VETENSKAPSRÅDET
THE SWEDISH RESEARCH COUNCIL

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2007-11299-54784-39	2007-8703

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*Linnéstöd och Berzelius Center

Area of science
Vetenskapsrådet

Announced grants
Linnaeus Grant 2007

Total amount for which applied (kSEK)

2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
4500	9000	9000	9000	9000	9000	9000	9000	9000	9000	4500

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Academic title
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Position
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Organisation
Karolinska Institutet

DESCRIPTIVE DATA

Project title, English (max 200 char)
Center for Research on Inflammation and Cardiovascular Disease

Abstract (max 1500 char)
We propose to establish a center of excellence for research on inflammation and cardiovascular disease (CERIC) at Karolinska Institutet (KI). Its goal is to be an internationally leading center in chronic inflammation, the pathobiological process that links inflammatory disorders such as multiple sclerosis, rheumatoid arthritis and psoriasis with atherosclerotic cardiovascular disease. For this purpose, we will build on existing, strong research in inflammatory mediators, autoimmunity, chronic inflammatory diseases, and cardiovascular disease at KI. To complement the current PIs, we will invest in recruitments of outstanding young scientists. Together, the CERIC research team will identify mechanisms of chronic inflammation leading to cardiovascular disease. The following research aims will be addressed: Aim 1. To determine why chronic inflammation sometimes, but not always, results in increased atherosclerosis and leads to myocardial infarction or stroke (cardiovascular disease (CVD)). Aim 2. To identify novel therapy targets and investigate the effects of targeted therapies against CID and CVD. Taken together, these two approaches will allow us both to understand the etiology and pathogenesis of CID and CVD and provide a basis for improved prevention and therapy for CID and inflammatory CVD, two major challenges to health in the population.

Abstract language

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Kod
2007-11299-54784-39

Name of Applicant
Wallberg Henriksson, Harriet

Date of birth
560525-1924

English

Research areas
*Medicin

Review panel
VR-M

Classification codes (SCB) in order of priority
182301, 182204,

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Academic title	**Date of doctoral exam**
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Academic title Professor	**Date of doctoral exam** 1989-05-10

CO-OPERATING HEI

ENCLOSED APPENDICES

A, B, C, U, V, S

BUDGET

Funding period (planned start and end date)
2008-07-01 -- 2018-06-30

Funds applied for (kSEK)	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Linnéstöd och Berzelius Center	4500	9000	9000	9000	9000	9000	9000	9000	9000	9000	4500
Total (kSEK):	4500	9000	9000	9000	9000	9000	9000	9000	9000	9000	4500

Total amount for which applied (kSEK)

2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
4500	9000	9000	9000	9000	9000	9000	9000	9000	9000	4500

POPULAR SCIENCE DESCRIPTION

Popularscience heading and description (max 4500 char)
Populärvetenskaplig sammanfattning CERIC

Bakgrund, betydelse och övergripande mål: Kardiovaskulära sjukdomar som hjärtinfarkt och stroke (KVS) utgör tillsammans den största orsaken till död i Sverige och många andra länder. Kroniska inflammationssjukdomar, bland dem reumatiska tillstånd och psoriasis,

är inte bara allvarliga tillstånd i sig själva utan medför en kraftigt ökad risk att drabbas av kardiovaskulär sjukdom. Ökad kunskap om de mekanismer som är gemensamma för kroniska inflammationssjukdomar och kardiovaskulär sjukdom skulle både möjliggöra bättre behandlig av kroniska inflammationssjukdomar och bättre prevention av den kardiovaskulära sjukdom som är orsakad av inflammation. Vårt mål med CERIC är att utnyttja och utvidga en infrastruktur för forskning i gränslandet mellan inflammation och KVS, och därigenom attrahera både svenska och internationella forskare som kan genomföra molekylär forskning och terapiutveckling i en unik klinisk forskningsmiljö.

Specifika mål och genomförande: 1. Att förstå varför kronisk inflammation ibland, men inte alltid, resulterar i ökad risk för KVS : Vi kommer att undersöka vilka gener, omgivningsfaktorer och immunreaktioner som bestämmer å ena sidan utvecklingen av olika inflammationssjukdomar, å andra sidan utvecklingen av KVS. Vi kommer att studera både den situation där KVS uppkommer som en komplikation till kronisk inflammation och som fristående sjukdom. Möjligheten att studera inflammationen (vid bl.a. reumatoid artrit) före debut av följdsjukdomen (KVS) ger unika förutsättningar för molekylära och kliniska studier av utvecklingen av den kardiovaskulära processen innan individen drabbats av hjärtinfarkt eller stroke. De humana studierna kommer att utföras i nära anslutning till djurexperimentella studier där djurmodeller för inflammation och KVS kopplas samman. Med hjälp av dessa modeller kan inflammation och kärlsjukdom studeras i stor detalj och nya målmolekyler för terapi av båda sjukdomsgrupperna identifieras. 2. Att förstå hur olika terapier mot inflammationssjukdomar påverkar utvecklingen av KVS: Många nya terapier som riktas mot specifika celler och molekyler i immunsystemet utvecklas och används nu vid reumatoid artrit, psoriasis och andra inflammationssjukdomar. Dessa terapier utvecklas och används också i djurexperimentella modeller. Genom att studera hur dessa terapier påverkar utvecklingen av KVS kan vi nå helt ny kunskap om mekanismer som driver KVS, och samtidigt bestämma vilka terapier som kan användas som ”prevention” mot KVS hos patienter med reumatoid artrit och andra kroniska inflammationssjukdomar.

För att kunna genomföra denna forskning krävs den miljö som vi nu önskar skapa, genom att existerande starka forskargrupper inom inflammation och KVS kombineras och nya grupper specialiserade på molekylära studier knyts till dessa grupper. De nya grupperna blir dels yngre forskare som rekryteras från hela världen, dels gästforskare som inbjuds att utnyttja vår unika forskningsmiljö och samtidigt dela med sig av sina idéer och tekniker till forskarna i denna miljö.

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Kod
2007-11299-54784-39

Name of applicant
Wallberg Henriksson, Harriet

Date of birth
560525-1924

Title of research programme
Center for Research on Inflammation and Cardiovascular Disease

Appendix A

Research programme

Vetenskapsrådet, SE-103 78 Stockholm, tel. +46 (0)8 546 44 000, vetenskapsradet@vr.se

Center for Research on Inflammation and Cardiovascular Disease (CERIC)

Applicants:

Göran K Hansson (coordinator) Professor of cardiovascular research in the Department of Medicine and Center for Molecular Medicine (CMM), principal investigator. Expertise in molecular medicine, vascular immunology and atherosclerosis research.

Cecilia Söderberg-Nauclér (vice coordinator) Associate Professor, Dept of Medicine and CMM. Expertise in virology, infection biology, vascular biology, and organ transplantation.

Marie Wahren-Herlenius (vice coordinator) Professor of experimental rheumatology, Dept of Medicine and CMM. Expertise in humoral immunology, autoimmunity, and autoimmune diseases.

Birgitta Agerberth, Associate Professor, Dept of Medical Biochemistry and Biophysics (MBB). Expertise in innate immunity, antibacterial peptides, and peptide biochemistry.

Anders Hamsten, Professor of cardiovascular diseases, Dept of Medicine and CMM. Expertise in genomics and molecular epidemiology of cardiovascular disease, atherothrombosis and myocardial infarction.

Rikard Holmdahl, Professor of medical inflammation research, currently at Lund University but recently appointed to the Karolinska Institutet, will be at MBB and CMM. Expertise in molecular biology, experimental genetics, immunology, and autoimmunity.

Jesper Z Hæggström, Professor of biochemistry, MBB. Expertise in lipid biochemistry, molecular biology, eicosanoid signaling, and lipidomics.

Lars Klareskog, Professor of rheumatology, Dept of Medicine and CMM. Expertise in clinical and experimental rheumatology, immunology, and rheumatoid arthritis research.

Tomas Olsson, Professor of molecular medicine, neurologist, Dept of Clinical Neuroscience and CMM. Expertise in neuroimmunology, immunogenetics, and multiple sclerosis.

Mona Ståhle, Professor of Dermatology, Dept of Medicine and CMM. Expertise in dermatology, inflammation and innate immunity.

Contents:

(References given in text; those published by CERIC investigators in *italics*).

1. CERIC Research Strategy

We propose to establish a center of excellence for research on inflammation and cardiovascular disease (CERIC) at Karolinska Institutet (KI). Its goal is to be an internationally leading center in chronic inflammation, the pathobiological process that links inflammatory disorders such as multiple sclerosis, rheumatoid arthritis and psoriasis with atherosclerotic cardiovascular disease. For this purpose, we will build on existing, strong research in inflammatory mediators, autoimmunity, chronic inflammatory diseases, and cardiovascular disease at KI. To complement the current PIs, we will invest in recruitments of outstanding young scientists. Together, the CERIC research team will identify mechanisms of chronic inflammation leading to cardiovascular disease.

