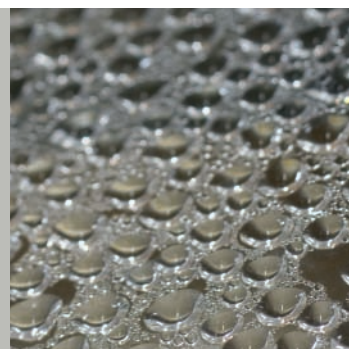
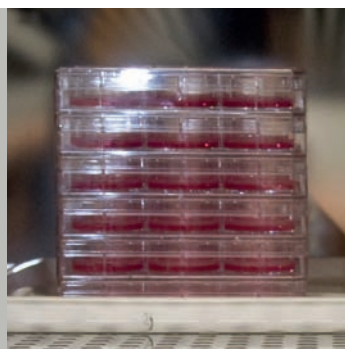
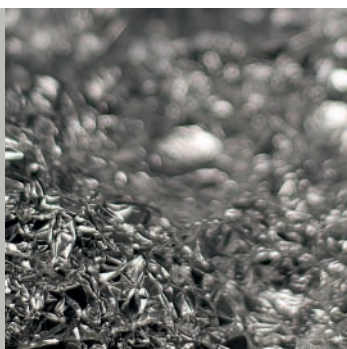


**MINERVA FOUNDATION
AND
MINERVA FOUNDATION INSTITUTE
FOR MEDICAL RESEARCH**



50TH ANNIVERSARY

1959-2009



Minerva Foundation Institute for Medical Research
BIOMEDICUM Helsinki 2U
Tukholmankatu 8 00290 HELSINKI,
Finland Tel. +358-9-191 25700
Fax +358-9-191 25701

[Www.helsinki.fi/minerva](http://www.helsinki.fi/minerva)

CONTENTS

4 How it all started

7 Summary of research and activities

8 Research groups

- 10** Unit of Neuroscience
- 12** Unit of Cardiovascular Research
- 14** Unit of Endocrinology
- 16** Unit of Metabolism
- 18** Unit of Cellular Physiology
- 20** Unit of Clinical Physiology
- 22** Unit of Biochemistry

24 Interviews

31 Dissertations 1959-2009

How it all Started

Space was needed. In the postwar period, Finland was a very poor country and in Helsinki the University hospital was small and worn-down. Therefore, clinical instruction was also given in the city hospitals of Helsinki. The Fourth Department of Internal Medicine, headed by Professor Bertel von Bonsdorff, was located in the Maria City Hospital. In this Department, scientific activity was intense, to a great extent due to the inspiring chief who in the 1930's had been trained in cardiology in Göttingen and hematology in Boston. His main topic of interest was the megaloblastic anemia caused by the fish tapeworm, a traditional and hotly debated research topic among Finnish medical scientists. Another research theme of the Department was goiter, which was endemic in Finland. Both projects utilized radioactive techniques, and the necessary equipment was consequently acquired at a cost considered to be enormous at the time. This became the first nuclear medicine laboratory in Finland, founded in the late 1940s, and a very early one even on European scale. In addition, the Department was a pioneer in nephrology.

External space is rented. While the scientific activity was prodigious, the laboratory space available was minimal. Professor von Bonsdorff came up with the idea that the scientists pool their grants and rent a facility suitable for a laboratory. Such space was found in the small hospital Konkordia, owned by the Methodist congregation. Three small research teams moved there: a parasitological one headed by Wolmar Nyberg (1919-1973), an endocrinological one headed by Bror-Axel Lamberg (1923-), and a biochemical one headed by Ralph Gräsbeck (1930-). An experienced lawyer pointed out

that the laboratory had to be governed by a legal person, otherwise it would have difficulties in dealing with the authorities. Thus a foundation was created, on ridiculously small capital, and given the name Minerva Foundation for Medical Research (Minerva being the Roman goddess of wisdom and science). A number of distinguished doctors were elected as members of its Board.

Two institutes in one. A few years later, a welcome source of money was discovered: a fund possessed by the Folkhälsan (People's Health) organization and bequeathed to it by Professor Ossian Schauman and his wife Betsy and intended for the establishment of an institute of genetics. However, war-time inflation had reduced the capital so that it was no longer sufficient for the founding of a true institute. However, a few rooms of the Minerva Institute were named the Folkhälsan Institute of Genetics, and research in the field was begun under the leadership of Albert de la Chapelle. In 1962, he produced the first dissertation from the Institute. It dealt with cytogenetic findings in female gonadal dysgenesis. In 1997, the Folkhälsan Institute separated from Minerva to become an independent and relatively large institute, but remaining in close contact with Minerva.

The history of the first 30 years of Minerva's existence has been published*. The institute has moved several times, but since 2001 it has been located in the Biomedicum Helsinki building in the vicinity of the Helsinki University Hospital. Biomedicum is a conglomerate of laboratories mostly belonging to Helsinki University but also to other institutions. In 2008, Minerva moved to brand-new facilities with 480 m² of space and located in an expanded part of the Biomedicum complex.



The Institute around 1970. From left B-A Lamberg (director of the Institute 1959-1971), R Gräsbeck, A Gordin, A Eriksson, J Fellman.

Research. The early research in the Institute was first a continuation of that in the Fourth Department of Medicine. The state-of-the-art methods used included chromosome analysis (karyotyping), radioimmunoassays of numerous hormones, and sophisticated protein chemical techniques resulting in the isolation and characterization of “new” proteins, including human intrinsic factor and mitogens. The research on the thyroid contributed to the eradication of endemic goiter and the development of refined diagnostic methods. In the late 1960s, Minerva was the most quoted Finnish biomedical institution after Helsinki University, being more cited in the literature than our new universities.

Since then, new research teams have established themselves and others have finished or moved elsewhere. Worth mentioning are the former Units of Cell Biology (head Teddy Weber), Nutrition (previously Vitamin D and Calcium, head Christel Lamberg-Allardt), Reproductive Endocrinology (head Fredrika Pekonen, now Forsskåhl), Experimental and Clinical Nephrology (head Carola Grönhagen-Riska) and that of Nuclear Medicine (head Kristian Liewendahl). The main topic of the Unit of Endocrinology was the thyroid until Professor Bror-Axel Lamberg, one of the founders of the Institute, retired in 1993. A new Unit with the same name is now mainly dealing with diabetes. Noteworthy research

topics successfully pursued are hormones and other factors involved in hypertension, cardiovascular disease, reproduction and cancer. Research on vitamin D has given results especially significant in a country with little sunlight. Mitogens causing lymphocytes to divide were once a hot topic. For many years, radioactive techniques were very popular research tools, but lately their role has diminished. Many of the investigators have obtained high academic positions in Finland and abroad, held leading positions in domestic and international scientific societies and obtained prestigious prizes. The main achievements of the first 30 years are found in the History of the Institute.* Later in this booklet, the principal achievements of the present research Units are described. An idea of the results of the research can also be obtained by examining the titles of the dissertations published from Minerva found at the end of this booklet.

It should be pointed out that most of the scientists have held posts outside the Institute and thus have only been able to perform research at Minerva part-time or during leaves of absence financed by stipends.

Commercial spin-off. To investigate interesting patients and diseases, the scientists set up a number of sophisticated laboratory tests such as assays for thyroid hormones, angiotensin II and vitamin B₁₂, karyotyping, etc. Many of the tests gradually became routine clinical analyses, and Minerva received numerous requests to perform such assays on hospital patients. By law, the Foundation was not permitted to charge for such services. To take over the routine work, in 1964 the

scientists decided to found a separate service laboratory. They paid for the shares themselves and donated them to the Minerva Foundation, the Folkhälsan and the Liv och Hälsa (Life and Health) Societies, with the provision that the profit of the company be used to support the research in the Minerva and Folkhälsan Institutes. The company was named Medix, which has since grown enormously, now being the largest private clinical reference laboratory in Finland. The profit generated by Medix has enabled Minerva to purchase its present laboratory facilities and also covers the salaries of the people servicing the laboratory as a whole. Most of the research proper is paid for by grants, which the researchers apply for and often obtain from external sources. Substantial grants have been obtained from the Sigrid Jusélius Foundation, the Academy of Finland and numerous other sources mentioned in connection with the research groups.

Medix subsequently also began to manufacture biochemicals and reagents. This activity has now been taken over by a separate company, Medix Biochemica. It is one of the biggest manufacturers of monoclonal antibodies in the world. Medix also donates a yearly prize to be awarded by Helsinki University for the best medical publication of the year to originate from Finland.

The Minerva-Medix conglomerate is an outstanding example of how free basic research can produce results that not only contribute to the advancement of medicine but also enable research to finance itself.

*Minerva 30 år. Finska Läkaresällskapets Handlingar 1989;133:1-76.

SUMMARY OF RESEARCH ACTIVITIES

The Minerva Foundation Institute for Medical Research is a privately owned biomedical institute currently consisting of seven research groups. The research at Minerva is focused on the study of basic cellular and molecular mechanisms underlying important human diseases, including cardiovascular diseases, diabetes and neurological degenerative disorders. The objectives range from studying single cells and molecules to analyses of experimental animals and human patient material.

As explained in the historical background, the Minerva Institute began as a rather small endeavor that has since developed into an active research entity. The uniqueness of the Institute lies in its good mix of basic and clinical research, and in a creative atmosphere of interaction with the freedom to address important research questions. Funding primarily comes from private and public sources. Presently, a substantial amount of grants come from sources such as the Academy of Finland.

The Minerva Institute has recently moved to a new location in Biomedicum-2 as part of the larger Biomedicum-Helsinki conglomerate of research laboratories with ultramodern facilities and new laboratory space. This move will further contribute to the development of the Institute and will create an inspiring scientific environment to meet new challenges in the future.

At the time of celebrating the 50th anniversary of the Institute, it is perhaps important to remember that scientific research also faces difficulties and threats. Some of these are well-known to most researchers, whilst others are related to general issues in society. It is striking to see that some of these difficulties are the same as those discussed in 1989 when the Institute celebrated its 30th anniversary. Thus, the current economical crisis, looming also in this country, may have a bearing on the



future grant situation and lead to worsened possibilities of investing in research. Recruiting new students into science is also a problem. It is likely that with decreasing resources fewer people will stay in research or plan for a scientific career. In recent years, it has also been noted that particularly among students of medicine fewer students choose or get interested in medical research. The reasons for this are of course complex and reflect a general tendency that may also change in the future. Minerva as a medical research institute strives to promote medical research in this country by recruiting talented and devoted researchers and students to the different groups.

