ANNUAL REPORT

MINERVASTIFTELSEN

Verksamhetsåret omfattar perioden 1.1.2006–31.12.2006. Fr.o.m. 1.1.2006 bestod stiftelsens styrelse av:

Professor Jim Schröder, ordförande
Professor Christian Ehnholm, vice ordförande
Professor Krister Höckerstedt, sekreterare
Professor Carl Gustav 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 1.1.2006–31.12.2006 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
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:

Finansutskottet Stipendieutskottet Valutskottet
Jim Schröder, ordf.
Carola Grönhagen-Riska
Christian Ehnholm
Tauno Palotie
Carl G Gahmberg, ordf.
Caj Haglund
Carl Gustaf Nilsson
Christer Holmberg
Krister Höckerstedt
Carina Wallgren-Pettersson
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 via the Minerva Foundation Institute for Medical Research. This annual review covers the period from January 1, 2006, to December 31, 2006.

The board of trustees included the following persons:

Professor Jim Schröder, Chairman
Professor Christian Ehnholm, Vice Chairman
Professor Krister Höckerstedt, Secretary
Professor Carl Gustav Gahmberg
Professor Carola Grönhagen-Riska
Professor 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
Professor Hannele Yki-Järvinen
Docent Ilkka Tikkanen
FM Tuulikki Nyman, Secretary
Carita Estlander-Kortman, financial manager

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

Within the Foundation three working groups are active:

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SUMMARY OF RESEARCH ACTIVITIES IN THE YEAR 2006

At the Minerva Foundation Institute for Medical Research six groups are actively working in different areas of medical and biomedical research. The Minerva Institute has an about 480m² large laboratory space situated at Biomedicum-Helsinki that is a large conglomerate of modern laboratories mostly from the Helsinki University with research groups in the biomedical and medical research fields. In year 2008 it is planned that the Institute will move to the new building, Biomedicum-2 that will be located nearby.
The research at Minerva is focused on the study of basic cellular and molecular mechanisms underlying important human diseases, such as heart, kidney and cardiovascular diseases, as well as diabetes and neurological degenerative disorders. To accomplish this, we use different cell and molecular biology methods and biochemical approaches. The objectives of the research range from studies of single cells and molecules to analyses of experimental animals and human patient samples. In year 2006 the infrastructure and the research facilities at the Minerva Institute have been developed further with the purchase of some new equipment and the development of the cell culture facilities.

The research activities have developed well for all the groups at Minerva Institute. Among achievements this year was the work on neural stem cells and their regulation by stress and steroids published by Sundberg et al., in the Journal of Neuroscience, and the publication done together with the Department of Genetics, Helsinki University (Professor J. Schröder) on the characterization of novel monoclonal antibodies towards human villous cytotrophoblasts (Hallikas et al, published in the Journal of Histochem& Cytochem).

During this year Dr. Thomas Blom belonging to the Unit of cellular Physiology, headed by Professor Kid Kid Törnquist, defended his thesis on ‘Sphingolipid-mediated regulation of cellular calcium signaling and survival’.

Dr. Sandra Falck, in the Unit of Neuroscience received grant and a Postdoctoral research position at the Finnish Academy for the coming 3 years.

Generous funding has been obtained from Minerva Foundation, Sigrid Jusélius Foundation, Medicinska Understödsföreningen Liv och Hälsa, Finnish Academy and from other sources. A detailed description of the research in the different groups is given below.

UNIT OF CLINICAL PHYSIOLOGY

Members of the unit

Frej Fyhrquist, MD, DMSc, professor, head
Anders Eriksson, DVM
Outi Saijonmaa, PhD, Docent
Maarit Piisilä, pharmacist, MSc.
Anna Tiitu, B.Sc., student (genetics)
Berent Munsterhjelm, medical student project work

Collaborators

Professor Kimmo Kontula, Department of Internal Medicine, Helsinki University Cental Hospital, Docent Per-Henrik Groop, The Folkhälsan Research Institute, Biomedicum Helsinki.

