1. Introduction

Vascular disease constitutes a major cause of death and disability in developed countries and will soon become a health threat worldwide. This trend motivates major efforts on multiple fronts to fight cardiovascular disease, with the goals of prevention as well as improved therapy. One prerequisite for success in this quest is increased understanding of the very dynamic environment represented by the vascular wall, where several cell types interact and undergo profound phenotypic modulation in development and in diseases such as atherosclerosis/restenosis and tumour neovascularization. This problem can best be approached as a combined effort of preclinical scientists specialized in research on different aspects of these cells and tissues and their signalling mechanisms together with clinical scientists specialized in the vascular disease process, treatment, and patient care.

The Faculty of Medicine at Lund University is fortunate in having a strong set of research groups in Lund and Malmö with matching competence required for this task. We have assembled a group of scientists covering a repertoire of approaches focusing on various critical aspects of vascular disease and propose a program to enhance the interaction between these groups. During the process of formulating the program, we have increasingly realized the considerable potential in a close collaboration within this already existing research environment, and the proposal includes measures to exchange experience, generate ideas and support collaborative work.

An important goal is to promote the careers of young investigators and to recruit new researchers to the field. Thus, the program is designed as a platform where young researchers will find opportunities to reach out from their immediate environment of training to broaden their experience and generate new research projects. Furthermore, a plan to improve translational training between preclinical and clinical scientists has been designed. We foresee that with initial support from the Faculty of Medicine, this network will grow in size and complexity to become sufficiently competitive to attract significantly increased external support from both national and international grant sources.

Within the vascular wall, endothelial cells (ECs), smooth muscle cells (SMCs), pericytes and adventitial cells communicate continuously in response to various external and internal stimuli. These signals regulate blood vessel development, structure and contractility, and hence the blood flow needed to satisfy the nutritional demands of tissues. This communication depends on the expression of receptors that allow cells to respond to the stimuli. In many cases the cells also produce the receptor ligands, including extracellular matrix (ECM) proteins, growth factors, and various autacoids. The nature of the stimuli varies with the state of the blood vessel and may be short-term signals such as neural, endocrine or myogenic stimuli to modulate the contractile state of the vessel or long-term growth signals to stimulate angiogenesis in vessel development or respond to pathological insults in disease processes. Dysregulation of the formation of new blood vessels is a major problem in the pathological conditions named above, and the list of diseases that are characterized by abnormal angiogenesis is growing. This program proposes to study these signals and processes in their integrated setting, with an emphasis on the pathophysiology and its clinical relevance.

2. Objective and aims

The program intends to analyse the interaction between the different components of the vascular wall, the endothelium and the pericytes/smooth muscle cells and their response to external signals such as proinflammatory cytokines, blood pressure changes, oxygen radicals and other stress factors to improve our understanding of those signalling events which can go astray and lead to vascular disease.

The research activities covered by the program have a direct bearing on the following determinants of vascular wall function and pathology: angiogenesis, atherosclerosis/restenosis, hypertension, inflammation, permeability. These themes are cornerstones in the development of vascular
disease. Knowledge about defined signalling events, under normal and pathological conditions, will be used to identify future targets for vascular disease therapy. These will be developed in close collaboration with clinicians from the Lund and Malmö university hospitals.

2. The endothelium

3.1 Overview

The endothelium lines all vessels on their luminal side, separating the local tissue from the blood compartment. In most blood vessels it forms a “continuous endothelium”, which is characterized by tight junctions and actively prevents cells and soluble proteins from randomly transversing it. An extreme example of this barrier function is the formation of the blood-brain-barrier, which does not even allow free diffusion of amino acids into the brain. In addition, the endothelium actively transports nutrients and has specialized signalling mechanisms for the exchange of information between the blood compartment and the local environment. Morphological specializations of the endothelium in exocrine and endocrine glands, like the adrenals, the pancreatic islets or the choroid plexus in the brain, include the formation of diaphragmed fenestrations with a pore-diameter of 50-100 nm, nondiaphragmed fenestrations in the kidney glomerulus, and larger pores (200 nm) in the discontinuous endothelium of the liver and the spleen. Most endothelium with the exception of that in pancreas, liver and heart appears to be derived from the same cell lineage and therefore, the maturation of different specialized EC characteristics depends on signalling by the local microenvironment during embryonal development, and probably, also in the adult organism.

An integral part of all blood vessels is the basement membrane (BM) of the endothelium, which consists of a number of ECM components, collagens, laminins, nidogen and proteoglycans. These ECM molecules form networks in the BM which can act as a barrier per se, but which can also bind cytokines and other signalling molecules in close proximity to the endothelium. Furthermore, ECM molecules such as the laminins occur in different isoforms in different blood vessels. It is therefore envisaged that the BM itself acts as a signalling entity on the endothelium. Interestingly, the pericytes, embedded into the endothelial BM, and other mural cells contribute to the local composition of the BM, and are to be included among the cell types that build the blood vessels. All blood vessels larger than the capillary are lined by SMC layer(s) with which the vascular endothelium exchanges a plethora of signals including e.g. nitric oxide (NO), endothelial-derived hyperpolarizing factor (EDHF), platelet-derived growth factor (PDGF), transforming growth factor β (TGFβ), and endothelin. The research program proposed here intends to analyse the paracrine signals that are exchanged between the ECs and other components of the vascular wall, including the BM and the SMC. The response of the vascular wall as a functional unit to external stimuli caused by changes in the body physiology such as blood pressure elevation, altered metabolic activity or pathological conditions like cardiovascular diseases, solid tumour formation, retinopathy and transplant arteriopathy, will be studied.

3.2. Targeting signalling between endothelium and other wall components in vascular disease

Numerous blood-borne vasoactive agonists released in response to various stimuli and mechanical factors such as shear stress influence the vascular endothelium to trigger the release of endothelial-derived contractile and relaxant factors, which subsequently act on SMC. Endothelial-derived NO is a common and critical second messenger to many vasodilator agonists, as it mediates their actions on vascular smooth muscle relaxation by stimulating guanylate cyclase activity and cGMP production, which then acts on cGMP-dependent protein kinase (PKG). Endothelial-derived NO is also an important regulator of cardiovascular homeostasis. However, it is considered a double-edged sword since low amounts produced by tonic endothelial nitric oxide synthase (eNOS) activity are beneficial as they inhibit leukocyte diapedesis, whereas elevated amounts from eNOS and inducible NOS (iNOS) increase two important inflammatory events, vascular permeability and angiogenesis. Furthermore, NO regulates smooth muscle proliferation. Consequently, understanding the regulation of vascular NO is critical in uncovering novel routes for vascular disease treatment.

F. Leeb-Lundberg’s group investigates the structure, function, and regulation of G-protein coupled receptors (GPCR) for vasoactive agonists such as bradykinin, among the most efficacious vasodilator agonists and stimulators of endothelial NO production. Furthermore, they study the coupling mechanisms between these receptors and eNOS. This group also investigates the interaction of GPCR with neuronal NOS (nNOS) as well as the pathways leading to induction of iNOS.

Mechanical pressure and shear stress exerted by the luminal blood flow is also thought to regulate
eNOS activity, but the sensors mediating this effect have not been identified. Mechanically induced signalling in the vascular wall is addressed by P. Hellstrand. Together with K. Swärd, he also investigates endothelin (ET), a long-acting vasoconstrictor secreted from the ECs upon mechanical stimuli. The ECs synthesize three isoforms (ET-1, ET-2 and ET-3) coded by three separate genes. Each of these isoforms may affect contractile and trophic signals, opening possibilities for specific pharmacological therapy.

It is increasingly clear that the organization of receptors and effectors in the plasma membrane is important for the function and integration of cell signalling. Caveolae represent critical plasma membrane components, which can serve as platforms for a number of signalling events in the vascular wall. Targeting of endothelial NO synthase (eNOS) to membrane caveolae is absolutely required for responses to agonist stimulation through GPCR as well as growth factor stimulation by e.g. vascular endothelial growth factor (VEGF). F. Leeb-Lundberg’s group has found that bradykinin receptors physically interact with eNOS in caveolae, and the binding epitopes are currently being mapped. R. Hallmann’s group also studies the critical roles of caveolae in signalling. The have identified a caveolae-associated membrane protein, MECA-32, which defines a subclass of caveolae and their function as origin of intracellular \( \text{Ca}^{2+} \) waves in ECs. K. Swärd has found that ET-1 receptors probably are localized in plasma membrane caveolae of the vascular SMCs. He has extensively studied the influence of cholesterol on caveolar structure, receptor responses and \( \text{Ca}^{2+} \) signalling in SMC, and together with R. Hallmann now expands these studies to the role of EC caveolae for signalling in the intact vascular wall.

The groups of P. Hellstrand, K. Swärd, and F. Leeb-Lundberg also study the importance of angiotensin-converting enzyme (ACE) on vascular function. This enzyme synthesizes the potent vasoconstrictor angiotensin II from its precursors angiotensin I and degrades the potent vasodilator bradykinin to bradykinin(1-7). It is through the decrease in angiotensin II and the increase in the bradykinin level and subsequent elevation of endothelial NO that angiotensin-converting enzyme (ACE) inhibitors are thought to accomplish many of their beneficial effects on myocardial and kidney functions. Also, antagonism of the angiotensin II AT1 receptor improves endothelial function through a bradykinin receptor mechanism. Furthermore, angiotensin II AT2 receptor activation inhibits fibrosis through the bradykinin/NO system. These agonists are not only associated with regulation of contractility but also implicated in regulation of vascular SMC differentiation and proliferation. In these projects, the relationship between contractile and relaxant agonists and their receptors in the caveolae structure of the vascular SMC and EC plasma membrane is being characterized. Identification and characterization of these signalling pathways will make it possible to understand the interplay between endothelial cells and vascular SMCs.

A. Arner studies the role of the NO-cGMP axis in smooth muscle contraction and growth as it relates to atherosclerosis. PKG plays a critical role in these events, and the exact mechanisms and PKG phosphorylation sites are investigated using PKG knock-out mice. With expertise in cardiac catheter interventions, J. Harnek and D. Erlinge have set up a pig model for balloon angioplasty and stenting. It has also been modified to a model of myocardial ischemia in vivo, where blood flow and the release of substances can be measured via doppler flow transducers and catheters in the coronary sinus. Microdialysis is used for improved measurement of endothelial release (nucleotides, t-PA and more). This technique is also used for improved sampling from patients.

The projects relating to endothelial signalling described here have much in common, although based in different research groups and utilizing different technology. Clearly, a critical weight exists for a major effort towards unravelling the role of numerous important endothelial components such as receptors, NOSs, and caveolae. A close interaction between the presented cell biological and physiological projects is expected to bring rapid progress towards understanding the communication between the endothelium and other vascular wall components in disease.

### 3.3 The endothelial cell and its basement membrane in inflammation and angiogenesis

The EC is the first cell in the vascular wall to respond to signals from the blood stream or the microenvironment, and it is speculated that it does not only react to these signals, but also plays an active role by releasing signals itself. This is apparent in inflammatory situations where systemic presence of proinflammatory agents like bacterial products in septic shock activates the EC, i.e. the expression of leukocyte adhesion molecules and NO-synthases that cause changes of the composition of their BM. These changes result in progression of the inflammatory reaction and include increased permeability and leukocyte infiltration into the tissue. The effect of
NOS on the progression of the inflammatory response and the regulation of the inflammatory reaction by NOS-modifying reagents will be studied by M. Bodelsson with input from the R. Hallmann group.