The following research aims will be addressed:

Aim 1. *To determine why chronic inflammation sometimes, but not always, results in increased atherosclerosis and leads to myocardial infarction or stroke (cardiovascular disease (CVD)).*

Which genes, environmental factors and immune reactions determine on one hand the development of different chronic inflammatory diseases (CID) and on the other hand development of CVD? Which events (such as metabolic disturbance, mechanical strain, infections and specific immune reactions) determine organ specificity, and particularly cardiovascular involvement, in chronic inflammation?

Aim 2. *To identify novel therapy targets and investigate the effects of targeted therapies against CID and CVD.*

Which steps in the molecular pathways leading to chronic inflammation are suitable targets for development of novel therapy against CID and CVD? How does current treatment with biological response modifiers affect CVD?

Taken together, these two approaches will allow us both to understand the etiology and pathogenesis of CID and CVD and provide a basis for improved prevention and therapy for CID and inflammation-dependent CVD.

Importance: The development of CVD is dependent both on metabolic and inflammatory events and it is the most common cause of premature death in many CID. In spite of this, our understanding of the chronic inflammatory mechanisms that contribute to CVD is limited. CERIC will address this problem in a novel way, utilizing resources and opportunities already at hand in experimental and clinical research to form a world-leading research environment, where it will be possible to study the molecular pathogenesis of CID and CVD in well defined clinical materials and animal models.

2. Organization of the CERIC consortium

We will create a research environment with two main components:

A1. **Establish a multidisciplinary team for translational research on inflammation in CID and CVD** by building on our combined expertise and research structures available at Karolinska Institutet, Karolinska University Hospital, and through national and international collaborations. Our goal is to offer a world-leading environment for research into these major challenges to health in the population.

The CERIC infrastructure will permit access to:

- Longitudinal cohorts of patients with several different CID and CVD, including registered co-morbidities, and with many patients treated with new biological response modifiers.
- Animal models that are tailored to mimic various types of CID and CVD. A novel and important feature will be the construction of crosses between mouse models of CVD and CID.
- A network structure in which studies of pathogenetic mechanisms involving cellular, viral, and immune processes can be performed in sophisticated animal models and well defined patient groups.

A2. Strengthen and renew our network by **recruitment of new outstanding research groups** that focus on mechanisms involved in the development and protection against CID and CVD. We expect to recruit young, dynamic scientists who will be offered opportunities to start up new groups. These groups will be able to work with experimental models and clinical materials available within the consortium and should complement and strengthen the existing network. Key features of the CERIC consortium will be:

- A recruitment and training program to build up a new generation of scientists in chronic inflammation. We will recruit new junior faculty members by international recruitment efforts and also support, on a competitive basis, current postdoctoral fellows to build up their own groups as junior faculty members.
- A program for visiting scientists (senior and junior) will be offered access to our translational research organization in order to address their own scientific questions. These scientists will transfer new ideas and technologies to our environment.

In order to achieve these goals, CERIC will build on two existing nodes, one at the Dept of Medical Biochemistry and Biophysics (MBB) at KI Campus and one at the Center for Molecular Medicine (CMM) at Karolinska University Hospital across the street from campus. At each site, participating groups will share facilities, equipment and space. The two nodes will be fused into one organization by collaborative research projects, shared postdoctoral fellows, shared core facilities, a weekly seminar series, biannual retreats, a webpage based information system, and a joint PhD program.

CERIC will be led by a steering group consisting of the 10 PIs. This group will take all strategic decisions whereas the daily operations will be led by the coordinator, assisted by the deputy coordinators. An administrative assistant will be hired to support the CERIC organization.

CERIC is suggested to be run under the Board for Research of KI, which is chaired by the Dean for Research. A Scientific Advisory Board (SAB) of 3-4 international top scientists will evaluate CERIC every second year, assess progress and report changes. Their reports will be submitted to the Dean for Research. In addition to overall evaluations of strategy and research

progress, the SAB will be consulted on recruitments as these are considered vital for the program (see below).

The proposed CERIC coordinator, Göran K Hansson, has a long track record of academic leadership, which includes positions as chairman of the Nobel Committee for physiology or medicine (2004-6), chairman of the European Vascular Biology Association (1998-2000), member of the Board of Research at Karolinska Institutet (2000-2006), member of the search committee for president of KI (2003), European editor of the journal Arteriosclerosis, Thrombosis and Vascular Biology (2000-2007), Consulting editor for Journal of Clinical Investigation (2002-), director of the graduate program at Gothenburg University (1990-94), scientific advisor to several biotech and pharma companies, and active partner in several EU grants. For further details, please see the attached CV.

3. Value added by CERIC

Estimated value added attributable to the research environment

CERIC is launched to bring together leading expertise (clinical and experimental) in the fields of CID, CVD, innate immunity, adaptive autoimmunity and inflammatory mediators. This unique constellation of research leaders and groups will address key issues related to the etiopathogenesis, therapy and prevention of CVD in subjects with CID. The substantial excess morbidity and mortality from CVD in many common forms of CID has only recently been identified and poses a significant health problem as well as a challenge to health care providers. CERIC possesses the complementary expertise, the critical intellectual mass and the diverse tool box required to elucidate the implicated biological mechanisms and to define novel targets for treatment and prevention. Needless to say, the questions asked by the CERIC investigators go far beyond the capacity of the individual groups, both with respect to scale and technical complexity.

Based on the biobanks, clinical cohorts, model systems, experimental techniques and general research infrastructure already available in the 10 core groups, CERIC will realistically attract outstanding, international junior research group leaders who get a head start through the start-up packages and existing resources offered by the Center. This is of considerable strategic importance and a priority for the allocation of funding since it secures the next generation of scientific leaders in translational medicine, including the much-needed clinician-scientists. Similarly, CERIC will benefit from the intermediate-term presence/input of high-profile senior scientists attracted from abroad who will consider the Center as an attractive source of novel ideas, biobanks and databases for interrogation and collaborations. Both categories – junior group leaders and senior top scientists – will ensure a continuous infusion of new ideas and concepts into CERIC and safeguard the vitality of the research environment.

Substantial investments have already been made by major national and international funding bodies in individual core partners or subsets of the core partnership, in most instances focusing on fairly narrow aspects of CID or CVD, whereas integrated approaches remain sparse. The proposed investment in CERIC will be a leverage, allowing innovative, joint and accelerated use of existing resources and recent advances brought to the Center by the individual partners.

4. BACKGROUND AND PREVIOUS CONTRIBUTIONS

4. 1. Atherosclerotic cardiovascular disease (CVD) is an inflammatory condition triggered by metabolic and environmental factors

Atherosclerosis is the result of an inflammatory process in the vessel wall. A certain metabolic profile, with hyperlipidemia, is necessary for triggering it. The inflammatory properties of the human atherosclerotic lesion were characterized by Göran Hansson (PI of this application), who discovered evidence for local activation of T cells and macrophages (review: *Hansson GK, N Engl J Med 2005;352:1685*). Further studies have identified key mediators of atherosclerosis-associated immunity but the initiating antigens remain incompletely understood. Adaptive immunity towards oxidatively modified lipoproteins is a major candidate promoting vascular inflammation and atherogenesis (Fig 1)(Stemme S, PNAS 1995;92:3893). In addition, innate immune responses triggered by modified lipoproteins and other macromolecular components may contribute to atherogenesis, as shown by Birgitta Agerberth (co-PI)(*Edfeldt K et al, Arterioscl Thromb Vasc Biol 2006;26:1551*). The downstream effectors of vascular inflammation involves not only cytokines and costimulatory factors but also lipid mediators, in particular those of the leukotriene pathway. As shown by Hansson together with Jesper Haeggström (co-PI), this pathway is activated in the atherosclerotic plaque and modulates vascular cell function (*Qiu H et al, PNAS 2006;103:8161*). Genetic epidemiology provides strong support for this notion (Helgadottir et al, Nat Gen 2004;36:233) and also imply genes regulating the major histocompatibility complex (MHC) and immune cell activation, as shown by Anders Hamsten, Lars Klareskog and Tomas Olsson (co-PIs)(*Swanberg M et al, Nat Genet 2005;37:486*).