A detailed description of the research performed in the different groups at the Minerva Institute is given below and also at the Institute's homepage (<http://www.helsinki.fi/minerva>).

RESEARCH GROUPS

Unit of Neuroscience

Dan Lindholm, MD, PhD, Professor, head

The Unit studies basic mechanisms underlying neurodegenerative diseases with a focus on cell death pathways and associated proteins, with the aim of contributing to better therapies to combat cell degeneration. It also studies synaptic degeneration, protein ubiquitination and neurotrophic factor signaling in neurons, as well as neural stem cells and their differentiation and responses.

Unit of Cardiovascular Research

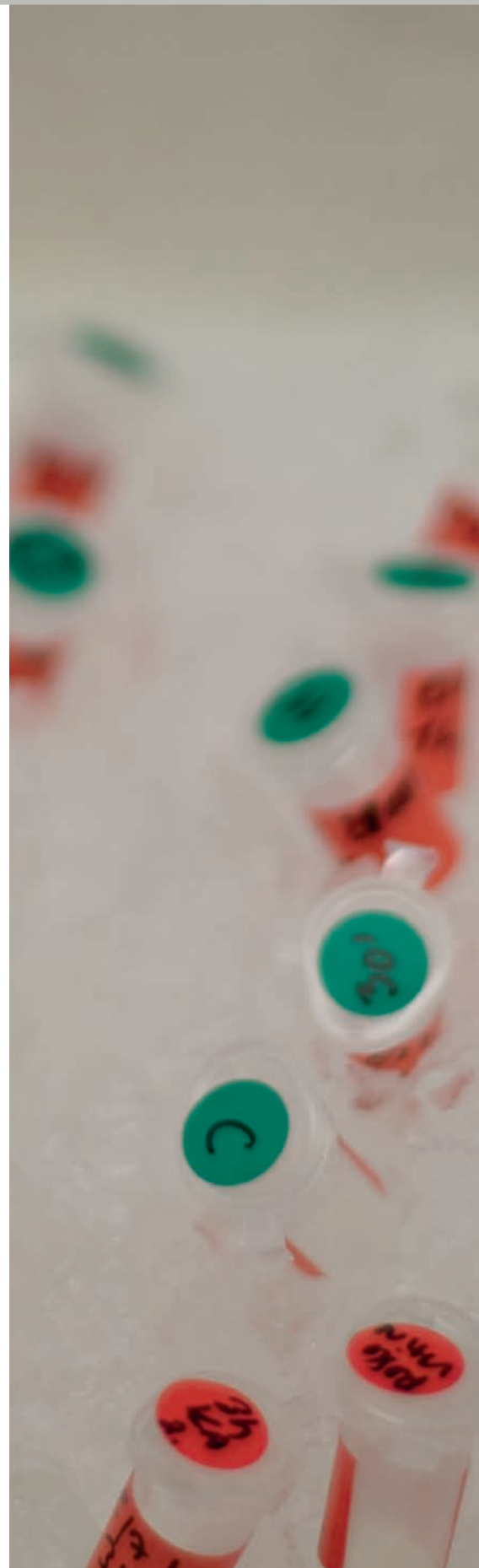
Ilkka Tikkanen, MD, PhD, Docent, head

The group studies mechanisms of end-organ damage and repair in cardiovascular and renal diseases, notably the local expression and regulation of vasoactive factors and apoptosis in hypertension, heart failure, and progression of renal damage. In addition, the properties of new cardiovascular drugs are being evaluated.

Unit of Endocrinology

Hannele Yki-Järvinen, MD, PhD, FRCP, Professor, head

The main goal of the Unit is to study the causes and consequences of insulin resistance in humans with a special focus on the role of fat accumulation in the liver.



Unit of Metabolism

Heikki Koistinen, MD, PhD, Docent, head

The main interest of the Unit is to clarify the molecular mechanisms regulating insulin sensitivity in skeletal muscle. The Unit is particularly interested in how lipid excess contributes to skeletal muscle insulin resistance, and how lipid-induced insulin resistance can be reversed.

Unit of Cellular Physiology

Kid Törnqvist, PhD, Professor, head

The main topic of the Unit's research is to understand the physiological significance of sphingolipid derivatives as regulators of calcium and potassium channels, and the role of sphingolipids as regulators of thyroid cancer cell function.

Unit of Clinical Physiology

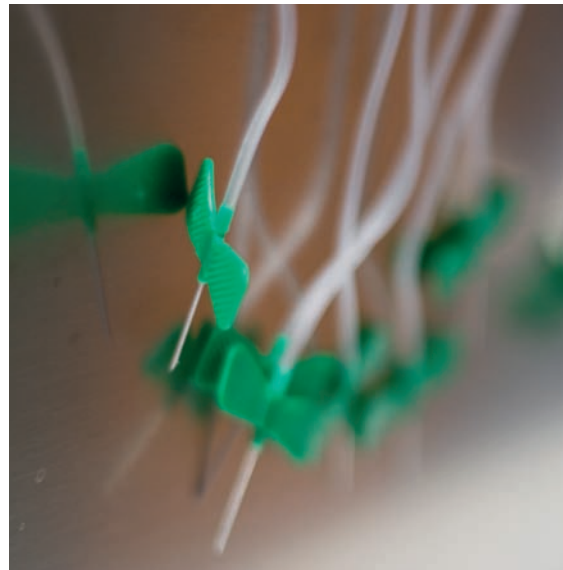
Frej Fyhrquist, MD, PhD, MDhc, Professor, head

The Unit has focused on the functions and receptors of vasoactive peptides. More recently, the role of telomeres in cardiovascular disease has become its new field of interest.

Unit of Biochemistry

Ralph Gräsbeck, MD, PhD, Dhc, Professor, head

The Unit investigates the physiological and pathological transport and metabolism of vitamin B₁₂ and related compounds. Reference values are a traditional specialty of this Unit.





► Members:

Dan Lindholm, MD, PhD, Professor
 Laura Korhonen, MD, PhD.
 Tuulikki Nyman, MSc, Laboratory Manager
 Minna Kairisalo, MSc (Pharm), PhD student
 Noora Putkonen, MSc, PhD student (HBGS)
 Sami Reijonen, MSc, PhD student
 Raili Rajala, MSc, PhD student (FGSN)
 Jenny Kivinen, undergraduate student
 Miia Lehtinen, undergraduate student
 Maria Sippel, undergraduate student
 Ulrika Furustrand, undergraduate student

Technical personnel

Eeva Lehto, technician
 Johanna Mäkelä, MSc, technician

Funded by the Minerva Foundation, the Sigrid Jusélius Foundation, the Liv och Hälsa Society, Signe and Ane Gyllenberg Foundation, Arvo and Lea Ylppö Foundation, Magnus Ehrnrooth Foundation, the Finska Läkaresällskapet and the Academy of Finland

UNIT OF NEUROSCIENCE

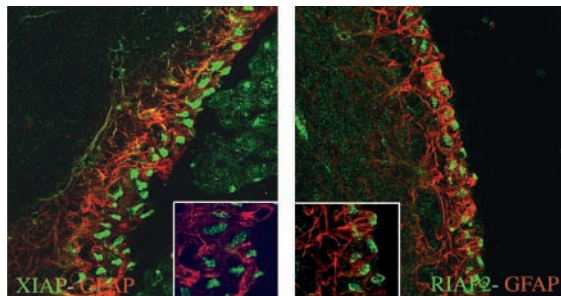
The Unit studies basic mechanisms underlying neurodegenerative diseases with a focus on cell death pathways and associated proteins, with the aim of contributing towards better therapies to combat cell degeneration. In this context, it studies particular changes in organelle dysfunctions and synaptic changes as early signs of the cell degeneration accompanying various human neurological diseases. Cell replacement using stem cells has emerged as a promising therapy in many diseases of the brain. The Unit studies proteins and other factors that govern the proliferation and differentiation of neural stem cells and their self-renewing potential.

Endoplasmic reticulum (ER) stress is involved in the pathogenesis of diabetes and other degenerative diseases. The Unit has shown that neuronal cell death involves specific pathways in the ER. In Huntington's disease (HD) and in glutamate-triggered excitotoxic cell death in neurons, there is rapid involvement of the ER, but the molecular mechanisms behind this have yet to be delineated.

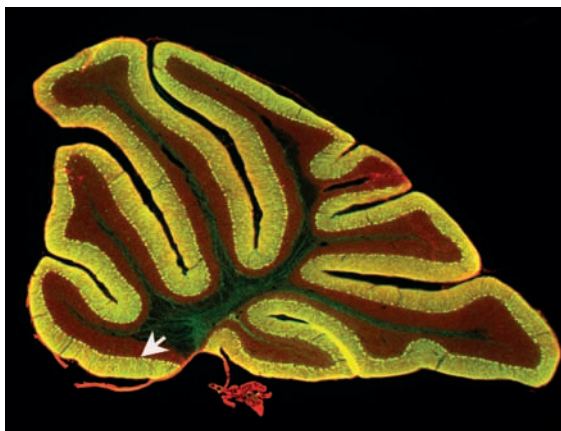
The Ubiquitin Proteasome System (UPS) plays a pivotal role in synapse formation and local protein control. Disturbances in UPS are linked to neurological disorders with synaptic dysfunction and loss of connectivity. The Unit has found that different deubiquitinating enzymes are expressed in neurons, including the Ubiquitin-specific protease-14. This enzyme is important for synaptic signaling and plasticity and its role and that of proteins interacting with it in neurons is currently under investigation.

Neural progenitor cells (NPCs) are localized in discrete neurogenic areas (niches) in brain tissue. In culture, these cells preferentially grow as neurospheres, indicating that local cell contacts and surface interactions are important.

The Unit has observed that particular membrane-associated proteases are crucial for the regulation of cell proliferation and self-renewal of NPCs. The exact mechanisms for this and how the pathway is regulated by known factors are currently under investigation.



