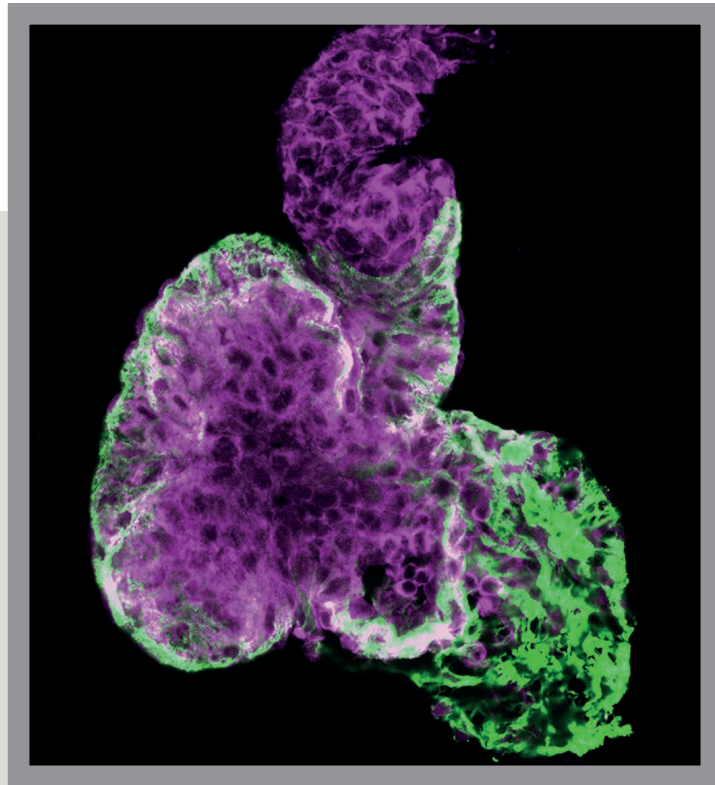




MINERVA FOUNDATION &
MINERVA FOUNDATION INSTITUTE
FOR MEDICAL RESEARCH



Scientific Report 2020



Front page image. Immunostaining of embryonic zebrafish heart at 4 days post fertilization showing high expression of Tankyrase 1 (magenta). Green represents myosin heavy chain staining for myocardium (courtesy of Hong Wang, Cardiovascular Research).

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SUMMARY OF RESEARCH AND ACTIVITIES IN 2020

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 2020 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 in 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 in 2020, covered half of the total Institute budget. During the year 2020, a total of 62 articles were published, from which 58 in international peer-reviewed journals, the median impact being 4.56. Moreover, M.Sc. Amr Abouelezz, M.D. Veijo Salo, M.Sc. Dan Duc Pham and M.Sc. Hanna Ruhanen defended their doctoral theses in 2020.

The year 2020 was exceptional due to the global Covid-19 pandemic, which reached Finland after the winter holiday season at the end of February. For the first time since the Second World War, the government employed an emergency law, which allowed, for example, restrictions on gatherings of people and their mobility in and out of the Uusimaa district. Along with the University of Helsinki, Minerva applied from the latter half of March a recommendation to work remotely and limited the number of laboratory personnel simultaneously present at the institute premises initially, in March-April to two, and then in May-June to six at a time, and work in two shifts was implemented. At the time of writing, the remote work recommendation is still valid, the maximum number of persons allowed in each office room is two, and use of a breathing mask is strongly recommended when working in common laboratory spaces. At the moment we are experiencing the second wave of the pandemic; It is possible that new, strict restrictions for work at Minerva could again become necessary. A third wave of the pandemic is predicted to occur in early 2021, but on the other hand, several efficient vaccines are on the way, bringing hope that the disease will finally be conquered in 2021.

Despite the Covid-19 pandemic, the Institute thrived in 2020 both scientifically and financially, and moves into 2021 with optimism and determination.

EVENTS AT MINERVA 2020

Seminar and Symposium

MINERVA SEMINAR, BIOMEDICUM HELSINKI

Christophe Leterrier, Institute of Neurophysiopathology, Faculty of Medical and Paramedical Sciences, Marseille, France.

The axonal cytoskeleton at the nanoscale. February 27, 2020.

MINERVA AND WIHURI INSTITUTES SYMPOSIUM

Translational insights into organ-specific vasculature

Read more on page 10.

Prizes and Grants

MEDIX PRIZE OF THE MINERVA FOUNDATION

Award Ceremony and Prize Lectures, webinar, September 14, 2020.

The winning article:

Notum produced by Paneth cells attenuates regeneration of aged intestinal epithelium. *Nature*. 2019;571:398-402.

Authors: Penttimikko N, Iqbal S, Mana M, Andersson S, Cognetta AB 3rd, Suciu RM, Roper J, Luopajarvi K, Markelin E, Gopalakrishnan S, Smolander OP, Naranjo S, Saarinen T, Juuti A, Pietiläinen K, Auvinen P, Ristimäki A, Gupta N, Tammela T, Jacks T, Sabatini DM, Cravatt BF, Yilmaz ÖH, Katajisto P.

Read more on pages 6–7.

RALPH GRÄSBECK SCHOLARSHIP FOR RESEARCH IN LABORATORY MEDICINE

Panu Luukkonen, Department of Internal Medicine, Yale University School of Medicine, New Haven, USA.

Read more on pages 8–9.

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

From Selma and Maja-Lisa Selander's fund 16 grants were awarded 2020, in all 119.500 EUR.

The following theses were accepted at the University of Helsinki in 2020:

DOCTORAL THESES

Amr Abouelezz: The structure and dynamics of the actin cytoskeleton in the axon initial segment. University of Helsinki, February 28, 2020. (Cellular Neuroscience)

Veijo Salo: Lipogenic subdomains of the ER: the role of seipin. University of Helsinki, April 17, 2020. (Membrane Biology)

Dan Pham Duc: Novel roles of p75 neurotrophin receptor in Low-density lipoprotein receptor regulation and lipid signaling. University of Helsinki, June 4, 2020. (Neuronal Signaling)

Hanna Ruhanen: Hepatic lipid metabolism in cardiometabolic diseases – protective and adverse effect of genetic variants. University of Helsinki, October 13, 2020. (Lipid Signaling and Homeostasis)

MASTER'S THESES

Jenny Lindholm: Metaboliska och antropometriska skillnader hos pre-eklamptiska respektive icke pre-eklamptiska mödrar samt deras barn. (Cardiovascular Research in the Young)

Lauri Vanharanta: High-content imaging and structure-based predictions reveal functional differences between Niemann-Pick C1 variants. (Membrane Biology)

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, 2020.

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MEDIX PRIZE OF THE MINERVA FOUNDATION

STEM CELLS CAN BE REJUVENATED BY INHIBITING SIGNALS FROM NEIGHBOURING CELLS

The Minerva Foundation's Medix Prize, worth €20,000, has been awarded to a team researching the rejuvenation of the functioning of aged tissue by inhibiting signals between stem cells and their niche cells. The prize was awarded for an article published in the science journal Nature by a research group from the University of Helsinki. The research group is headed by Associate Professor and Director of the Academy of Finland's Centre of Excellence in Stem Cell Metabolism Pekka Katajisto.

The mechanism discovered by the research group may represent a safer way to treat gastrointestinal complications in elderly people, reduce the harmful side-effects of chemotherapeutic agents and support the recovery of older patients.

According to the head researcher of the project, PhD student Nalle Pentinmikko, compromised tissue function in elderly people has been known for a good while. In addition, reduced function of stem cells is known to have a role in poor regeneration of old tissues.

"Research has so far focused on the intrinsic mechanisms in the functional decline of stem cell. Our research is amongst the first to examine the role of the neighbourhood, the niche, of ageing stem cells. To our surprise, we discovered that incorrect signals are sent from the niche to stem cells which deteriorates the functional capacity of stem cells and therefore negatively affects their ability to regenerate damaged gut tissue," Head Researcher Pentinmikko says.