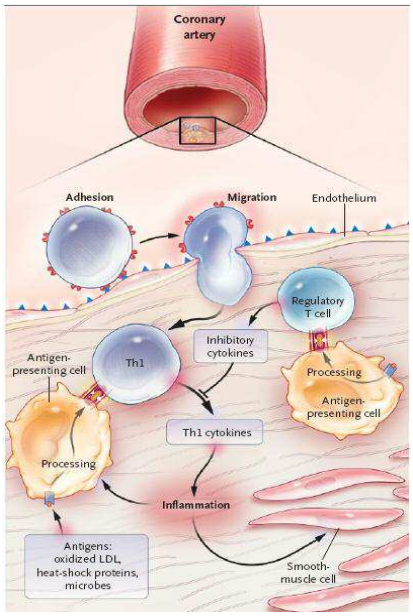


Fig. 1. Activation of antigen-specific T cells in the forming atherosclerotic plaque. Proinflammatory Th1 cells are activated by local antigens including oxidized LDL. This elicits production of proinflammatory mediators and leads to a chronic inflammatory state in the artery wall.
From *GK Hansson, N Engl J Med 2005;352:1685-95*

Mouse models of human disease have become indispensable for hypothesis-testing studies of atherosclerosis. By using compound knockout mice, Hansson and others have established that adaptive immunity confers proatherosclerotic activity in hyperlipidemic animals but also generates atheroprotective immune responses (*Zhou X et al, Arterioscl Thromb Vasc Biol 2001;21:108; Robertson AK et al, J Clin Invest 2003;112:1342*). These findings provide a basis for identification of novel therapy targets against CVD. Clinical and epidemiological studies have demonstrated that inflammatory biomarkers such as C-reactive protein (CRP) are risk factors for CVD (*Hansson GK, N Engl J Med 2005;352:1685*). However, CRP does not per se cause atherosclerosis but rather reflects ongoing chronic inflammation. Hypothetically,

this could reflect CID and/or chronic infection contributing both to CID and CVD. The Herpes family viruses, in particular, cytomegalovirus (CMV) have been implicated in these processes. Cecilia Söderberg-Nauclér (co-PI of this application) has discovered that latent CMV is reactivated in macrophages by inflammatory stimuli and that CMV infection may spread to vascular endothelial and smooth muscle cells and contribute to atherosclerosis and thrombosis (*Rahbar A et al, J Virol 2005;79:2211; Gredmark S et al, J Virol 2007;81:5112*). Interestingly, CMV can promote inflammation by inducing leukotriene production in vascular smooth muscle cells, as recently discovered by Söderberg-Nauclér and Haeggström (unpubl obs).

In summary, currently available data support a key role for immune activation and inflammatory responses in the pathogenesis of atherosclerosis. However, more research will be necessary to obtain a comprehensive picture of the process and also to identify the precise inflammatory reactions that may drive different types and phases of atherosclerosis, atherothrombosis and clinically manifest CVD.

4.2 Chronic inflammatory diseases (CID) are heterogeneous conditions but improved understanding of disease mechanisms will lead to delineation of more pathobiologically relevant disease entities.

CID are most often defined by criteria, without deeper knowledge about disease mechanisms. Recent studies of genes, environment and immune reactions in CID have revealed striking differences in all these three aspects between different subsets, thus providing evidence for different pathogenetic pathways being responsible for disease development in these CID subsets. A striking example is provided in rheumatoid arthritis (RA) in which two major subsets of disease can be defined based on the presence or absence of antibodies to poststranslationally modified (citrullinated) autoantigens (ACPA); These two categories have completely different genetic and environmental susceptibility factors. Lars Klareskog (co-PI) has contributed to the emergence of this new picture (*Klareskog et al Arthritis Rheum 2006;54:38*) and formulated an etiologic hypothesis for RA that involves specific genes, environmental agents and pathogenetic immune reactions (review: *Klareskog et al, Nature Clin Pract 2006;2:425*). Psoriasis has also been subdivided based on genetic, environmental and clinical features (*Holm SJ et al, J Invest Dermatol 2005;125:721*); and a similar subdivision may also be relevant for MS (Lassmann H, Brain Pathol 2007;17:210; *Olsson T et al, Curr Opin Immunol 2006;18:643*). Epidemiological studies have convincingly demonstrated that CVD morbidity as well as CVD mortality is increased in patients with established RA (*Björnådal L et al, Ann Rheum Dis 2006;6:741*) and psoriasis as well as in other rheumatic conditions such as Sjögrens disease. Tomas Olsson, Lars Klareskog and Anders Hamsten of this consortium have recently discovered that MS, RA and myocardial infarction (MI) share genetic risk factors (*Swanberg M et al, Nat Genet 2005;37:486*); this obviously points to shared pathogenetic steps between CID and CVD.

However, we do not yet fully understand which features of CID are related to an increased risk for CVD, and more specifically which genes, which immune reactions and which triggering factors that may be involved in CID as well as in CVD.

4.3 CID are long-standing diseases that often lead to CVD

CID as well as CVD are long-lasting diseases in which pathogenetic immune reactions often occur many years before the onset of clinical CID. Therefore, it is important to distinguish between those environmental triggers and immune reactions that act early “preclinically”, those factors that trigger clinical disease, and those factors that lead to chronicity (*Klareskog*

L et al, Nature Clin Pract 2006;2:425). It will also be important to identify genes that regulate each of these phases. Studies on associations between CVD and CID have most often been performed using cross-sectional studies of CVD in CID populations compared with controls. Thus, it has been unclear whether the link between CID and CVD is due to shared genetic or environmental risk factors, or alternatively, if the inflammation in active CID is a necessary component for CVD to occur. A recent study in a new-onset RA cohort (from KI) demonstrated no significantly increased risk in newly diagnosed RA patients, whereas the risk was still substantial in patients with long-standing RA (*Askling et al, unpublished observation).* At the same time, there is evidence both for shared genetic risk factors between RA, MS and CVD (*Swanberg M et al, Nat Genet 2005;37:486)* and for shared environmental risk factors (for example smoking) in CVD and certain CID. Of note, some CID appear not to be associated with risk for CVD; in our setting this may particularly be the case for MS.

In conclusion, we need longitudinal studies to determine which events associated with CID that associate with an increased risk for CVD, and when these events occur. Such knowledge would help to determine which immune reactions trigger CVD in different CID and thus also provide a basis for prevention of CVD.

Genes and environment as risk factors for CID and CVD

It is likely that many of the mechanisms underlying immune auto-aggression are shared between the different CID; some of these may also promote the formation of inflammatory atherosclerotic lesions in the vasculature. Studies on gene polymorphisms associated with increased susceptibility for CID and CVD have, for a long time, focused on candidate genes emerging from experimental studies. They have shown that several susceptibility loci are shared between different CID as well as between CID and CVD.

Thanks to the detailed careful phenotypic characterization of patients in the cohorts of our consortium, we have been able to describe how subsets of patients with CID such as RA have very different genetic risk factors (*Källberg et al Am J Hum Gen 2007;80:867)*, and thus should be considered separate entities from genetic and etiologic points of view. Recent research using genome-wide association studies (GWAS) in humans and experimental studies employing comparative genetics and advanced intercrosses in mice and rats have made it possible to compare different CID and CVD in a more productive fashion than before. This creates new opportunities to use genetics to define potentially important pathways in human diseases and in their models, and approach the question of shared and non-shared pathways. Examples of recent work from our consortium, in collaboration with our extensive national and international networks, include mapping of a number of CVD genes (*Farrall M et al, PLoS Gen 2006;2:e72*) and MS genes such as *Il7r* (*Lundmark F et al, Nat Gen 2007;39:1108*), GWAS and linkage studies for RA and CVD (*Plenge et al New Engl J Med 2007;357:1199*) and identification of a number of psoriasis genes. Studies in rodent models for arthritis and encephalitis have identified a large number of susceptibility regions, which by advanced intercrosses and the use of congenic strains have been mapped down to small gene regions (see *Olsson T et al, Curr Op Immunol 2006;18:643 and Holmdahl R, Nat Clin Pract Rheumatol 2007;3:104*). In a few important proof-of-concept studies, information from the rodent gene mappings have been transferred to the human situation and permitted the identification of new human susceptibility alleles such as *Il7r* and the shared susceptibility gene *Mhc2ta*.

However, there is still a paucity of data on which genes and environmental influences that are shared between these different CID and between CID and CVD. Our consortium has

the potential to be in the forefront of the unraveling of common genetic and environmental risk factors for these diseases.

4.5 The molecular pathogenesis of CID and CVD show important shared steps, overlaps, and interactions.

A main area for several of the groups in the consortium has been functional studies in the various CID as well as in CVD, using a combination of human and rodent studies. Prime examples of such studies are:

- *Interactions between metabolic factors and immunity in atherosclerosis)*: LDL accumulation in the artery wall leads to complement deposition, Toll-like receptor expression, HLA class II expression, T cell activation, cytokine secretion, antimicrobial peptide production, and a local inflammatory condition (Review: *Hansson GK & Libby P Nature Rev Immunol 2006;6:508*). In atherosclerosis, T cell responses are mounted towards LDL peptides (CD4+ cells) (*Stemme S et al, PNAS 1995;92:3893*) and also CD1 restricted lipid antigens (*Tupin M J Exp Med 2004;199:417*). Mediators of inflammation, in turn, modulate key steps in lipid metabolism including expression of lipases, scavenger receptors, and cholesterol transporters (*Hansson GK, Science 2007;316:206*).
- *Genes regulating oxidation and immune activity in arthritis, encephalitis and atherosclerosis*: We have identified major gene regions associated with CID (arthritis, encephalomyelitis and psoriasis) in mouse and rat inbred strains (*Vingsbo-Lundberg C, Nat Genet 1998;20:401; Kuokkanen S, Nature Gen 1996;13:477; Kess D, J Immunol 2006;177:4612*). These gene regions often overlap suggesting that the genes control shared pathways. Several of the underlying genes have subsequently been identified in both experimental animals and in human cohorts. A major gene that was cloned in the rat controls the oxidative burst and surprisingly, a low oxidative burst led to more severe CID (*Olofsson P, Nat Genet 2003;33:25; Hultqvist M, PNAS 2004;101:12646*). In-depth analysis showed that reactive oxidative species exert a regulatory effect on T cell autoimmunity underlying the inflammatory process (*Gelderman KA, PNAS 2006;103:12831*); this opens up possibilities to develop a new therapy based on oxidants (*Hultqvist M, PLoS Med 2006;3:e348*). Furthermore, this novel findings are of obvious interest in atherosclerosis, a condition in which lipoprotein oxidation has been proposed to play a major role (*Hansson GK, N Engl J Med 2005;352:1685).*
- *The role of microbial agents, in particular CMV, in the development of multiple CID as well as CVD:* By using highly sensitive methods for virus detection, a previously unknown, low-grade active CMV infection has been detected in patients with chronic inflammatory diseases including RA, psoriasis, and IBD (*Rahbar et al, Inflamm Bowel Dis 2003;9154* and unpubl obs). A reactivated CMV infection may therefore be a hitherto undiscovered common pathogen in CID. Interestingly, CMV is also a common passenger in the atherosclerotic lesion and has striking modulatory effects on vascular cell function (*Rahbar A et al, J Virol 2005;79:2211; Gredmark S et al, J Virol 2007;81:5112).* In addition, CMV infection most likely contributes to development and accumulation of CD28- T cells (Pourgheysari B et al, J Virol 2007;81:7759). T cell receptors recognizing CMV virus derived peptides are enriched in the CD28-negative T cell population (Weekes M, J Immunol. 1999;162:7569) and CD28 negative cells are also enriched in atherosclerosis (Liuzzo G, Circ 2000;101:2883). Taken together, these studies provide a basis for further studies on the role of CMV, and possibly other similar viruses, in CID and CVD.

