MINERVASTIFTELSEN

Verksamhetsåret omfattar perioden 1.1.2007-31.12.2007. Fr.o.m. 1.1.2007 bestod stiftelsens styrelse av:

Professor Jim Schröder, ordförande
Professor Christian Ehnholm, vice ordförande
Professor Krister Höckerstedt, sekreterare
Professor Carl G. Gahmberg
Professor Carola Grönhagen-Riska
Docent Caj Haglund
Professor Christer Holmberg
Professor Carl Gustaf Nilsson
Advokat Tauno Palotie
Docent Carina Wallgren-Pettersson

Till revisorer för perioden 1.1.2007-31.12.2007 valdes:
EM Martin Grandell, CGR, ordinarie revisor
EM Kim Karhu, CGR, ordinarie revisor

MEDICINSKA FORSKNINGSINSTITUTET MINERVA

Direktionen bestod av följande personer:

Professor Dan Lindholm, ordförande
Professor Frej Fyhrquist
Professor Ralph Gräsbeck
Docent Heikki Koistinen
Professor Kid Törnquist
Professor Hannele Yki-Järvinen
Docent Ilkka Tikkanen
FM Tuulikki Nyman, sekreterare
DK Carita Estlander-Kortman, ekonomichef

Institutchef var professor Dan Lindholm och ekonomichef DK Carita Estlander-Kortman.

I stiftelsen har verkat tre arbetssutskott:

1. Finansutskottet
   Jim Schröder, ordf.
   Carola Grönhagen-Riska
   Christian Ehnholm
   Tauno Palotie

2. Stipendieutskottet
   Carl G Gahmberg, ordf.
   Caj Haglund
   Carl Gustaf Nilsson
   Christer Holmberg
   Krister Höckerstedt
   Carina Wallgren-Pettersson
3. Valutskottet
   Jim Schröder, ordf.
   Christian Ehnholm
   Carl G Gahmberg
   Carola Grönhagen-Riska

Minerva har fått mottaga betydande understöd från Medicinska Understödsföreningen Liv och Hälsa.

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 annual review covers the period from January 1, 2007, to December 31, 2007. The board of trustees included the following persons:

   Professor Jim Schröder, Chairman
   Professor Christian Ehnholm, Vice Chairman
   Professor Krister Höckerstedt, Secretary
   Professor Carl G. Gahmberg
   Professor Carola Grönhagen-Riska
   Docent Caj Haglund
   Professor Christer Holmberg
   Professor Carl Gustaf Nilsson
   Advocate Tauno Palotie
   Docent Carina Wallgren-Pettersson

THE MINERVA FOUNDATION INSTITUTE FOR MEDICAL RESEARCH

Board of directors:

   Professor Dan Lindholm, Chairman
   Professor Frej Fyhrquist
   Professor Kid Törnquist
   Professor Ralph Gräsbeck
   Docent Heikki Koistinen
   Professor Hannele Yki-Järvinen
   Docent Ilkka Tikkanen
   FM Tuulikki Nyman, Secretary
   DK Carita Estlander-Kortman, financial manager

Head of the Institute was Dan Lindholm. Carita Estlander-Kortman was financial manager.

The administration is handled by following groups:

4. Financial Committee
   Jim Schröder, chairman
   Carola Grönhagen-Riska
   Christian Ehnholm
   Tauno Palotie
SUMMARY OF RESEARCH AND ACTIVITIES DURING THE YEAR 2007

The Minerva Foundation Institute for Medical Research is a privately owned biomedical institute 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 studies of single cells and molecules to analyses of experimental animals and human patient material.

Minerva Institute has currently a 480 m² large laboratory space situated at the Biomedicum-Helsinki building that is a large conglomerate of modern laboratories mostly belonging to the Helsinki University with research groups in the biomedical and medical research fields. In the spring of 2008 the Minerva Institute will move to the new building, Biomedicum-2 that is located nearby, with ultramodern facilities and new laboratories spaces. The change in location of Minerva will contribute to the development of the Institute and will create an inspiring environment for performing research with new challenges for the future.

