obtained from the Helsinki Biobank and Tartu University (manuscript under preparation).

Awards, honors, and positions of trust

Prof. Dan Lindholm: Chair of the Biology section in The Finnish Society of Sciences and Letters.

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Original articles

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

Tel. +358 2 941 25701

www.minervafoundation.fi
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