- *Immunity to post-translationally modified autoantigens in the development of arthritis, and CVD*: During recent years, antibodies to autoantigens generated by peptidylarginases that alter arginine residues in proteins to citrulline have emerged both as prime diagnostic tools to detect RA and as prognostic tools defining a subset of patients with more severe disease course. Potentially even more important, immunity to citrullinated autoantigens such as collagen II (*Lundberg et al, Arthritis Res Ther 2005;7:R458*) or fibrinogen (Kuhn et al JCI 2006; 116:961) appear to promote arthritis, as demonstrated in rodent disease models. We have proposed a working hypothesis to explain how genes (such as HLA-DRB1 alleles) and environment (including smoking and other airway stimuli) may interact to induce these pathogenic autoantibodies several years before overt disease occurs (*Klareskog et al. Curr Opin Immunol. 2006;18:650*). This may represent a paradigm for gene-immunity-environment interactions in CID, and contribute also to atherosclerotic CVD co-morbidity. Molecular studies will now be needed to critically test these hypotheses.
- *Pivotal role of proinflammatory lipid mediators in CID and CVD*: Eicosanoids, a family of lipid mediators derived from arachidonic acid, are implicated in the development and maintenance of pain, fever and inflammation. Drugs targeting the formation and action of eicosanoids are widely used as antipyretic, analgesic and antiphlogistic medications (NSAIDs) as well as in the treatment of bronchial asthma (montelukast). Recently, biochemical and genetic evidence have indicated that leukotrienes are involved in vascular inflammation and atherosclerosis. We have recently discovered that the leukotriene synthesis pathway is highly upregulated in culprit atherosclerotic lesions (*Bäck M et al, Proc Natl Acad Sci 2005;102:17501; Qiu H et al, Proc Natl Acad Sci 2006;103:8161*), whereas other investigators found that three genes required for leukotriene synthesis confer increased risk for CVD (Dwyer et al, N Engl J Med 2004;350:29; Helgadottir et al, Nat Gen 2004;36:233; Nat Gen 2006;38:68).
- *Innate immune reactions are shared between CID and CVD.* Innate immune mechanisms constitute an early response against pathogens and are also involved in CID. Recent studies show rare alleles in pattern recognition receptor genes to be associated with inflammatory bowel disease and also, as shown by us, with CVD (*Edfeldt et al, Circ 2002, Eur Heart J 2004*). Furthermore, antimicrobial peptides are induced in CID such as psoriasis and rheumatoid arthritis, and also in atherosclerosis (*Edfeldt et al, Arterioscl Thromb Vasc Biol 2006;26:1551*). Recent data show that these peptides may have proinflammatory effects in addition to their antimicrobial ones. Further analysis of innate immunity as a potential link between CID and CVD will be an important task within this consortium.

4.6 Therapeutic interventions as tools to explore molecular pathways in CID and CVD

The increasing use of targeted therapies for CID and CVD does not only provide opportunities for better treatment for the patients, but also opportunities for in vivo studies of molecular pathways that may be shared between CID and CVD. Of note, these therapies may be beneficial not only for the treated disease itself but also for its co-morbidities (as for TNF-blockade on RA and CVD in RA patients; *(Jacobsson L et al: Ann Rheum Dis. 2007 66:670).* However, undesired effects may also occur, an obvious example being the increased CVD morbidity in patients treated with COX-2 inhibitors. A number of upcoming potential therapies in the eicosanoid field should benefit from early studies of shared and non-shared pathways in eicosanoid metabolism in different CID and CVD. Another example is TNF-blockade, which has excellent effects in many, but not all patients with RA, psoriasis and IBD

and decreases RA-associated CVD while it increases disease activity in some cases of MS. We have established large clinical surveillance and safety programs for the biologics used in CID (for TNF-blockade, anti-CD20 and CTLA4Ig in RA, for TNF-blockade in psoriasis and for anti-VLA-4 (Tysabri) in MS). This program can be used to obtain blood (for genotyping and biomarkers) and tissues (for arrays and functional studies) before and after therapies, in order to investigate molecular mechanisms that may be responsible for the diverse effects of these treatments.

So far, few mechanistic studies have been designed that focus on molecular pathways involved in CVD pathogenesis in CID patients treated with different targeted therapies. Monitoring targeted therapy should provide excellent opportunities both to understand the regulation of critical events in CID and CVD, and to help us design therapies for prevention against CVD in patients with CID.

4.7 Problems and potentials of molecular studies aimed at understanding CID, their inter-relationships and the relation between CID and CVD

In vitro studies of immune and inflammatory reactions contributing to CID and CVD can be performed using an increasing repertoire of sophisticated methodologies and continue to provide ideas and hypotheses regarding pathogenetic pathways. However, critical testing of such hypotheses requires different approaches. The development of gene-targeted mouse models offers unique possibilities to test the causal role of specific genes and their products in disease development. Therefore, the exploration of gene-targeted murine models of human disease is a key component in our research program. Since we still lack information regarding the molecular mechanisms linking CID to CVD, we will allocate resources to create mouse models for such investigations. By crossing mice with established disease conditions such as the atherosclerotic *Apoe*$^{-/-}$ mouse with mice carrying targeted deletions in genes regulating immunity and inflammation, by crossing CVD models with CID-prone mice, and by using organ-specific (Cre-lox) deletions of candidate genes, we expect to arrive at a comprehensive understanding of the molecular pathogenesis underlying CID/CVD co-morbidity.

As a parallel step in research, findings in models must be validated in humans. Here, unique biobanks generated by us and others at the KI provide excellent opportunities for molecular pathogenesis research. Studies of gene polymorphisms in relation to disease are addressed in cohorts and case-control studies of CID and CVD. The meticulous documentation of clinical phenotypes in these materials makes it possible to perform subset analysis and longitudinal studies needed for co-morbidity analysis.

In addition, we have generated biobanks of pathological tissues and cells that are linked to clinical databases and DNA samples. These biobanks are interrogated for expression analysis including transcriptome, proteome and metabolome; this provides opportunities for unbiased exploration of molecular events. Furthermore, tissue biobanks are used to validate, in the human setting, key features of discoveries made in rodent models. Finally, we expect that our combined molecular and clinical phenotypic analysis will prompt the definition of novel subsets of CID with different genetic features and differential susceptibility to CVD.

5. Research plan

The overall strategy has two major goals:

A. Build a research infrastructure for CID-CVD research.

A1. Establish a multidisciplinary team for research on pathogenetic mechanisms in CID, CVD and their interactions by building on our combined expertise and the research structures available at Karolinska Institutet, Karolinska University Hospital, and through national and international collaborations. Our goal is to offer a world-leading environment for research into these major challenges to health in the population.

A2. Recruit innovative research groups that focus on mechanisms involved in the development and protection against CID and CVD. We expect to recruit young, dynamic scientists who will be offered opportunities to start up new groups. These groups will be able to work with experimental models and clinical materials available within the consortium and should complement and strengthen the existing network. The recruitment and promotion of these scientists will provide a strategy for building careers in translational medicine and renewing this field of research.

B. Make major contributions to the understanding of chronic inflammation and its cardiovascular complications.

B1. Determine why chronic inflammation sometimes, but not always, results in increased atherosclerosis and leads to myocardial infarction or stroke (cardiovascular disease (CVD)).

B2. Identify novel therapy targets and investigate the effects of targeted therapies against CID and CVD.

5.1. Establish a multidisciplinary team (Goal A1)

5.1.1 The current CERIC network

An existing core of collaborating groups working on CVD (experimental and clinical) and CID (rheumatology, neuroimmunology, dermatology) have decided to combine forces with groups providing expertise in innate immunity, adaptive autoimmunity, and inflammatory mediators. Currently existing national and international networks and clinical study teams will be introduced into the center. These combined resources will be utilized to form a research environment without barriers and encompassing research groups that utilize different technologies and expertise to address major issues related to the etiopathogenesis, therapy and prevention of CID leading to CVD. Current research collaborations between CERIC partners are illustrated in Fig. 2.