The crucial role of the endothelial BM for the function of the vessel wall and the mural cells themselves is central in E. Gustafsson’s EC work. She has produced and analysed EC-specific perlecan knockout mice, which show impaired vessel integrity leading to bleeding during embryonic blood vessel formation. The BM molecule family laminin is the topic of L. Sorokin’s and J. Talts/P. Ekblom’s EC studies: these groups have a considerable expertise on the role of these basement membrane proteins in development and during inflammation. The α6β1 integrin is a central laminin receptor on ECs, leukocytes, and bone marrow stem cells. This integrin is also present on all T lymphocytes but its function appears to be regulated by additional associated molecules, like the tetraspanins. To understand the signals that ECs and invading leukocytes receive from the presence of laminins in the local BM in inflammatory situations, L. Sorokin’s group employs in vitro and in vivo functional adhesion and migration studies. The in vivo experiments will include EC-specific and smooth muscle specific laminin-knockout mice and their response in inflammation models like experimental autoimmune encephalitis. In a related project, M. Ekblom, M. Durbeej and L. Sorokin study the role of laminin receptors (integrin, dystroglycan) for migration of hematopoietic stem cells. E. Gustafsson also studies the role of integrin β1 and will analyse the signalling cascade of these receptors with an endothelial-specific knockout mouse for the integrin-linked kinase ILK. J. Talts & P. Ekblom also focus on the role of laminins in the endothelial BM: they will analyse the inhibitory effects of laminin fragments on angiogenic processes. J. Talts has shown laminin cleavage in endothelial basement membranes. He will study the effect of laminin fragments on angiogenesis in a wound-healing model and by in vitro assays together with E. Gustafsson, T. Hjalt and M. Ekblom analyze the roles of endothelial PITX transcription factors, thought to modulate the ECM. Finding target genes of these PITX genes might aid in our understanding of vascular disorders.

The role of the endothelium to prevent leakage of fluid and proteins is compromised in inflammation, leading to hypovolemia and tissue edema, factors of adverse impact for the outcome in patients suffering from severe inflammatory conditions. The mechanisms behind these effects are investigated in vivo by P.-O. Grände, on the basis of the hypothesis that endothelial permeability under relatively normal conditions is affected by the contractile state of intraendothelial actomyosin filaments, while inflammation also involves a disturbed glycocalyx function. The endogenously produced substances prostacyclin and NO are expected to decrease actomyosin contractility, whereas activation of RhoA would increase sensitivity to Ca^{2+}, and thereby contractility. Addition of agonists or inhibitors of these signalling systems affect fluid and protein permeability in vivo, consistent with the hypothesis, and further work is directed to defining the role of this process in relation to factors affecting the glycocalyx during severe inflammation (sepsis).

B.-O. Nilsson will study the estrogen-mediated regulation of the NOS activity in ECs and SMC. The group has reported that the lack of estrogen receptors in the vascular wall is correlated with a loss of iNOS activity. The systemic effect of estrogen as an immunomodulator will be investigated in combination with proinflammatory signals in vitro and in an in vivo model of atherosclerosis (ApoE knockout mouse).

### 3.4 Role of endothelial factors in gene expression

M. Dictor analyses the function of a latency-associated protein encoded by human herpesvirus 8 in ECs, LANA, which induces constitutive signalling in the wnt signalling pathway. This pathway has been shown in dermal microvascular endothelium to be crucial for EC proliferation when LANA binds GSK-3β thus preventing degradation of β-catenin. M. Dictor has transfected LANA DNA driven by the hPECAM-1 promoter in endothelium differentiating in murine stem cell-derived embryoid bodies and intends to study the downstream effects of this gene activation. B. Dahlbäck, who has a long-standing interest in blood coagulation, investigates the signalling cascade triggered by the receptor tyrosine kinase Ax1 on ECs and SMC. Ax1 is a kinase with homology to cell adhesion molecules like NCAM, and has been described to have transforming potential. Furthermore, the vitamin K-dependent Ax1-ligand Gas6 (growth arrest specific gene 6) activates the Akt-1 pathway and can prevent apoptosis. The group has produced Gas6 knock-out mice, which show platelet dysfunction and are protected against thrombosis. However, Gas6 is expected to have effects on both endothelium and smooth muscle, which will be investigated in collaborative work. It is hypothesized that this
signalling pathway will shed new light on the growth and survival of ECs and SMCs.

A critical aspect of vascular development is the cross-talk that must occur between endothelial cells and the surrounding embryonic mesenchyme for correct patterning. This process has been shown to require signalling via the Ca²⁺-dependent transcription factor NFAT, since NFATc3 and c4 null mice die at E10.5 with vascular patterning defects, and blocking NFAT translocation in adult animals with CsA prevents the growth of vessels into tumors. M. Gomez investigates the endothelial role of NFAT signalling in vascular development, focusing on VEGF, which activates NFAT translocation and transcription in endothelial cells and has also been identified as an NFAT target gene. This work will have the following therapeutic implications: (1) inhibitors of NFAT signalling might be effective modulators of tumour angiogenesis, (2) the downstream genes (secreted cytokines) induced by NFAT signalling could be useful as inhibitors of tumour angiogenesis.

### 4. Vascular smooth muscle

#### 4.1 Overview

Unlike cardiac and skeletal myocytes, which are terminally differentiated, the SMC exhibits significant phenotypic plasticity. Dispersed SMCs in culture rapidly progress from a non-proliferating, “contractile” into a proliferating, “synthetic” state. Phenotypic modulation occurs not only in culture but also during the atherosclerotic process. This is associated with neointima formation, partly due to migration of synthetic SMC, which exhibit decreased contractility and altered expression of contractile/cytoskeletal proteins, receptors and ion channels. Other pathophysiological conditions involve instead adaptive changes of the primarily contractile myocyte. In hypertension, remodelling of the vascular wall normally occurs by a rearrangement and increased mass of differentiated and fully contractile myocytes.

#### 4.2 Ca²⁺ signalling in smooth muscle activation

Ca²⁺ can enter the cytosol from the extracellular space or be released from the sarcoplasmic reticulum (SR). Extracellular Ca²⁺ can pass the cell membrane through voltage- (VOC) operated channels, regulated by the membrane potential, or by receptor-operated channels (ROC), gated by specific ligands. VOC have been shown to play a dominant role in the activation of smooth muscle contraction. ROC constitute a less homogenous group of “non-selective” cation channels, which may have a relationship to homologues of the TRP (Transient Receptor Potential) channels first described in the Drosophila photoreceptor, which are now implicated in Ca²⁺ entry in SMC both in response to receptor activation and to depletion of intracellular Ca²⁺ stores.

The initial signal for contraction of smooth muscle is an increase in [Ca²⁺], which activates a Ca²⁺-calmodulin-dependent kinase to produce myosin phosphorylation, resulting in cross-bridge interaction with actin. Dephosphorylation of myosin occurs by a phosphatase, which is in itself not sensitive to Ca²⁺ but can be affected by agonists (for example, α₁-adrenergic), leading to altered sensitivity of myosin phosphorylation to Ca²⁺, since it is determined by the kinase/phosphatase activity ratio. A. Arner and K. Swärd both investigate the Ca²⁺-dependent regulation of contraction using using intracellular Ca²⁺ measurements and permeabilized preparations in addition to biochemical methods.

In contrast to the role of Ca²⁺ in regulating contraction, little is known about how Ca²⁺ signals are translated to changes in transcription factor activity in this tissue. Ca²⁺ transients in vascular SMC may be global, i.e. distributed throughout the cytoplasm, or local in the form of sparks (released from the SR), or waves/oscillations travelling along the cell. These Ca²⁺ signals encode different cellular outcomes (e.g. membrane hyperpolarization, contraction, transcription) that are inter-linked at multiple levels.

The research of M. Gomez focuses on decoding the different Ca²⁺ signals with respect to their impact on the activation of the prototypical Ca²⁺-sensitive transcription factor NFAT in native vascular smooth muscle. It has been implicated in the pathogenesis of cardiac and skeletal muscle hypertrophy and might be predicted to play a similar role in smooth muscle growth associated with, e.g., hypertension and atherosclerosis. Plans are to dissect the initial, Ca²⁺/calcineurin-dependent events in NFAT activation, to identify specific NFAT targets, and to test whether NFAT might regulate differentiation-specific genes in native vascular smooth muscle. Using human myometrial arteries, two different modes of vascular hypertrophy will be studied: “physiological” in normal pregnancy vs. “pathological” in pre-eclampsia (PE). Pregnancy induces growth and remodelling of myometrial arteries, with hypertrophy and hyperplasia of the vascular wall leading to larger and more distensible vessels. In PE, arteries develop media hyperplasia,
characteristic of hypertensive and early ath erosclerotic changes.

4.3 Signalling role of the cytoskeleton.

The group of A. Arner has developed animal models for vascular growth in vivo and studied differentiation/dedifferentiation aspects of smooth muscle. During recent years the group has explored the function of the smooth muscle intermediate filament cytoskeleton using desmin deficient mice, which show impaired contractility. The interaction with matrix via integrins has been studied using a novel in vitro knock-out technique. This affords new possibilities for investigation of the signalling between integrins and the contractile system.

Considerable evidence implicates the actin cytoskeleton in mechanotransduction, as a link between integrins and focal adhesions, on the one hand, and the molecular regulation of gene transcription, on the other. P. Hellstrand’s group investigates the role of stretch (blood pressure) on growth and differentiation. Their hypothesis is that stretch promotes polymerisation of actin filaments. This would reduce the pool of unpolymerised actin, which is known to negatively regulate the expression of a group of proteins associated with the contractile phenotype (“differentiation markers”). They investigate the different steps in the pathways controlling actin polymerization, including RhoA activation and downstream effects via pathways controlling actin polymerisation and depolymerisation, respectively. The MAP kinase pathway is activated by stretch in several ways, including endogenous release of growth factors such as Ang II and ET-1. Mechanically stretched blood vessels in vitro show increased protein synthesis and particularly differentiation marker expression. This is analysed using proteomics methodology.

4.4 Phenotype modulation in vascular injury

Using a mouse model of in vivo neointima formation, A. Hultgärdh-Nilsson investigates the expression of the ECM components osteopontin and cartilage oligomeric matrix protein, which are present in increased amounts in atherosclerotic lesions. Knock-out mice for these proteins are being present in increased amounts in atherosclerotic lesions. Analysis of signalling pathways and screening of changes in protein expression induced by various lipids and lipoproteins in SMCs is therefore proposed as a way to explain the effects of lipid accumulation on cellular function.

4.5 Fatty acid-induced cell activation

Certain lipids and lipoproteins can activate vascular cells, thus contributing to fibrosis and inflammation. For example, VLDL and fatty acids have been shown to induce monocyte adhesion to ECs. Furthermore, fatty acids have been shown to modulate the expression of proteoglycan core proteins. Many effects of lipoproteins are likely related to their fatty acid content, even though cholesterol is the main type of lipid deposited in atherosclerotic lesions. Analysis of signalling pathways and screening of changes in protein expression induced by various lipids and lipoproteins in SMCs is therefore proposed as a way to explain the effects of lipid accumulation on cellular function.

Very low density lipoprotein (VLDL) is an independent risk factor for atherosclerosis. M. Ares will study the effects of VLDL and various fatty acids on the production of ECM, activity of ion channels, inflammation, and expression of proteins involved in lipid metabolism in macrophages and SMCs. VLDL and fatty acids potentiate inflammatory activation of macrophages. Furthermore, VLDL seem to elevate cellular fatty acid levels so much that a stress response is induced. The best-
known fatty acid receptors are the peroxisome proliferator-activated receptors (PPARs). PPARδ can suppress PPARα and PPARγ transcriptional activity by competitive binding to PPRE. The main physiological function of PPARδ and PPARγ is to promote lipid storage, while PPARα induces genes involved in oxidation of fatty acids. Therefore, the balance of these PPARs may determine whether cells accumulate or burn triacylglycerols. PPARδ is up-regulated during vascular lesion formation and promotes post-confluent cell proliferation in vascular smooth muscle cells and fibroblasts.