To develop the Institute further, a new group, the Unit of Metabolism, was recruited in the year 2007. This group is headed by Docent Heikki Koistinen, MD and focuses on the study of insulin signaling and fatty acid metabolism in skeletal muscle specimens from humans. The Unit will further deepen and strengthen the already actively ongoing research in diabetes on causes of insulin resistance in type-2 diabetes that is successfully carried out at Minerva.

Apart from diabetes, cardiovascular research, cell physiology, cell biology and neurobiology are all strongly represented at the Institute. The research activities have developed well for all the groups at Minerva Institute. Among achievements this year can be mentioned the work in the Unit of Endocrinology on the pathogenesis of metabolic syndrome in humans showing that adipose tissue inflammation is a key event that distinguishes between obese subjects with and without fatty liver (Kolak et al, Diabetes 56:1960-1968) Another seminal finding is the collaborative work between the Unit of Neuroscience and University of Zurich on the anti-apoptotic protein, XIAP and cell death regulation in acute lymphoblastic leukemia cells (Bornhauser et al, Blood 110:2084-209).

During this year, Dr. Cia Ramström belonging to the Unit of Cellular Physiology, headed by Professor Kid Törnquist, defended her doctoral dissertation on ‘Ceramides and DAG as regulators of potassium channel function’.
Additionally, a total of four Master thesis (Pro gradu thesis) were finished at Minerva during this year.

Generous funding has been obtained from The Minerva Foundation, The Sigrid Jusélius Foundation, Medicinska Understödfsöreningen Liv och Hälsa, The Finnish Academy and other sources.

A detailed description of the research in the different groups at Minerva is given below and in the recently updated homepage (please see under http://www.helsinki.fi/minerva).

UNIT OF NEUROSCIENCE

Members of the unit

Dan Lindholm, M.D., Ph.D., Professor (head)
Laura Korhonen, M.D., Ph.D., (on maternal leave)
Tuulikki Nyman, M.Sc., Laboratory Manager
Sandra Falck, Ph.D. (on maternal leave)
Kirs Jänkälä, B.Sc. student
Minna Kairisalo, M.Sc. (Pharm), Ph.D. student
Eeva Lehto, Laboratory Assistant
Johanna Mäkelä, M.Sc., Laboratory Assistant
Noora Putkonen, M.Sc., Ph.D. student (HBGS)
Sami Reijonen, M.Sc., Ph.D. student
Raili Rajala, M.Sc., Ph.D. student (FGSN)
Mikko Koskinen, M.Sc., Ph.D. student (HBGS)

In addition students in biology and medicine have worked part time in the group.


Collaborators include U. Arumäe Inst for Biotechnology, K. Blomgren Gothenburg University, B Bornhauser University of Zurich, L. Andersson, Dept of Pathology University of Helsinki, T. Otonkoski, Biomedicum-Helsinki, O.Eriksson, Biomedicum, G.Mudo and N. Belluardo Palermo Italy, H Kataoka, Faculty of Medicine University of Miyazaki, Japan, Jim Schröder Dept of Genetics, Helsinki University.

The group is interested in basic mechanisms underlying neurodegenerative diseases and excitotoxic damage by focusing on cell death pathways and proteins in disease pathogenesis with the aim to contribute to better therapies to combat cell death and degeneration. Particular interests are the roles of cellular organelles such as mitochondria and endoplasmic reticulum (ER) stress in cell death control in neurons as well as alterations in protein ubiquitination via the ubiquitine proteasome system (UPS) in pathogenesis. In this context we also study changes in synaptic function and degeneration as these are early findings in many brain disorders as well as alterations in neurotrophic factor signaling. The group also pursues studies of neuronal stem cells and of factors that influence their proliferation, cell differentiation and plasticity in the brain and in disease conditions.
Figure 1. *In vitro* model to study Huntington’s disease by the expression of mutant fluorescent huntingtin-EGFP fusion protein construct forming aggregates in cultured neurons visualized using fluorescent microscopy (green dots) (Reijonen et al, in press).