Stem cells require Wnt molecules, which regulate their ability to proliferate. In old tissue, Paneth cells, surrounding the stem cells, produce an enzyme called Notum, which is an extracellular Wnt inhibitor. This results in the decreased regeneration capacity of stem cells which, in turn, negatively affects the recovery of damaged gut tissue. Whereas Notum was already known to researchers, its connection to stem cell biology has now been established for the first time.

The discovery of the mechanism allows for correcting miscommunication between cells by means of pharmacological inhibition or genetic targeting of Notum.

"At the end of the research, we found a pharmacological molecule that may create a basis for future medical treatment. The US-

based research group that has developed the molecule had discovered its Notum inhibiting function, but they didn't know when and where this kind of molecule could be used," Head Researcher Pentinmikko says.

According to Katajisto's vision, there could in ten years' time be treatments and medicines to rejuvenate the stem cells function of elderly patients in such a way that their ability to repair damaged tissue would be closer to that of young tissue.

"This will be of great importance in cancer treatment, for example, where the most commonly used treatments often result in serious damage to healthy tissue, in particular in older individuals. Currently, the risks associated with such harmful side-effects can influence treatment decisions for elderly patients even in cases where the treatment could be beneficial" says Katajisto.

The newly discovered mechanism cannot be used for preventing or curing illnesses, but it can be used for facilitating recovery from certain conditions and the severe side-effects of treatments in the future. The research group has already launched research into the role of Notum in the onset of colorectal cancer.

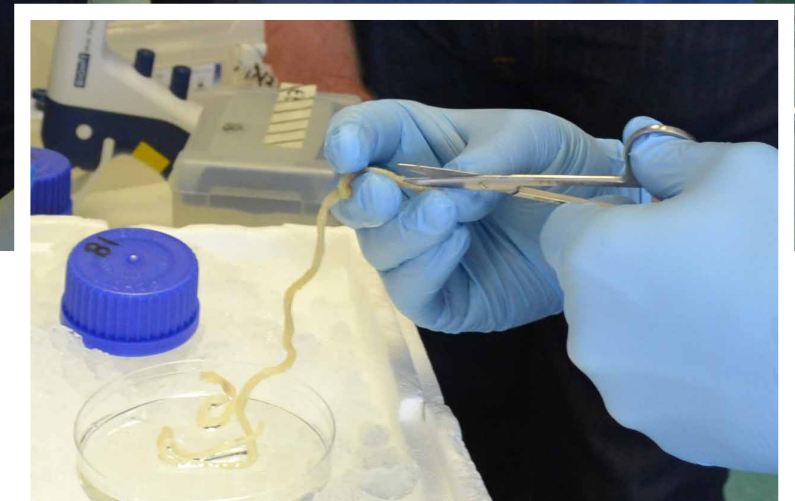
The Medix Prize by the Minerva Foundation is an important annual award for internationally high-level Finnish medical research. This year the Medix Prize will be awarded for the 33rd time. The Medix Prize is awarded by the University of Helsinki, and is donated to the university by the Minerva Foundation.

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

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



The research group used mice and human source materials. Director Pekka Katajisto (rear) observes Head Researcher Nalle Pentinmikko preparing a small intestine dissected from an aged mouse (courtesy of Martti Ahlström, Viestintätoimisto Verbi Oy).



RALPH GRÄSBECK SCHOLARSHIP FOR RESEARCH IN LABORATORY MEDICINE

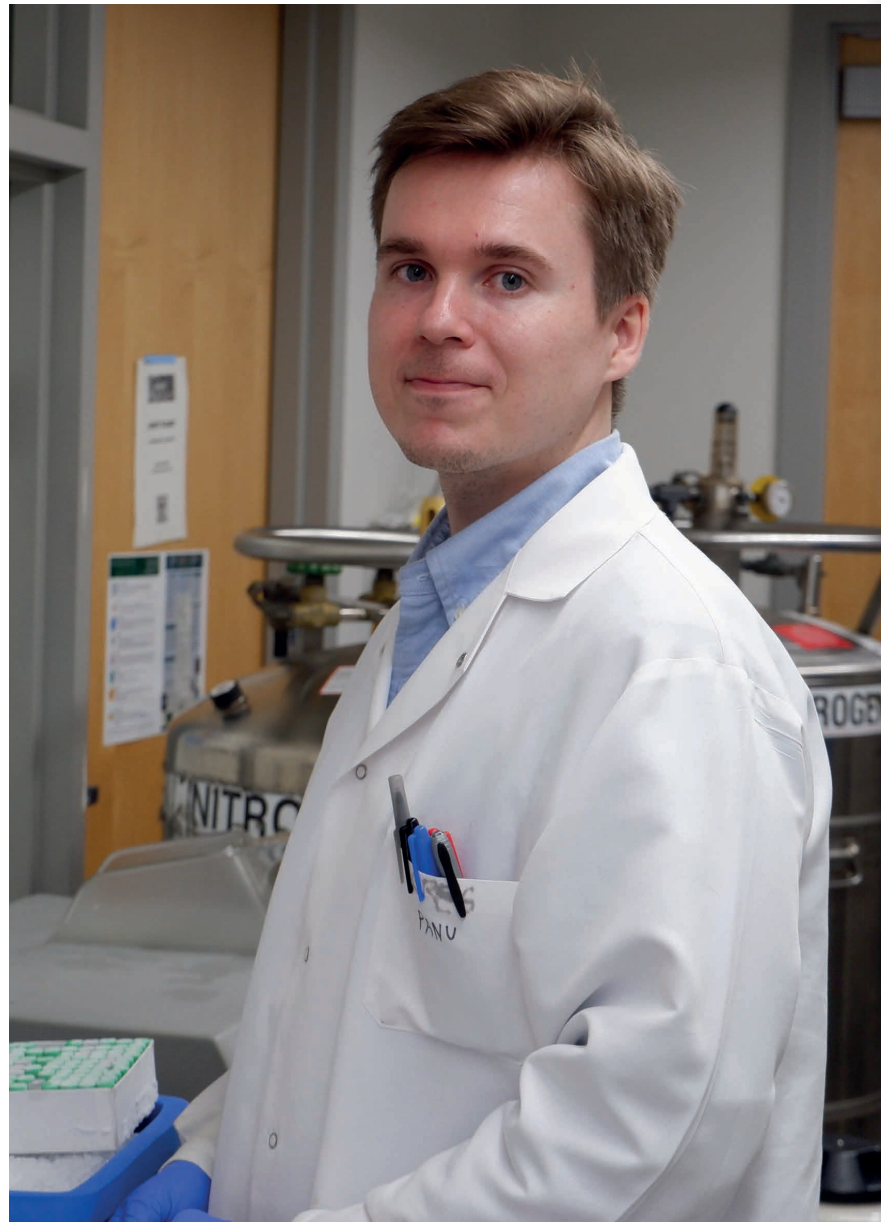
In 2018, Minerva Foundation decided to commemorate Professor Ralph Gräsbeck, one of the founders of Minerva Foundation and the associated Medical Research Institute, by establishing a new scholarship in his name. The first scholarship was granted in 2018 to Dr. Pirkka-Pekka Laurila on the recommendation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

The Ralph Gräsbeck Scholarship totals EUR 10,000 and will be 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 2020 Ralph Gräsbeck Scholarship for Research in Laboratory Medicine is awarded to M.D., Dr.Med. Sci., **Panu Luukkonen** at the Department of Internal Medicine, Yale University School of Medicine, New Haven, USA. The Ralph Gräsbeck Scholarship is granted to Luukkonen for his research “A mendelian randomization study of non-alcoholic fatty liver disease in humans.”

Panu K. Luukkonen investigates non-alcoholic fatty liver disease (NAFLD), particularly the mechanisms driving its progression from simple steatosis to more severe forms, including non-alcoholic steatohepatitis (NASH) and cirrhosis in humans, by combining genetic and metabolic approaches. The Ralph Gräsbeck Scholarship was granted to him for research aiming to identify novel biomarkers and therapeutic targets for treatment of NAFLD and NASH.

Dr. Luukkonen's research has been published in high-impact journals including *PNAS*, *Journal of Hepatology*, and *Diabetes Care*, and he speaks regularly at international meetings. He has previously received the Biomedicum Helsinki Foundation Prize (2018), the Finnish Diabetes Research Society Young Investigator Award (2019), the Thesis of the Year Award for the best doctoral thesis in medicine in Finland (2019) and the Unto Uotila Award from the Finnish Endocrine Society (2020).