Neuronal stem cells in the wall of the brain ventricle



Immunostaining of rat cerebellum for the anti-apoptotic protein XIAP (red fluorescence) and for calbindinD (green fluorescence). Purkinje cells appear yellow (arrow) showing coexpression of the proteins. Cerebellar granule cells are also positive for XIAP.

Selected publications

- Korhonen L., Lindholm D. The ubiquitin proteasome system in synaptic and axonal degeneration: A new twist to an old cycle. *J Cell Biol* 2004;165(1): 27-30
- Lindholm D., Wootz H., Korhonen L. ER stress and neurodegenerative diseases. *Cell Death and Diff* 2006;13:385-392
- Sundberg M, Savola S, Hienola A, Korhonen L, Lindholm D. Glucocorticoid hormones decrease proliferation of embryonic neural stem cells through ubiquitin-mediated degradation of cyclin D1. *J Neurosci* 2006;26:5402-10
- Sokka AL, Putkonen N, Mudo G, Pryazhnikov E, Reijonen S, Khiroug L, Belluardo N, Lindholm D. and Korhonen L. Endoplasmic reticulum stress inhibition protects against excitotoxic neuronal injury in the rat brain. *J Neurosci* 2007;27:901-908
- Bornhauser B.C., Bonapace L., Lindholm D., Martinez R., Cario G., Schrappe M., Niggli F.K., Schäfer B.W., and Bourquin J-P. Low dose arsenic trioxide sensitizes glucocorticoid-resistant acute lymphoblastic leukemia cells to dexamethasone via an Akt-dependent pathway. *Blood* 2007;110:2084-2091
- Reijonen S., Putkonen N., Nørremølle A., Lindholm D. and Korhonen L. Inhibition of endoplasmic reticulum stress counteracts neuronal cell death and protein aggregation caused by N-terminal mutant huntingtin proteins. *Exp Cell Res* 2008;314:950-960
- Korhonen L, Hansson I, Maugras C, Wehrle R, Kairisalo M, Borgkvist A, Jokitalo E, Sotelo C, Fisone G, Dusart I, Lindholm D. Expression of X-chromosome linked inhibitor of apoptosis protein in mature Purkinje cells and in retinal bipolar cells in transgenic mice induces neurodegeneration. *Neuroscience* 2008;156(3):515-526



► Members

Ilkka Tikkanen, MD, Ph.D., Docent, head
 Mika Laine, MD, PhD, Docent
 Eeva Palojoki, MD, PhD
 Tom Bäcklund, MD., PhD student
 Hanna Forsten, VMD, PhD student
 Tina Grönholm, MD, PhD student
 Päivi Lakkisto, MD, PhD student
 Kirsi Lastunen, MD, PhD student
 Jere Paavola, MD, PhD student
 Heli Segersvärd, PhD student
 Juha-Matti Siren, PhD student

Laboratory technicians

Riina Hatakka, Katariina Immonen, BSc, Riikka Kosonen, MSc and Jarkko Lakkisto

Collaborators

Ari Harjula, MD, PhD, Professor, Helsinki University
 Esko Kankuri, MD, PhD., Helsinki University
 Markku Kupari, MD, PhD, Professor, Helsinki University
 Eero Mervaala, MD, PhD, Professor, Helsinki University
 Kari Pulkki, MD, PhD, Professor, Kuopio University
 Ilkka Pörsti, MD, PhD, Professor, Tampere University

Funded by The Minerva Foundation, the Sigrid Jusélius Foundation, Helsinki University Research grants (EVO) and the Finnish Foundation for Cardiovascular Research.

UNIT OF CARDIOVASCULAR RESEARCH

Main research activities

The group was founded in 1997 when the group leader returned from Australia after a year of research as a visiting professor in the Department of Medicine at the University of Melbourne. It studies the mechanisms and repair of end-organ damage in cardiovascular and renal diseases. In this context, the Unit has studied the local expression of components of the renin-angiotensin-aldosterone system, other vasoactive factors, and apoptosis in hypertension, heart failure, and in the progression of renal damage. In addition, the cardiovascular and renal protective properties of new cardiovascular drugs have been evaluated.

The Unit has characterized and studied vasopeptidase inhibitors (VPIs; dual inhibitors of angiotensin converting enzyme, ACE, and neutral endopeptidase, NEP) in models of hypertension and cardiac and renal disease. The results provide evidence that VPIs have beneficial cardiovascular effects beyond their blood pressure-lowering efficacy. They may thus prove a useful approach for reducing blood pressure and retarding the progression of hypertensive cardiovascular changes.

The Unit has studied apoptotic cardiomyocyte loss and adverse cardiac remodelling after myocardial infarction (MI) in diabetic and non-diabetic rats. The results suggest that cardiomyocyte loss could be an important mechanism contributing to the progressive dilatation of the heart and the poor prognosis after MI in diabetes.

In experimental renal insufficiency, the Unit has found the existence of an important link between calcium-phosphorus balance, vitamin D, and ACE expression in the kidney and cardiovascular tissues. This could

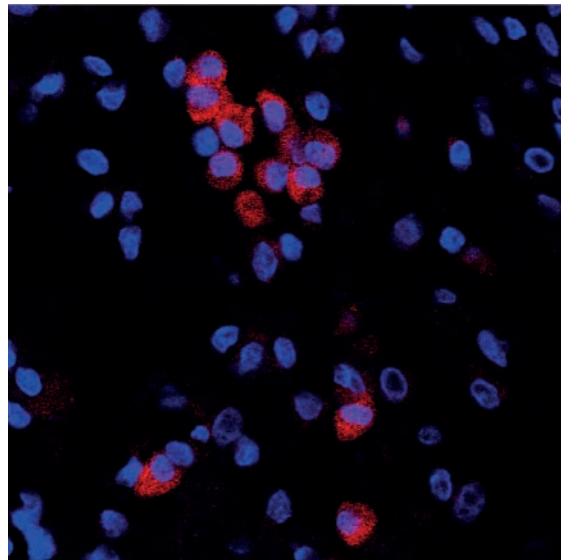
be important in the progression of renal and vascular damage in chronic renal failure.

Mutations of cardiac ryanodine receptors (RyR2s) in familial catecholaminergic polymorphic ventricular tachycardia was found to generate delayed afterdepolarizations. These were due to the increased propensity of Ca^{2+} waves predisposing to arrhythmias and sudden death during exercise.

Recently, the Unit's research has focused on exploring the regenerative and reparative mechanisms of tissue damage in cardiovascular diseases. In agreement with the findings of Anversa and coworkers, the Unit was able to show that the heart contains stem cells (see Figure), which are capable of activating, proliferating and forming new cardiomyocytes and vascular structures after MI. The Unit could also demonstrate that this regenerative process can be favourably influenced by various interventions. Its studies have shown for the first time that induction heme oxygenase-1 (HO-1), a cytoprotective enzyme exerting many of its beneficial effects through carbon monoxide (CO), promotes cardiac regeneration and angiogenesis after MI. Modulation of the HO-1/CO axis may thus provide a new tool for repairing cardiac injury and preventing post-MI cardiac failure. These novel findings on cardiac stem cells offer a very promising opportunity to improve the treatment of chronic heart failure.

Selected publications

- Bäcklund T, Palojoki E, Saraste A, Grönholm T, Eriksson A, Lakkisto P, Vuolteenaho O, Nieminen MS, Voipio-Pulkki L-M, Laine M, Tikkanen I. Effect of vasopeptidase inhibitor omapatrilat on cardiomyocyte apoptosis and ventricular remodelling in rat myocardial infarction. *Cardiovasc Res* 2003;57:727-737
- Bäcklund T, Palojoki E, Saraste A, Eriksson A, Finckenberg P, Kytö V, Lakkisto P, Mervaala E, Voipio-Pulkki L-M, Laine M, Tikkanen I. Sustained cardiomyocyte apoptosis and left ventricular remodelling after myocardial infarction in experimental diabetes. *Diabetologia* 2004;47:325-330



C-kit positive stem cells in the infarct area after myocardial infarction

- Pörsti I, Fan M, Kööbi P, Jolma P, Kalliovalkama J, Vehmas TI, Helin H, Holthöfer H, Mervaala E, Nyman T, Tikkanen I. High calcium diet down-regulates kidney angiotensin-converting enzyme in experimental renal failure. *Kidney Int* 2004;66:2155-2166
- Cheng ZJ, Grönholm T, Louhelainen M, Finckenberg P, Merasto S, Tikkanen I, Mervaala E. Vascular and renal effects of vasopeptidase inhibition and angiotensin-converting enzyme blockade in spontaneously diabetic Goto-Kakizaki rats. *J Hypertens* 2005;23:1757-1770
- Paavola J, Viitasalo M, Laitinen-Forsblom PJ, Pasternack M, Swan H, Tikkanen I, Toivonen L, Kontula K, Laine M. Mutant ryanodine receptors in catecholaminergic polymorphic ventricular tachycardia generate delayed afterdepolarizations due to increased propensity to Ca^{2+} waves. *Eur Heart J* 2007;28:1135-1142



► Members

Hannele Yki-Järvinen, MD, PhD, FRCP, Professor,
head

Robert Bergholm, MD, PhD

Anja Cornér, MD

Janne Makkonen, MD

Kaisa Makkonen, MSc

**In addition, the following group members
work at the Section of Internal Medicine**

Leena Juurinen, MD

Kirsi Pietiläinen, MD, PhD

Ksenia Sevastianova, MD

Jussi Sutinen, MD, PhD

Jukka Westerbacka, MD, PhD

Anna Kotronen, MD

Technical personnel

Mia Urjansson, technician

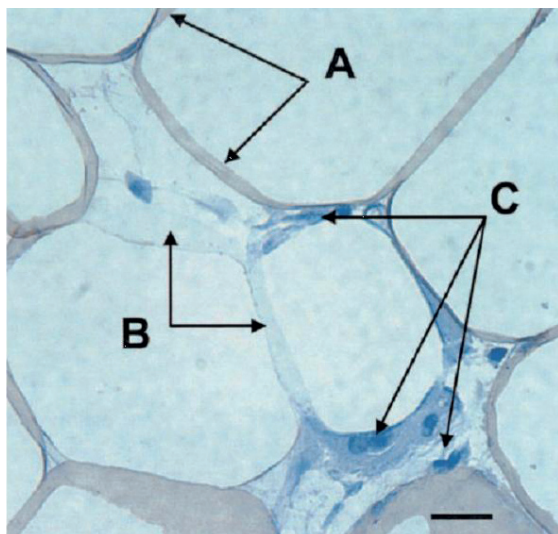
Funded by the Minerva Foundation, EU-
HEPADIP, the Sigrid Jusélius Foundation, Helsinki
University Research grants (EVO) and the
Academy of Finland and the Sanofi-Aventis,
MSD and Eli Lilly companies.