The group is a member of Finnish Graduate School in Neuroscience (FGSN) and Helsinki Biomedical Graduate School (HBGS) and collaborates with the Biomedicum Stem Cell Center on stem cells.

**Publications:**


**In Press:**


of human osteosarcoma cells and binds the X-linked inhibitor of apoptosis protein. Biochem Biophys Res Commun, In press


The following Pro Gradu theses were accepted:


UNIT OF CARDIOVASCULAR RESEARCH

Members of the Unit are:

Ilkka Tikkanen, M.D., Ph.D., Docent, head
Mika Laine, M.D., Ph.D., Docent
Eeva Palojoki, M.D., Ph.D.
Tom Bácklund, M.D., PhD student
Tina Grönholm, M.D., PhD student
Päivi Lakkisto, M.D., PhD student
Kirsi Lastunen, M.D., PhD student
Jere Paavola, Cand. Med. PhD student
Heli Segersvärd, Cand. Med. PhD student
Hanna Tikkanen, DVM. PhD student
Riina Hatakka, Laboratory technician
Riikka Kosonen, Laboratory technician
Jarkko Lakkisto, Laboratory technician

Collaborators are: Eero Mervaala, M.D., Ph.D., Professor, University of Helsinki; Kari Pulkki, M.D., Ph.D., Professor, University of Kuopio, Ilkka Pörsti, M.D., Ph.D., Professor, University of Tampere.


Main research findings and activities:
The major interest of the group has been to study mechanisms of end-organ damage in cardiovascular and renal diseases, notably local expression of vasoactive factors and apoptosis in hypertension, heart failure, and in progression of renal damage. In this connection, the cardiovascular and renal protective properties of new cardiovascular drugs have been studied. Recently, the focus of our research has been shifted to study more regenerative and reparative mechanisms after tissue injury in cardiovascular diseases. In this context we aim to study:
a. the role of cardiac stem cell proliferation and mobilization in cardiac tissue repair and regeneration after myocardial infarction,
b. cellular mechanisms mediating cardiovascular protection following tissue injury, and
c. the role and regulation of novel components of the renin-angiotensin-aldosterone system in the adaptation to and treatment of end-organ damage in cardiovascular diseases

The novel findings on cardiac stem cells (CSC) open a completely new possibility to achieve cardiac repair and treatment of cardiac failure after myocardial infarction. We have been able to show that cardiac niches contain stem cells (CSC), which are able to activate, proliferate and form new myocytes and vascular structures after myocardial injury (Anversa P et al., Circulation 113:1451-1463, 2006). In agreement with these findings, we have been able to show increased amounts of new cardiomyocytes after experimental myocardial infarction in the rat utilizing immunohistochemical characterization of proliferating cardiomyocytes and cardiac stem cells (see Figure).

Figure 2. Cardiac regeneration after acute myocardial infarction. Cells are stained with different markers for cell proliferation (BrdU,Ki67) and cardiac stem cells (c-Kit, MHC).

Publications:


In Press:

UNIT OF ENDOCRINOLOGY

Members of the Unit

Hannele Yki-Järvinen, MD, Ph.D., F.R.C.P, Prof. of Medicine, University of Helsinki, head
Robert Bergholm, MD, Ph.D.,
Anja Cornér, MD
Leena Juurinen, MD
Kirsi Pietiläinen, MD, Ph.D.,
Ksenia Sevastianova, MD
Jussi Sutinen, MD, Ph.D.,
Jukka Westerbacka, MD, Ph.D.,
Anna Kotronen, MB
Janne Makkonen, MB
Katja Tuominen, technician
Mia Urjansson, technician
Tuija Mård, nurse

Funded by The Minerva Foundation, EU-HEPADIP, Sigrid Jusélius, EVO and Academy of Finland, Sanofi-Aventis, MSD and Eli Lilly.