Bibliometric analysis of the CERIC network shows its investigators to be at the forefront of their respective fields. Several of their discoveries have been published in top rank journals and they have also been invited to publish review articles in leading journals. This reflects on the high profile publication policy, high quality and novelty, and leading positions in the field of the CERIC investigators. A total of 161 papers have been published in journals with impact factor >10, including Nature (6 papers), Science (3), Cell (3), N Engl J Med (9) Lancet (18), Nature Medicine (3), Nature Genetics (9), Nature Rev Immunol (1), J Clin Invest (14), J Exp Med (9), J Cell Biol (2), EMBO J (2), PLos Med (2), Proc Natl Acad Sci (34), Immunol Rev (9), Am J Hum Gen (7), and Circulation (41). During 2006-7 alone, 20 papers were published

in top journals (IF>10), including papers in Nature, Science, Nature Medicine, and N Engl J Med. In addition, a steady flow of papers are published in leading journals of each respective

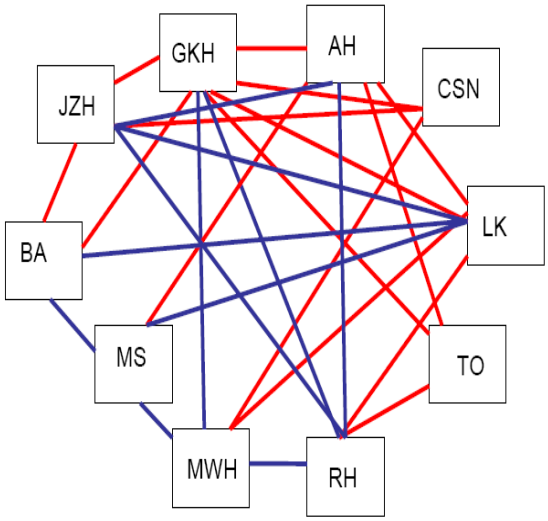
Published/submitted (red lines):

BA-JZH	Peptide-lipid signaling in immunity
BA-GKH	Innate immunity in atherosclerosis
JZH-CSN	Virus modulate leukotriene cascade
JZH-GKH	Leukotrienes in atherosclerosis
GKH-AH	Genetics of atherosclerosis
GKH-LK	Shared molecular steps CID/CVD
GKH-TO	Cellular immunity in CNS
AH-LK-TO	Genetics of CID and CVD
CSN-MWH	Molecular pathogenesis of CID
LK-TO	Genetics of MS and RA
TO-RH	Molecular genetics of CID
LK-RH	Pathogenesis of RA
MS-AH	Metabolic disturbance in CID

Ongoing (blue-black lines):

BA-MS-LK	Innate immunity in CID
MWH-GKH	Autoimmunity in heart disease
GKH-RH	Autoimmunity of CVD
AH-RH	Genetics of CVD and CID
MWH-RH	Autoimmunity of CID

Fig. 2.



field, such as Am J Pathol, Ann Neurol, Arterioscl Thromb Vasc Biol, Arthr Rheum, Blood, Circ Res, Hypertension, JAMA, J Biol Chem, J Immunol, J Infect Dis, I Invest Derm, J Virol, PLoS Gen and Stroke. Four of the CERIC investigators (AH, GKH, LK and TO) have been cited more then 10,000 times. Together, CERIC PIs are cited 71,792 times and 17 of their papers were cited more than 300 times.

5.1.2. Clinical resources. Sweden is well suited for studies of the genetic epidemiology of complex diseases, including studies of their interrelationships. This is due to our population-based longitudinal cohorts, national health care registers, and organization of academic medicine. Due to efforts from several Swedish agencies, EU and NIH, several such cohorts and case control studies have been established. The biobanks include a large genome-wide scan for susceptibility loci in precocious CVD (PROCARDIS, organized by Anders Hamsten together with Hugh Watkins, Oxford; >2500 affected sib pairs and >5000 matched controls); and also several case-control studies of myocardial infarction (Hamsten; 1700 patients and matched controls), RA (organized by Lars Klareskog, > 3000 cases and matched controls), and MS (organized by Tomas Olsson and Jan Hillert, > 1000 cases and matched controls).

Equally important, tissue biobanks for transcript profiling of atherosclerosis and arthritis (organized by Göran Hansson and Lars Klareskog, respectively) will also be available for CERIC investigators. Genetic and biopsy material will also be available from patient cohorts with psoriasis (Mona Ståhle), Sjögren's syndrome and SLE (Marie Wahren-Herlenius). Finally, the unique Swedish Twin Registry (director Prof Paul Lichtenstein) can be accessed and provides opportunities for genetic exploration and identification of disease associated genes. Bioinformatic exploration of these biobanks will provide unbiased information on disease genes and their expression, form the basis for formulation of specific hypotheses by CERIC investigators, and initiate research activities in preclinical and clinical laboratories.

We plan to perform a proteomics-based analysis of protein biomarkers in selected cohorts (in collaboration with the Human Proteome Resource center at the Royal Institute of Technology (KTH; Mathias Uhlén, Joakim Lundeberg et al) in order to detect whether posttranslational

modifications mark risk for CID and/or risk for CVD development in individuals with inflammatory processes.

5.1.3. Resources for experimental research:
We plan to create **a new mouse/rat genetic center at KI**. It will be localized at the Department of Medical Biochemistry and Biophysics (MBB) at KI Campus with an annex at the Center for Molecular Medicine (CMM), is planned to start in January 08, and will be operating in full scale from 1 July 08. This animal house will contain 9000 cages and is a complete animal resource center designed for genetic and immunological research. The creation and rent of this facility is fully financed by KI. A complementary facility for rodent research, with breeding of mice and rats, is already in operation at CMM at the Karolinska University Hospital across the street from KI Campus.

Several **gene-targeted mouse models** have been established, and in some cases created – at CERIC. For atherosclerosis, the hypercholesterolemic *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ mice represent a major resource and are used extensively in experiments, with standardized protocols for analysis of pathology, metabolism and immunology, and with crosses into a variety of different strains with specific defects in the immune system (e.g. *Scid*, *Il10*$^{-/-}$, *Il18*$^{-/-}$, CD4dnTGFβRII carrying defective TGFβ receptors on T cells, and most recently DEREG mice with conditional ablation of FoxP3^{+} regulatory T cells). Similarly, several powerful arthritis models are in use, including targeted genes (including point-mutated *Ncf1* and human HLA-DR1 transgenics) on B10.Q background. Neuroimmunological mouse models on the DBA/1 background include compound knockouts with CD4, CD8 and other immunologic defects.

A large number of common as well as disease-specific susceptibility genes for CID have been identified and many (more than a hundred) **congenic strains** have been bred in the mouse and rat. In this way, the role of selected genes, triggers and immune reactions promoting disease development can be investigated in detail. Gene dissection will also benefit from unique heterogeneous stocks (HS) of mice and rats. Ongoing experiments include more than 2000 mice subjected to experimental arthritis and 2000 rats subjected to experimental MS-like disease (EU project EURATools). Whole genome SNP mapping in both species will likely reveal very narrow Quantitative Trait Loci (QTL) confidence intervals, with options for rapid gene positioning.

An important new initiative that will be taken in the context of the current program is the construction of mouse strains that both contain various susceptibility genes for CID and carry a metabolic disturbance promoting atherosclerosis. This will initially be done by crossing mice carrying CID susceptibility genes with the *Apoe*$^{-/-}$ mouse. Later on in the program, we propose to assess the contribution of different dysmetabolic conditions by using other gene-targeted models mimicking human dyslipidemic conditions more closely, such as the Apob100^{tg} x *Ldlr*$^{-/-}$ mouse. Furthermore, we plan to assess the role of organ selectivity by constructing tissue-specific gene-targeted constructs, for instance by mating mice with floxed genes with others carrying Cre recombinase under promoters selectively active in endothelial and smooth muscle cells, neurons, chondroblasts, macrophages, and T and B cells.

Together, these approaches should provide novel information on the role of specific genes and their products in the development of CID and CVD and on the interactions between immunity and metabolism in the development of tissue-specific inflammation and atherosclerosis.

5.1.4 Bioinformatics

Our bioinformatics program will be aimed both towards capturing structured information from patients, further analysing and combining databases with genetic and biomarker

information, and using bioinformatics tools to identify molecular pathways. Many components of this strategy will be applicable in experimental models as well as in clinical studies .We will rely on systems established in rheumatology and cardiovascular medicine as well as experience from the KI Biobank Information Management System (BIMS) as building stones in the development of these systems. For integrating animal data with those from human biobanks, we plan to use the publicly available Arexis Genome Database that was originally developed in Sweden.