Funded by the Minerva Foundation, Sigrid Jusélius Foundation, Else & Wilhelm Stockmann Foundation and Medicinska Understödsföreningen 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 during he 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 sub study of the LIFE trial, in collaboration with members of the LIFE Genetics sub study (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. To the above mentioned project has been added a study on telomere length and its association with cardiovascular endpoints in the LIFE study. This work is ongoing, with telomeres analyzed from roughly 1400 DNA samples at present. A study of telomere length and telomere shortening in diabetic patients with or without albuminuric nephropathy is ongoing in collaboration with Docent Per-Henrik Groop (the FinnDiane project at the Folkhälsan Research Center, Biomedicum Helsinki). Further, a study on telomeres in renal transplantation in collaboration with Docent Eero Honkanen, Department of Nephrology, Helsinki University Central Hospital.

Publications


UNIT OF CARDIOVASCULAR RESEARCH

Members of the unit

Ilkka Tikkanen, M.D., Ph.D., Docent, head
Mika Laine, M.D., Ph.D., Docent
Eeva Palojoki, M.D., Ph.D.
Tom Bäcklund, 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
Pia Stewen, M.Sc.
Heli Tikkanen, Med. student

Laboratory technicians are Riina Hatakka and Riikka Kosonen, M.Sc

Collaborators

Kari Pulkki, M.D., Ph.D., Docent, 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.

1. Our data has provided evidence that vasopeptidase inhibition (dual inhibition of angiotensin converting enzyme, ACE, and neutral endopeptidase, NEP) may prove a useful therapeutic approach for reducing blood pressure and retarding progression of cardiac and renal disease. Results in a number of studies suggested that vasopeptidase inhibitors exert cardio- and vasculoprotective properties beyond their blood pressure-lowering effects. The tissue NEP and ACE inhibitory profile of the novel vasopeptidase inhibitor AVE 7688 was characterized utilizing quantitative in vitro autoradiography. Compared to the NEP/ACE inhibitor omapatrilat and the selective ACE inhibitor ramipril, AVE 7688 was proven a superior inhibitor of ACE in cardiovascular tissues while the NEP inhibitory capacity of AVE 7688 was similar to that of omapatrilat.

2. Expression of the profibrotic, bradykinin degrading enzyme NEP and bradykinin (BK) receptors were studied in stenotic aortic valves obtained at valve replacement surgery in collaboration with Doc. M. Kupari and coworkers. NEP activity was increased in stenotic aortic valves in parallel with increased expression of BK-receptors. Up-regulation of NEP and BK type 1 receptors has the potential to promote valvular fibrosis while increase in BK type 2 receptors may represent a compensatory antifibrotic response. The findings suggest that NEP-inhibitory compounds could prove a novel therapeutic possibility to retard progression of aortic stenosis.

3. To clarify mechanisms behind impaired prognosis after myocardial infarction in diabetes, series of experiments have been conducted to study the course of myocardial infarction, cardiac apoptosis and expression of vasoactive factors in experimental models of type 1 and type 2 diabetes. After myocardial infarction (MI), sustained cardiomyocyte apoptosis, left ventricular enlargement, increased cardiac fibrosis and enhanced profibrogenic connective tissue growth factor (CTGF) expression were detected in diabetic compared with non-diabetic rats. In collaboration with Prof E. Mervaala and co-workers, Institute of Biomedicine, apoptotic gene profile was found to be activated in spontaneously diabetic Goto Kakizaki rats as assessed by apoptosis specific microarray. In addition, the results suggested the importance of decreased Akt phosphorylation and activation of the pro-apoptotic FOXO3a transcription factor in the pathogenesis of post-infarction ventricular remodelling in diabetes. Apoptotic myocyte loss could thus be an important mechanism contributing to progressive dilatation of the heart and poor prognosis after MI in diabetes. Interestingly, the calcium-sensitizing agent levosimendan prevented post-infarct heart failure and cardiac remodelling as well as sustained cardiomyocyte apoptosis and induction of apoptotic genes after MI in diabetic Goto Kakizaki rats. Sustained cardiomyocyte apoptosis at 12 weeks after MI was found to be associated with increased expression of angiotensin type 1 (AT1)-receptors and ACE, while expression of both the novel angiotensin converting enzyme-2 (ACE2) and angiotensin type 2 (AT2)-receptors were down-
regulated at week 1. This unbalanced activation of the renin-angiotensin system may play part in the pathophysiology of myocardial injury in diabetes after MI.