UNIT OF ENDOCRINOLOGY

The goal of the group is to study insulin resistance in humans. Its main interest is to define the causes and consequences of fat accumulation in the liver.

Metabolic syndrome is a cluster of risk factors (abdominal obesity, increased serum triglycerides, low serum HDL cholesterol, elevated blood pressure and hyperglycemia) considered to increase the risk of cardiovascular diseases and type 2 diabetes more than any one of the risks factors alone. Although metabolic syndrome is relatively common, how the syndrome develops is poorly understood and consequently predicting who will suffer from it is difficult. A fatty liver due to non-alcoholic causes is considered to be a key player in the pathogenesis of metabolic syndrome and may distinguish subjects who are likely to develop the syndrome. Subjects with a fatty liver are characterized by features of metabolic syndrome, and those fulfilling the criteria for metabolic syndrome usually have a fatty liver. The adipose tissue in obese subjects is often inflamed, and the expression of insulin-resistant genes and the local production of their protein products by macrophages is increased and may regulate liver fat.

In a recent key study, the Unit has demonstrated that adipose tissue inflammation distinguishes between obese subjects with and without a fatty liver. The liver fat content of 20 obese women was measured using proton magnetic resonance spectroscopy. The women were divided into a high and a normal liver fat group and matched for age and body mass index. A surgical biopsy of subcutaneous adipose tissue was taken for immunohistochemistry and gene expression studies (Professor Hamsten's group, King Gustaf V Research Institute, Karolinska Institutet, Stockholm, Sweden). Adipose tissue lipidomic



Light microscopy of subcutaneous adipose tissue from an obese woman. A arrows, perilipin-positive staining; B arrows, perilipin-negative staining; and C arrows, macrophages. Scale bar: 20 μ m

analyses were performed using ultra-performance liquid chromatography combined with mass spectrometry to characterize and quantitate hundreds of lipid species (Matej Oresic's group, VTT Technical Research Centre, Espoo, Finland).

In addition, the Unit has recently shown that adipose tissue is infiltrated by macrophages and that its content of long-chain triacylglycerols and ceramides is increased in subjects with increased liver fat compared with equally obese subjects with normal liver fat. Ceramides or their metabolites could contribute to the adverse effects of long-chain fatty acids on insulin resistance and inflammation. Studies exploring the causes for adipose tissue inflammation and liver fat accumulation continue.

Selected publications

- Kottronen A, Juurinen L, Tiikkainen M, Vehkavaara S and Yki-Järvinen H. Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes. *Gastroenterology* 2008;135:122-130
- Mustelin L, Pietiläinen K, Rissanen A, Sovijärvi A, Piirilä P, Naukkarinen J, Peltonen L, Kaprio J and Yki-Järvinen H. Acquired obesity and poor physical fitness impair expression of genes of mitochondrial oxidative phosphorylation in monozygotic twins discordant for obesity. *Am J Physiol Endocrinol Metab* 2008;295(1):E145-54
- Sevastianova K, Sutinen J, Jannisto K, Hamsten A, Ristola M and Yki-Järvinen H. Adipose tissue inflammation and liver fat in patients with highly active antiretroviral therapy-associated lipodystrophy. *Am J Physiol Endocrinol Metab* 2008;295:E85-E91
- Westerbacka J, Corner A, Kolak M, Makkonen J, Turpeinen U, Hamsten A, Fisher RM and Yki-Järvinen H. Insulin regulation of MCP-1 in human adipose tissue of obese and lean women. *Am J Physiol Endocrinol Metab* 294:E841-E845,2008
- Juurinen L, Kottronen A, Granér M, Yki-Järvinen H. Rosiglitazone reduces liver fat and insulin requirements and improves hepatic insulin sensitivity and glycemic control in patients with type 2 diabetes requiring high insulin doses. *J Clin Endocrinol Metab*. January 2008,93(1):118-124



► Members

Heikki Koistinen, MD, PhD, Docent, head
Paulina Skrobuk, MSc, (Engineering and
Biotechnology), PhD student
Eveliina Leppäniemi, MSc student

Funded by the Minerva Foundation, the Finnish Cultural and Novo Nordisk Foundations, the Finnish Foundation for Cardiovascular Research and Helsinki University.

UNIT OF METABOLISM

The Unit focuses on the regulation of insulin sensitivity in skeletal muscle. Obesity, a sedentary lifestyle and a diet with an excessive content of fatty acids are the main nongenetic reasons for the current type 2 diabetes pandemic. Increased systemic fatty acid availability and reduced fatty acid oxidation in the skeletal muscle of obese type 2 diabetic people favor the ectopic storage of fat in muscles, resulting in adverse metabolic effects. We aim to identify effective strategies to combat lipid-induced insulin resistance.

Type 2 diabetes and insulin resistance are characterized by defects in skeletal muscle glucose transport and fatty acid metabolism. Since the major part of insulin-stimulated glucose disposal in humans occurs in skeletal muscle, the intramuscular transfer of fatty acids to oxidative or lipogenic pathways must be important in the regulation of insulin sensitivity. AMP-activated protein kinase (AMPK) plays a central role in the regulation of metabolic pathways and is an important determinant of insulin sensitivity. The Unit previously observed that defects in insulin-stimulated glucose transport and the translocation of GLUT4 in type 2 diabetic muscle could be normalized in response to AMPK activation. This makes AMPK an attractive target in the treatment of insulin resistance in humans.

Several endogenous hormones and cytokines, such as interleukin-6 (IL-6) activate AMPK signaling, and thus could affect insulin sensitivity. In a collaborative project with the Karolinska Institute, we have recently demonstrated that IL-6 acutely increases glucose metabolism in intact human skeletal muscle strips as well as in primary human skeletal muscle cells. Adiponectin, which is almost exclusively secreted from adipocytes, activates AMPK signaling and improves insulin sensitivity in diabetic animal models. Insulin resistant states, such as obesity, cardiovascular

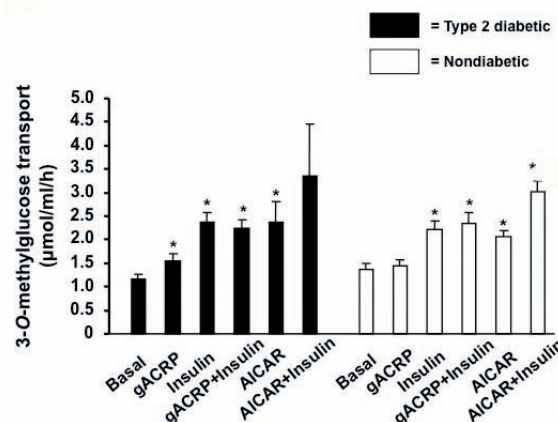
disease and type 2 diabetes, are characterized by hypoadiponectinemia, suggesting that adiponectin is also an important determinant of insulin sensitivity in humans. Interventions aimed at increasing circulating adiponectin concentrations are expected to improve insulin resistance in an adiponectin-dependent fashion. Thus, biological validation of the metabolic actions of adiponectin in human insulin-sensitive tissues is warranted. The Unit has therefore determined the effect of globular adiponectin on glucose transport in isolated skeletal muscle strips from *vastus lateralis* muscle biopsies obtained from a cohort of type 2 diabetic and nondiabetic men. As expected, insulin and AICAR (a nucleotide analog widely used to activate AMPK) increased glucose transport in isolated skeletal muscle strips (Figure). Globular adiponectin led to a 1.3-fold increase of the glucose transport rate in type 2 diabetic muscle.

The ongoing projects of the Unit include the interaction between glucose and fatty acid metabolism in isolated human skeletal muscle strips as well as in cultured muscle cells. The Unit is particularly interested in how lipid excess contributes to skeletal muscle insulin resistance, what are molecular lipids that mediate this effect, and how lipid-induced insulin resistance can be reversed. Currently, the role of AMPK and inflammatory modulators in the regulation of these processes are being explored.

Diabetes is a life-long condition and often leads to severe complications such as heart and kidney disease, blindness and nerve damage. Through identifying molecular mechanisms by which fatty acids interfere with insulin sensitivity, it should be possible to develop pharmacological and physiological intervention strategies aimed to prevent the development of type 2 diabetes and to improve glucose and lipid homeostasis.

Selected publications

Koistinen HA, Galuska D, Chibalin AV, Yang J, Zierath JR, Holman GD, Wallberg-Henriksson H: AICAR (5-amino-imidazole carboxamide riboside) increases glucose transport and cell-surface GLUT4 content in skeletal muscle from Type 2 diabetic subjects. *Diabetes*



Open muscle biopsies were obtained from vastus lateralis muscle from 12 men with type 2 diabetes and 15 nondiabetic men. Muscle strips were exposed to globular adiponectin insulin or AICAR for 60 min. Globular adiponectin increased glucose transport in type 2 diabetic muscle. AICAR increased glucose transport in both groups, and enhanced insulin-stimulated glucose transport 52% in type 2 diabetic and 31% in nondiabetic muscle.