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

The metabolic syndrome is a cluster of risk factors (abdominal obesity, increased serum triglycerides, low serum HDL cholesterol, elevated blood pressure and hyperglycemia) that is considered to increase the risk of cardiovascular diseases and type 2 diabetes more than one risk factor alone. It is poorly understood to whom this common syndrome develops.
Fatty liver due to non-alcoholic causes is considered to be a key player in the pathogenesis of the metabolic syndrome, and may distinguish subjects who develop the syndrome. Subjects with fatty liver are characterized by features of the metabolic syndrome and those fulfilling the criteria for metabolic syndrome usually have a fatty liver (Kotronen et al J Clin Endocrinol Metab 92:3490-7, 2007). Adipose tissue in obese subjects is inflamed and expression of insulin-resistant genes and the local production of their protein products by macrophages are increased and may regulate liver fat (Westerbacka Diabetologia 49:132-40, 2007).
In the recent key study, we have demonstrated that adipose tissue inflammation distinguishes between obese subjects with and without fatty liver (Diabetes 56:1960-1968, 2007). In 20 obese women, the liver fat content 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 performed for immunohistochemistry and gene expression studies (Prof. Hamsten's group, King Gustaf V Research Institute, Karolinska Institutet, Stockholm, Sweden). Adipose tissue lipidomic 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).

Also, we have recently shown that adipose tissue is infiltrated with macrophages, and its content of long-chain TAGs and ceramides is increased in subjects with increased LFAT compared with equally obese subjects with normal LFAT. Ceramides or their metabolites could contribute to 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.

Publications:


In Press:


UNIT OF METABOLISM

Members of the unit
Heikki Koistinen, M.D., Ph.D., Docent, head
Paulina Skrobuk, M.Sc (Biotechnology), Ph.D. student
Heidi Kuoppamaa, student of biochemistry, Master's student
Maarit Sihvo, student of biochemistry, Master's student
Riitta Päivärinta, technician

Funded by The Minerva Foundation, University of Helsinki, Finnish Cultural Foundation, Finnish Foundation for Cardiovascular Research and Novo Nordisk Foundation

Type 2 diabetes and insulin resistance are characterized by defects in skeletal muscle glucose transport and fatty acid metabolism. In particular, the intracellular fate of fatty acids is a major determinant of insulin sensitivity, as increased intramuscular fatty acid metabolites can affect intracellular signaling and impair insulin-stimulated glucose transport. The main interest of the group is to explain the molecular mechanisms regulating insulin sensitivity in skeletal muscle. We study the regulation of glucose and fatty acid metabolism directly in isolated human skeletal muscle strips obtained using open muscle biopsy technique. We are particularly interested in how lipid excess contributes to skeletal muscle insulin resistance, and how lipid-induced insulin resistance can be reversed. We are currently exploring the role of AMP-activated protein kinase in the regulation of these processes.
The unit collaborates closely with the groups of professor Juleen R Zierath, associate professor Anna Krook and associate professor Alexander V Chibalin from Karolinska Institutet, Stockholm, Sweden

**Publications:**

The following *Pro gradu theses* were accepted:

**Kuoppamaa H:** Adiponektiinin vaikutus ihmisen luurankoliikaisessa. Helsinki University, 2007. (The action of adiponectin in human skeletal muscle)

**Sihvo M:** Angiotensin II:n vaikutus sokeriaineenvaihduntaan ihmisen luurankoliikaisessa. Helsinki University, 2007. (The action of angiotensin II on sugar metabolism in human skeletal muscle)

**UNIT OF CELLULAR PHYSIOLOGY**

**Members of the Unit are:**
Kid Törnquist, Ph. D., Professor (head)
Cia Ramström, Ph. D.
Pia Stewen, M. Sc.
Tero Viitanen, M. Sc.
In addition the following researchers are working at Åbo Akademi:
Sonja Balthasar, Ph. D.
Tomas Blom, Ph. D.
Emad Afrasiabi, M. D.
Nina Bergelin, M.Sc.
Dan Gratschev, M. Sc.
Christoffer Löf, M.Sc.
Michael Pasternack, Ph. D. (Affiliated member)
Hugh Chapman, B. Sc. (Affiliated member)