M. Ares collaborates with B. Olde who has identified a novel GPCR named FFA1R, which is activated by medium- to long-chain free fatty acids. Together, they study the possible role of this receptor in the activation of vascular cells by fatty acids. Protein expression in SMC treated with VLDL or fatty acids will be studied at the Swegene proteomics laboratory in Lund. Changes in protein levels will be traced back to mechanisms that regulate gene expression, which are subsequently studied in separate experiments. B. Olde has found that FFA1R is also present on pancreatic β cells, where they regulate the release of insulin. Indeed, they have found that antidiabetic drugs of the thiazolidinedione class also activate this receptor. In collaboration with Stefan Hansson at the Department of Obstetrics and Gynaecology they have found that this receptor is highly expressed in certain parts of the kidney in accordance with the acute effects of these drugs and fatty acids on blood pressure. This group will continue to pursue the role of this receptor in the regulation of vascular function as well as in lipid and carbohydrate metabolism as a whole.

5. Translational research

M. Ares and collaborators study human atherosclerotic plaques removed from carotid arteries by endarterectomy. The matrix and lipid composition, protein kinase and transcription factor profiles of these carotid plaques are investigated and correlated with the susceptibility to rupture as determined echographically. Preliminary results indicate that the activity of transcription factor AP-1 is higher in plaques from symptomatic patients. Furthermore, plaques from symptomatic patients contain increased levels of non-cross-linked elastin (presumably being degraded) and less calcium than plaques not associated with symptoms. In addition, unpublished data show that calcium (not collagen, elastin or lipid) content is the main determinant of plaque echostructure. These plaques are analysed for the presence of cartilage proteins by A. Hultgårdh-Nilsson.

Collaboration between A. Arner, E. Zoucas and J. Harnek has lead to a patented technology to prevent restenosis. Events at the onset of injury are crucial for the development of intimal hyperplasia and can be modified by local application of NO in association with angioplasty, which down-regulates NOS expression and SMC proliferation. The cGMP-dependent NO-pathway is essential in vessel injury since blocking the pathway significantly increases neointimal formation. By placing artificial NO-donors in the arterial lumen they are attempting to prevent unwanted vascular SMC proliferation.

Based on principles of physiological volume regulation, P.-O. Grände has developed a widely used 'volume-targeted' protocol (Lund concept') for the treatment of increased intracranial pressure. Its physiological and biochemical effects have been evaluated utilizing intracerebral microdialysis. The clinical experience has been favourable.

Effects of clinically used inhibitors of restenosis, such as rapamycin, are evaluated by D. Erlinge and P. Hellstrand, who examine gene expression and function after balloon dilatation in vitro of human arteries in organ culture. Release of extracellular nucleotides that stimulate cell proliferation and platelet aggregation has been found to be elevated and to correlate with platelet activation in patients with acute coronary syndromes. A drug development project in collaboration with organic chemistry, KI, has generated three leads that are of interest for cardiovascular drug development. One is a potentiator of P2X1 receptors by allosteric interaction.

6. Scientific interaction and joint projects

The program will strongly increase synergies between the different existing research teams in the faculty. Already now in the planning phase, new interactions are formed and will be promoted by this initiative. Connections between the research on signalling cascades and those working on vascular activation and inflammation models will be formed. Below is a summary of areas where functional connections between the research activities of participants in this application exist and will be further strengthened by the program.
The Vascular Wall program has a strong and unique technological platform where expertise from the fields of molecular biology, cell biology, cell physiology and biochemistry are joined together.

**Molecular biology** – To clone sequences and manipulate cDNAs coding for proteins and perform site-directed mutagenesis to introduce point mutations. Standard methods for RNA and DNA isolation and analysis including RT-PCR, quantitative real-time PCR, Northern blot, in situ hybridization, Southern blot etc. Eukaryotic cell transfection and infection

**Protein purification, analysis and chemistry** – Electrophoresis, spectrophotometry, fluorescence and immunological methods (ELISA, SDS-PAGE, Western blot analysis by 1D- and 2D-PAGE, autoradiography). Mass spectrometry, gene arrays (in collaboration with SWEGENE), protein sequencing, peptide synthesis and receptor structure modeling. High-performance thin-layer chromatography for lipid analysis and gas chromatography.

**Surface plasmon resonance (Biacore)** – Receptor–ligand interactions to measure on and off rates of ligand binding. Utilized here for protein-protein and protein-carbohydrate interactions

**Confocal microscopy/deconvolution system** – To study protein localization/co-localization and perform cytosolic Ca\(^{2+}\) measurements. 3D-Reconstruction of serial sections at high resolution (<1µm).

**PALM laser capture microscope** – For microdissection of individual cells or areas of interest for further molecular biology analysis

**Phase contrast/DIC/fluorescence microscopy and video microscopy** – Immunohistochemistry/-fluorescence to identify proteins. Time-lapse video microscope equipped with CO\(_2\) and temperature control, plus image analysis software, for in vitro cell migration experiments. Stress response to cultivated adherent cells can be applied by a defined shear stress system under linear (parallel) medium flow.

**Cell biology methods** – Expertise in cell adhesion and migration assays, FACscan flow cytometry, assays of cellular receptors and their signalling pathways and subcellular fractionation.

**Cell physiology methods** – Equipment for measurements of vascular smooth muscle and sympathetic nerve function in vitro, force and vessel diameter in isometric and pressure myograph systems. Patch-clamp techniques for membrane
potential, whole cell current and single-channel measurements. Tools to study nitric oxide, protein and DNA synthesis rates and apoptosis.

**Mouse models** –
*Transgenic mice*:
SM22-human COMP over-expressing mice.
ROSA26 reporter strain to monitor Cre recombinase expression.

*Knockout mice*:
Mutants lacking ECM components; osteopontin, COMP and perlecan knockouts.
Gas6 knockout.
SM22α knockout.
JNK1 and JNK2 knockouts
ApoE and LDL receptor knockouts that develop spontaneous aortic lesions and are widely used as atherosclerotic animal models.

*Floxed mice* for making conditional knockouts using the Cre LoxP recombination system:
osteopontin, perlecan, laminin α5, integrin β1, integrin-linked kinase

*Cre mice* to delete genes in:
smooth muscle cells (SM22 promoter, tamoxifen-inducable), ECs (tie1 promoter),
macrophages (class A scavenger receptor promoter, tamoxifen-inducible?)

**Human cardiovascular tissue** – obtained from cardiopulmonary bypass operations, transplantation, myocardial biopsies during catheterisations and blood samples from patients with cardiovascular disease. Myometrial vessels from non-pregnant, pregnant and pre-eclamptic women are obtained from the Department of Obstetrics and Gynaecology.

**Clinical studies** – The Heart & Lung Division contains most clinical methods in the treatment of heart disease: coronary care unit, PCI/Cath-lab, CABG, valvular surgery, heart transplantation, cardiac assist devices, electrophysiology, pacemaker/ICD and echocardiography. The Department of Cardiology has a unit for research patient visits. Conditions are excellent for interaction between basic laboratory research and clinic. Hemodynamic measurements are done routinely and can be used to confirm preclinical findings.

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## 8. Research – clinical rotations

At present we see a clear trend towards a polarization, where medical research is done by researchers educated in biology, biomedicine and chemistry, while medical students focus on the clinic, without getting a research education. Recruitment of medical students to research has been very difficult in the last years. In the clinical departments, advanced diagnostic procedures and treatments are performed that have potentials for research but they are not fully recognized by the basic researchers. Vice versa, the basic researchers have advanced methodology that could be used for clinical research that the clinicians are unaware of. One important part of the program will be to offer possibilities for clinicians to get research training and to familiarize basic researchers with clinical activities.

The basic research groups will offer possibilities for clinicians to do research for periods of a few months while they are residents or earlier. The aim will be to give insights into research methodology and to stimulate new ideas or collaboration. Some clinicians may continue research to a PhD, but this is not the main objective of these rotations. It will also give the basic researchers contacts in the clinical departments that could be of importance in the translation of their basic science into a clinical setting. The salary of the clinician is expected to be paid by the clinic, but the program will offer a minor compensation to the research unit, to cover chemicals and material. The clinical departments will offer rotations/auscultations for basic researchers, mostly PhD’s and post-docs. These will be individualized, with the aim to meet patients, to see actual clinical problems, current treatment strategies and to establish contacts. During these rotations both clinicians and basic researchers will be encouraged to give oral presentations, to further increase communication.

### 9. Organisation and management

A board of five members, one of whom will serve as director, will manage the program. The board will be elected annually among the members of the program on a rotational basis. It should represent basic as well as clinical research and should include researchers at different career stages. The board will take decisions on budget and activities within the program, and the director will be responsible for implementation of board decisions. It is suggested that for the first year the board will be composed of **Per Hellstrand** (director), **Maria Gomez**, **David Erlinge**, **Rupert Hallmann** and **Fredrik Leeb-Lundberg**.
A panel of internationally renowned scientists will form an external advisory board, which will review the progress of the program, suggest new initiatives, and participate in a yearly retreat for program members. We are pleased that Professor **Ulrich Pohl**, Institute of Physiology, Ludwig Maximilians University, Munich, and Professor **Anthony M Heagerty**, Director, Cardiovascular Research Group, University of Manchester, have both agreed to serve in this advisory board.

**10. Planned activities and budget**

The principal instrument for carrying out the task intended here is the increased scientific collaboration foreseen. The activities of the program are designed to promote this goal.

The program will only fund activities directly generated by the interaction within the program and involving several program members as detailed below. Supports for post-doc positions will be for 2-year periods and will generally provide partial coverage, with the expectation that the recipient group can provide matching funds.

Main activities of the program will be:

1. A yearly retreat for all participants and the advisory board, to review progress and formulate strategies. Amount applied for here: 200 kSEK/year.

2. Collaborative projects in specific areas. These will include research collaboration as well as joint seminars, minisymposia, journal clubs and grant applications. Projects will be supported by the program for postdoc positions with bench fees, provided they include substantial interaction between at least three participating research groups. Amount applied for here: 1 400 kSEK (post-doc packages) + 250 kSEK (meetings).

3. Support for young investigators in career positions (assistant professor), but not yet having permanent faculty positions. This will include partial support for building an independent research group. Amount applied for here: 1 000 kSEK.

4. The program will be active in seeking grant support at the national and international level. This will include the promotion of the program as a Center of Excellence, as well as identifying grant sources and stimulate collaboration likely to generate successful applications. Administrative support for this includes part time secretarial service and a web page. Amount applied for here: 150 kSEK/year.

5. Total budget asked for: **3 000 kSEK/year**.

6. It is foreseen that long-term success of the program will create a demand for relocation of research groups to a common physical environment, as well as additional administrative responsibilities, which will increase the strength and autonomy of the program.