5.1.5. Computational and systems biology. Due to the enormous number of molecules and the complexity of interactions between molecules, cells, organs and the environment, it is necessary to employ computational analysis, modelling techniques and systems thinking in order to deepen our understanding of disease etiopathogenesis. This challenge will be addressed in CERIC by the integration in the Center of professor Jesper Tegnér, who is currently affiliated with the Hamsten group. Jesper Tegnér is professor of computational biology in the Department of Physics, Institute of Technology, Linköping University. His group will provide cutting-edge competence in mathematical modeling and machine-learning analysis and provide tools for identifying biological pathways and disease mechanisms from complex datasets comprising data obtained from various high-throughput platforms, in-depth clinical phenotypes and information on outcome from national registries. The basis for this activity rests equally on computational sciences, mathematics and physics.

5.1.6 External collaborations

The CERIC investigators have teamed up with a significant number of international research centers, by informal scientist-to-scientist collaborations but also in formally organized and funded networks and integrated projects. Major current collaborations include:

National networks:
COMBINE (Lars Klareskog coordinator, Anders Hamsten, Göran Hansson, Rikard Holmdahl, Tomas Olsson, Mona Ståhle, Marie Wahren-Herlenius partners), funded by Swedish public foundations Vinnova and Stratfo to support applied research and development into inflammatory diseases.
Chronic inflammation CIDaT (coordinator Jesper Haeggström, partner Göran Hansson), a similar project on development of new diagnostics and drugs in inflammatory diseases.

European and international networks and integrated projects:

European Vascular Genomics Network (Göran K Hansson partner), an EU network linking leading European vascular biology and CVD research laboratories.
EICOSANOX (Jesper Haeggström coordinator, Göran Hansson partner), an EU integrated project focusing on eicosanoids and nitric oxide in pathophysiology.
PROCARDIS (Anders Hamsten vice coordinator, Göran Hansson partner), an EU integrated project on the genomics of CVD.
AtheroRemo (Göran Hansson and Jesper Haeggström, partners), an EU integrated project on atherosclerosis and remodeling.
Neuropromise (Tomas Olsson, partner), an EU integrated project on MS research.
AutoCure (Lars Klareskog coordinator), an EU integrated project on mechanisms and therapy targets for rheumatic diseases.
EURATools (Tomas Olsson, partner), an EU integrated project in neuroimmunology.
Leducq Translational Network of Excellence in Atherothrombosis (A Hamsten, GK Hansson partners), coordinated from Harvard Medical School.

5.2 Recruitment program with focus on the junior faculty level (Goal A2)

The CERIC team has analysed the needs for career development and training within Swedish biomedicine and in particular, translational medicine relating to CID and CVD. We believe, as does KI, that the most urgent needs are at the junior faculty level. Contemporary Swedish biomedicine has a large cohort of professors and a very large group of PhD students. In contrast, there is a shortage of postdoctoral fellows and particularly of junior faculty scientists. Few positions are announced for promising young scientists who wish to develop an independent research career and form their own groups. This is a problem not only for the individuals themselves; it threatens the renewal of our biomedical research. We have therefore decided to give high priority within CERIC to developing a junior faculty program.

CERIC will recruit exceptionally gifted young scientists on an international basis. Successful candidates will be appointed at the **junior faculty** level and receive generous start-up packages to initiate research projects, including salaries for postdocs and running costs. These projects will focus on chronic inflammation and complement the approaches and expertise of existing CERIC laboratories. Although scientific quality (CV, research program) of candidates will be the major criteria for recruitment, we hope to strengthen certain areas through external recruitments, including the vascular biology of inflammation, cell therapy, proteomics, and bioinformatics. Junior faculty projects will be evaluated biannually by the scientific advisory board (SAB) and successful project leaders will be offered tenured positions at Karolinska Institutet.

In addition to the junior faculty program, we will initiate a **postdoctoral program** with international recruitment of talented young scientists to perform research in CERIC projects for approximately 2 years. Translational projects will be given priority and it is intended that CERIC postdocs shall work in two collaborating laboratories. It is expected that the most successful postdoctoral fellows within CERIC will compete successfully for some of the junior faculty positions that open up midterm in the program.

Research training at the PhD student/postgraduate level will also be an important component of the CERIC program. We will stimulate PhD students to choose translational projects that link two CERIC laboratories. Since physician-scientists with experience from molecular research are of key importance for translational research of the CERIC type, we will allocate special funds to MD/PhD students. However, we will not duplicate the PhD student programs of our respective academic departments. Instead, we will rely on the departmental organization, the research courses organized by the KI graduate school, and supplement them with courses and training focused on CERIC research.

5.3 Molecular pathogenesis at the CID-CVD junction (Goal B)

The focus of CERIC on the pathogenetic mechanisms that lead from CID to CVD should, together with the intellectual and structural resources within the Center, put us at the forefront of research worldwide into this major medical problem and help us make major contributions to its solution. We will here outline specific projects that will be running from day 1 of CERIC. Obviously, the precise research project development 5 years down the line will depend on our findings at earlier stages and the general progress of medical research. Therefore, it is impossible to provide a detailed research plan for the entire 10 years of life of CERIC.

We will try to make each of the specific projects add to the more overall aims, described in the introduction; i.e. (1) which factors determine whether an inflammation becomes chronic

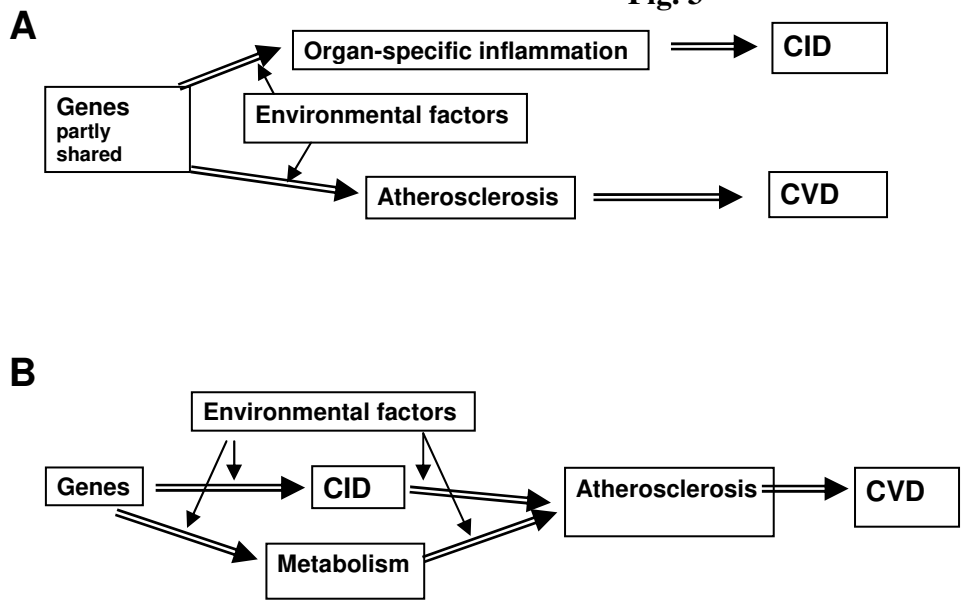
and which organ(s) will be affected? Specific emphasis will be placed on why and how the cardiovascular system is affected; (2) To use the increasing availability of targeted therapies as a tool both to understand which pathogenetic pathways are of importance for various CID and to find out how these targeted therapies influence future risk for CVD.

The schematic figure (below) is aimed to give an idea of how we hope to use longitudinal studies of our patients and animal models in order to understand disease development and ultimately prevent or treat in very early phases, preferably before the first symptoms of disease.

5.3.1. Relationship between CID and CVD

There is much epidemiological evidence that different CID are associated with each other. For instance, different CID are enriched in certain families. There is also ample evidence that some CID are associated with a highly increased risk for CVD. Within this project, we will define how CID and CVD are interconnected and in which phases of CID that a risk for other CID and for CVD are seen. We will consider two theoretical alternatives, a parallel or a serial connection between CID and CVD (Fig 3). The former implies that CVD occurs in CID patients since a set of risk factors (genetic and environmental) promote the development of atherosclerosis as well as CID. The latter proposes that the presence in the patient of a CID accelerates the development of atherosclerotic CVD. A parallel CID-CVD connection is supported by genetic epidemiology; for instance, an *Mhc2ta* allele conveys increased risk both for myocardial infarction, RA and MS. It would fit with the observation that smoking increases the risk both for RA and coronary artery disease. A serial connection, on the other hand, is compatible with experimental data showing increased atherosclerosis in mice with autoimmune conditions such as lupus.

Fig. 3



5.3.1.1. Studies on the relationships between CID and CVD in patient cohorts

Our access to several well characterized longitudinal cohorts of CID (RA, Psoriasis, SLE. Myositis, MS) as well as CVD (mainly coronary artery disease) will enable us to investigate in detail both the parallel development of CID and CVD and also the role of CID as driving forces behind development of CVD. In the latter case, we will have a unique advantage of access to “pre-CVD patients”, i.e. cohorts of individuals in which the risk for CVD is greatly

increased. This is the case in cohorts of RA, SLE, myositis and psoriasis. This permits a phenotypic characterization of these patients before the onset of clinical ischemic CVD. We plan to prospectively follow the development of CVD in a high-risk group of such RA patients, which will be characterised with regard to immunophenotype, metabolic profile, environmental exposure, and a large panel of genetic polymorphisms. This cohort will be monitored for RA activity (clinical score) and clinical symptoms of CVD. In a subgroup, we will perform carotid ultrasound investigations at regular intervals to follow intima-media thickness and development of plaques. For this study, we will select CID patients expected to be at high and low risk, respectively, with regard to their systemic immune/inflammatory profile (anti-citrulline antibodies, anti-oxLDL antibodies, $CD28^{null}$ T cells, CRP).