4. The role of renin-angiotensin system in the renal and cardiovascular effects of calcium supplementation in chronic renal failure has been studied in collaboration with Prof. I. Pörsti and Co-workers, University of Tampere. AT1-receptor antagonism has been shown to normalize impaired relaxation of resistance arteries in experimental renal failure by enhancing relaxation via potassium channels. In addition we have been able to show that high calcium diet down-regulates kidney angiotensin converting enzyme, reduces albuminuria and blood pressure, and favourably influences kidney morphology in experimental renal failure. Moreover, renal CTGF expression is decreased and renal cortical AT1-receptor density is reduced. These results suggest an important link between calcium metabolism and ACE expression in the kidney and cardiovascular tissues that could be important in the progression of renal and vascular damage in chronic renal failure. Our recent findings demonstrated that increased cardiac perivascular fibrosis and CTGF expression associate with low plasma calcitriol levels in rats with renal failure. Paracalcitol, the non-calcemic analogue of 1,25(OH)2D3, further suppressed calcitriol levels and aggravated fibrosis suggesting that low circulating calcitriol may predispose to perivascular fibrosis in chronic renal insufficiency.

5. Real time confocal microscopy was applied to study calcium signalling in cardiac atrial cells utilising dynamic intracellular Ca++-measurements. Increased propensity to calcium waves may generate triggered arrhythmias due to delayed after depolarisations. Mutated ryanodine receptors (RyR) from two different families with catecholaminergic polymorphic ventricular tachycardia (CPVT) were expressed in HEK-293 cell line and calcium signals were compared with native RyRs. No differences in calcium signals between mutated and native channels were found at baseline. However, mutated RyRs showed increased propensity to spontaneous calcium waves upon cAMP stimulation. The increased sensitivity of ryanodine receptors to cAMP may explain the occurrence of clinical arrhythmias in CPVT syndrome during exercise or emotional stress.

6. New research projects started in 2006. Focus of research will be shifted from end-organ damage mechanisms to studies on cellular protective and reparative mechanisms in cardiovascular diseases. Notably in this connection, we aim to study the role of cardiac stem cell (CSC) proliferation and mobilization in cardiac tissue repair and regeneration after myocardial infarction and in myocardial hypertrophy, as well as cellular mechanisms mediating cardiovascular protection following tissue injury, and 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 CSC open a completely new possibility to cardiac repair and treatment of cardiac failure after myocardial infarction. It has been shown that cardiac niches contain stem cells, 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 our preliminary studies we were able to show increased amounts of c-kit positive CSC:s after experimental myocardial infarction in the rat, while hepatocyte growth factor receptor (c-met) positive cells localized mainly in the vascular wall. The Ki67-positive cell proliferation was most marked at the border zone of myocardial infarction.

Publications


In press


UNIT OF CELLULAR PHYSIOLOGY

Members of the unit

Kid Törnquist, Ph.D., Professor (head)
Tomas Blom, Ph.D.
Sonja Balthasar, M.Sc.
Cia Ramström, M.Sc.
Emad Afrasiabi, M.D.
Nina Bergelin, M.Sc.
Christoffer Löf, M.Sc.
Pia Stewen, M.Sc.
Catharina Alam, M.Sc.-student
Janiina Ahlgren, M.Sc.-student
Hugh Chapman, B.Sc. (Affiliated member)

Funded by the Minerva Foundation, Medicinska Understödsföreningen Liv och Hälsa, Magnus Ehrnrooth Foundation and Åbo Akademi.

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. We also aim 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 specific 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, our 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. Our first completed investigation on this topic shows that sphingosine 1-phosphate potently stimulates migration of some thyroid cancer cell types, whereas the migration of other cancer cell types is blocked. Furthermore, an effort is being made to understand the regulation of the expression of the S1P-family of sphingolipid receptors. Preliminary data also suggest that sphingosine 1-phosphate may have an autocrine effect in some cancer cell types.