**11. Added value to the Medical Faculty**

All activities supported by the program will aim at promoting interaction and collaboration. One particular reason for this is that several of the participants in the program are internationally prominent scientists who have been recently recruited to the Faculty. We therefore see a considerable potential in rapidly bringing this competence to bear on the important problems covered here. Several established research groups have strong records in their respective areas, but in the rapidly changing environment of modern science it is vital that new impulses are received and synergies exploited. The program combines researchers representing divergent but closely related fields in terms of integrated functions of the vascular wall, yet all with an interest in cellular signalling mechanisms and therefore speaking a common scientific language. This should ensure optimal conditions for fruitful collaboration and also utilization of the considerable investments made by the Faculty with respect to scientific and clinical competence, cutting edge equipment, and scientific infrastructure.
12. Supplements

Short presentations of participating groups:

- Cardiovascular Physiology
- Clinically Applied Vascular Physiology
- Connective Tissue Biology
- Endothelial Cell Biology
- Lipids, Plaques and Vascular cells
- Molecular Cardiology
- Molecular Pharmacology
- Physiology of Peripheral Circulation
- Regulation of Endothelial Cell Functions by the Tyrosine Kinase Receptor Family Axl-Sky-cMer and its Vitamin K-Dependent Ligand Gas6
- Tube Formation and Extracellular Matrix
- Vascular Biology Research Group at the Department of Anesthesiology and Intensive Care
- Vascular Extracellular Matrix
- Vascular Physiology
Cardiovascular Physiology

Affiliation and location
Division of Cardiovascular Physiology,
Department of Physiological Sciences, BMC F11, SE-221 84 Lund

Research interests
Mechanisms of smooth and cardiac muscle contraction. Regulation of the contractile process via cellular signalling (e.g. Ca\(^{2+}\) regulation, small G-proteins). Long-term modulation of muscle structure and function during adaptive growth, hypertension and vascular injury.

Translational research activities
Extensive international collaboration regarding smooth muscle function in different transgenic mouse models (e.g. Max Delbrück Centrum, Berlin, Karolinska Institute, Stockholm, University of Paris) and regarding muscle function (Moscow, Aarhus, St Petersburg, London, Charlottesville). Clinical collaboration regarding smooth muscle (vascular and detrusor) contraction in the urinary tract organs (Clinical Pharmacology and Urology, Lund), protein expression in vessels after coronary angioplasty (Dept Radiology and Surgery, Lund), pharyngeal muscles (Radiology, Malmö), cardiac muscle during atrial fibrillation (Cardiology, Lund), effects of purinoreceptors (Cardiology, Lund).

Group composition

<table>
<thead>
<tr>
<th>Project leaders</th>
<th>Postdocs</th>
<th>PhD students</th>
<th>Technical staff</th>
</tr>
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<tbody>
<tr>
<td>Anders Arner, professor</td>
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<td>3</td>
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<tr>
<td>Paul Edman, professor emeritus</td>
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Current research funding

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<td>VR/MFR</td>
<td>AA</td>
<td>Contractile mechanism in smooth and cardiac muscle</td>
<td>495</td>
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<td>SSF</td>
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<td>Forskarskolan Läkemedelsvetenskap, Ph.D. project</td>
<td>650</td>
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<td>Heart-Lung</td>
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<td>Wallenberg</td>
<td>AA</td>
<td>Vascular and cardiac contraction in transgenic mice (PI: Dr P. Thorén, Stockholm)</td>
<td>250 (Lund)</td>
<td>2003 (2004)</td>
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<td>Fondation</td>
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CV: Anders Arner

Education

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Postdoctoral training

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<tr>
<td>University of Heidelberg</td>
<td>1984-85 (1 yr)</td>
<td>Prof. J.C Rüegg</td>
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Clinical training

About 11 months (medicine, psychiatry).

Positions held

- 2002-current: Elected head of Dept Physiological Sciences
- 1999-current: Professor (Physiology), Lund University
- 1999: Visiting professor (6 months) Dept Molecular Physiology and Biological Physics (G. Owens, AP and AV Somlyo), University of Virginia
- 1988-1999: Associate professor (physiology), Lund University
- 1985-1988: Assistant professor (physiology), Lund University

Awards and honours

- 2003: Organizer: Annual meeting of the National Network for Functional Studies in Mice
- 2001: Co-organizer, Baltic Summer School on Cardiovasc System in Health & disease, Lund
- 2001: Member of Steering group for European Society for Muscle Research
- 1995 - current: Member and secretary of the committee for physiology of Royal Swedish Academy of Science
- 1994: Dr Fernströms’s prize to young Swedish scientists
Selected publications from the research group since 1998


Clinically Applied Vascular Physiology

Affiliation and location
Department of Surgery, University Hospital Lund 221 85 Lund
Heart Radiology, Heart Lung Division, University Hospital Lund
Experimental Radiology BMC, in-vivo Department SE 22184 Lund

Research Interests:
The influence of Nitric Oxide after injury such as balloon angioplasty, vascular anastomosis and organ transplant on vascular smooth muscle cells, endothelial cells and progenitor cells as well as extracellular matrix components in the vasculature.
The effect of P2Y and P2X receptors on vascular homeostasis and preconditioning after balloon angioplasty and in cardiogenic shock in experimental and human settings.

Translational research activities:
Coronary and peripheral studies on the development of intimal hyperplasia after balloon injury and surgical anastomosis. Coronary and peripheral studies on intimal hyperplasia after stent insertion. Studies on nucleotide release, cardiac blood flow, and ventricular arrhythmia during early cardiac ischemia and reperfusion in preconditioning and cardiogenic shock. Studies on pancreas and liver transplants.

Group composition

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<tr>
<th>Project leaders</th>
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<tbody>
<tr>
<td>Evita Zoucas MD PhD Ass. Professor</td>
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<tr>
<td>Jan Harnek, MD PhD</td>
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<tr>
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<tr>
<td>Lund University</td>
<td>PhD</td>
<td>1981</td>
<td>Surgery</td>
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<tr>
<td>Lund University Hospital</td>
<td>Specialist in Surgery</td>
<td>1988</td>
<td>General Surgery</td>
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<tr>
<td>Dept of Surgery</td>
<td>Consultant</td>
<td>1999</td>
<td>Lower GI-Surgery</td>
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Clinical training

1977 02- 1979 06  Guest scientist Lund Univ. Dept. of Surgery. Sweden (2 theatre,10 research sessions/w)
1982 08 - 1985 01  Senior House Officer (Medicine, Surgery, Aneasthetics,ICU, Psychiatry, GP ) University Hospital Lund ( training post)
850211 - 880831   Registrar, Dept. of Surg. Regional Hospital Trelleborg (training post)
880901 - 890228   Consultant Gen. Surgeon, Dept. of Surg. Regional Hospital Trelleborg (locum)
890305 - 950731   Specialist Senior Registrar, Dept. of Surg. University Hospital Lund ( 24 months Vacular unit, 51 months HPB unit)
950801 - 960131   Senior registrar, Dept. of Thoracic Surg. Univ. Hospital Lund (locum)
960201 - 960828   Specialist Senior registrar, Dept. of Surgery. University Hospital Lund ( HPB unit)
960829 - 960930   Consultant (locum) Dept. of surg. University Hospital Lund Sweden.
961001- 990731   Specialist Senior Registrar, Dept. Surgery, University Hospital Lund (Colorectal Unit)
990801 – present  Consultant , Dept. Surgery, Univ.Hosp. Lund (Colorectal Unit )

Positions held

9701 - 2001  CEO Department of Exp Surgical Research (including the administration of the research departments of Surgery, Urology, Radiology, Orthopedics and Neurosurgery.
0305 -  CEO of the colorectal unit. University Hospital Lund
**CV: Jan Harnek**

### Education

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<td>Lund University Hospital</td>
<td>Specialist in Radiology</td>
<td>1994</td>
<td>Radiology</td>
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<tr>
<td>Heart Radiology</td>
<td>Consultant</td>
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<td>Thoracic Radiology</td>
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<td>Lund University</td>
<td>Ph.D.</td>
<td>2003</td>
<td>Interventional Radiology</td>
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### Clinical training:

- **Radiology Dept., Helsingborg**: 870727 – 880731 House-officer – UL/AT
- **Orthopedic Dept, Landskrona**: 880718 - 881002 House-officer
- **Surgical Dept, Landskrona**: 881003 - 890402 House-officer
- **Internal Med., Landskrona**: 890403 - 891001 House-officer
- **Rad. Dept., Helsingborg**: 891002 - 910401 Senior-House-officer - FV
- **Rad. Dept., Lund**: 910402 – 930331 Senior-House-officer
- **Rad. Dept, Lund**: 930401 – 940220 Senior House officer
- **Thorasic Surg., Lund**: 940221 - 940626 Senior House-officer
- **Rad. Dept, Lund**: 940627 - 950830 Registrar-AL
- **Rad. Dept., Lund**: 950901 - 990331 Consultant-BÖL/ÖL
- **Rad Dept, Lund**: 990401 - 990916 Consultant
- **Heart-Lung Division Lund**: 990917 - 001231 Consultant
- **Heart-Lung Division Lund**: 010101 - Consultant

### Current Position

Consultant, Heart Radiology / Heart Lung division
Selected publications from the research group since 1998


Affiliation and location
Division of,
Department of Cell and Molecular Biology, BMC C12, SE-221 84 Lund

Research interests
Remodelling of the extracellular matrix during atherosclerosis and restenosis with focus on the extracellular matrix proteins osteopontin, COMP, fibromodulin, biglycan and decorin. How do these proteins affect inflammation, smooth muscle cell migration and proliferation and collagen fiber assembly during the atherosclerotic process.

Translational research activities
Studies of the expression of COMP, collagen II and aggrecan in human carotid paques.

Group composition

<table>
<thead>
<tr>
<th>Project leaders</th>
<th>Postdocs</th>
<th>PhD students</th>
<th>Technical staff</th>
</tr>
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<tbody>
<tr>
<td>Anna Hultgårdh-Nilsson, senior lecturer</td>
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<tr>
<td>Ahnders Franzén, researcher</td>
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Current research funding

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<td>VR/MFR</td>
<td>AHN</td>
<td>Expression and functional importance of extracellular matrix proteins in the atherosclerotic process</td>
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<td>Heart-Lung Foundation</td>
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<td>A functional study of extracellular matrix proteins in the atherosclerotic process</td>
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<td>AFAs Hälso-fond</td>
<td>AHN</td>
<td>Studies of osteopontin, an inflammatory cytokine with multifunctional roles in cardiovascular disease</td>
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<td>SSF (NNCR)</td>
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<td>Various Foundations</td>
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CV: Anna Hultgårdh-Nilsson

### Education

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<th>Field of study</th>
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<tr>
<td>Karolinska Institutet</td>
<td>DDS</td>
<td>1985</td>
<td>Dentistry</td>
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<tr>
<td>Karolinska Institutet</td>
<td>Ph.D</td>
<td>1991</td>
<td>Vascular smooth muscle cell differentiation and proliferation</td>
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### Postdoctoral training

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<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
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<tr>
<td>Cedars Sinai Medical Center, UCLA</td>
<td>1992-1993</td>
<td>Prof. James Fagin</td>
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</table>

### Positions held

- 2000-current: senior lecturer (lektor), Lund University
- 1994-1997: assistant professor (fo.ass), Karolinska Institutet

### Awards and honours

- 2001-current: Member of the working group for clinical science 1, The Swedish Research Council
- 2002-current: Chairperson of the working group for medicine, STINT (The Swedish Foundation for International Cooperation in Research and Higher Education)
- 2002-current: Member of the board, STINT


Affiliation and location
Department of Experimental Pathology
Jubileumsinstituten, Sölvegatan 25, Se-22362 Lund

Research interests
Work is focused on the endothelium of the blood vessel wall; Interaction with the microenvironment in the different organs. This interaction manifests itself during embryonic development and in inflammatory as well as in regenerative processes. One protein, MECA32 shows a regulated expression during embryonic development. We have analyzed this protein and its gene in detail and discuss its function in relation to the formation of endothelial cell caveolae and caveolae mediated signaling. The role of the endothelium in the extravasation of leukocytes during inflammatory processes is a second focus: The function of the endothelial cell specific E-selectin as adhesion molecule for lymphocytes and granulocytes is studied with transgenic endothelium expressing E-selectin deletion mutants in functional assays of leukocyte adhesion to cultivated endothelial cells. The work hypothesis is that the interaction of different leukocyte subsets with E-selectin is dependent on the leukocyte subset. Inhibition of leukocyte adhesion to the adhesion molecules presented by endothelial cells is another focus in the lab.