These clinical studies will allow us to identify genetic and environmental risk factors for CVD as well as potential risk factors specific for the inflammatory disease and its treatment. Having identified the risk factors and subsets of patients where these risk factors are operative, we will be able to obtain biologic samples from the various patient groups (CID patients with high and low risk for CVD), and perform a series of functional in vitro experiments, for example concerning immune reactivity to appropriate autoantigens (such as oxidised lipoproteins and heat shock proteins) and concerning immune regulation. We will also be able to investigate in detail the effects of immunomodulating treatments that may modulate CVD development (such as anti-TNF treatment). In this way, we should be able both to define pathways of relevance for development of CVD in CID patients, and interventions that reduce the risk for CVD in CID patients.

A number of specific subprojects addressing specific questions can now be carried out in these unique patient cohorts. Examples of such studies are:

- The role of various autoreactivities in the development of CVD in CID patients. We will investigate the occurrence of a number of adaptive (mainly antibody mediated) immune reactions in pre-CVD patients and see how these immune reactions relate to risk for CVD;

- The occurrence of CMV as well as CMV reactive T cells (mainly of the $CD28^{null}$ T cells) in different phases of CID and CVD. This should clarify to what extent CMV infection and anti-CMV responses are causatively involved in development of CVD;

- The interactions between environmental factors such as smoking, immune reactivities to post-translationally modified proteins that are induced by smoking, and actual development of CVD in this cohort.

5.3.1.2 Studies on the relationship between CID and CVD in mouse models

In gene-targeted mouse models, we will assess the effect of an inflammatory assault (such as collagen-induced arthritis or MOG induced encephalomyelitis) on atherosclerosis. We will also determine to what extent perturbations, by gene targeting, of the adaptive and innate parts of the immune system contribute to parallel increases in atherosclerosis, arthritis, and encephalomyelitis. For this purpose, the *Apoe* knockout mouse that develops spontaneous atherosclerosis has already been backcrossed to the B10.Q background that is susceptible to collagen induced arthritis.

A number of new genes controlling CID have been identified in the mouse models and an additional number is localized in small congenic fragments determining specific inflammatory pathways. These are selected to control arthritis and/or encephalomyelitis, see Figure 4. Susceptibility genes identified by using this strategy will now be tested for development of atherosclerotic CVD. Ongoing experiments to determine the role of oxidative enzymes in antigen presentation, autoimmunity, and arthritis will be expanded to include atherosclerosis (collaborative studies with Dr Jan Nilsson, Lund University).

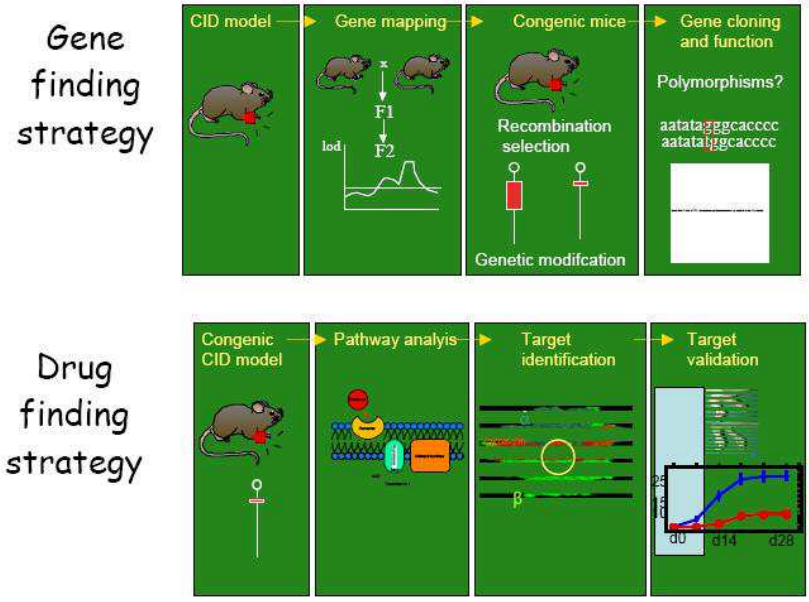


Fig. 4. General strategy for gene finding and drug target identification in CID.

In the first phase, the role of the *Ncf1* ($p47^{phox}$) gene will be analyzed; this gene would be expected to inhibit atherosclerosis due to its role in antigen presentation. However, it is also expected to mediate lipoprotein oxidation, which could promote disease development. A mouse carrying a mutant *Ncf1* gene (carrying a point mutation in exon 8; *Hultqvist M et al, J Immunol. 2007;179:1431*) will be crossed with the *Apoe*$^{-/-}$ mouse. This experiment should provide information about the relative importance of antigen processing vs lipoprotein oxidation for development of atherosclerosis.

The role of oxidation in atherosclerosis is likely to be complex and we will follow up these studies using a set of unique mice in which the *Ncf1* gene is expressed in specific antigen presenting cells such as dendritic cells, macrophages and thymic endothelial cells. The thymic endothelial cells will be of particular interest as they determine central immune tolerance. By this approach and also targeted deletion of the *Aire* gene, we should be able to determine the role of central tolerance for development of atherosclerotic inflammation in *Apoe* deficient mice.

We will evaluate the role of MHC alleles in atherosclerosis, by breeding the *Apoe* knockout onto MHC class I and II congenic backgrounds and assess the effects on vascular lesions. In a second phase, APOB transgenic mice expressing human LDL protein will be crossed with mice transgenic for human HLA class II alleles; the effect will be determined on atherosclerosis, collagen-induced arthritis, spontaneous arthritis, and MOG-EAE.

The shared susceptibility gene *Mhc2ta*, which conveys risk for RA, MS, and MI and controls MHC class II expression, will also be analyzed with regard to atherosclerosis. We have recently found that different mouse strains possess variants in the promoter III regions leading to differential MHC molecule expression, similar to our previous findings in the rat and human species (*Swanberg M et al, Nat Genet 2005;37:486)*. These variants have now been isolated in congenic strains that will be crossed into the atherosclerosis-prone *Apoe*$^{-/-}$ mouse.

If we obtain evidence for significant interactions between arthritis and atherosclerosis in the collagen-induced *Apoe*$^{-/-}$/B10.Q model, we will evaluate the role of immunoregulatory feedback in this situation by crossing the mouse with two transgenic models currently available in the laboratory. The CD4dnTGFβRtg with dominant-negative TGFβ receptors on

T cells lacks TGFβ mediated Treg function (*Robertson AK et al, J Clin Invest 2003;112:1342; Ait-Oufella et al Nat Med 2006;12:178*) and the DEREG mouse has an inducible defect in FoxP3+ T cells (ongoing studies).

Through all these studies, we expect to develop a matrix of different genetic and environmental risk factors for inflammatory disease and an assessment of their respective importance as pathogenetic factors for atherosclerosis. Originating from these data, it will be possible to analyze pathways leading to CVD in various CID and to study these pathways both in vitro and by additional targeted interventions in vivo. In addition, comparisons of CID induction in hyperlipidemic vs normolipidemic mice should provide clues regarding metabolic regulation of inflammation.

5.3.2. Sjögren´s syndrome resulting in CVD as a paradigm for pathological immune interaction

Patients with Sjögren´s syndrome often develop anti-Ro52 autoantibodies. Newborn children of mothers with Sjögren´s syndrome can develop congenital heart blocks (CHB) that may be fatal; this was recently shown to be due to maternofetal transfer of Ro52 antibodies that block transmission in the conductance system of the heart (*Salomonsson S et al, J Exp Med 2005;201:11*). However, the recurrence risk in subsequent pregnancies is only 20% despite persisting maternal autoantibodies, indicating that additional factors are required for disease development. Marie Wahren-Herlenius et al, collaborating with Tomas Olsson´s group, have shown that immunization with specific Ro52 peptides can cause CHB in rat fetuses (*Salomonsson S et al, J Exp Med 2005;201:11*). Certain genotypes determine the mother´s immune response to the Ro52 peptide, whereas other genotypes determine the effects of the binding of the anti-Ro52 antibodies to the fetal cardiomyocytes, and thus whether the presence of a given set of autoantibodies will result in disease.

Further work within CERIC will now be directed towards understanding the molecular events involved in causing the fetal heart defects, using experimental animal models and human cardiomyocyte cultures exposed to the autoantibodies. We will also make extended analyses to identify genetic and environmental factors that determine the emergence of CHB in human fetuses. Here, we will utilize the databases and biobanks (including information on genetic risk factors for other CID and CVD) and clinical materials as described above.