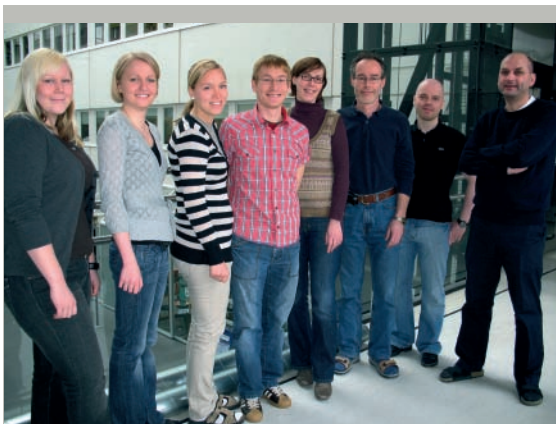
2003;52:1066-1072

Karlsson HKR, Ahlsén M, Zierath JR, Wallberg-Henriksson H, Koistinen HA: Insulin signaling and glucose transport in skeletal muscle from first-degree relatives of type 2 diabetic patients. *Diabetes* 2006;55:1283-1288

Bouzakri K, Zachrisson A, Al-Khalili L, Zhang BB, Koistinen HA, Krook A, Zierath JR : siRNA based gene silencing reveals specialized roles of IRS1/Akt2 and IRS-2/Akt1 in glucose and lipid metabolism in human skeletal muscle. *Cell Metabolism* 2006;4:89-96

Al-Khalili L, Bouzakri K, Glund S, Lönnqvist F , Koistinen HA, Krook A: Signaling specificity of interleukin-6 action on glucose and lipid metabolism in skeletal muscle. *Molecular Endocrinology* 2006;20:3364-75

Kuoppamaa H, Skrobuk P, Sihvo M, Hiukka A, Chibalin AV, Zierath JR, Koistinen HA: Globular adiponectin stimulates glucose transport in type 2 diabetic muscle. *Diabetes/Metabolism Research and Reviews* 2008;24:554-62



► Members

Kid Törnquist, PhD, Professor, head
Tero Viitanen, MSc, PhD student
Nina Bergelin, MSc, PhD student
Sara Fagerstedt, BSc

In addition, the following group members work at Åbo Akademi University:

Sonja Balthasar, PhD
Emad Afrasiabi, MD, PhD
Christoffer Löf, MSc
Paramod Sukumaran, MSc
Kati Kemppainen, MSc
Marika Hietamäki, BSc
Veronica Kalhori, BSc
Dan Gratshev, MSc (Affiliated member)

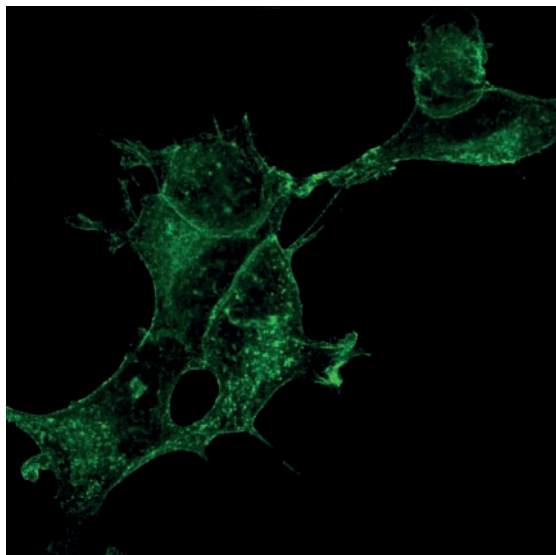
Funded by the Minerva Foundation, the Liv och Hälsa Society, The Sigrid Jusélius Foundation, the Academy of Finland, the Center of Excellence in Cell Stress (Åbo Akademi University).

UNIT OF CELLULAR PHYSIOLOGY

The main interest of the Unit was initially to investigate the regulation of calcium entry in various epithelial cells, at the beginning concentrating on thyroid epithelial cells in particular. In addition to receptor-mediated entry mechanisms, the regulation of store-operated calcium entry was investigated. In pituitary cells, both agonist-evoked calcium signals, as well as the regulation of L-type voltage-operated calcium channels, were of particular interest. In these studies, sphingomyelin derivatives (ceramide, sphingosine and sphingosine 1-phosphate, S1P) proved to be very effective modulators of calcium signals.

At present, the Unit studies the importance of sphingomyelin derivatives (sphingosine 1-phosphate, ceramide) on several aspects of cellular regulation. In addition, the investigations aim at understanding the physiological significance of the putative sphingosine-sphingosine 1-phosphate (S1P) "rheostat". Currently, the Unit is working at elucidating the mechanisms by which S1P and sphingosine kinase, *i.e.* the kinase phosphorylating sphingosine to S1P, regulate calcium entry. Especially the interactions of S1P, sphingosine kinase and members of the TRPC family of calcium channels are under investigation, both in normal and cancer cells. Furthermore, the modulation of intracellular calcium stores and the processing of mitochondrial calcium are of interest.

One important research area concerns the effect of S1P on the proliferation and migration of both normal thyroid cells and thyroid cancer cells. The investigations show that S1P potently stimulates the migration of some thyroid cancer cell types, whereas the migration of some other tumor cell types is blocked. The receptor profile for S1P is of crucial importance in this phenomenon.



Immunostaining of HERG potassium channels in HEK cells overexpressing HERG

Furthermore, recent studies clearly show that S1P may stimulate the migration of thyroid cancer cells by an autocrine mechanism. Considering that sphingosine kinase may function as an oncogene, these observations may be of significant clinical relevance. Furthermore, in thyroid cancer cells, vascular endothelial growth factor (VEGF) receptor 2 is an important part of the signaling complex activated by S1P. This is emphasized by recent results, which show that blocking VEGF receptor 2 potentially attenuates the migratory response evoked by S1P, and that S1P phosphorylates VEGF receptor 2.

An exciting series of investigations aim at understanding the mechanisms of ceramide action on potassium channels. Investigations of the Unit have shown that ceramide evokes internalization and ubiquitin-mediated degradation of the HERG potassium channel. Understanding the mechanisms by which ceramide (*i.e.* as a result of cellular stress) regulates HERG channel function is of great importance, given the central role of HERG in the repolarization of *e.g.* cardiac action potentials. An important issue is to investigate the mechanisms by which ceramide internalizes HERG and which ubiquitin ligase

participates in this process. Another recent observation is that HERG is expressed in several types of human thyroid cancer cells (at least follicular and anaplastic) and regulates both proliferation and migration in these cell types. Interestingly, HERG seems to be without a regulatory role in normal thyroid cells.

Selected publications

- Törnqvist K, Blom T, Shariatmadari R, Pasternack M. Ceramide 1-phosphate enhances calcium entry through voltage-operated calcium channels by a protein kinase C-dependent mechanism in GH4C1 rat pituitary cells. *Biochem J* 2004;380:1-8
- Blom T, Slotte JP, Pitson SM, Törnqvist K. Enhancement of intracellular sphingosine-1-phosphate production by inositol 1,4,5-trisphosphate-evoked calcium mobilisation in HEK-293 cells: Endogenous sphingosine-1-phosphate as a modulator of the calcium response. *Cell Signal* 2005;17:827-836
- Chapman H, Ramström C, Korhonen L, Laine M, Wann KT, Lindholm D, Pasternack M, Törnqvist K. Down-regulation of the HERG (KCNH2) K⁺ channel by ceramide: Evidence for ubiquitin-mediated lysosomal degradation. *J Cell Sci* 2005;118:5325-5334
- Blom T, Bergelin N, Slotte JP, Törnqvist K. Sphingosine kinase is a regulator of voltage-operated calcium channels in GH4C1 rat pituitary cells. *Cell Signal* 2006;18:1366-73
- Balthasar S, Samulin J, Ahlgren H, Bergelin N, Lundqvist M, Toescu EC, Eggo MC, Törnqvist K. Sphingosine 1-phosphate receptor expression profile and regulation of migration in human thyroid cancer cells. *Biochem J* 2006;398:547-556
- Balthasar S, Bergelin N, Löf C, Vainio M, Andersson S, Törnqvist K. Interaction between sphingosine 1-phosphate and vascular endothelial growth factor signaling in ML-1 follicular thyroid cancer cells. *Endocr-Relat Cancer* 2008;15: 521-534



► Members

Frej Fyhrquist, Professor, MD, PhD, MDhc, head
 Outi Saijonmaa, PhD, Docent
 Anders Eriksson, DVM
 Anna Tiitu, BSc, undergraduate student
 Emilie Kvist, MSc

Collaborators

Per-Henrik Groop, MD, PhD, Docent,
 Folkhälsan Institute, Biomedicum Helsinki
 Timo Strandberg, MD, PhD, Professor,
 Oulu University
 Kimmo Kontula, MD, PhD, Professor,
 Helsinki University
 Karri Silventoinen, PhD, Docent,
 Helsinki University

Funded by the Minerva Foundation, the
 Sigrid Jusélius Foundation, Else och Wilhelm
 Stockmann Foundation and the Liv och Hälsa
 Society.

UNIT OF CLINICAL PHYSIOLOGY

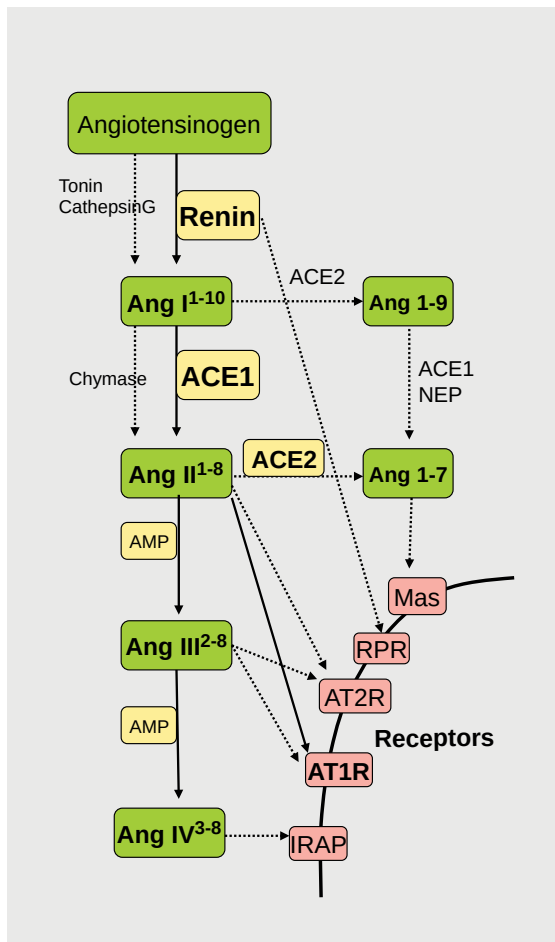
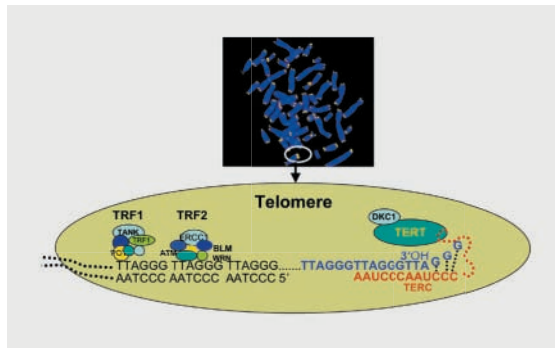
Established in 1975, more than 250 publications, mostly on vasoactive peptides and the renin-angiotensin system, have emerged from the Unit.