Translational research activities
The work on the mechanisms of leukocyte adhesion in inflammation is highly relevant for the analysis and the treatment of inflammatory diseases, especially in chronic inflammation.

Group composition

<table>
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<tr>
<th>Project leaders</th>
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<th>PhD students</th>
<th>Technical staff</th>
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<tbody>
<tr>
<td>Prof. Dr. Rupert Hallmann</td>
<td>Dr. Markus Hammel</td>
<td>Dipl.biol. Olaf Zilles</td>
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Current research funding

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<td>Semaphorins as inhibitors of leukocyte adhesion to endothelium in inflammation</td>
<td>260</td>
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<td>ALF</td>
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<td>Functional analyses of normal and pathological vascular and lymphatic endothelial cell growth and differentiation</td>
<td>2241</td>
<td>2003 3yr</td>
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<td>Foundations</td>
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<td>Cell-cell and cell matrix interactions in vascular endothelium &amp; in inflammation</td>
<td>300</td>
<td>2002&amp;2003 1-2yr</td>
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CV: Rupert Hallmann

Education

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<tr>
<td>Eberhard-Karls-Universität</td>
<td>Diploma in Biochemistry</td>
<td>1984</td>
<td>Monoclonal antibodies against DNA binding proteins in Drosophila</td>
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<td>Tuebingen, Germany</td>
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<td>Eberhard-Karls-Universität</td>
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<td>1988</td>
<td>Vascular development in the chicken embryo</td>
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<td>University of Erlangen</td>
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<td>Immunology</td>
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Postdoctoral training

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<tr>
<td>Stanford Medical School, USA</td>
<td>1988-1990</td>
<td>Dr. E.C. Butcher</td>
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</table>

Positions held

- 1990-1993 Group Leader in the Clinical Research Unit for Rheumatology, Max-Planck Society, Erlangen, Germany, headed by Prof. K. von der Mark
- 1994-2002 Group Leader in the Institute for Experimental Medicine, University Erlangen-Nuernberg, Germany, headed by Prof. K. von der Mark
- 1998 Promoted ‘Privatdozent’ (C2-Professor), Member of the Medical Faculty, University of Erlangen, Germany


Lipids, Plaques and Vascular Cells

Affiliation and location
Experimental Cardiovascular Research
Department of Medicine
Wallenberg-laboratory, Entrance 46, Floor 1
Malmö University Hospital
SE-20502 Malmö

Research interests
Regulation of gene expression (cytokines; transcription factors) and apoptosis in the context of experimental atherosclerosis research. Effects of lipids and lipoproteins on cultured cells. Analysis of the composition of atherosclerotic plaques.

Translational research activities
The purpose of this project is to analyse the composition of carotid plaques, the susceptibility of which to rupture has previously been echographically classified in separate studies (the established echographic methods are being used to determine which patients should be operated). Preliminary results indicate that calcium is the main determinant of plaque echostructure. Plaques associated with clinical symptoms are characterized by echolucency (black echographic appearance), increased levels of non-cross-linked elastin (presumably being degraded), increased activity of transcription factor AP-1 and less calcium than plaques not associated with symptoms.

Group composition

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<td>Mikko Ares, Associate Professor</td>
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<td>Foundations</td>
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<td>Cellular responses to atherogenic lipids</td>
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CV: Mikko Ares

Education

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<td>Åbo Akademi University</td>
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<td>Ph.D.</td>
<td>1998</td>
<td>Experimental Cardiovascular Research</td>
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Positions held

1998-: Assistant professor (Experimental Cardiovascular Research), Lund University
1) M. Isabella Pörn-Ares, Takaomi C. Saido, Tommy Andersson and Mikko P. S. Ares: Oxidized low-density lipoprotein induces calpain-dependent cell death and ubiquitination of caspase-3 in HMEC-1 endothelial cells. *Biochemical Journal*, vol. 374 (2003), 403-411. This paper was chosen as a ‘Featured article of the month’ (July 2003) by the Association for Eradication of Heart Attack (AEHA), and is presented at [www.VP.org](http://www.VP.org).


Molecular Cardiology

Affiliation and location
Molecular Cardiology, BMC C12, SE-221 84 Lund
Department of Cardiology, Lund University Hospital

Research interests
The extracellular nucleotides ATP, ADP, UTP and UDP acting on the large family of P2 receptors constitute an important system for cardiovascular regulation. We study: 1. The mechanisms of P2 receptor mediated vasodilatation, t-PA-release, vasoconstriction, mitogenic effects on SMC and platelet aggregation. 2. Regulatory mechanisms for P2 receptor expression. 3. Release of nucleotides during coronary syndromes and PCI. 4. Develop antagonists for P2 receptors.

Translational research activities
Group leader David Erlinge works 50% as physician at the Cardiology clinic, with interventional cardiology (coronary angiography, PCI). Research is focused on human material where responses to balloon dilatation in vitro of human left internal mammary artery, is studied. The effect of clinically used inhibitors of restenosis such as rapamycin is evaluated. Basal gene expression in the vascular wall with microarray after laser dissektion microscopy is compared between patient groups (e.g. diabetics). Release of extracellular nucleotides that stimulate EC, VSMC proliferation and platelet aggregation has been found to be elevated in patients with acute coronary syndromes and correlate with platelet activation. A drug development project in collaboration with organic chemistry, KI has generated three leads that are of interest for cardiovascular drug development. One is a potentiator of P2X1 receptors by allosteric interaction.

Group composition

<table>
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<td>2003</td>
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**CV: David Erlinge**

**Education**

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<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund University</td>
<td>M.D.</td>
<td>1990</td>
<td>Medicine</td>
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<tr>
<td>Lund University</td>
<td>Ph.D.</td>
<td>1994</td>
<td>Medicine</td>
</tr>
<tr>
<td>Lund University</td>
<td>Docent</td>
<td>1999</td>
<td>Medicine</td>
</tr>
</tbody>
</table>

**Visiting researcher**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
</thead>
</table>

**Clinical training**

- Assistant Physician, (Underläkare), Virology, Lund 1.5 m: 1988
- Assistant Physician, (Underläkare), Medicine, Trelleborg 1.5 m: 1989
- Assistant Physician, (Underläkare), Medicine, Lund 4.0 m, 50%: 1991
- Assistant Physician, (Underläkare), Medicine, Lund 1.0 m: 1995
- Internship, Lund University Hospital: 1995-1996
- Specialist of Cardiology: 2003-

**Academic positions held**

- Amanuens, Pathology (40% and 20%): 1987-1988
- PhD-student 100%, Medicine, Lund University: 1990-1994
- (Utbildningsbidrag and Doktorandtjänst)
- 50% research and education position: 1997-2005
- (Klinisk Assistent, ALF, Forskningsutrymme för Yngre Forskare)

**Current Position**

- Specialist of Cardiology, Lund (permanent position): 2003-
  - combined with
  - 50% research and education position: 1997-2005
  - (Klinisk Assistent, ALF, Forskningsutrymme för Yngre Forskare).
Selected publications from the research group since 1998


Affiliation and location
Division of Molecular Neurobiology
Institute of Physiological Sciences, BMC A12, SE-22184, Lund

Research interests
Structure, function and regulation of G protein-coupled receptors (GPCR); identification of novel natural ligands for orphan receptors; ligand receptor binding; conformational changes involved in receptor activation; protein-protein interactions occurring between receptors and effectors; trafficking of receptor signals; cellular localization and trafficking of receptors and effector components.

The Division of Molecular Neurobiology at Wallenberg Neuroscience Center, Lund University currently represents the largest single academic group in Sweden focusing on the superfamily of GPCR. The various components present in this division synergize to create a broad approach to the molecular biology, molecular pharmacology, and cell physiology of vascular inflammatory mechanisms.

Translational research activities
Activation of FFA1R by dietary fatty acids and its relation to first-phase insulin release and rosiglitazone (Avandia) therapy. Study of the mechanism of action of drugs against inflammatory pain.

Group composition

<table>
<thead>
<tr>
<th>Project leaders</th>
<th>Postdocs</th>
<th>PhD students</th>
<th>Technical staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fredrik Leeb-Lundberg, Professor</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Björn Olde, Associate Professor</td>
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<td>3</td>
<td>1</td>
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Current research funding

<table>
<thead>
<tr>
<th>Granting agency</th>
<th>Main holder</th>
<th>Project title</th>
<th>kSEK/year</th>
<th>Granted (years)</th>
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<tbody>
<tr>
<td>VR/MFR</td>
<td>BO</td>
<td>Functional genomics of orphan G protein-coupled receptors</td>
<td>260</td>
<td>3</td>
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<tr>
<td>Other</td>
<td>FLL/BO</td>
<td>Structure, function and regulation of G protein-coupled receptors</td>
<td>3000</td>
<td>4</td>
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<tr>
<td>Other</td>
<td>FLL/BO</td>
<td></td>
<td>1000</td>
<td>1</td>
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</table>
CV: Fredrik Leeb-Lundberg

Education

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<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
</tr>
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<tbody>
<tr>
<td>Lund University</td>
<td>Fil. kand.</td>
<td>1976</td>
<td>Biological chemistry</td>
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<tr>
<td>Univ. of California</td>
<td>Ph.D.</td>
<td>1981</td>
<td>Biochemistry</td>
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Postdoctoral training

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<tr>
<th>Institution</th>
<th>Years</th>
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<tr>
<td>Univ. of California</td>
<td>1981-1982</td>
<td>Prof. R.W. Olson</td>
</tr>
<tr>
<td>Duke University Medical Center</td>
<td>1982-1986</td>
<td>Prof. R.J. Lefkowitz</td>
</tr>
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</table>

Honors and Awards

1977-1978 Education Abroad Program Reciprocity Student Fellowship
1981-1984 USPHS Postdoctoral National Research Service Award
1986-pres. Ad hoc reviewer (2-3 manuscripts/journal/year) for about 6 scientific journals
1987-1988 Leonard D. Ormsby Endowment Award
1988-1992 NIH First Independent Research Support and Transition Award
1990-1994 American Heart Association, Central Research Review Committee, Member
1994-1998 American Heart Association, Research Allocation and Advisory Committee, Member
1994-1996 Molecular Pharmacology, Editorial Board, Member
1995 National Institutes of Allergy and Infectious Diseases, Review Committee for Asthma, Allergic, and Immunological Diseases’ Cooperative Centers, Member
1996 Cortech, Inc., Consultantship
1998 Astra Hassle, Inc., Consultantship
1998 Promotion Prize, E.K. Frey - E. Werle Foundation, in recognition of work in the field of scientific research on the kallikrein-kinin system in relation to physiology and pathophysiology (presented in Nara, Japan)
2001-pres International Union of Pharmacology (IUPHAR) Nomenclature Committee, Chairman, Subcommittee for Bradykinin Receptors
1999 Laboratoire Fournier, S.A., Consultanship
2001-pres. Molecular Pharmacology, Editorial Board, Member
2002 Elected President, International Kinin Conference Kinin 2005

Positions held

2002 Professor (tenured), Cell and Molecular Physiology, Institute of Physiological Sciences, Lund University, Lund, Sweden
1992 Adjunct Professor, Department of Biochemistry, The University of Texas Health Science Center, San Antonio, Texas, USA
1998 Professor (tenured), Department of Biochemistry, The University of Texas Health Science Center, San Antonio, Texas, USA
1992 Associate Professor (tenured), Department of Biochemistry, The University of Texas Health Science Center, San Antonio, Texas, USA
1986 Assistant Professor (tenure-track), Department of Biochemistry, The University of Texas Health Science Center, San Antonio, Texas, USA
## CV: Björn Olde

### Education

<table>
<thead>
<tr>
<th>Institution</th>
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<tr>
<td>Chemistry</td>
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<td>Biochemistry</td>
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### Postdoctoral training

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<th>Years</th>
<th>Supervisor</th>
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<tbody>
<tr>
<td>NIH</td>
<td>1989-1993</td>
<td>Prof. J.C. Venter</td>
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<tr>
<td>Georgetown University</td>
<td>1993-1994</td>
<td>Prof. A. Sidhu</td>
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</table>
Selected publications from the research group since 1998


Affiliation and location
Division of Cardiovascular Physiology,
Department of Physiological Sciences, BMC F11, SE-221 84 Lund
Division of Anesthesia and Intensive Care,
Department of Cardiovascular, renal and Ethics, University Hospital of Lund, SE 221 85 Lund

Research interests
Mechanisms controlling blood flow and transvascular exchange with special reference to microvascular permeability under normal as well as pathophysiological states in the intensive care. Mechanisms controlling brain volume and microvascular effects of prostacyclin and rho kinas inhibition.