A very 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 underway 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, investigations are planned to examine the role of HERG channels in thyroid cancer cells.
The group is acting mostly at the Department of Biology (Åbo Akademi University, BioCity, Åbo, Finland) where about 80% of the activities take place. However, all the electro-physiological measurements and several applications using confocal microscopy are made at the Minerva Institute.

Publications


Dissertations

The following thesis work from the Unit was accepted by the Faculty of Mathematics and Natural Sciences of Åbo Akademi University:


UNIT OF ENDOCRINOLOGY

Members of the unit

Hannele Yki-Järvinen, D.M.Sc., F.R.C.P, Professor of Medicine, University of Helsinki
Jukka Westerbacka, M.D., Ph.D.
Jussi Sutinen, M.D., Ph.D.
Robert Bergholm, M.D., Ph.D.
Kirsi Pietiläinen, M.D., Ph.D.
Leena Juurinen, M.D.
Anja Corner, M.D.
Anna Kotronen, medical student
Janne Makkonen, medical student
Ksenia Sevastianova, medical student
Technicians are Katja Tuominen, Mia Urjansson and Tuija Mård.

Funded by the Minerva Foundation, EU-HEPADIP, Sigrid Juselius, EVO and Academy of Finland, Sanofi-aventis, MSD and Eli Lilly.

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

The group leader is one of the 10 Project Board members of an EU project entitled ‘adipohepatic signaling’ (www.hepadip.org) which started in November 2005 and will continue for a 5-year period. Our research line focuses on studies in humans. Dr. Robert Bergholm is continuing studies addressing alterations of vascular function in insulin resistance and other conditions characterized by endothelial dysfunction (in rheumatoid arthritis in collaboration with professor Marjatta Leirisalo-Repo and in CADASIL patients together with professor Hannu Kalima and coworkers).

During the past year, we have demonstrated that gene expression and its regulation by insulin are altered in insulin resistant subjects with a high liver fat content – not only is the response of genes mediating insulin sensitivity blunted but the response of genes mediating insulin resistance is exaggerated. We have shown by studying monozygotic twins discordant for obesity that such alterations are in part acquired. Regarding regulation of liver fat content, we have shown in multiple studies that serum insulin concentrations and liver fat are positively correlated, which have raised the question of whether insulin increases liver fat content or vice versa. In a 7 month study performed by Leena Juurinen, insulin therapy was shown to decrease significantly liver fat content thus supporting the idea that fat accumulation in the liver is a cause and not a consequence of hyperinsulinemia. Current activities include search for a marker of the fatty liver and the metabolic syndrome using a lipidomics approach in collaboration with Matej Oresic at the VTT (member of HEPADIP), and definition of the cellular pathways which mediate adverse effects of saturated fat on adipose tissue i.e. causing inflammation and macrophage accumulation and changes which lead to fat deposition in the liver. Dr. Jukka Westerbacka is performing a study addressing FFA fluxes across the fatty liver in Stockholm at the catheterization lab at the Karolinska Institute and has performed a study addressing gene expression in the human liver (submitted, in collaboration with Drs Petri Auvinen and Dario Greco in Viikki and with the Karolinska Institute). A treatment study addressing effects of endocannabinoid blockade on liver fat and adipose tissue gene expression is ongoing (Robert Bergholm). An investigator-initiated trial comparing exenatide and insulin treatment effects (1 year of treatment) on insulin sensitivity and beta-cell and alpha-cell function is ongoing and is being performed with Anja Corner.

Dr. Jussi Sutinen, MD, PhD is continuing studies addressing the molecular mechanisms and treatment of HIV-associated lipodystrophy. Dr. Ksenia Sevastianova is preparing her thesis on this topic and has 2 articles published (one in 2005 and 1 in press, not included below). Tissues samples are in part being analyzed in collaboration with Ullrich Walker in Germany.

The group is funded by EU-HEPADIP, Sigrid Juselius, EVO and Academy of Finland, sanofi-aventis, MSD and Eli Lilly.