Panu Luukkonen (courtesy of Kitt Falk Petersen).

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 Laboratories) 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.

MINERVA AND WIHURI INSTITUTES SYMPOSIUM 2020

In December 2019, scientists of the Minerva and Wihuri Research Institutes started organizing a joint scientific symposium under the title 'Translational Insights into Organ-Specific Vasculature.' The aim was to combine resources in an effort to assemble a high-end event with global top specialists as invited lecturers. The planned time point was August 24-25, 2020, and the event was to comprise six scientific sessions. The COVID-19 pandemic surged over Europe and the US from February 2020 onwards, and it soon became evident that arranging any symposium at which the speakers and the audience were physically present would be impossible. In order to vitalize scientific interactions and stimulate new ideas despite the pandemic V. Olkkonen and K. Alitalo decided in September 2020 that the symposium should be arranged as a series of virtual mini-symposia, each of which would represent one session of the original physical symposium. This plan was executed: the first virtual mini-symposium was held on October 29, 2020, and the series is continuing in early 2021.

MINERVA AND WIHURI INSTITUTES MINI-SYMPOSIUM SERIES *Translational insights into organ-specific vasculature*

Session I. Cardiovascular disease and regeneration, October 29, 2020.

Eldad Tzahor, Weizmann Institute of Science, Rehovot, Israel / *Novel strategies for cardiac regeneration*

Martin R Bennett, Centre for Clinical Investigation, Cambridge, UK / *Regulation of vascular smooth muscle cell senescence in atherosclerosis*

Short talk, **Martina Lorey**, Wihuri Research Institute, Helsinki, Finland / *Lipoprotein(a) induces inflammasome activation in macrophages*

Session II. Adipose tissue plasticity, November 24, 2020.

Christian Wolfrum, ETH Zürich, Switzerland / *The role of adipose tissue heterogeneity and plasticity in metabolism*

Philipp Scherer, Touchstone Diabetes Center, Dallas, TX, USA / *Adipocyte plasticity: Implications for metabolism and cancer through angiogenesis and fibrosis*

Short talk, **Eija Pirinen**, University of Helsinki, Finland / *Novel 3D culture model of human adipose spheroids*

Session III. Brain circulation and cerebrospinal fluid homeostasis I, December 3, 2020.

Nanna MacAulay, University of Copenhagen, Denmark / *Cotransporter-mediated water transport underlying cerebrospinal fluid formation*

Nathalie Jurisch-Yaksi, Kavli Institute for Systems Neuroscience, Trondheim, Norway / *Biophysics and function of motile cilia-mediated flow in the brain ventricles, lessons learned from the zebrafish*

Session IV. Cellular level analysis of organ development, December 17, 2020.

Joakim Lundberg, Royal Institute of Technology, Stockholm / *Molecular and data driven annotation of organs in development - from technology to an atlas*

Friedemann Kiefer, European Institute for Molecular Imaging, Münster, Germany / *The journey defines the destination: Another look at mesenteric lymphatic vessels*

Session V. Brain circulation and cerebrospinal fluid homeostasis II, January 13, 2021.

Steven Proulx, Theodor Kocher Institute, Bern, Switzerland / *In vivo imaging of cerebrospinal fluid outflow via lymphatic vessels*

Maria Lehtinen, Harvard University, Boston, MA, USA / *Illuminating the choroid plexus brain barrier*

IN MEMORIAM PROFESSOR ALBERT DE LA CHAPELLE

Academician, Professor Albert de la Chapelle passed away on December 10, 2020. He was born in Helsinki on February 11, 1933. He made a remarkable contribution to the activity of Minerva Foundation and its Research Institute, serving on the Executive Board of the Foundation in 1974-1990 as well as on those of the enterprises Oy Medix Ab and Medix Biochemica, formerly owned by Minerva Foundation. Moreover, he served as Vice Chair of Minerva's Board of Directors in 1963-1980 and 1983-1987.

de la Chapelle was one of the first junior researchers to join the Minerva circle in 1959, and his doctoral thesis 'Cytogenetical and Clinical Observations in Female Gonadal Dysgenesis' was the first to be completed at Minerva Institute. He finished his M.D. degree in 1957 and his Ph.D. in 1962. From 1962, de la Chapelle was affiliated to the Folkhälsan Institute of Genetics, which he led for more than three decades, but he maintained close contacts with Minerva, as the two institutes shared the same workspaces. de la Chapelle became Docent in Medical Genetics in 1965 and served as Senior Scientist of the Finnish State Medical Research Council 1965-1974, for part of which time he worked at Columbia University (NY, USA) 1966-1968, and at the Medical Research Council (London, UK) (1974). After this, he became the first Professor of Medical Genetics at the University of Helsinki, holding this position in 1974-1997. He served as Senior Physician at the Helsinki University Central Hospital, 1977-1997, and two terms as Research Professor of the Academy of Finland in 1985-1990 and 1990-1995. From 1997, after retiring from the Chair of Medical Genetics in Helsinki, de la Chapelle worked as Professor of Cancer of Molecular Genetics at the newly founded Ohio State University, USA. He was awarded the Matti Äyräpää prize in 1989 and the Anders Jahre prize in 1990, and was a member of the Royal Swedish Academy of Sciences. He was the second Finn ever to be awarded membership of the National Academy of Sciences, USA. The scientific production of Prof. de la Chapelle comprises approximately 650 published articles and a large number of medical patents. A great number of young students and coworkers have had the benefit of learning from his enthusiastic and inspiring dedication to science.

Professor de la Chapelle's major contributions were in medical genetics and molecular cell biology, including cancer pathogenesis. He was among the first to set up chromosome analysis in Finland and was the first to describe a male with XX sex chromosomes, which later led to the discovery of the sex-determin-



ing region of the Y chromosome. Together with his colleagues, he identified a number of disease-causing chromosomal aberrations, and made major contributions to the discovery of the Finnish disease heritage. He augmented our understanding of the genetic and molecular etiology of cancers. Above all, in collaboration with the group of Prof. Bert Vogelstein, he discovered germline mutations affecting the mismatch repair system as a novel mechanism of hereditary susceptibility to cancer.

Professor de la Chapelle stated that Minerva Institute was of enormous importance to his career, and that Minerva also meant a lot to him at the emotional level (interview with Docent Annette Forsén on September 23, 2020). We have lost a nationally and internationally highly respected colleague whose work was one of the cornerstones on which the present Minerva Institute was built.

Vesa Olkkonen, Carina Wallgren-Pettersson

IN MEMORIAM PROFESSOR CHRISTIAN EHNHOLM

Professor Christian “Enis” Ehnholm passed away after a short sickness, on September 7, 2020 in Grankulla, Finland. He made a remarkable contribution to the activity of Minerva Foundation and its Research Institute, serving on the Executive Board of the Foundation in 1990-2008 and as vice chair of the Board in 1996-1997 and 2003-2008.

Dr. Ehnholm received his medical degree at the University of Helsinki in 1966 and his Ph.D. in 1970. He worked at the University of Helsinki, Department of Serology and Bacteriology, as a researcher in 1965-1971. During this time he was among the first to purify, quantify, and resolve the protein and carbohydrate composition of Lipoprotein(a) in collaboration with Kåre Berg, Kai Simons, Henrik Garoff, and Ossi Renkonen. Throughout the coming years his main research interest was in cardiovascular diseases, with an emphasis on plasma lipoprotein metabolism. He visited Cornell University, Ithaca in 1971-72 as a NIH Fellow, working in the group of Prof. Donald B. Zilversmit, and worked in 1972-73 as an NIH Fellow at the University of California, San Diego, La Jolla together with W. Virgil Brown, Daniel Steinberg, Andre Bensadoun, and Heiner Greten. After his return to Finland, he worked as a senior scientist of the Academy of Finland in 1974-77 and continued successful lipoprotein and lipase research together with Esko Nikkilä, Marja-Riitta Taskinen, Jussi Huttunen, and Paavo Kinnunen.