Translational research activities
Circulatory effects of trauma, especially brain trauma, and of sepsis.

Group composition

<table>
<thead>
<tr>
<th>Project leaders</th>
<th>Postdocs</th>
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<th>Technical staff</th>
</tr>
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<tbody>
<tr>
<td>Per-Olof Grände, professor</td>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>Peter Bentzer, MD, PhD</td>
<td></td>
<td></td>
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</table>

Current research funding

<table>
<thead>
<tr>
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<th>Granted (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR/MFR</td>
<td>POG</td>
<td>Physiological, pathophysiological and clinical aspects on microcirculatory control</td>
<td>339</td>
<td>2001-2004</td>
</tr>
<tr>
<td>ALF</td>
<td>POG</td>
<td>Microcirculation and capillary permeability during sepsis and after trauma</td>
<td>1100</td>
<td>2003-2005</td>
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</table>
CV: Per-Olof Grände

**Education**

<table>
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<th>Field of study</th>
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<tbody>
<tr>
<td>Lund Technical High school</td>
<td>M.S. (civilingenieur)</td>
<td>1969</td>
<td>Mechanical, hydraulic, rheology</td>
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<tr>
<td>Lund University</td>
<td>M.D.</td>
<td>1976</td>
<td>Medicine</td>
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<tr>
<td>Lund University</td>
<td>Ph.D.</td>
<td>1979</td>
<td>Circulatory Physiology</td>
</tr>
<tr>
<td>Lund University Hospital</td>
<td>Specialist</td>
<td>1986</td>
<td>Anaesthesia and Intensive Care</td>
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**Postdoctoral training**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
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<tbody>
<tr>
<td>Lund University</td>
<td>1979-1982</td>
<td>Prof S. Mellander</td>
</tr>
</tbody>
</table>

**Clinical training**


**Positions held**

- 2002-current: professor (anaesthesia and intensive care)
- 1995-2002: Associate professor (physiology)
- 1990-1995: Senior Consultant in intensive care
- 1993-1990: Various position in clinical work

**Awards and honours**

- Volvo Award Prize in neurotraumatology 1993
- Upjohn Trauma scholarship for 1993
- Swedish Medical Society Jubileum Prize 1996
- Wallenberg Scholarship on 10.0 milj Swe crowns 1996-2002
- Mångbergs prize 1999
- Co-organizer, Baltic Summer School on cardiovascular System in health and Disease, Lund
Selected publications from the research group since 1998


2) Möller AD, Grände PO. 1999. Low-dose prostacyclin is superior to terbutaline and aminophylline in reducing capillary fluid permeability in cat skeletal muscle in vivo. Crit Care Med. 27: 130-136


20) **Lundblad C, Grände PO, Bentzer P.** A mouse model for evaluation of capillary density, capillary surface area, cortical blood flow, and cortical edema, in the traumatized brain. J of Neurotrauma. Accepted
Regulation of Endothelial Cell Functions by the Tyrosine Kinase Receptor Family Axl-Sky-cMer and its Vitamin K-Dependent Ligand Gas6

Affiliation and location
Division of Clinical Chemistry, Department of Laboratory Medicine
University of Lund, University Hospital, Malmö
Wallenberg laboratory
SE-20502 Malmö

Research interests
Regulation of endothelial functions by the Axl-Sky-cMer family, which is a group of tyrosine kinases that are stimulated by the vitamin K-dependent protein Gas6, is the focus of the research. Gas6 stands for growth arrest specific gene 6, the gene being induced by growth arrest. Gas6 being a vitamin K-dependent protein binds to negatively charged phospholipids, e.g. to apoptotic cells. In addition it binds and stimulates the Axl-Sky-cMer family of tyrosine kinases, a binding that results in intra-cellular signalling events. The functional consequences include anti-apoptosis, mitogen stimulation, and mobility changes. We are interested in determining the role of this ligand-receptor system in vascular biology with focus on the endothelium.

Translational research activities
Being part of a laboratory medicine department, we have excellent opportunities in establishing research activities in close connection to the clinical laboratory and clinical department. Using reagents created in the laboratory, we establish methods to measure the involved proteins in blood and tissue samples. Such assays are used to elucidation of the clinical significance of measuring the involved protein components in clinical medicine. We have a proven record of such activities in the field of blood coagulation research.

Group composition

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<tr>
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<th>Technical staff</th>
</tr>
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<tbody>
<tr>
<td>Björn Dahlbäck</td>
<td>3</td>
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Current research funding

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<thead>
<tr>
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<th>Project title</th>
<th>kSEK/year</th>
<th>Granted (years)</th>
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<tbody>
<tr>
<td>VR/MFR</td>
<td>BD</td>
<td>Regulation of Blood Coagulation/the Gas6/Axl pathway</td>
<td>1,000</td>
<td>2003-2009</td>
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<td>ALF</td>
<td>BD</td>
<td>As above</td>
<td>3,600</td>
<td>2003-2005</td>
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<tr>
<td>EU</td>
<td>BD</td>
<td>Marie Curie Fellowship</td>
<td>750</td>
<td>2002-2003</td>
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<td>SSF (NNCR)</td>
<td>BD</td>
<td>ApoM a novel apilipoprotein</td>
<td>400</td>
<td>-2004</td>
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<td>Söderbergs stifelse</td>
<td>BD</td>
<td>Regulation of blood coagulation on lipoproteins</td>
<td>1,500</td>
<td>2003-2005</td>
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<td>Cancer foundation</td>
<td>BD</td>
<td>The Gas6/Axl pathway</td>
<td>400</td>
<td>2003-2004</td>
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<tr>
<td>Local foundations</td>
<td>BD</td>
<td>As above – blood coagulation – apoM- or Gas6/Axl</td>
<td>500</td>
<td>2003</td>
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</table>
CV: Björn Dahlbäck

Education

<table>
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<tr>
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<tbody>
<tr>
<td>Lund University</td>
<td>M.D.</td>
<td>1974</td>
<td>Medicine</td>
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<td>Lund University</td>
<td>Ph.D.</td>
<td>1981</td>
<td>Laboratory Medicine</td>
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Postdoctoral training

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
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<tbody>
<tr>
<td>Scripps Clinic and Research found-</td>
<td>1982-1983</td>
<td>Prof. H Müller-Eberhard</td>
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</tbody>
</table>

Clinical training

Internship (1974-1976 University Hospital in Malmö)
Internal Medicine and infectious diseases in total 2 years (1972 -1977 University Hospital in Malmö)
Clinical chemistry/Blood coagulation since 1977

Positions held

1989-current: Professor of Blood Coagulation Research, Lund University
1986-1989: Associate Professor, Lund University
1983-1986: Assistant Professor, Lund University
1982-1983: Fogarthy Postdoctoral Fellow: Scripps, LaJolla
1977-1982: Resident in Clinical Chemistry, University Hospital, Malmö


Tube Formation and the Extracellular Matrix

Affiliation and location
Section for Cell and Developmental Biology, BMC B12
Department of Cell and Molecular Biology, 22184 Lund

Research interests
Role of laminins and their receptors for epithelial and endothelial tube formation. Influence of recombinant laminin fragments and monoclonal antibodies against laminins on development of endothelial and epithelial cells. The molecular profile of hematopoietic stem cells.

Translational research activities
Role of extracellular matrix for the development of bone marrow stem cells.

Group composition

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<tr>
<th>Project leaders</th>
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<th>Technical staff</th>
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<tbody>
<tr>
<td>Peter Ekblom</td>
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<td>1 (secretary)</td>
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<tr>
<td>Jan Fredrik Talts</td>
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<td>2</td>
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</tr>
<tr>
<td>Madeleine Durbeej</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Marja Ekblom</td>
<td></td>
<td>1</td>
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<tr>
<td>Tord Hjalt</td>
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Current research funding

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<th>Project title</th>
<th>kSEK/year</th>
<th>Granted (years)</th>
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<tbody>
<tr>
<td>Cancer Fund</td>
<td>P.E.</td>
<td>Basement membranes in cancer</td>
<td>1 600</td>
<td>2001-2004</td>
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<td>Pediatric Cancer Fund</td>
<td>P.E.</td>
<td>Cell-specific nuclear pores in development and inWilms tumor</td>
<td>300</td>
<td>2002-2004</td>
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<td>Cancer Fund</td>
<td>M.E.</td>
<td>Laminins in hematopoiesis</td>
<td>200</td>
<td>2003-2004</td>
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<tr>
<td>Smaller Foundations</td>
<td>J.F. MD. T.H. M.E.</td>
<td>Laminins and their receptors, etc.</td>
<td>1 300</td>
<td>2002</td>
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CV: Peter Ekblom

Education

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<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
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<tr>
<td>Helsinki University</td>
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<td>Pathology</td>
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<tr>
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<td>Ph. D.</td>
<td>1981</td>
<td>Developmental Biology</td>
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Postdoctoral training

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<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
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<tbody>
<tr>
<td>Helsinki University</td>
<td>1981-1984</td>
<td>Lauri Saxén</td>
</tr>
</tbody>
</table>

Clinical training

Clinical Pathologist, Helsinki University 1977-1984

Positions held

1999-current: Professor (molecular cell biology), Lund University
1990-1999: Professor (zoophysiology), Uppsala University
1984-1990: Group Leader, Max-Planck-Society, Friedrich-Miescher Lab., Tübingen
1982-1984: Assistant Professor, Department of Pathology, Helsinki University
1977-1983: Junior Pathologist, Department of Pathology, Helsinki University

Professional Service

Editorial Boards
Member, Editorial Board of “Experimental Nephrology “ 1992-present
Member, Editorial Board of “Int. J. Dev. Biol ” 1999-1995.
Member, “Faculty of 1000”, Cell Biology Section. 2000-present
Associate Editor, “Matrix Biology“.1999-present

Grant committees and other committees
Committee for Biology, Swedish Natural Science Research Council (NFR), 1994-2000.
Board of the Uppsala Biomedical Center, 1996-1999.
Board of the Biology Education Center, Uppsala University, 1995-1998.
Advisory Board, Center for Molecular Medicine, Erlangen, 1999-present
Board of the International Society for Differentiation, 2001-present
Grant committee for Biology, Swedish Cancer Fund, 2002-present
Committee for Molecular Biology, Swedish Research Council. 2002-present

Elected Memberships in Scientific Societies.
European Molecular Biology Organization (EMBO), 1991-present
Royal Society of Sciences, Uppsala, Sweden. 1992-present

Member of Organizing Committees for International Symposia
The 10th International Sigfrid Juselius Symposium, Helsinki, Finland, 1984.
European Science Foundation., Molecular Biology of Cellular Interactions, Germany, 1995.
2nd European Kidney Research forum, Bergamo, Italy, 1996

Invited lectures at international conferences.
Over 100 invitations, including several plenary lectures at major meetings.