Publications


In press


UNIT OF BIOCHEMISTRY

Members of the unit

Prof. Ralph Gräsbeck, M.D., Ph.D., D.h.c. (head)
Mirkka Sarparanta, M.Sc.
Prof. Benoît Dugué, Ph.D.

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

The unit has continued its studies on the transport and metabolism of vitamin B12. Two main lines were pursued.

The genes and mutations causing the Imerslund-Gräsbeck syndrome (IGS). The project was pursued together with Albert de la Chapelle and his coworkers in Columbus, Ohio. The Finnish cases are caused by a mutation in the cubilin gene in chromosome 10 and the Norwegian cases by an error in the amnionless gene in chromosome 14. Gräsbeck published an invited review on the disease in Orphanet Journal of Rare Diseases. After this, a large number of doctors in different countries contacted him for mutational analysis. In addition, new cases were actively sought. Most cases are caused by mutations in the two genes mentioned. However, 5 families had cases related to a gene in chromosome 11 coding for gastric intrinsic factor. The cases had been wrongly diagnosed as having IGS. Our conclusion is that in suspected cases of IGS mutational analysis is the best test to reach the correct diagnosis. If positive at an early stage, a large number of radioactive vitamin B12 and other tests become unnecessary. A manuscript containing this message was prepared for submission to a suitable journal.

Some cases could not be related to a known gene. We are searching for it.

Another interesting problem is the benign but persistent proteinuria, which is often absent. In addition it may occur in close relatives without B12 malabsorption. The cubilin gene is large and apparently contains regions responsible for the binding of its different ligands. This problem will be attacked with genetic and biochemical techniques.

Our second project is biosynthesis of vitamin B12 labelled with 32P and 57Co. Then the behaviour of the two labelled compounds in the rat is studied, the idea being that they would behave differently as they are located in different parts of the cobalamin molecule. We thought it especially likely that phosphorus dissociates as it is situated in a side-chain which moves when the coenzyme forms of the vitamin take part in enzyme functions. Also, phosphorus is a very mobile atom in biochemistry.

The project is approaching its end. Following considerable efforts we managed to develop a rapid method to biosynthesise 32P-cobalamin with sufficient specific activity. The product was then administered together with the 57Co labelled compound by injection or orally to rats and the distribution in organs of the two isotopes was measured. Many difficulties had to be surmounted because of the short half-life of 32P.

The results are now clear, the distribution is the same and no phosphorus dissociates. -It is truly remarkable that one of the biggest small molecules, a "crystalloid", is so stable in metabolism and has a biological half-life in man of over one year.

The group previously observed differences in the behaviour of the two labels. We thought that a phosphorous-free breakdown product cobinamide could have been produced or been present as an
impurity. Accordingly, we synthesized 57Co-labelled cobinamide and studied its behaviour together
with 32P-cobalamin. Both compounds exhibited remarkably similar behaviour. Other explanations for
our early findings had to be sought. We focussed on the different forms of the vitamin commonly used
(and one often transforming into the other): cyanocobalamin (CN-Cbl) and hydroxocobalamin (OH-
Cbl). The former is widely used, but gradually it has become regarded as an artefact. For instance, its
concentration in blood is increased in smokers. OH-Cbl is the physiological vitamin form, and when
administered, it is rapidly transformed into coenzymes. -We synthesised both vitamin forms and gave
them simultaneously to rats. Shortly after administration relatively more of the cyano form
accumulated in the liver, later the two compounds behaved similarly. Incidentally, also cobinamide
accumulated somewhat more in the liver shortly after injection. In these cases the liver may exert a
detoxifying function, such as removal of cyanide or excretion of cobinamide into the bile.
Dugué, who worked for more than a decade in the Unit, is now Professor of Sports Medicine in
Poitiers, France, but spends several months a year in Finland studying the influence of muscle
exercise and stress on handicapped persons. His main coworkers are employed by Orton Hospital.
Interesting results were published: Muscle work in the upper extremities also strengthened the
function of the legs of patients undergone hip joint arthroplasty. -Dugué’s interest in problems related
to stress originate in his early studies on the effect of stress on the expression of the intestinal receptor
for the vitamin B12-intrinsic factor complex.