In 1977, Ehnholm joined the National Public Health Institute as Head of the Department of Forensic Science and later as head of the Department of Biochemistry. In 1982 he returned for a year to the U.S., to the Gladstone Foundation Laboratories in San Francisco, the laboratory of Robert Mahley. In Gladstone he focused on apoE and continued this research in Finland, publishing several reports on the role of apoE in human lipoprotein metabolism and its association with disease, some of them together with Antero Kesäniemi and Tatu Miettinen. Along with apoE studies, Ehnholm studied apoA-I, apoA-IV, and apoB-100 polymorphisms and their relevance in lipoprotein metabolism. In the 1980s he was involved in the North Karelia project headed by Pekka Puska. In 1987-1988 he continued research at the Baker Medical Research Institute, Melbourne, and in 1998-99 at the University of Adelaide, Australia, in the laboratory of Phil Barter and Kerry-Anne Rye; later he returned to work with Barter and Rye at the Heart Research Institute, Sydney, during 2004-2005. From the early 1990s, Ehnholm started to investigate plasma phospholipid transfer protein (PLTP) together with Matti Jauhiainen and Vesa Olkkonen,

and also collaborated on this topic with Arie van Tol, Miranda van Eck, Phil Barter, and Kerry-Anne Rye. Furthermore, Ehnholm had a long-lasting collaboration with Prof. Marja-Riitta Taskinen, their study areas including familial combined hyperlipidemia, HDL metabolism, LPL and hepatic lipase (HL) function. In addition to basic research, he participated actively in several clinical trials and studies, including the European Atherosclerosis Research Study (EARS) I-II, the Diabetes Atherosclerosis Intervention Study (DAIS), EUFAM (European Multi-center Study on Familial Dyslipidemias in Patients with Premature Coronary Heart Disease) and the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study. Ehnholm's last research interest was the role of Angiopoietin-like 3 and 4 (ANGPTL) in lipoprotein metabolism.

Ehnholm's scientific production included more than 470 original publications in peer-reviewed international scientific journals and books. Moreover, he served on the Editorial Board of a number of journals in the atherosclerosis field. Ehnholm was one of the Founders of the European Atherosclerosis Society (EAS) and the European Lipoprotein Club (ELC), a Member of the Executive Committee of the European Atherosclerosis Society (1996-99) and a Board Member of the International Atherosclerosis Society (2000-02).

Ehnholm's character was special and his outspoken nature with simultaneous compassion enabled people to relate to him readily. His advice was invariably wise and often leavened by black-humorous puns. He was always willing to help solve any problem, scientific or other, by utilizing a pragmatic problem-solving approach. Prof. Ehnholm was an internationally renowned cardiovascular researcher who made pioneering discoveries. We have lost a warm-hearted research personality, who left a remarkable legacy both nationally and internationally.



Matti Jauhiainen, Vesa Olkkonen



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., postdoc autumn 2020
Mari Ylinen, M.D., Dr.Med.Sci.
Linda Litwin, M.D.
Rasmus Olander, M.D.
Essi Karikoski, M.Sc.
Michelle Renlund, M.D.
Jenny Lindholm, Medical student
Max Nurmi, Medical student
Maria Finne, M.Sc., Research coordinator

External funding

Foundation for Pediatric Research
Medical Society of Finland
Medicinska understödsföreningen Liv och Hälsa r.f
Sigrid Juselius Foundation
Stiftelsen Dorothea Olivia, Karl Walter och Jarl Walter Perkléns minne
Research Funding of the Helsinki-Uusimaa Hospital District
(state funding for university-level health research)

CARDIOVASCULAR RESEARCH IN THE YOUNG

Main research activity during 2020

During the year, the main research activities were in the project domains of fetal cardiovascular programming and prevention of cardiovascular disease. Study subject visits were arranged in the Clinical Trial Unit at the Children's Hospital within the FINN-CARE project (A lifestyle intervention for families with a history of pre-eclampsia – primary prevention of cardiovascular disease) during the spring and autumn. Michelle Renlund and Anni Kivelä (collaboration with Tiina Jääskeläinen and Hannele Laivuori) have been assigned to the project as Ph.D. students. During the year, Jenny Lindholm finalized her Master's thesis, co-supervised by Tiina Jääskeläinen. Furthermore, maternal and offspring cardiovascular morphology and function data from the RADIEL (Finnish Gestational Diabetes Prevention Study) 5-year-from-birth project has been processed by Ph.D. student Linda Litwin, with one accepted manuscript reporting no effect of gestational diabetes or pre-gestational obesity on 6-year offsprings' left ventricular function. A manuscript on maternal-offspring cardiovascular health associations was submitted in late autumn 2020. Postdoc Johnny Sundholm continued his work within the project during the autumn, analyzing maternal data relating adiposity and cardiovascular risk to arterial structure and function. Finally, Ph.D. student Rasmus Olander returned to the group in July to continue full-time research within the Fetal programming on cardiovascular and bone health at 5 years from birth (SIVELU) project. During the year, one manuscript was accepted for publication concluding that the nature of the relationship between body size and cardiac dimensions may be influenced by adiposity in preterm and term newborns with abnormal fetal growth and body size at birth.

Postdoc Johnny Sundholm's manuscript on arterial changes in young adults following childhood hematopoietic stem cell transplantation (HSCT;

collaboration with Prof. Kirsi Jahnukainen) was published. The manuscript concluded that long-term childhood HSCT survivors show early arterial aging related to radiation, metabolic, and CVD risk factors, and that prevention of risk factors could potentially decelerate early arterial wall thickening.

Recruitment to the randomized controlled trial ORALPEDHEART (Oral Health and Dental Care in Children with Congenital Heart Disease; NCT03329170) with co-investigator postdoc My Blomqvist and Ph.D. student Essi Karikoski was continued.

A manuscript on vascular health from the randomized controlled MIAD trial (Motivational Interview in Adolescent Diabetes; NCT02637154; collaboration with Dr Mari-Anne Pulkkinen) on vascular health was published. The study found no effect of motivational interviewing added to standard educational care on vascular health in adolescent type 1 diabetes. Disease duration and glycemic control were associated with vascular health at baseline; only limited associations between glycemic control and vascular health parameter changes were found. Vascular health parameter changes were interrelated during follow-up consistent with the clustering of cardiovascular risk.

Healthy control subject recruitment to the Cardiovascular structure and function in Mulibrey nanism study was finalized by Taisto Sarkola during spring 2020, with the first manuscript submitted in late autumn 2020.

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

Figure. Ultrasound images of the common carotid artery (CCA), femoral artery (FA) and its superficial (SFA) and deep (DFA) branches, and brachial artery (B) from a 6-year-old girl in the SIVE-LU study using non-invasive very-high resolution ultrasound. Ultrasound frequency and scale bars are marked in the images. Lumen diameter (LD) and far wall arterial layers (IMT, intima-media thickness; IMAT, intima-media-adventitia thickness; AT, adventitia thickness) are marked on the left hand side.

Thesis completed in the group in 2020

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

Jenny Lindholm: Metaboliska och antropometriska skillnader hos pre-eklamptiska respektive icke pre-eklamptiska mödrar samt deras barn. Faculty of Medicine, 2020.