Supervisor of Ph.D. studies
11 Ph. D. Theses, Tübingen, and Uppsala/Lund, 1984-2002
CV: Marja Ekblom

Education

<table>
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<tr>
<th>Institution</th>
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<tr>
<td>Helsinki University</td>
<td>M.D.</td>
<td>1975</td>
<td>Medicine</td>
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<tr>
<td>Transplantation laboratory, Helsinki</td>
<td>Ph.D.</td>
<td>1985</td>
<td>Hematology</td>
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Postdoctoral training

<table>
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<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max-Planck-Institute, Tübingen</td>
<td>1986-1990</td>
<td>Peter Ekblom</td>
</tr>
</tbody>
</table>

Clinical training

About 5 years in Finland (Medicine, Hematology)
About 8 years in Uppsala (Hematology)
About 4 years in Lund (Hematology)
Specialist in Internal Medicine 1981
Specialist in Hematology 1999

Positions held

Various positions as Junior or Senior Physician, Helsinki (1975-1990) and Uppsala (1992-1999)
Assistant Professor (50 %) Dept. of Laboratory Medicine, Lund (Hematology), 1999-present
Senior Physician (50%). Hematology. University Clinic, Lund, 1999-present

One year leave of absence three times, 1983, 1985 and 1990 because of children.

Professional Service

Supervisor of Ph.D. studies
CV: Madeleine Durbeej

Education

<table>
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<tr>
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<th>Year(s)</th>
<th>Field of study</th>
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<tbody>
<tr>
<td>Uppsala Univ.</td>
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<td>1997</td>
<td>Developmental Biology</td>
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Postdoctoral training

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<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard Hughes Medical Inst., Iowa</td>
<td>1997-2001</td>
<td>Kevin P. Campbell</td>
</tr>
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</table>

Positions held

Assistant professor, Lund University, 2001- present
Howard Hughes Associate, Iowa, 1999-2001

Two leaves of absence because of two children.
# CV: Tord Hjalt

## Education

<table>
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<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
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<tr>
<td>Uppsala University</td>
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<td>1995</td>
<td>Microbiology</td>
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## Postdoctoral training

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<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
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<tbody>
<tr>
<td>Uppsala University</td>
<td>1995-1997</td>
<td>Peter Ekblom</td>
</tr>
<tr>
<td>University of Iowa, Dept. Pediatrics</td>
<td>1997-2000</td>
<td>Jeffrey C. Murray</td>
</tr>
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</table>

## Positions held

Assistant Professor, Lund University, 2001- present
**CV: Jan Fredrik Talts**

### Education

<table>
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<td>Developmental Biology</td>
</tr>
</tbody>
</table>

### Postdoctoral training

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
</thead>
</table>

### Positions held

Assistant Professor, Lund University, 1999- present
Selected publications from the group since 1998


Vascular Biology Research Group at the Department of Anaesthesiology and Intensive Care

Affiliation and location
Affiliation: Division of Cardio-Pulmonary and Renal Sciences and Ethics, Department of Anaesthesiology and Intensive Care, Lund University, SE-221 85 Lund, Sweden.

Location: University Hospital. Laboratory at Department of Molecular Pathogenesis at BMC B14, Lund University.

Research interests
Effects of sepsis on the vascular wall especially endothelial and smooth muscle nitric oxide mechanisms and the interaction with bacterial products and antimicrobial peptides. Influence of antibacterial peptides on vascular smooth muscle cell apoptosis and development of atherosclerosis. The vascular pharmacology of anaesthetic drugs, especially the function of the sympathetic vascular neurons and the endothelium/smooth muscle cross-talk.

Translational research activities
Development of candidate drugs for the treatment of septic shock based on antimicrobial peptides and analogs as well as antiinflammatory strategies for the treatment of atherosclerosis.

Group composition

<table>
<thead>
<tr>
<th>Project leader</th>
<th>Postdocs</th>
<th>PhD students</th>
<th>Technical staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikael Bodelsson, assoc. professor</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Current research funding

<table>
<thead>
<tr>
<th>Granting agency</th>
<th>Main holder</th>
<th>Project title</th>
<th>kSEK/year</th>
<th>Granted (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR/MFR</td>
<td>MB</td>
<td>On the therapeutic potential of antibacterial peptides in septic shock</td>
<td>209</td>
<td>2003-2004</td>
</tr>
<tr>
<td>ALF (project)</td>
<td>MB</td>
<td>Effects of sepsis and anaesthesia on the blood vessel wall</td>
<td>685</td>
<td>2003-2005</td>
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<tr>
<td>ALF (salary)</td>
<td>MB</td>
<td>Fellowship for especially promising young clinical researchers</td>
<td>542</td>
<td>2001-2003</td>
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<tr>
<td>Misc. foundations</td>
<td>MB</td>
<td>On the therapeutic potential of antibacterial peptides in septic shock</td>
<td>213</td>
<td>2003</td>
</tr>
</tbody>
</table>
CV: Mikael Bodelsson

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund University</td>
<td>MD</td>
<td>1987</td>
<td>Medicine</td>
</tr>
<tr>
<td>Lund University</td>
<td>PhD</td>
<td>1990</td>
<td>Surgery and Medical Cell Research</td>
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Clinical training

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Surgery</td>
<td>1 year and 11 months</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>11 months</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>3 months</td>
</tr>
<tr>
<td>General Practice</td>
<td>7 months</td>
</tr>
<tr>
<td>Anaesthesiology and Intensive Care</td>
<td>(Resident) 3 years and 5 months</td>
</tr>
</tbody>
</table>

Positions held

Postgraduate positions at the Department of Medical Cell Research 1987-1990 (about 3 ½ years)

Visiting Postgraduate Research Fellow at Heart Science Centre, Harefield Hospital, Middlesex, U.K., 1987-1989 (about 6 months)

Undergraduate Course Manager at the University Department of Anaesthesiology and Intensive Care, Lund, 4 September 1995 to 31 December 1997 (2 years and 4 months).

Attending anaesthesiologist, Department of Anaesthesia and Intensive Care, Lund University Hospital 1992-2001.

Consultant anaesthesiologist, Department of Anaesthesia and Intensive Care, Lund University Hospital 2001-current

Awards and honours

The Millennium Scholarship from Swedish Society of Anaesthesia and Intensive Care (SEK 40.000:-) 2000 to an outstanding researcher within the field of anaesthesia and intensive care. This scholarship has been awarded only once and will not bee awarded in the future.

First prize in the European Society of Anaesthesiologists 2002 research competition for trainee anaesthesiologists (Euro 3.000:-).

Third prize in a scientific competition in conjunction with the meeting of the Scandinavia Society of Anaesthesia and Intensive Care in Tromsø 2001 (“Radiometerpriset”).
Selected publications from the research group since 1998


Affiliation and location
Dept. Experimental Pathology, Jubeliums Institute,
Sölvegatan 25, SE-22185 Lund

Research interests
The main efforts of the group are investigations of cell-cell and cell-matrix interactions in vascular endothelium in inflammation. The groups of Sorokin and Gustafsson focus on the role of the basement membrane and of the β1 integrins, respectively, in vascular endothelial cell function, including extravasation of leukocytes into inflammed tissues. One of research focuses is the laminin family of basement membrane proteins. Each laminin is composed of an α, β and γ chain which associate to form an approximately crossed-shaped heterotrimeric molecule. Twelve genetically distinct laminin chains have been identified, two of which were first identified and characterized in our laboratory (laminin α4 & α5). These two laminins are expressed in the endothelial and smooth muscle basement membranes and, therefore, are important in the vessel wall. Evidence to date suggests that they play crucial roles in defining the permeability of the vessel wall. There are two main aspects to our work: 1) in vitro assays using purified laminin isoforms or recombinant fragments to define structure-function relationships e.g. what portions of the laminins interact with cells, which receptors mediated such interactions and what are the signal transduction pathways activated; and 2) in vivo manipulation of the laminin molecules to define function. This involves the use of the Cre-loxP recombinase system to eliminate specific laminin isoforms in defined tissues or at defined times in development. Further, we generate mice carrying deletions/mutations in specific domains in the laminin molecules to define structure-function relationships and to provide disease models.

Translational research activities
We have produced tools for studies of human tissues including monoclonal antibodies to all know laminin chains, that will be available to the program grant members. These antibodies have been successfully utilized for studies of human lupus nephritis.

Group composition

<table>
<thead>
<tr>
<th>Project leaders</th>
<th>Postdocs</th>
<th>PhD students</th>
<th>Technical staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lydia Sorokin, professor</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Erika Gustafsson, assistant professor</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Uwe Rauch, senior lecturer</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Michael Dictor, senior lecturer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granting agency</td>
<td>Main holder</td>
<td>Project title</td>
<td>kSEK/year</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td>VR/NFR</td>
<td>LMS</td>
<td>Funktionell karakterisering av basalmembrans proteinet laminin-10 (α5β1γ1)/</td>
<td>900</td>
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<tr>
<td>VR/NFR</td>
<td>LMS</td>
<td>Investigation of the Functional Significance of the Basement Membrane in Leukocyte Extravasation in a Mouse Experimental Autoimmune Encephalomyelitis (EAE)</td>
<td>430</td>
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<tr>
<td>VR/NFR</td>
<td>EG</td>
<td>The role of β1 integrins and integrin-linked kinase (ILK) in vascular development</td>
<td>208 + 643(FoAss)</td>
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<tr>
<td>ALF</td>
<td>LMS RH MD EG UR</td>
<td>Functional analyses of normal and pathological vascular and lymphatic endothelial cell growth and differentiation</td>
<td>2241</td>
</tr>
<tr>
<td>Various Foundations</td>
<td>All</td>
<td>Cell-cell and cell matrix interactions in vascular endothelium &amp; in inflammation</td>
<td>700</td>
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</table>
CV: Lydia Sorokin

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
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<tbody>
<tr>
<td>University of Western Australia</td>
<td>B.Sc.(Hons)</td>
<td>1977-1981</td>
<td>Biochemistry, Physiology, Zoology</td>
</tr>
<tr>
<td>University of Western Australia</td>
<td>PhD</td>
<td>1984-1987</td>
<td>Biochemistry/Physiology</td>
</tr>
<tr>
<td>Medical Faculty, University of Erlangen-Nuremberg, Germany</td>
<td>Docent</td>
<td>1999</td>
<td>Biochemistry/ Cell Biology</td>
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</table>

Postdoctoral training

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friederich-Meischer Laboratories of the Max-Planck Society, Tübingen, Germany</td>
<td>1988-1990</td>
<td>Prof. P. Ekblom</td>
</tr>
<tr>
<td>Max-Planck Society, Connective Tissue Research Group, Erlangen, Germany</td>
<td>1990-1992</td>
<td>Prof. K. von der Mark</td>
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Positions held