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

The group is mainly interested in understanding the mechanisms regulating calcium entry, the modulation of intracellular calcium stores and the processes regulating proliferation and migration in endocrine cells. It also aims at understanding the importance of sphingomyelin derivatives as modulators of endocrine cells. Currently the regulation and importance of plasma membrane receptors and intracellular receptors for sphingomyelin derivatives is a topic of interest. The aims are to understand by which mechanisms sphingosine derivatives modulate voltage-dependent calcium channels, and by which mechanisms intracellular sphingolipid receptors regulate intracellular calcium levels (i.e. by interacting with 1,4,5-trisphosphate- and ryanodine receptors). In addition, the investigations aim at understanding the physiological significance of the putative sphingosine - sphingosine 1-phosphate “rheostat”. One important research area
concerns the effect of sphingosine 1-phosphate on the proliferation and migration of both normal thyroid cells and thyroid cancer cells. The investigations on this topic show that sphingosine 1-phosphate potently stimulates migration of some thyroid cancer cell types, whereas the migration of other cancer cell types is blocked. Furthermore, VEGF receptor 2 is an important component of the signaling complex activated by S1P. Preliminary data also suggest that sphingosine 1-phosphate may have an autocrine effect in some cancer cell types.

An exciting series of investigations aim at understanding the mechanisms of action of ceramide on potassium channels. Our investigations have shown that ceramide evokes an internalization and ubiquitin-mediated degradation of the HERG channel. Further investigations are currently under way to clarify the mechanisms responsible for the internalization of the HERG channel. It appears evident that protein kinase C is a major player in regulating channel internalization. In addition, HERG channels seem to be of importance in thyroid cancer cells.

The group is acting mostly at the Department of Biology (Åbo Akademi University, BioCity, Åbo, Finland) where about 70% of the activities take place. However, all the electro-physiological measurements and several applications using confocal microscopy are made at the Minerva Institute.

Publications:

In Press:


Thesis Examination
The Faculty of Mathematics and Natural Sciences of Åbo Akademi University accepted the following Theses work from the Unit:

Cia Ramström: Ceramides and DAG as regulators of potassium channel function. ISBN952-12-1819-3

UNIT OF CLINICAL PHYSIOLOGY

Members of the Unit
Frej Fyhrquist, Professor, M.D., Ph.D., head
Anders Eriksson, DVM
Outi Saijonmaa, Ph.D., Docent
Anna Tiitu, B.Sc., student

Collaborators are: Docent Per-Henrik Groop, M.D., Ph.D., Folkhälsan Institute, Biomedicum Helsinki. Docent Ilkka Immonen, M.D., D.M.Sc., Helsinki University Central Hospital. Professor Kimmo Kontula, M.D., D.M.Sc., Department of Internal Medicine, University of Helsinki. Adjunct professor Karri Silventoinen, Ph.D., University of Helsinki

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

Major interests of the Unit are blood pressure regulation, endothelial physiology and telomere functions. The Unit has focused on vasoactive peptides, notably angiotensin, bradykinin, and endothelin, their functions and receptors. More recently, the role of telomeres in cardiovascular disease and in diabetes has become our new field of interest.

1. Angiotensin-converting enzyme (ACE) was studied in cultured human endothelial cells, monocytes, and macrophages. We have shown that statins, notably atorvastatin and simvastatin, are powerful inhibitors of ACE expression, while nicotine caused upregulation of ACE expression, during the process of maturation of human monocytes to macrophages, like the effect shown earlier by us in endothelial cells. This observation may add a novel pleiotropic effect of statins to our present knowledge.

2. Genetic profiling of left ventricular hypertrophy (LVH), a substudy of the LIFE trial; in collaboration with members of the LIFE Genetics substudy (a Nordic consortium). For this purpose, cDNA has been extracted from blood samples of 4132 patients with LVH, and single nucleotide polymorphism (SNP) analysis of 13 candidate genes has been performed at the Finnish Genome Center, Biomedicum Helsinki. LVH was shown to be associated with the 16 I/D polymorphism of ACE and with the angiotensinogen Met235Thr polymorphism (manuscript submitted).