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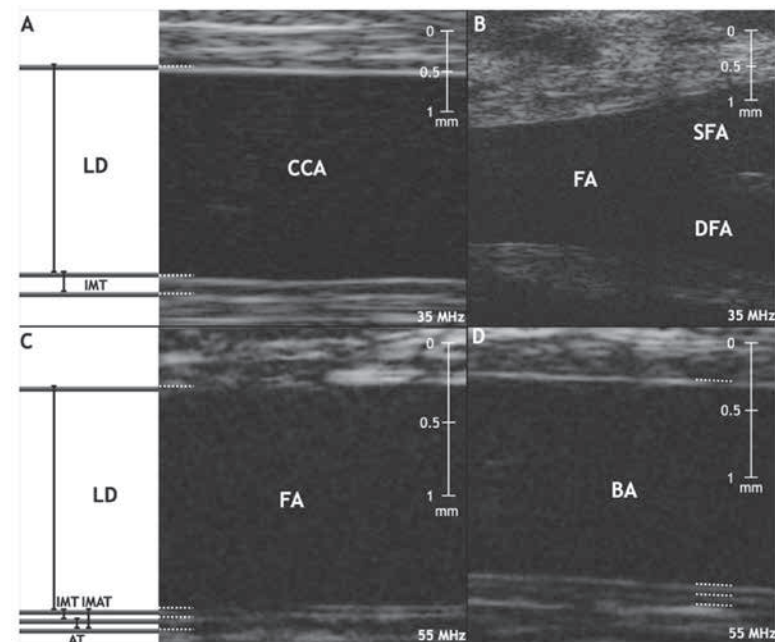
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CARDIOVASCULAR RESEARCH

Main research activities

Our research group studies mechanisms of end-organ damage in cardiovascular and renal diseases. In addition, we evaluate the cardiovascular and renal protective properties of new cardiovascular drugs and treatments. During recent years, the group's research has focused on exploring the molecular mechanisms of cardiac injury and repair after myocardial infarction (MI) 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 2020 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 cardiac failure and repair is needed to advance the discovery of novel drug target molecules and novel biomarkers for more personalized diagnostics and outcome prediction.

Septins are small GTPases that are associated with actin and are important in the organization of the cytoskeleton. We have shown in collaboration with Prof. Sanna Lehtonen, HU, that septin7b, the zebrafish ortholog of human septin7, is essential for the subcellular organization of cardiomyocytes and cardiac function in zebrafish. Moreover, knock-down of septin7b diminished the expression of retinaldehyde dehydrogenase 2 (raldh2), which catalyzes the synthesis of retinoic acid shown to modulate ischemic injury and stimulate cardiac regeneration. Our studies elucidating the role of septins in cardiac recovery after myocardial injury continued during 2020.

Vezf1 encodes a nuclear protein containing six zinc finger motifs of the C2H2 type (krüppel-like) and a proline-rich transcriptional transactivation domain. The role of Vezf1 in stress-induced cardiac hypertrophy and development of heart failure in embryonic zebrafish was studied in collaboration with Prof. Risto Kerkelä, University of Oulu. We employed loss of function methods using antisense oligomer molecules that block the translation or splicing of Vezf1. We were able to demonstrate that Vezf1 regulates the development of stress-induced cardiac hypertrophy by modulating β MHC expression and cardiac contractile function by stabilizing cardiomyocyte calcium cycling. Our results indicate a clinically relevant role for Vezf1 in the heart.

MicroRNAs are short noncoding RNA molecules widely involved in the regulation of gene expression. Circulating miRNAs have emerged as potential diagnostic and prognostic biomarkers of car-

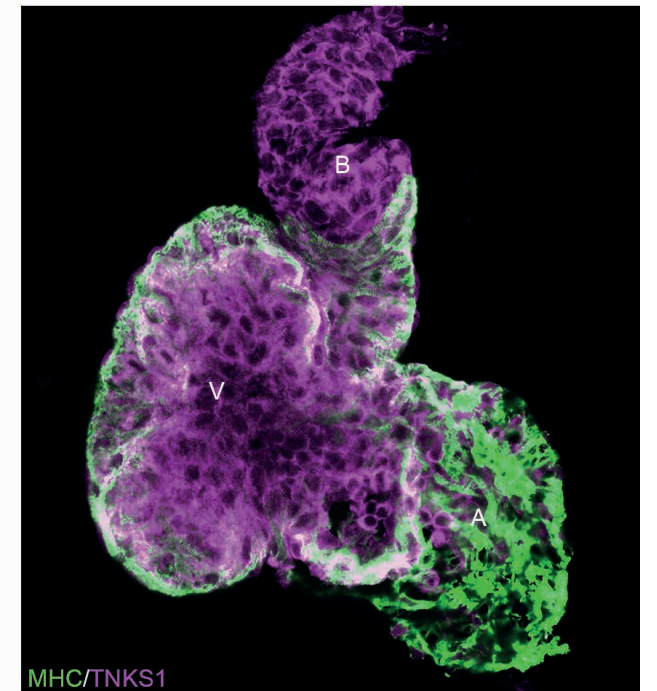
diovascular disease. Cardiogenic shock (CS) is a severe state of inadequate systemic tissue perfusion due to low cardiac output, often resulting in multi-organ failure. In-hospital mortality is close to 40% even with current treatment. New biomarkers to stratify CS patients according to their risk and optimize treatment are needed. In collaboration with Adj. Prof. Veli-Pekka Harjola, HUCH, and Dr. Yvan Devaux, the Luxembourg Institute of Health, Luxembourg we have identified several potential miRNA biomarker candidates using microarray profiling. We were able to show that miR-21-5p, miR-122-5p and miR-320a-3p plasma levels were significantly elevated in nonsurvivors of CS and associated with markers of hypoperfusion. Furthermore, high plasma levels of miR-21-5p and miR-320a-3p were independent predictors of 90-day all-cause mortality, indicating the potential of miRNAs as biomarkers for risk assessment in CS.

During 2020, 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 starting from November 2020 as a co-leader of the Working Group: Best Practices and Experimental Standards.

Clinical hypertension

High blood pressure is the leading risk factor for death worldwide. Despite developments in anti-hypertensive 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 embryonic zebrafish heart at 4 days post fertilization showing high expression of Tankyrase 1 (TNKS1). V, ventricle; A, atrium; B, bulbus; MHC, myosin heavy chain (courtesy of Hong Wang).



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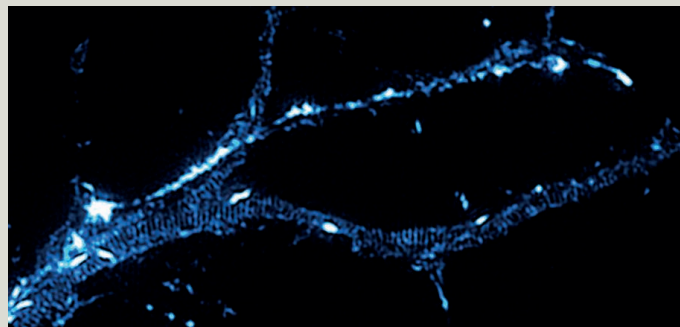


Figure. Super-resolution SIM reconstruction of F-actin in a rat hippocampal neuron. Periodic actin rings (stripes) are visible throughout the axon, but not the dendrite. The distance between each actin ring is 190 nm (courtesy of Amr Abouelezz).

CELLULAR NEUROSCIENCE

Main research activities

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

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

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

Single neurons

The neuron itself is a mini-computer. It evaluates different signals and calculates, depending on the strength and number of the signals, whether the signal is taken forward. Appropriate organization of neuron subunits is needed for normal function. The axon initial segment (AIS) is the site of action potential initiation. At same time, the AIS serves as a barrier between dendrites and axons, by sorting vesicles and proteins to the axon or somato-dendritic compartment. The majority of excitatory synapses in the central nervous system exist on small bulbous structures on dendrites known as dendritic spines. The dendrites of a single neu-

ron can contain hundreds to thousands of spines. During learning, new spines will appear. At the same time, other spines and synapses will be removed. Thus, dendritic spines can be considered 'memory units' or 'stuff that memories are made of.' Through adding or removing, or strengthening or weakening, these units, the brain modulates its function. By reorganizing synaptic pathways, new skills are stored in the brain. Precise control of the dendritic spine morphology and density, as well as the length and location of AISs, 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? The possibilities seem to be alterations in dendritic spine initiation, dendrite branching, and axonal branching. Too much of any of these leads to overload of contacts and vice versa. Poor selectivity can be at least partially explained by altered spine/synapse stabilization mechanisms. Altered excitatory/inhibitory synapse balance is often associated with psychiatric diseases.