Other activities. Gräsbeck has received numerous requests to write articles related to the history of
medicine, principally biographies, but also on the topic of reference values. He wrote a biography of
Professor Anders Langeskiöld, famous orthopedic surgeon and member of the Board of the Minerva
Foundation. The article is in print in Biografiskt lexicon för Finland, eds. H. Knif and F. Hertzberg.
He also wrote or completely revised about 30 articles in the last volume of the encyclopaedia
Uppslagsverket Finland part 5 (S–O). As member of the library committee of the Finska
Läkareälskaptet he took part in the translation from ancient Swedish to modern Finnish of the oldest
medical book of Sweden-Finland, published by Benedictus Olai in 1573.

Publications

Gräsbeck R: Imerslund-Gräsbeck syndrome (Selective vitamin B12 malabsorption with proteinuria).
Orphanet J rare Dis 1:17–22, 2006 (http://www. OJRD.com/content/1/1/17).

Gräsbeck, R: Approx. 30 articles in Uppslagsverket Finland, part 4 (O–S), Schildts, Helsinki 2006

Maire J, Dugué B, Faillenet-Maire A-F, Smolander J, Tordi N, Parratte B, Grange C, Rouillon
J-D: Influence of a 6-week arm exercise program on walking ability and health status after hip

The following Pro gradu thesis was accepted by Helsinki University:

Sarpapanta M: 32P- ja 57Co-radioleimatun B12-vitamiinin valmistus ja sen käyttäytyminen
nisäkkäään aineenvaihdunnassa. (Production of 32P and 57Co labelled vitamin B12 and its behaviour

UNIT OF NEUROSCIENCE

Members of the unit

Dan Lindholm, MD PhD, Professor (head)
Laura Korhonen, MD PhD, Docent
Sandra Falck, PhD, postdoc
Ras Trokovic, PhD, postdoc
Tuulikki Nyman, MSc, Laboratory Manager
Johanna Mäkelä, MSc, Biochemist
The main focus of the group is the study of various aspects of neurological disorders by applying modern methods of cell and molecular biology. In particular we aim to:

1. Characterize the pathophysiology and mechanisms underlying different neurodegenerative diseases, such as Huntington's disease, epilepsy and ALS. Hereby we study specific factors and proteins, such as the Inhibitor of Apoptosis Proteins and the calcium binding proteins, in addition to cellular pathways in the mitochondria and endoplasmic reticulum that are involved in the control of nerve cell death and survival. As protein aggregation and intracellular accumulation are parts of many human neurological disorders we also study the roles of protein degradation and the activity of the ubiquitin proteasome system (UPS) and the action of ubiquitin ligases and deubiquitinating enzymes (DUBs) in the regulation of neuronal and synaptic proteins.

2. Study of neural stem cells (NSC) by analysing factors influencing cell proliferation, differentiation and plasticity of these cells in vivo and in vitro. We have recently also developed methods to for the study and differentiation of human embryonic stem cells in collaboration with groups at the Biomedicum. Using the technology for production of monoclonal antibodies, we also search for novel surface markers expressed by NSC and radial glial cells that serve as progenitor cells in the brain. We have particularly focused on the role of the hepatocyte growth factor system and the protein HA1 that was found to be expressed in human cytotrophoblasts and in neural stem cells. Recently, we have encountered an interesting regulation of neural stem cells by various cytokines that will be explored in more detail.

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

Other collaborations

U Arumäe, Inst for Biotechnology,
K Blomgren, Gothenburg University,
L Andersson, Dept of Pathology, Helsinki University,
T Otonkoski, Biomedicum Helsinki,
O Eriksson, Biomedium,
S Naaby-Hansen, Ludwig Institute London,
I Dusart, Inserm-Paris,
G Mudo and N Belluardo, Palermo Italy,
H Kataoka, Faculty of Medicine University of Miyazaki, Japan
Jim Schröder, Dept of Genetics, Helsinki University.
Publications


In press


The following Pro gradu thesis and Examensarbete were accepted

**Putkonen N:** Synaptisen ubikitiini-spesifisen proteaasin, synUSP:n, merkitys Huntingtonin taudin patogeneesissä (in Finnish). Helsinki University, 2006.