Examples of important publications from the group are: 1. An assay method for determining the activity of plasma renin which is used world-wide and acknowledged as a Classic Citation. 2. The first demonstration of atrial natriuretic peptide in human plasma and its association with the degree of heart failure.

The Unit is presently focusing on components of the renin-angiotensin system, notably angiotensin-converting enzymes (ACE1 and ACE2) and angiotensin peptides. Another major interest of the Unit is the role of telomeres in vascular aging and cardiovascular disease.

The Unit has measured the telomere length of DNA samples from 1271 Finnish subjects who participated in the LIFE-study. Short telomeres were associated with an increased Framingham risk score at the baseline, and were predictive of cardiovascular disease during the follow-up study. In collaboration with Docent P-H Groop, Folkhälsan Institute, the Unit observed that short telomere length is predictive of progression of nephropathy in patients with type I diabetes.

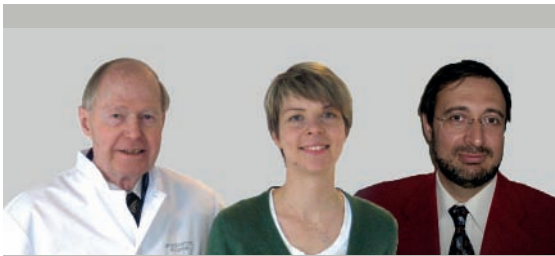
Regulation of ACE1 was studied in cultured cells. Statins, notably atorvastatin and simvastatin, were shown to be powerful inhibitors of ACE expression. This may add a novel aspect to the pleiotropic actions of statins. Furthermore, nicotine caused upregulation of ACE expression, suggesting a possible proinflammatory role for nicotine in the vascular endothelium.



Selected publications

Dahlöf B, Devereux R, Julius S, Kjeldsen S, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm L, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359:995-1003

Fyhrist F, Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Hille DA, Lyle PA, Edelman JM, Snapinn SM, Wedel H. Pulse pressure and treatment effects of losartan or atenolol in patients with hypertension and left ventricular hypertrophy. *Hypertension* 2005;45:580-585



► Members

Ralph Gräsbeck, MD, PhD, Dhc, Professor, head
 Benoît Dugué, PhD, Docent, Professor, Poitiers
 University
 Mirkka Sarparanta, MSc, PhD student

Collaborators

Albert de la Chapelle, MD, PhD, Academician,
 Ohio State University, Columbus, Ohio
 Stephan Tanner, PhD, Research Assistant
 Professor, Ohio State University, Columbus,
 Ohio
 Shoji Yamada, PhD, Professor, Hokkaido
 University of Education, Sapporo

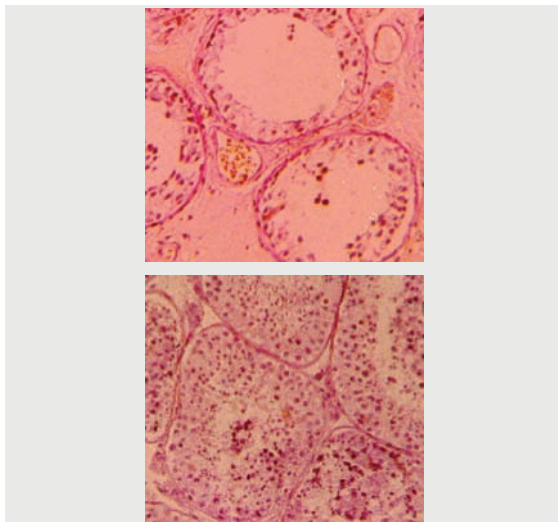
Funded by the Minerva Foundation, Medicinska
 Understödsföreningen Liv och Hälsa, and the
 Magnus Ehnrooth Foundation.

UNIT OF BIOCHEMISTRY

The Unit of Biochemistry is as old as the Institute of which Professor Gräsbeck is one of the founders. The starting point was research on the then common anemia caused by the fish tapeworm. It was shown to be due to the lack of vitamin B₁₂, which substance then became the main research topic of the Unit. In this field, the Unit has made numerous important discoveries, *e.g.* it was the first to isolate human intrinsic factor, discovered R-protein (now called haptocorrin), and described the congenital syndrome which carries the names of Gräsbeck and Imerslund, who discovered it simultaneously (abbreviated IGS). The Unit also did basic research on other hematology-related problems, *e.g.* showed the existence of a receptor for heme in the intestine and immature red cells, that anti-leukocyte immune serum was highly mitogenic, and crystallized kidney bean leucoagglutinin. In 1969 Gräsbeck together with Professor N-E Saris introduced the concept of reference values, a term or philosophy which is now universally used (but not always fully understood).

Because of Professor Gräsbeck's high age, most of his former collaborators have obtained posts elsewhere and consequently the Unit is small. Thus, only Gräsbeck works full-time, and Professor Dugué and Mrs. Sarparanta work only periodically at Minerva. The Unit collaborates with Professor de la Chapelle and Dr. Stephan Tanner in Columbus, Ohio, in characterizing the genes responsible for congenital vitamin B₁₂ deficiency diseases. The Unit now investigates the proteinuria present in about half of the cases of IGS and offers worldwide advice in diagnosing new cases.

In another project, the Unit studies the fates of the parts of the cobalamin molecule in metabolism. The reason is that it has been axiomatically accepted that in radioactive



Testicular biopsy before and after treatment of a patient with vitamin B12 deficiency. Gräsbeck R and Salonen E-M: Prog Food Nutr Sci 1976;2:193-231

vitamin B₁₂, radiocobalt reflects the behavior of the entire molecule. One project was to elucidate whether the phosphorus in a side chain dissociates from the central cobalt atom. ³²P-labelled cobalamin was biosynthesized, given to rats and compared with ⁵⁷Co-cobalamin and cobinamide. Phosphorus was found not to dissociate. These results were published in the Journal of Labelled Compounds and Radiopharmaceuticals. The fates of other parts of the molecule are now being studied.

Lately, Gräsbeck has written educational articles on reference values. In addition, being able to read numerous languages, he has written summaries of old medical books in the antique library of the Finska Läkaresällskapet and biographies of notable scientists, including Linnaeus, whose 300th anniversary was celebrated in 2007. Dugué, Professor of sports medicine in Poitiers, France, became an expert on stress while working in the Unit, studying the effect of stress on the expression of the vitamin B₁₂-intrinsic factor receptor. He has now studied the effects of cold on hormone concentrations in women and the beneficial effect for handicapped people of physically exercising healthy limbs.

Selected publications

- Wahlstedt-Fröberg V, Pettersson T, Aminoff M, Dugué B and Gräsbeck R. Proteinuria in cubilin-deficient patients with selective vitamin B12 malabsorption. *Pediatr Nephrol* 2003;18,417-421
- Gräsbeck R. The evolution of the reference value concept. *Clin Chem Lab Med* 2004;42,692-697
- Tanner SM, Li Z, Perko JD, Öner C, Çetin M, Altay Ç, Yurtsever Z, David KL, Faivre L, Ismail EA, Gräsbeck R and de la Chapelle A. Hereditary juvenile cobalamin deficiency caused by mutations in the intrinsic factor gene. *Proc Natl Acad Sci US* 2005;102,4130-4133
- Gräsbeck R. Imerslund-Gräsbeck syndrome (selective vitamin B12 malabsorption with proteinuria). *Orphanet Journal of Rare Diseases* 2006. <http://www.ORJD.com/content/1/1/17> (Length 6 pages)
- Gräsbeck R, Sarparanta M. Preparation and biodistribution of ³²P-labelled hydroxocobalamin and comparison with ⁵⁷Co-labelled cobinamide and cyanocobalamin. *J Labelled Compounds and Radiopharmaceuticals* 2008;51:451-456



In the Name of the Goddess of Science

In the year 1959, a group of researchers from the Faculty of Medicine in Helsinki University thought about how they could realize their interest towards scientific research. The problem was very tangible; the university clinics, situated in different locations across the city, did not have enough space to start a research laboratory.

"Professor Bertel von Bonsdorff, the head of the Fourth Department of Internal Medicine, which at the time was a subtenant in the Maria City Hospital, suggested that we should rent the space needed for research outside the hospital. To begin with, we hired premises from the private Konkordia Hospital. The administration also required thinking about, and we came to the solution of setting up a foundation", Professor **Ralph Gräsbeck**, one of the founders of the Minerva Foundation, tells us.

"It was I that came up with the name. Minerva is the goddess of wisdom and science; it very aptly describes what we do", Gräsbeck mentions.

In the beginning, the Foundation only had a very small amount of money, and to start with the researchers covered the costs of renting from their own research grants. The research work itself did not differ in the way it was carried out, although there was less knowledge and the equipment was simpler. Even at these early stages, the scientists had very practicable facilities at their disposal. For example, a cold room was built in the laboratory, containing equipment for the purification of proteins. It was also possible to handle radioactive materials.