Our projects aim at clarifying how the excitation/inhibition balance is regulated at the level of a single neuron. We started this with small screening-type study, testing the effects of ASD mutations on five actin-binding proteins. We detected changes in both dendritic spines (excitation) and inhibitory synapses (Hlushchenko et al., 2018) but we could not conclude any common defect or clear mechanism that was regulating the excitation/inhibition balance. We are now continuing these studies by studying the role of myosin XVI in excitatory and inhibitory synapses. Myosin XVI is an interesting protein, as it is down-regulated in ASD and over-expressed in schizophrenia. We have already studied spine initiation by showing that MIM protein is a mechanism to initiate dendritic spines (Saarikangas et al., 2015). Now we are elucidating other mechanisms, particularly focusing on proteins initiating spines in an activity-dependent manner. We have studied the spine stabilization mechanisms or mechanisms regulating synaptic plasticity with myosin IIb (Koskinen et al., 2014), actin phosphorylation (Bertling et al., 2016), and gelsolin (Hlushchenko et al., 2019).

In 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 this year. The main article of the thesis was published in March 2020 (Abouelezz et al., 2020).

Neuronal networks

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

The brain

At the level of the brain, our main question is, how does the brain control behavior and especially, how do defects in brain anatomy affect behavior? At the level of the brain, we have mainly studied the role of MIM in development, controlling behavior, and aging (Saarikangas et al., 2015; Minkeviciene et al., 2019). In the future, we will extend these studies to myosin XVI knock-out mice.

Thesis completed in the group in 2020

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

Amr Abouelezz: The structure and dynamics of the actin cytoskeleton in the axon initial segment. February 28, 2020.

Publications 2020

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ENDOCRINOLOGY

Main research activities

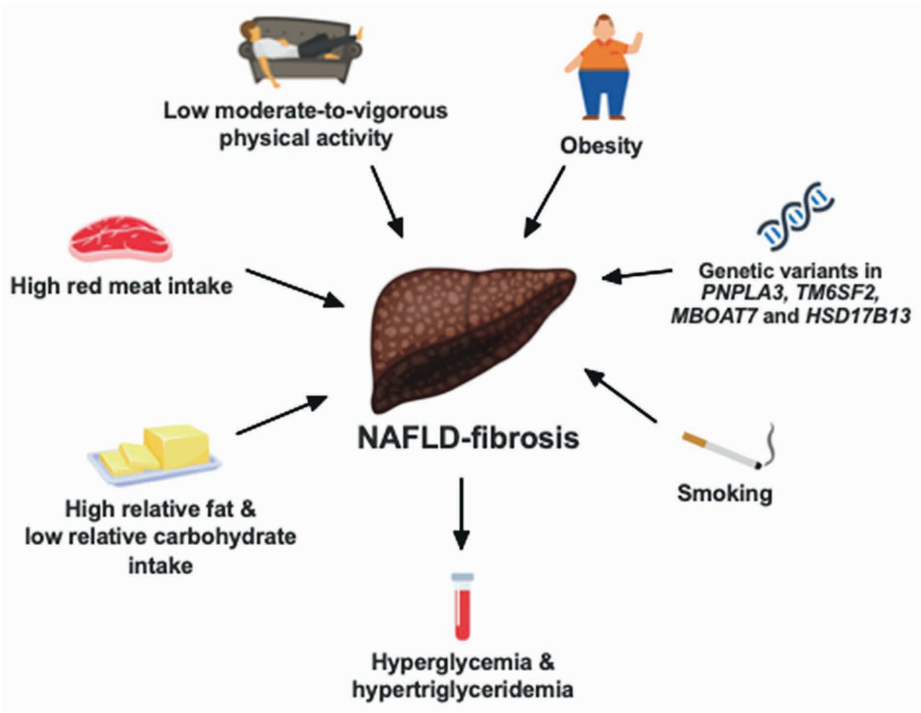
We have continued mechanistic in vivo and in vitro studies addressing the mechanisms underlying subtypes of NAFLD in humans caused by the common genetic risk variants in PNPLA3 and MBOAT7 and the protective effects of variants in HSD17B13 and MARC1. Regarding the PNPLA3 I148M variant, we have shown,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

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

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

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

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



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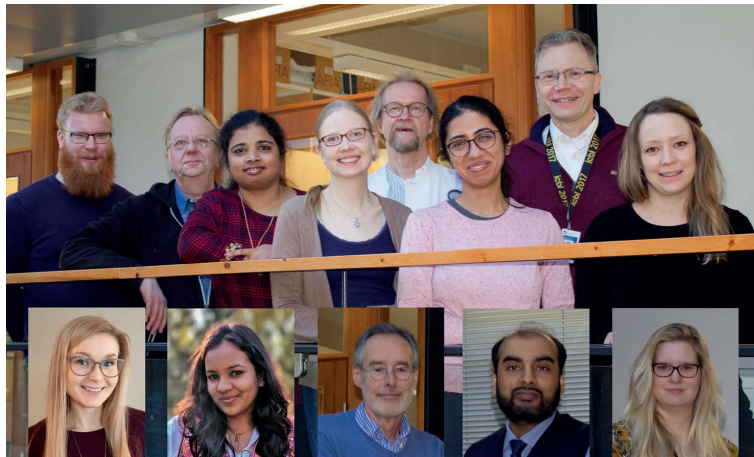
Luukkonen PK, Tukiainen T, Juuti A, Sammalkorpi H, **Haridas PAN**, Niemelä O, Arola J, Orho-Melander M, Hakkarainen A, Kovanen PT, Dwivedi O, Groop L, Hodson L, Gastaldelli A, Hyötyläinen T, Orešič M, **Yki-Järvinen H**. Hydroxysteroid 17-β dehydrogenase 13 variant increases phospholipids and protects against fibrosis in nonalcoholic fatty liver disease. *JCI Insight*. 2020; 5:e132158.

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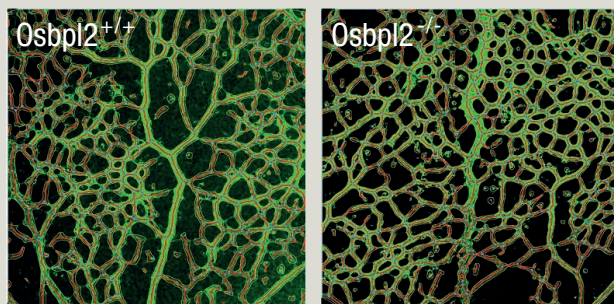


Figure. Retinal vasculature of *Osbp12*^{+/+} and *Osbp12*^{-/-} mice, stained with FITC-isolectin B4. The images were analyzed with Image Pro Plus 6.0; branches are highlighted in red and branchpoints in blue.

LIPID SIGNALING AND HOMEOSTASIS

Main research activities

One of the interests of the unit is membrane contact sites (MCSs), zones of close contact between the limiting membranes of intracellular organelles. In 2020, major activity in the group was directed at understanding the role of two MCS components, the OSBP-related protein ORP2, a counter-current transporter of cholesterol and PI(4,5)P₂, and Protrudin/ZFYVE27, in EC functions such as angiogenesis. Our findings in cultured EC revealed crucial roles for functions of ORP2 in VEGF signaling. Consistently, study of ORP2/*Osbp12* knock-out mice demonstrated a defect in retinal angiogenesis in vivo. A similar study on Protrudin function in endothelial cell (EC) in vitro and in vivo is in progress. A long-term project addressing the functional cross-talk of the ORP/Osh lipid transfer proteins in mammalian and yeast cells with the SNARE protein machinery of transport vesicle fusion revealed a new interaction and coordination between these two membrane-associated machineries (Weber-Boyvat et al., 2020).

A second major activity in the group in 2020 focused on the dysregulation of adipocyte metabolism and communication with other cell types relevant for human disease. We focused on a miRNA associated with both cancers and metabolic disease, miR-221-3p, and produced data suggesting that its expression in adipocytes plays an important role in the communication between adipocytes and breast cancer cells during tumor development (Ahonen et al., 2020). Furthermore, study of Angiopoietin-like 3 (ANGPTL3) in cultured hepatocytes demonstrated key roles of this protein in controlling the polyunsaturated fatty acid (PUFA) content, cholesterol esterification and synthesis of PUFA-derived lipid mediators in human hepatocytes (Ruhanen et al., 2020). Our observations support the potential of this gene/protein as a future cardiovascular therapy target.