<table>
<thead>
<tr>
<th>Year</th>
<th>Position and Institution</th>
</tr>
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<tbody>
<tr>
<td>2003-</td>
<td>Professor, Experimental Pathology, Lund University, Sweden.</td>
</tr>
<tr>
<td>1999-2002</td>
<td>Associate Professor, Interdisciplinary Center for Clinical Research, Nikolaus Fiebiger Center, University of Erlangen-Nürnberg, Germany.</td>
</tr>
<tr>
<td>1996-1998</td>
<td>Assistant Professor; Institute for Experimental Medicine, University of Erlangen-Nürnberg, Erlangen, Germany.</td>
</tr>
<tr>
<td>1992-1995</td>
<td>Assistant Professor, Max-Planck Society, Connective Tissue Research Group, Erlangen, Germany.</td>
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</table>

Awards and honours

<table>
<thead>
<tr>
<th>Year</th>
<th>Award</th>
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<tbody>
<tr>
<td>2001</td>
<td>NFR (National Research Council) Senior Researcher.</td>
</tr>
<tr>
<td>1989</td>
<td>DAAD Post-doctoral Fellowship.</td>
</tr>
<tr>
<td>1988</td>
<td>Awarded the Athelstan and Amy Saw Medical Research Fellowship.</td>
</tr>
<tr>
<td>1987</td>
<td>1) Biochemistry Prize by the Australian Biochemistry Society.</td>
</tr>
<tr>
<td></td>
<td>2) Foundation Bursary by Australian Federation of University Women.</td>
</tr>
<tr>
<td>1984</td>
<td>Awarded Commonwealth Post-Graduate Scholarship to undertake PhD.</td>
</tr>
</tbody>
</table>
CV: Erika Gustafsson

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
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<tbody>
<tr>
<td>Uppsala University</td>
<td>B.Sc.</td>
<td>1993</td>
<td>Biology and chemistry</td>
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<tr>
<td>Uppsala University</td>
<td>Ph.D.</td>
<td>1997</td>
<td>Reproductive immunology</td>
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Postdoctoral training

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPI for Biochemistry/ Lund University</td>
<td>1998-2002</td>
<td>Prof. R. Fässler</td>
</tr>
</tbody>
</table>

Positions held

- 2003-current: Assistant professor funded by Vetenskapsrådet, Department of Experimental Pathology, Lund University.
- 1993: Teaching position, Department of Zoophysiology, Uppsala University.
CV: Uwe Rauch

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
</tr>
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<tbody>
<tr>
<td>Univ. Muenster</td>
<td>B.Sc.</td>
<td>1985</td>
<td>Chemistry</td>
</tr>
<tr>
<td>Univ. Muenster</td>
<td>Ph.D.</td>
<td>1989</td>
<td>Biochemistry</td>
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Postdoctoral training

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
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</thead>
<tbody>
<tr>
<td>New York University</td>
<td>3.5</td>
<td>R U Margolis</td>
</tr>
</tbody>
</table>

Positions held

1993 – 1997   Research assistant, Max-Planck Institute for Biochemistry
1998 – now   Lecturer, Lund University

Research interests

Extracellular matrix molecules, in particular hyaluronan and proteoglycans, carbohydrate mediated interactions, extracellular matrix of the brain, and it’s remodelling (EAE, gliomas/angiogenesis).
CV: Michael Dictor

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Illinois</td>
<td>B.Sc.</td>
<td>1968</td>
<td>Physiology, linguistics</td>
</tr>
<tr>
<td>University of Wisconsin</td>
<td>M.D.</td>
<td>1972</td>
<td>Medicine</td>
</tr>
<tr>
<td>Lund University</td>
<td>Ph.D.</td>
<td>1990</td>
<td>Pathology</td>
</tr>
</tbody>
</table>

Clinical training

29 years (1973-1975, 1977-present, anatomic pathology)

Positions held

1996-present: Senior Pathologist, Assoc. Prof., (docent överläkare), Lund University Hospital; regional consultant in lymphoma (1990-present), oncologic pathology and head & neck diseases (1990-1999)

1985-1995: Senior Pathologist, Lund University Hospital

1981-1985: Pathologist, University of California

Research interests

Selected publications from the research group since 1998


13) Sixt, M., Baumeister T., Samson T., Scharffetter-Kochanek K., Foerster R., Schuler G., Lutz M. B., and Sorokin, L. M. CCR7-binding chemokines, and cell- and matrix-binding integrins play essential but distinct roles in dendritic cell migration within lymph nodes. Submitted


**Vascular Physiology**

**Affiliation and location**
Division of Molecular and Cellular Physiology, Department of Physiological Sciences, BMC F12, SE-221 84 Lund

**Research interests**
Vascular smooth muscle contraction, differentiation and growth. Effects of the tissue environment, mechanical forces (blood pressure), and ion channels in determining cellular phenotype. Role of cholesterol-rich membrane regions (caveolae) in vascular signalling. Intracellular Ca\(^{2+}\) handling and the role of Ca\(^{2+}\)-dependent transcription factors (NFAT) in vascular growth and differentiation. Regulation of vascular inflammation responses by estrogen receptors.

**Translational research activities**
Studies of ion channel plasticity and phenotype modulation in human vascular grafts following balloon dilatation and organ culture *in vitro*. Studies of NFAT expression and the effect of a novel NFAT inhibitor in human myometrial vessels from non-pregnant women as well as in normal pregnancy and preeclampsia. Importance of estrogen receptors in human gingival inflammation.

**Group composition**

<table>
<thead>
<tr>
<th>Project leaders</th>
<th>Postdocs</th>
<th>PhD students</th>
<th>Technical staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Hellstrand, professor</td>
<td>3</td>
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<td>1</td>
</tr>
<tr>
<td>Bengt-Olof Nilsson, senior lecturer</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karl Swärd, assistant professor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maria Gomez, assistant professor</td>
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<td>2</td>
<td></td>
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</table>

**Current research funding**

<table>
<thead>
<tr>
<th>Granting agency</th>
<th>Main holder</th>
<th>Project title</th>
<th>kSEK/year</th>
<th>Granted (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR/MFR</td>
<td>PH</td>
<td>Signals for differentiation and growth of smooth muscle in the vascular wall</td>
<td>350</td>
<td>2002-2004</td>
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<tr>
<td>SSF (NNCR)</td>
<td>PH</td>
<td>Ph.D. project</td>
<td>300</td>
<td>2001-2003</td>
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<tr>
<td>Heart-Lung Foundation</td>
<td>MG</td>
<td>Role of NFAT in smooth muscle: a mediator in vascular hypertrophy?</td>
<td>150</td>
<td>2003-2004</td>
</tr>
<tr>
<td>Heart-Lung Foundation</td>
<td>BON</td>
<td>Regulation of vascular gene and protein expression by estrogen</td>
<td>300</td>
<td>2002-2003</td>
</tr>
<tr>
<td>Various Foundations</td>
<td>MG</td>
<td>NFAT in smooth muscle</td>
<td>550</td>
<td>2003</td>
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<tr>
<td>Various Foundations</td>
<td>KS</td>
<td>Caveolae in vascular signalling</td>
<td>150</td>
<td>2003</td>
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</tbody>
</table>
CV: Per Hellstrand

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
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</thead>
<tbody>
<tr>
<td>Stockholm University</td>
<td>B.Sc.</td>
<td>1967</td>
<td>Mathematics, physics, philosophy</td>
</tr>
<tr>
<td>Stanford University</td>
<td>M.S.</td>
<td>1968</td>
<td>Physics</td>
</tr>
<tr>
<td>Lund University</td>
<td>M.D.</td>
<td>1975</td>
<td>Medicine</td>
</tr>
<tr>
<td>Lund University</td>
<td>Ph.D.</td>
<td>1979</td>
<td>Physiology</td>
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</table>

Postdoctoral training

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Cincinnati</td>
<td>1980 (1 yr)</td>
<td>Prof. R.J. Paul</td>
</tr>
</tbody>
</table>

Clinical training

About 8 months (1973-1976, medicine, psychiatry, general practice).

Positions held

1993-current: Professor (muscle research), Lund University  
1985-1993: Associate professor (physiology), Lund University   
1981-1985: Assistant professor (physiology), Lund University   
1996-2001: Chairman, Department of Physiological Sciences, Lund University   
1990-1993: Chairman, Department of Physiology and Biophysics, Lund University

Awards and honours

2003: Member, External evaluation committee, Cardiovascular Research Group, University of Manchester  
2001: Co-organizer, Baltic Summer School on Cardiovascular System in Health and disease, Lund  
1994-1999: Member, Board of the Medical Faculty, Lund University   
CV: Bengt-Olof Nilsson

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund University</td>
<td>D.D.S</td>
<td>1986</td>
<td>Odontology, medicine</td>
</tr>
<tr>
<td>Lund University</td>
<td>Ph.D.</td>
<td>1991</td>
<td>Physiology</td>
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</table>

Clinical training


Positions held

1998- current: Senior lecturer, associate professor
1991-1998: assistant professor
CV: Karl Swärd

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
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<th>Field of study</th>
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<tbody>
<tr>
<td>Lund University</td>
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<td>1989-92</td>
<td>Medicine</td>
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<td>Lund University</td>
<td>Ph.D.</td>
<td>1997</td>
<td>Physiology</td>
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Postdoctoral training

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<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Calgary</td>
<td>1997-99</td>
<td>Michael P. Walsh</td>
</tr>
</tbody>
</table>

Positions held

2002-current: Assistant professor (Physiology), Lund University

Awards

1997-1999 Heart and stroke foundation of Canada (fellowship award)
1997-1999 Alberta heritage foundation for medical research (fellowship award)
CV: Maria F. Gomez

Education

<table>
<thead>
<tr>
<th>Institution</th>
<th>Degree</th>
<th>Year(s)</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univ. de la Republica, Montevideo, Uruguay</td>
<td>B.Sc.</td>
<td>1989</td>
<td>Medicine</td>
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<tr>
<td>Lund University</td>
<td>M.S.</td>
<td>1994</td>
<td>Medicine</td>
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<tr>
<td>Lund University</td>
<td>Ph.D.</td>
<td>1998</td>
<td>Physiology</td>
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Postdoctoral training

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>Supervisor</th>
</tr>
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<tbody>
<tr>
<td>University of Vermont</td>
<td>2000-2001</td>
<td>Prof. M.T. Nelson</td>
</tr>
</tbody>
</table>

Positions held

- 1999: Research Assistant Prof., Dept. of Physiol. Sciences, Lund Univ.
- 2000-2001: Post-Doctoral Associate, Dept. of Pharmacology, Univ of Vermont.
- 2002-current: Assistant Prof., Dept. of Physiol. Sciences, Lund Univ.

Awards and honours

- 1994 – 1998: Graduate Fellowship, Faculty of Medicine, Lund Univ.
- 1999: Teaching Award, Dept. of Physiological Sciences, Lund Univ.
- 1999: Salubrin Druva Award, Dr. P. Håkansson’s Foundation, Sweden.
- 2000: Research Award, Wallenberg Foundation, Sweden.
- 2000: Research Award, Swedish Medical Research Council.
- 2002-03: Research award, M. Bervalls Foundation.
- 2002-4: Swedish Heart & Lung Association award.
- 2003: Research award, T. Zoégas Foundation.

Overseas collaboration

Dr. Mark T. Nelson. Pharmacology Department, University of Vermont, U.S.A.

Clinical collaboration

1) Dr. Marie-Louise Lydrup (Dept. of Surgery, Central Hospital, Kristianstad)
2) Dr. Dag Wide-Swensson (Dept. of Obstetrics & Gynecology, Univ. Hospital Lund)

Corporate collaboration

1) Dr. Yung-Wu Chen & Dr. Steven Djuric (Integrative Pharmacology at Abbott Laboratories), research collaboration, 2001-2003.
Selected publications from the research group since 1998