"Among other things, the subjects of our research included thyroid hormones, tapeworms and vitamin B₁₂. We were using new methods, so many doctors sent us samples from interesting and difficult-to-diagnose patients. We did these analyses for free in the beginning;

I Sinkkonen and R Gräsbeck isolating intrinsic factor in the cold room (1961)



after all, the Foundation was not allowed to take part in commercial enterprises. But as the amount of work grew, in 1964 we erected a service laboratory to take care of the routinely performed analyses. This was the company Medix, which is owned by the Minerva Foundation and which even today largely finances our activities. It is possible to make money through research – something I had realized while in the USA. It was still a foreign concept in the Finnish scientific community that research could pay for itself.”

Research Across Cultural Borders

Professor Gräsbeck acted as the director of the Institute during the years 1971-1993. At the moment, he leads the Unit of Biochemistry. His career has been a long one and has included a number of significant scientific discoveries. For example, in 1965 his group isolated human intrinsic factor from gastric juice. This is a protein which binds the vitamin B₁₂ in our food and transports it to the small intestine, where it attaches to a receptor on the intestinal wall, leading to the absorption of the vitamin. The gastric juice of a person suffering from pernicious anemia lacks this intrinsic factor.

A second noteworthy innovation was the discovery of a disease belonging to the Finnish disease heritage. This

disease is now known as Imersund-Gräsbeck syndrome. It is a congenital deficiency of vitamin B₁₂, which is caused by the inability of the intestine to absorb the vitamin from food. The problem lies in the receptor of the small intestine and the genes encoding it. This has been the object a great deal of interest, as it has recently been found that the same genes and proteins are also involved in the transport of many other substances. These genes are probably also mutated in some other diseases, which manifest as defects in the brain and eyes.

“It is surprising that diseases that are phenotypically entirely distinct could be caused by the same gene. Of course, in science anything new tends to be in some way surprising, Gräsbeck adds.

“I feel very privileged to have been involved in the development of science, and I have also been honored for my work. It is tremendously interesting to elucidate biochemical processes and the etiology of diseases. Science is also very international, and many foreign investigators have worked in my group. Finnish biochemical research has a good reputation, and the level is also high in genetics. Over the years, I have gained a large number of friends from different parts of the world. Everywhere in the world, we researchers are unified across cultural borders by the same zeal for science.”

Arja-Leena Paavola

A Pioneer of Many Fields in Finland

Professor **Frej Fyhrquist** heads the Unit of Clinical Physiology, where the research concentrates on hypertension in particular and on vasoactive factors more broadly. The group has published over 300 articles. During the years 1994-2003, Fyhrquist was also the director of the Minerva Research Institute.

Minerva is part of the network of research communities. The most important collaborator for Fyhrquist's group is the Helsinki University Central Hospital's Department of Internal Diseases.

"In practice, the collaboration means offering us patient material for research uses. We also work on common ventures in close contact with different departments of Helsinki University", Fyhrquist explains.

Hypertension belongs to the Finnish national diseases and it remains a notable problem, with plenty of research still to be done to understand it. Hypertension therapy could also be improved, as a high blood pressure is a significant risk factor in many diseases.

"The blood pressure of the Finnish population has decreased considerably over the past 30 years, but in spite of this beneficial development, the figures are still high when compared internationally. Also the morbidity and mortality due to stroke and coronary disease is prevalent. Strokes are very expensive for society and a harsh condition for all involved", Fyhrquist points out.

"Unfortunately, Finns are not very interested in even having their blood pressure measured, because hypertension remains symptomless for a long time. A late start in therapy is often the cause of the treatment being unsatisfactory."

Fyhrquist has supervised the production of sixteen theses. He considers the role of supervisor to be particularly rewarding.

"When I myself was young, research was done on top of other work. Funding was obtained by working days



in the hospital and then spending evenings and nights doing research in the laboratory. The atmosphere was one of great enthusiasm, but admittedly it was very tough and I don't recommend that kind of working pace for anybody."

In contrast, nowadays scientists' ardor may be curbed by the fierce competition for positions and funding. The researchers at Minerva also use a great deal of time for organising funding; many senior researchers spend up to a third of their working time writing grant applications. However, Fyhrquist doesn't see this as a purely bad state of affairs: writing grant applications forces one to think critically about the significance of the planned research.

"In addition to the Finnish Academy, also private foundations have an important role in research funding. In Finland, funding is almost always too temporary and young scientist have to live with a lot of anxiety and short-term employment. Perhaps the number of graduates are also a little too high nowadays", Fyhrquist ponders.

Work for National Health

In previous years, promising researchers could be recruited to projects simply by asking junior doctors whether they would be interested in doing research at Minerva. Presently recruiting is harder, because often good salaries elsewhere attract doctors more than working with rats in the laboratory. Consequently, the proportion of doctors among the investigators at Minerva has diminished while the number of researchers trained in the natural sciences has increased. The Institute can offer the possibility of doing a pro gradu thesis for a Master's degree or a Ph.D. thesis.

According to Fyhrquist, someone suited to research must have certain psychological prerequisites for the work.

"You have to be eager but also prepared to cope with set-backs and hard toil in the hope of finally getting recognition for the work. But it is very rewarding. I myself decided to concentrate on a career in research when I realized that my work as a junior doctor at Maria City Hospital didn't give me intellectual satisfaction. I became interested in the renin-angiotensin system. Even after many years, I am still very enthusiastic about furthering science."

Although not a large institute, Minerva still plays a significant role in the scientific circle of our country.

"We have produced a number of excellent theses, and in research we have even made it to the top. Many of the investigators who received their scientific training with us have attained high academic positions with merits obtained at Minerva, and now as professors they are in turn training new researchers. In some things Minerva has been a true pioneer, such as in protein chemistry, and we were the first in Finland to use isotopes in medicine", Fyhrquist expounds.

Arja-Leena Paavola

Persevering Work in Science

Docent **Laura Korhonen** has held the position of Academy Research Fellow at Minerva since autumn 2005. Her field is medical neurobiology and cell death research in particular.

"My research group is trying to deduce the earliest possible changes in nerve cell function to improve the diagnostics of neurodegenerative diseases and to create new kinds of possibilities for their treatment and prevention", Korhonen relates.

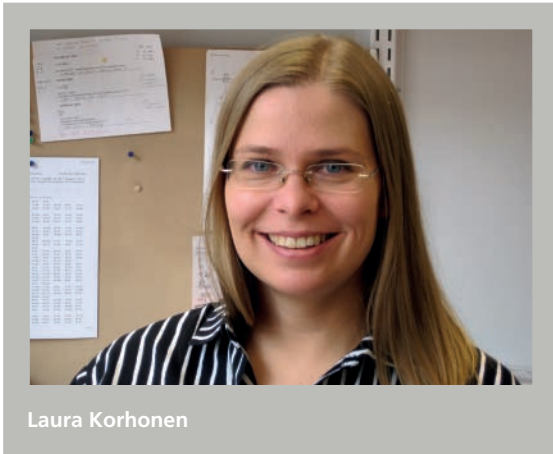
She is conducting experimental basic research, which utilises different biochemical, cell and molecular biological methods.

"We also use animal models, which help us to look for clues for the mechanisms of cell death in neurons. We are trying to find out how different organelles, such as the endoplasmic reticulum, are involved in cell death and its regulation. We are also very interested in the disturbances of synaptic functions as part of the pathogenesis of neurodegenerative diseases."

Several theses, both Master's and Ph.D., are being prepared in the various projects of the group; thus research work also has an educational aspect. There are currently four graduate students working in Korhonen's group. During the past few years, the research groups at Minerva have actively taken part in graduate training. For example, the course on neurobiology aimed at graduate students is very popular.

A Thirst for Knowledge as Motivation

Korhonen is one of the younger researchers at Minerva. The wide age distribution among the research staff is an asset, as it brings perspective to research work and helps in understanding the persistence required by the work. Knowledge accumulates over the decades from



Laura Korhonen

small fragments of information.

"The senior scientists at the institute have always staunchly supported and helped their youngers and hence have played a central role in building and maintaining the "Minerva spirit". Additionally, their presence helps remind me of what got me into scientific work, namely insatiable curiosity, a thirst for knowledge, and the joy of discovery", Korhonen gratefully tells us.

Her own field is currently at a very interesting stage. In many cases, the disease causing genes are known, but their function in the cell is not entirely understood. The methodology has also advanced remarkably, and in the coming years it may be possible to get precise answers to very basic mechanistic questions.

"We need this knowledge if we are to develop diagnostics and therapies", Korhonen asserts.

There have also been changes at Minerva over the past few years. The neuro group in particular has recruited several new students. Modern research methods, such as stem cell culture, siRNA techniques, cloning and imaging, are in use. Also contacts with the outside world have become tighter.

"Especially Professor Dan Lindholm has actively established contacts across borders, and many visits from international scientists have brightened the everyday life of the Research Institute over the last few years."

Arja-Leena Paavola

Top-Level Research Requires Collaboration

At the beginning of her scientific career, Professor **Carola Grönhagen-Riska** concentrated on laboratory work, which led to her working as a researcher at Minerva.

"For my Ph.D. thesis, I worked on isolating angiotensin converting enzyme, ACE, which among other things regulates blood pressure, from lung tissue. My supervisor was Professor Frej Fyhrquist. I continued in his research group until the mid-1980's, when I moved to the Helsinki University Central hospital to be head doctor in nephrology. Since then, my research subjects have principally been the patient groups at the Helsinki University Central Hospital Department of Nephrology, and the lab work has been carried out in the research laboratory of the Department. My research effort in recent years has largely been involved with the Finnish Registry for Kidney Diseases and the epidemiology and therapy of kidney conditions, Grönhagen-Riska explains.

In addition to her research work, she has been actively involved with Minerva, starting as the Foundation's secretary, then chairing the Foundation for five years before becoming a member of the Board.

"As a member of the Board, I'm involved in the activities of the Foundation and research institute in many ways. I'm also on the boards of the companies owned by the Foundation. We have divided responsibilities between the financial and stipend committees in a way that some Board members take part in managing the property, i.e. the companies owned by Minerva, whereas the others concentrate on the proper use of research funds to advance the scientific work."

When she started, the research institute was located in Kauniainen with the Medix laboratory. Research activity was very spirited and lively, but for a research institute it was not good to operate so far from the university.