We are actively continuing collaborative work on the critical role that hepatic LDL receptor plays in the flow of macrophage-derived un-esterified cholesterol to feces, termed macrophage-reverse cholesterol transport (m-RCT). Our results demonstrate that, besides the major HDL-dependent m-RCT

pathway via SR-BI (scavenger receptor class B type 1) to the liver, a CETP-independent m-RCT path exists, in which LDL mediates the transfer of cholesterol from macrophages to feces (Cedo et al., 2020). In another co-project, we demonstrated that disruption of phospholipid transfer protein (PLTP) activity reduces the atherosclerosis susceptibility of SR-BI-deficient mice, despite impairment of the metabolism of triglyceride-rich lipoproteins and the induction of phenotypic features of metabolic syndrome. Our studies highlight that the presence of an active PLTP protein in the plasma facilitates the uptake of triglyceride-rich lipoproteins from the circulation by the liver (Hoekstra et al., 2020). In addition, we have orchestrated two reports giving general fresh education to readers on the clinical relevance of lipoprotein (a), Lp(a) (Vuorio et al., 2020) and plasma ceramides (Öörni et al., 2020).

Investigations on the importance of calcium and lipid signaling in mainly human tumor-derived thyroid cancer cells have continued. Of special interest has been the importance of stromal interacting molecule 1 (STIM1) and Orai1, two important proteins regulating intracellular calcium storage and signaling. Furthermore, the effect of the interactions between calcium signaling and the sphingomyelin metabolite sphingosine 1-phosphate (S1P) on the regulation of thyroid cancer cell migration and invasion has been investigated. These investigations have also been conducted in collaboration with Professor Jessica Rosenholm (Åbo Akademi University) regarding the use of mesoporous silica nanoparticles (MSNs) as drug delivery systems in nanomedicine (Niemelä et al., 2020).

Thesis completed in the group in 2020

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

Hanna Ruhanen: Hepatic lipid metabolism in cardiometabolic diseases - protective and adverse effects of genetic variants. October 13, 2020

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The Academy of Finland
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 Jane and Aatos Erkko Foundation
 Leducq Foundation for Cardiovascular Research
 University of Helsinki, Research Excellence and Infrastructure Funding (HiLIFE)

MEMBRANE BIOLOGY

Main research activities

Our group focuses on understanding how membrane lipids are transported between subcellular compartments in mammalian cells and how cellular lipid storage at the predilection sites, such as lysosomes and lipid droplets, is controlled. These questions are key to understanding the pathogenic mechanisms underlying major human health threats, such as atherosclerosis and non-alcoholic fatty liver disease as well as less common but life-threatening diseases, such as lysosomal lipid storage diseases and inherited lipodystrophies. To this aim, we also develop novel techniques for lipid cell biological analyses, including lipid imaging, dissection of rapid metabolic fluxes of lipids, and manipulation of cells and tissues at improved spatio-temporal resolution.

The year 2020 was exceptional. Science in the group went virtual to a degree not witnessed before and experimental work suffered from limited access to the lab. Our Leducq Transatlantic Network of Excellence kick-off meeting still took place physically at the UCLA campus at the end of January, and Prof. James Olzmann from UC Berkeley managed to visit us in early March as the last Biomedicum Helsinki seminar speaker before the lockdown. Thereafter, all meetings became virtual, including weekly lab meetings and seminars, thesis progress reports, international conferences, etc. We also experienced our first virtual dissertation, with Prof. Robert Farese, Harvard Univ. functioning as the opponent of Dr. Veijo Salo. Dr. Tomas Blom, recruited to Orion Corporation, continued to work remotely as an affiliated team leader.

We made scientific discoveries in national and international networks, including collaboration with other researchers from Minerva Foundation Institute for Medical Research, at the cross-roads of cell biology and biophysics. For instance,

we found that a Niemann-Pick C1 (NPC1) protein commonly used by labs as a benign wild-type variant compromises NPC1 functionality in lysosomal cholesterol export. This is because the amino acid change disrupts the NPC1 intramolecular cholesterol transport tunnel (Vanharanta et al., 2020). We also discovered that the assembly of triglyceride lipid droplets depends critically not only on the ER membrane protein seipin (Salo et al., 2019) but also on biophysical membrane properties, such as curvature (Santinho et al., 2020). The principles of lipid droplet nucleation (Thiam and Ikonen, 2020), as well as the metabolism and physiological functions of lipid droplets (Klemm and Ikonen, 2020) are now starting to emerge.

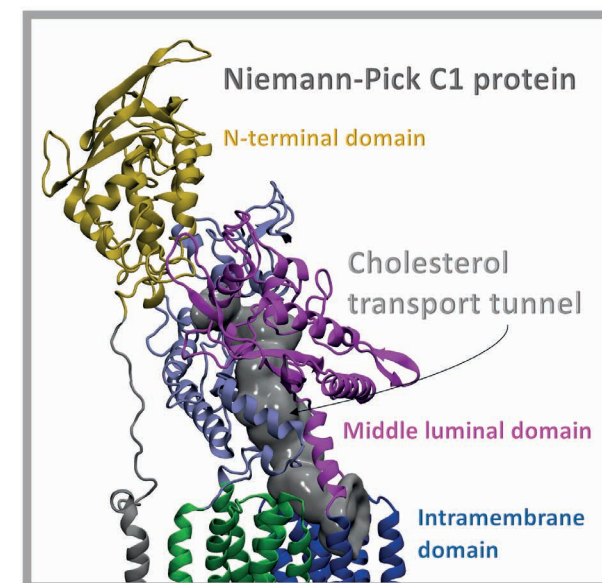


Figure. Intralysosomal domains of the NPC1 protein with the cholesterol transport tunnel highlighted (courtesy of Elina Ikonen).

Theses completed in the group in 2020

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

Veijo Salo: Lipogenic subdomains of the ER: The role of seipin. April 17, 2020.

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

Lauri Vanharanta: High-content imaging and structure-based predictions reveal functional differences between Niemann-Pick C1 variants.

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Koponen A, Pan G, **Kivelä AM**, Ralko A, **Taskinen JH**, **Arora A**, **Kosonen R**, Kari OK, Ndika J, **Ikonen E**, Cho W, Yan D, **Oikkonen VM**. ORP2, a cholesterol transporter, regulates angiogenic signaling in endothelial cells. *FASEB J.* 2020; 34:14671-14694.

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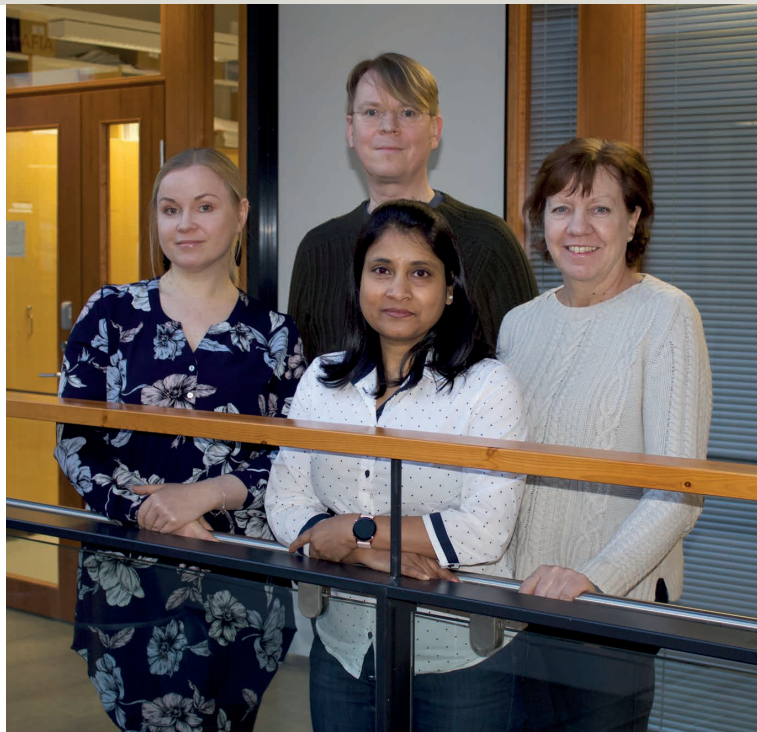
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Laboratoriolääketieteen edistämmissäätiö

METABOLISM

Main research activities

We study the molecular mechanisms of insulin resistance in human skeletal muscle, using primary human muscle cells as a research model.