3. We have measured telomere length of DNA-samples from 1300 Finnish patients of the LIFE-study (clinical results in Lancet 2002; 39:995). These results are currently being analyzed and compared with single nucleotide polymorphisms of the renin-angiotensin system determined previously. In collaboration with docent P-H Groop, (the FinnDiane project at the Folkhälsan Research Center, Biomedicum Helsinki), we are studying telomere length and rate of telomere shortening in patients with type I diabetes and healthy subjects. Together with docent Ilkka Immonen, Department of Eye Diseases, Helsinki University Central Hospital, we study telomere length in patients with degeneration of macula densa. Having access to clinical data and DNA-samples from DNA-samples of more than 4000 Scandinavian patients of the LIFE-study, we plan to measure telomeres of selected groups. Further, a study on telomeres in renal transplantation is performed in collaboration with Docent Eero Honkanen, Department of Nephrology, Helsinki University Central Hospital.

Publications:


In Press:


UNIT OF BIOCHEMISTRY

Members of the unit

Prof. Ralph Gräsbeck, M.D., Ph.D., D.h.c., head
Benoît Dugué, Ph.D., Docent, Professor (University of Poitiers)
Mirkka Sarparanta, M.Sc., Ph.D. student

Collaborators include Professor Shoji Yamada, University of Sapporo, Japan

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

The group is as old as the Institute of which Prof. Gräsbeck is one of the founders. Its main topics have been vitamin B12, its metabolism and related diseases, the transport of heme, leucocyte mitogens, reference values and recently, history of medicine. Only Prof. Gräsbeck works full time, Prof. Dugué periodically and Dr. Sarparanta now acts as an adviser. The group has isolated and characterized the central proteins in cobalamin transport and described the congenital disease which carries the name of Gräsbeck and Imerslund, who discovered it simultaneously. The Unit collaborates with Prof. Albert de la Chapelle and Dr. Stephan Tanner in Columbus, Ohio in characterizing the genes responsible for the syndrome. The Unit now investigates the proteinuria, present in about half of the cases and offers worldwide advice in diagnosing new cases. In another project the stability of the cobalamin molecule in metabolism was studied, especially whether the phosphorus in a side chain dissociates from the central cobalt atom. 32P-labeled cobalamin was biosynthesized, given to rats and compared with 57Co-cobalamin and cobinamide. Phosphorus was found not to dissociate. An
article appeared in J Label Comps Radiopharm. Professor Yamada in Sapporo (a former member of the unit) has participated in developing a suitable medium for biosynthesizing intrinsic B₁₂. Gräsbeck wrote an educational article on reference values (a term once introduced by himself). In addition, he has written summaries of antique medical books and biographies of medical scientists, including Linnaeus whose 300th anniversary was celebrated in 2007. Dugué, professor in sports medicine in Poitiers, France, investigated the effects of muscular training in handicapped patients.

Publications:
**Sarpalanta M & Gräsbeck R:** Biosynthesis of 32P- and 57Co-cobalamin and 57Co-cobinamide and their biodistribution in rats. Abstract, EANM'07, Annual Congress of the European Association of Nuclear Medicine, Copenhagen, Oct. 13-17, 2007.

**Others:**
**Gräsbeck R:** Approx. 30 articles in the last volume of the encyclopedia (S-Ö) Uppslagsverket Finland, Schildts, Helsingfors 2007.

**Gräsbeck R:** Böcker av Linné, de Sauvage och Sydenham: Finska Läkaresällskapets antika bibliotek. Hippokrates (Yearbook of the Finnish Society of Medical History) 2007, pp. 71-84

**In Press:**
**Gräsbeck R:** Anders Langenskiöld: Article in Biografiskt lexikon för Finland. Svenska Litteratursällskapet i Finland, In press.