"The most significant of the changes during my career was moving Minerva closer to Helsinki University and the Central Hospital. In hindsight, the first important step on the road of progression and expansion was precisely this move into the Aura building in Helsinki. Due to the move, cooperation with different university organizations improved substantially. The next milestone was moving into new facilities at the turn of the millennium in conjunction with the founding of Biomedicum."

At the Heart of Innovation

Currently, Minerva is situated in Biomedicum-2, where the Foundation purchased excellent new facilities. Being located in a building doing front-line medical research and where innovation is at its best is a huge advantage for what is after all a small research institute. In Biomedicum, collaborations arise naturally.

"I find it wonderful that we were able to buy research space in Biomedicum also because it shows that the Foundation's finances are in good hands," Grönhagen-Riska remarks.

"During the 50-year history of the Foundation, we have been through several different changes. One of the renovations, which I was instigating around the millennium, was a change in the structure of the administration. Now, Minerva's Board has more members and nearly all of them are professors or other researchers from Helsinki University. This consolidates cooperation with outside research, something we were striving at."

Top-notch research requires an open community, where researchers can meet face to face. In the words of Grönhagen-Riska, prerequisites of research are input and output. In this respect, the most successful in the world are those who have similar congregations to Biomedicum.

"I believe that Minerva must integrate even more closely into the big picture and continually make sure that we support developing and valuable medical research. We want to encourage good groups and good scientists by offering them resources and research space."

Arja-Leena Paavola

Benefits for Research from the Corporate World

Professor **Jim Schröder** first came to Minerva to work on his Ph.D. thesis on genetics in the year 1970. After defending, he went out into the world for several years.

"Professor Albert de la Chapelle and I showed that during pregnancy, cells cross from the placenta into the mother's bloodstream. This finding led to the idea that it might be possible to determine if the coming child was healthy by taking a blood sample from the mother. We published our study in 1972, and due to this I was able to go to Stanford University to continue investigating the subject," Schröder describes.

These studies initiated extensive research all over the world. Nowadays, it is possible to isolate fetal DNA from the blood of a pregnant woman. This year, a laboratory test kit for diagnosing inherited diseases in the fetus during the early stages of pregnancy will be coming out on the market. A venous blood sample from the mother has several advantages over the traditional way of taking a biopsy by puncturing the uterus, because it is much safer and the test can be administered at a much earlier stage.

Research funding in good shape

Schröder has been able to usefully combine business thinking and research, which has been advantageous to both Minerva and the companies it owns. In the year 1994, he returned to Minerva, this time as a member of the Foundation Board. Schröder has been the chair of the Board since 2003.

The Foundation is the major stockholder in three successful companies. The key to this success has to a



Jim Schröder

great extent been the close cooperation between Minerva and the Medix corporations.

"When I was a student, human genetics was in its infancy in Finland, and there was hardly any research in or teaching of medical genetics at the university. After Minerva was founded, in 1962 the Folkhälsan Department of Genetics was launched, which for 30 years was located in the same space as Minerva. In practice, there was no clear distinction between these institutions, and the scientists of the Folkhälsan Genetics Department were also researchers at Minerva, and vice versa. This arrangement was beneficial for both parties," Schröder narrates.

In the early years of Minerva, all funding was obtained from private foundations, but already in the 1960's the proportion of public funders, like the Academy of Finland,

grew to be predominant. Through the development of the Medix corporations, the significance of companies as funders of the research at Minerva has grown year by year. In 2008, over 40 percent of the whole research budget of the institute came from Medix corporation dividends.

"In my view, the funding situation for research in Finland is good. However, in some fields there are too many university graduates, and there isn't enough work for everybody. Many people become researchers because industry isn't offering jobs that correspond to their education. More should be invested into applied scientific research, though basic research must be given its due. Tighter cooperation between the university world and industry would profit everyone. Silicon Valley in the USA is a good example of this," Schröder points out.

Arja-Leena Paavola



DISSERTATIONS from the Minerva institute

2008

Anna Kotronen: Liver fat in the metabolic syndrome and type 2 diabetes

2007

Cia Ramström: Ceramides and DAG as regulators of potassium channel function

2005

Mirja Tiikkainen: Effects of weight loss, rosiglitazone and metformin on liver fat content, insulin resistance and gene expression in adipose tissue

2004

Marjo Tamminen: Vascular and platelet function in insulin resistance

Esa Leppänen: Experimental basis for standardization of blood specimen collection (started in Minerva but was completed in Jyväskylä)

2003

Elena Korshennikova: Molecular mechanisms of insulin resistance in human skeletal muscle and lipodystrophic adipose tissue

Robert Bergholm: Effects of weight loss, physical training and anti-inflammatory therapy on endothelial function in vivo



Biomedicum Helsinki, 2001-2008

Jussi Sutinen: Pathogenesis and treatment of lipodystrophy in HIV-infected patients receiving highly active antiretroviral therapy

2002

Nina Uhlenius: Angiotensin II and nitric oxide in chronic experimental nephritis

2001

Jukka Westerbacka: Insulin action on large artery stiffness in normal and insulin resistant subjects.

Satu Vehkavaara: Identification and treatment of endothelial dysfunction and cardiovascular risk markers in disorders of glucose metabolism and in postmenopausal women.

2000

Benoît Dugué: Variabilité biologique. Influence des facteurs préanalytiques *in vivo* (stress physique, stress psychologique, chronobiologie) sur les résultats d'analyses de marqueurs biologiques sanguins et cellulaires

1999

Markus Sundblom: Neuropeptide FF in human blood and cerebrospinal fluid

1998

Leena Karhapää: Effects of caffeine and thimerosal on the regulation of intracellular calcium concentration in GH₄C₁ rat pituitary cells

1997

Marja-Leena Sirviö: Endothelin-1; cardiopulmonal expression, metabolism and regulation of atrial natriuretic peptide release

1995

Antti Virkamäki: Mechanism and causes of abnormal carbohydrate metabolism during experimental and natural infections

1994

Outi Saijonmaa: Endothelin-1: Plasma levels in cold pressor test and regulation in endothelial cells

Karri Helin: Neutral endopeptidase inhibition in experimental heart failure



Auratalo, 1989-2001

1991

Sari Tikanoja: Free thyroid hormones in serum: performance of different assay methodologies in thyroid diseases and non-thyroidal illnesses

1989

Per-Henrik Groop: The relationship between gastric inhibitory polypeptide (GIP) and beta-cell function in man

Tuula Tikkanen: Atrial natriuretic peptide in experimental heart failure

Kaj Metsärinne: Renin substrate in human plasma and amniotic fluid

1987

Kid Törnquist: 1,25-dihydroxyvitamin D₃ and the secretion of thyrotropin and prolactin from the rat pituitary gland

Katarina Rosenlöf: Erythropoietin: receptor and comparison with renin substrate

1986

Virpi Oksanen: Neurosarcoidosis: A clinical, laboratory and neuroradiological study

1984

Markku M. Nieminen: Renin-Aldosterone axis in man following ingestion of ethanol

Christel Lamberg-Allardt: Serum 25-hydroxy-vitamin D concentration and vitamin D intake

Terje Forslund: Induction of rat angiotensin converting enzyme by captopril and enalapril

1983

Ilkka Immonen: Factors affecting human plasma renin substrate concentration with emphasis on estrogens and pregnancy

1982

Jaakko Linkola: Strain differences in water and electrolyte metabolism between alcohol preferring (AA) and alcohol avoiding (ANA) rats

Tom Petterson: Pleural effusions in infectious, neoplastic and connective tissue diseases. A study of cellular and immunological reactions with emphasis on the role of T and B lymphocytes

1981

Ilkka Kouvonen: Structure of the porcine intestinal intrinsic factor (IF) receptor



Kauniainen, 1972-1989

Ilkka Tikkanen: Hypertensive effect of autoimmune nephritis in DOCA-NaCl-treated and in spontaneously hypertensive rats

Georg Borgström: Clinical implications of chromosome aberrations in hematologic neoplasia

1980

Carola Grönhagen-Riska: Angiotensin converting enzyme and sarcoidosis

Fredrika Pekonen: The interaction of thyrotropin with its receptors

1978

Thomas Tötterman: Thyroid-infiltrating immunocompetent cells in human autoimmune thyroid disease

George Marcoullis: Soluble and membrane-bound proteins involved in vitamin B₁₂ transport

Pertti Soveri: Renin in human pregnancy and during oral contraception



Töölönkatu, 1964-1972

1975

Gustav Wägar: Effect of TSH and cyclic adenosine 3', 5'-monophosphate on thyroidal protein synthesis

Jim Schröder: Passage of blood cells between foetus and mother

1974

Ariel Gordin: Thyrotrophin in human serum; A methodological and clinical study in diseases of the thyroid gland

Ulf-Håkan Stenman: Studies on cobalophilin. Vitamin B₁₂-binding proteins of R-type

Ritva-Kajsa Selander: Kromosomala makromolekylerers effekt på vissa akridinderivats absorption och fluorescens

1973

Aldur Eriksson: Human twinning in and around the Åland Islands



Konkordia Hospital, 1959-1964



Albert de la Chapelle and Kai Simons

1972

Jorma Mäenpää: Hypothyroidism and autoimmune thyroiditis in childhood

Risto Kala: Venous plasma angiotensin II in man. Diurnal variation and response to various postural stimuli and exercise

1971

Johan Wennström: Effect of ionizing radiation on the chromosomes in meiotic and mitotic cells

Frej Fyhrquist: Radioimmunoassay of plasma angiotensin II in patients with hypertension, in renal transplant recipients, and in anephric patients

1970

Johan Edgren: Effect of cysteine on chromosome aberrations induced by radiation of human lymphocytes in vitro

1969

Teddy Weber: Isolation and characterization of a lymphocyte-stimulating leucoagglutinin from red kidney beans (*Phaseolus vulgaris*)

1968

Rolf Nordman: Endemic goitre in Finland in the light of thyroids of newborn in 1962-1965

Kristian Liewendahl: Iodochloroxyquinoline and the thyroid gland. Metabolism of iodochloroxyquinoline iodine and its effect on the thyroid iodine metabolism in rats

1964

Kai Simons: Vitamin B₁₂ binders in human body fluids and blood cells

1962

Albert de la Chapelle: Cytogenetical and clinical observations in female gonadal dysgenesis



1959-2009