Moreover, we collaborate closely with the FUSION study (Finland-United States Investigation of NIDDM Genetics, head principal investigator (PI) Prof. Michael Boehnke, University of Michigan, Ann Arbor, USA), with the head of the group, Docent Heikki Koistinen being one of the FUSION PIs.

Treatment of hypercholesterolemia with simvastatin has been found to be associated with increased risk for type 2 diabetes (T2D). Simvastatin exists in inactive lactone form, which is then converted into active acid form. We studied the effects of lactone- and acid-form simvastatin on glucose metabolism and mitochondrial respiration in primary human skeletal muscle cells. Exposure of primary human myotubes to lactone-form simvastatin increased glucose uptake and glycogen synthesis. In contrast, exposure to acid-form simvastatin did not affect glucose uptake and led to a decrease in glycogen synthesis. Exposure to either form of simvastatin led to a reduction in glycolysis, mitochondrial respiration, and ATP production. Thus, the lactone and acid forms of simvastatin impact non-oxidative glucose metabolism differentially, as lactone form increases and acid form impairs glucose storage into glycogen. Simvastatin impairs oxidative glucose metabolism and energy production in human skeletal muscle cells (Mäkinen et al., 2020).

As part of a large research collaboration, in which the FUSION study also participated, a genome-wide gene-smoking interaction study of mean arterial pressure (MAP) and pulse pressure (PP) was performed. More than 130 loci were significantly associated with MAP and/or PP (Sung et al., 2019). A large meta-analysis to study genetic regulation of blood pressure (BP) revealed more than 100 novel BP-associated genomic regions and >80 rare variant BP associations. Variants associated with blood pressure showed enrichment in regions of active chromatin in fetal tissues, which may link fetal development with future regulation of blood pressure (Surendran et al., 2020).

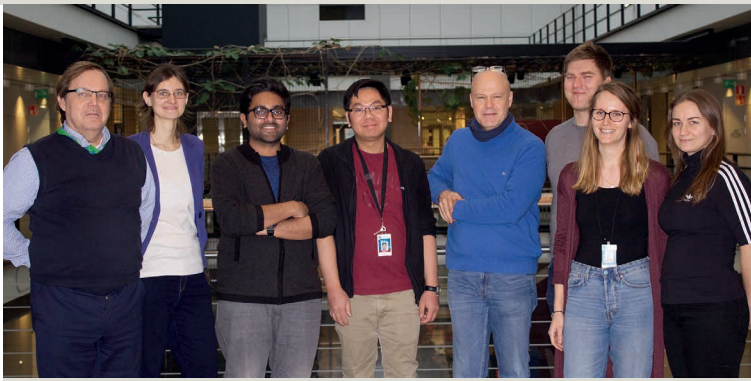
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The Finska Läkaresällskapet
 The Liv och Hälsa Foundation
 The Magnus Ehrnrooth Foundation
 EU H2020-MSCA-RISE project, SZ_TEST

NEURONAL SIGNALING

Main research activities

We study trophic factors in neurodegenerative diseases, such as Huntington's (HD) and Parkinson's disease (PD). We focus on the roles of endoplasmic reticulum (ER) stress and protein degradation pathways, including the ubiquitin proteasome and autophagy systems. We employ various biochemical, proteomic, molecular biology, and cell biology methods for our studies, such as primary neuron cultures and genetically modified mice. The majority of the group is housed in Medium, Faculty of Medicine of the University of Helsinki, and the group is actively engaged in research at Minerva. During 2020, we worked on three main areas of research.

1. Novel roles of USP14 in neuronal autophagy and in cell models of HD.

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

USP14 is a deubiquitinating enzyme associated with the proteasome and important for protein degradation. However, a significant proportion of the USP14 in the cell is in the cytosol. We observed that inhibition of proteasome activity reduced the amount of proteasome-bound USP14 with the possibility of additional protein interactions. We then performed proteomic analyses identifying the molecular chaperone, HSC70, and GABARAP as binding partners for USP14. Similarly, employing mutagenesis of the aminoterminal UBL domain of USP14 resulted in a W58A-USP14 mutant that did not bind to the proteasome (Srinivasan et al., 2019). Recent molecular modeling of wild-type and mutant W58A USP14 (in collaboration with Prof M. Karelson, Tartu University) revealed distinct changes in conformation that may have a bearing on the function of USP14. Furthermore, using quantitative mass spectrometry, we obtained evidence that

USP14 undergoes posttranslational modifications (PTMs) such as phosphorylation and methylation in human neuroblastoma cells. The functional significance of these PTMs for the physiology of USP14 in neurons and in models of HD will be studied further. A deeper understanding of USP14 and the mechanisms governing proteasome and autophagy processes can have therapeutic consequences in protein aggregation diseases.

2. Neurotrophic factors in cellular models of HD

Endoplasmic reticulum (ER) stress is closely linked to the pathophysiology of neurodegenerative diseases including HD (Lindholm et al., 2017). Cerebral dopamine neurotrophic factor (CDNF) is a protein with a unique mechanism of action, mitigating ER stress as demonstrated in models of PD (Voutilainen et al., 2015). We observed that CDNF is also protective in models of HD by reducing ER stress and the IRE1 signaling pathway in striatal neurons (Stepanova et al., 2020). The precise mechanisms for the beneficial effects of CDNF in HD are currently under investigation.

Along with this we are investigating the protein, Canopy 2 (CNPY2), which is also an ER resident protein that we have cloned before. CNPY2 can influence ER stress and may itself act as an initiator of the unfolded protein response, as shown in liver cells. We have evidence that overexpression of CNPY2 is neuroprotective. We further observed that CNPY2 is increased in striatal neurons expressing 109Q-containing mutant huntingtin protein. We are currently investigating the mechanisms and signaling functions of CNPY2 in HD and other brain diseases using gene knock-out mice, cell models, and proteomic and next-generation sequencing methods.

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

Peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α) is a master regulator of mitochondria biogenesis and cell stress playing a role in metabolic and degenerative diseases. We have

previously studied transgenic mice with overexpression of PGC-1 α in brain neurons (Mudo et al., 2012; Mäkelä et al., 2016). Our transcriptome and proteomic analyses showed an increase in specific GABA-A receptors in the PGC-1 α transgenic mice with an increase in anxiety-like behavior in the mice (Vanaveski et al., submitted manuscript). Dysfunctional GABAergic signaling is a consistent finding in neuropsychiatric diseases including schizophrenia (SZ). We will hence crossbreed our transgenic mice with those carrying risk genes for SZ in order to reveal possible novel therapies linked to PGC-1 α functions. Along with this, we are analyzing serum samples of SZ patients obtained from the Helsinki Biobank and Tartu University. This is an EU-funded collaboration called SZ_TEST, to facilitate early molecular diagnostics and novel treatments of SZ.

Thesis completed in the group in 2020

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

Dan Duc Pham: Novel roles of p75 neurotrophin receptor in Low-density lipoprotein receptor regulation and lipid signaling. June 4, 2020.

Publications 2020

- Khirug S, Soni S, Saez Garcia M, Tessier M, Zhou L, Kuleskaya N, Rauvala H, **Lindholm D**, Ludwig A, Molinari F, Rivera C. Protective role of low ethanol administration following ischemic stroke via recovery of KCC2 and p75^{NTR} expression. *Mol Neurobiol*. 2020 Oct 24. Online ahead of print.
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1. **Abouelezz A**, Stefen H, Segerstråle M, **Micinski D**, **Minkeviciene R**, Lahti L, Hardeman EC, Gunning PW, Hoogenraad CC, Taira T, Fath T, **Hotulainen P**. Tropomyosin Tpm3.1 is required to maintain the structure and function of the axon initial segment. *iScience*. 2020; 23:101053.

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