5.3.3 CID, CVD and CMV

Based on the evidence discussed elsewhere in this proposal that signs of CMV infection are common in multiple CID as well as in CVD, continued studies will focus on identifying factors that reactivate CMV infections and determine how active infection can contribute to inflammation and CVD. Our *a priori* hypothesis is that chronic CMV infection promotes CID and that CMV activation triggers clinically manifest, atherothrombotic CVD. By interrogation of global expression array data obtained from human atherosclerotic lesions, we have recently found that CMV induced proteins are present in atherosclerotic lesions (*Olofsson P et al, Arterioscl Thromb Vasc Biol 2005;25:e113*); this supports a role for CMV in CVD. Tissue biobanks available within CERIC will be screened for the presence of HCMV and other pathogens.

5.3.4. Effector molecules in chronic inflammation

The **antimicrobial peptide**, cathelicidin/LL37 can trigger autoimmunity in psoriasis by binding to self-DNA, leading to uptake, TLR-9 ligation and interferon production in dendritic cells (Lande R et al, Nature 2007;449:564). LL37, which is expressed also in atherosclerotic lesions, induces adhesion molecule (ICAM-1) and chemokine (MCP-1) expression in endothelial cells (*Frohm M et al, J Biol Chem 1997;272:15258; Edfeldt et al, Arterioscl*

Thromb Vasc Biol 2006;26:1551). Since ICAM-1 and MCP-1 promote atherosclerotic lesion development, LL37 may accelerate CVD under conditions of chronic inflammation. We will test this possibility by crossing *Apoe*$^{-/-}$ mice with LL37 deficient animals and also by assessing LL37 production in the model of collagen induced arthritis in hypercholesterolemic mice as discussed above. If experimental studies support a pathogenic role for LL37 in inflammatory CVD, clinical studies will be performed using patient materials described above.

Rececently, three genes controlling **leukotriene** synthesis were identified as susceptibility genes for CVD. Furthermore, our analysis of clinical biobanks and animal models show that the LTB_4 pathway is upregulated in culprit atherosclerotic lesions causing stroke, and that LTB_4 blockade inhibits atherosclerosis and restenosis (*Bäck et al, Proc Natl Acad Sci 2005; Qiu et al, Proc Natl Acad Sci 2006*). These results prompt us to investigate the potential of leukotriene synthesis inhibitors and receptor blockers to ameliorate atherosclerosis, arthritis, and other CID as well as the impact of targeted genetic defects in the leukotriene pathway on disease development. Furthermore, we will study the potential role of cysteinyl-leukotrienes, powerful smooth muscle contracting agents, in coronary spasm, heart ischemia and arrhythmia accompanying myocardial infarction, using a unique collection of human heart biopsies and animal models of myocardial ischemia, pharmacological tools and/or genetic ablations.

LTB_4 stimulates T-cell migration and function, thus acting as a link between the innate immune responses, adaptive immunity and autoimmune inflammation. We will test the hypotheses that pro- or anti-inflammatory eicosanoid pathways may be induced or silenced secondary to autoimmune disease processes. Moreover, several classes of immune modulatory/anti-inflammatory drugs are used in CID and their effects on eicosanoid pathways will be studied, possibly offering new therapeutic strategies. Finally, the construction of a mouse strain susceptible both to arthritis and atherosclerosis (see above) will be used to test whether LTB_4 blockade ameliorates inflammation-accelerated atherosclerosis. If this is the case, it would point to an obvious therapy target for drug development.

6. Milestones for the CERIC program

2 years:
- Establish compound mouse models for arthritis and atherosclerosis
- Establish high-throughput screening platforms for CVD risk in CID cohorts
- Establish computational biology exploration of databases for CID and CVD
- Recruit new PIs at junior faculty level, new postdoctoral fellows, and guest faculty

5 years:
- Clarify principles (serial/parallel) and major molecular mechanisms linking CID to CVD
- Discover a set of therapy targets for CID associated CVD
- Identify markers for CVD risk in CID patients
- Determine mechanistic role of a set of shared susceptibility genes for CID and CVD
- Successful junior faculty PIs established with dynamic groups and tenured positions
- Continue recruitment program

10 years:
- Novel therapies for CID and CVD in pharmaceutical development and clinical trials
- Training and mentoring program of junior faculty established as a model for academic medicine.

VETENSKAPSRÅDET
THE SWEDISH RESEARCH COUNCIL

Kod
2007-11299-54784-39

Name of applicant
Wallberg Henriksson, Harriet

Date of birth
560525-1924

Title of research programme
Center for Research on Inflammation and Cardiovascular Disease

Appendix B

Curriculum vitae

Vetenskapsrådet, SE-103 78 Stockholm, tel. +46 (0)8 546 44 000, vetenskapsradet@vr.se

Curriculum Vitae for Göran K Hansson

Office address: Center for Molecular Medicine, Karolinska Hospital, S-17176 Stockholm, Sweden; tel. (+46) 8-51776222; E-mail Goran.Hansson@ki.se

Education
Medical school, Gothenburg University; Med.kand. (Bachelor of Medicine) 1972; Läkarexamen (M.D.) 1977; Ph.D. 1980 in histology, Gothenburg University.

Positions/Appointments
Docent, histology, Gothenburg University 1981; Fogarty Postdoctoral Fellow, Dept. of Pathology, University of Washington, Seattle, WA., 1981-82; Internship and residency, Sahlgrenska University Hospital, Gothenburg, 1983-89. Forskarassistent (assistant professor) in cardiovascular diseases, Medical Research Council, 1986-88; Senior scientist in cardiovascular cell biology, Medical Research Council 1990-94; Professor of Cell Biology, Gothenburg University, 1994-95; Professor of Cardiovascular Research, Karolinska Institute, 1995-.

Awards, Honours etc (selected)
The Erik K. Fernström Prize for Medical Research, 1992; Visiting Professor, Dept of Cardiology, Università Catolica del Sacro Cuore, Rome 1996; Lars Werkö Prize for Heart Research, 1998; Meilahti lecture, Helsinki University Hospital, 2000; Russell Ross Memorial Lecture, Intl Soc Atherosclerosis, 2000; Pfizer Visiting Professor, Univ of Texas/Houston, 2001; Nikkilä Lecture, Scand Soc Atheroscler Res, 2002; Eijkman Medal, Utrecht University 2003; Vulnerable Plaque Lifetime Achievement Award, AEHA/ACC, Chicago 2003; Leducq Visiting Professor, Harvard Medical School, Boston 2005; Kennedy Visiting Professor, Imperial College, London 2005; David Geffen School of Medicine Visiting Professor, UCLA, Los Angeles 2006; Anitschkow Prize, European Atherosclerosis Society 2007; Hugh Sinclair Lecture, British Atherosclerosis Society/European Vascular Biology Organization, 2007; George Lyman Duff Memorial Lecture, American Heart Association 2007.

Commissions of trust
Prize committees: Nobel Assembly for physiology or medicine, 1997-; Member, Nobel Committee for physiology or medicine, 1998-; Chair, Nobel Committee 2004-06; Science Committee, Louis-Jeantet Foundation, 2000-. *Scientific societies and advisory boards:*: Chair, European Vascular Biology Association, 1998-2000; Chair, Gordon Conference on Atherosclerosis, 1999; *SAB* Heart Research Institute, Sydney 1994; Wihuri Research Institute, Helsinki, 1995-; Gladstone Foundation San Francisco 2001; Kuopio University, 2001; Oxford University, 2002; Academy of Finland, 2002-5; Medical University of Vienna 2005. *Intrauniversity tasks*: Director, graduate school, faculty of medicine, Gothenburg Univ 1991-4; Member, board of graduate school, Karolinska Institute 1996-98; Member, board for research, Karolinska Institute 1999-2005; Search committee for new president of Karolinska Inst 2005. *Scientific journals*: European Editor, Arteriosclerosis, Thrombosis, and Vascular Biology, 2000-07; Consulting Editor, Journal of Clinical Investigation, 2002-; Editorial Board, Circulation, 2000-; Annals of Medicine 2001-; Current Atherosclerosis Reports 2001-.

Publications
More than 185 original papers, 40 reviews, 25 book chapters, and one book.

Scientific supervision

17 graduate students awarded PhD degrees; 13 postdoctoral fellows, of whom 8 foreign fellows.

Curriculum Vitae for Cecilia Söderberg-Nauclér

Education: MD, Karolinska Institutet 1994; PhD in Clinical Immunology, Karolinska Institutet 1995. Thesis title: Biological Importance and Immunogenicity of Human Aminopeptidase N (CD13) in Cytomegalovirus Infection; supervisor: Prof. Erna Möller; Licensed to practise medicine 2001.

Post-doc: Post-doctoral fellow at the Dept. of Microbiology and Immunology, Oregon Health Sciences University, Portland, Oregon, USA 1995-1997. Mentor: Prof. Jay A. Nelson.

Docent (Associate professor): Karolinska Institutet 2002.

Current position: Research group leader for Cellular and Molecular Immunology in the Experimental Cardiovascular Research Unit, Department of Medicine, Center for Molecular Medicine since 2004. Most of my salary is covered by the Royal Swedish Academy of Sciences/Knut and Alice Wallenberg Foundation ("Akademiforskartjänst i Medicin") and the remainder by the Karolinska Institute "excellence program in biomedical research". I spend 10% of my time in clinical medicine as a consultant in Pediatric hepatology.

Previous positions: 1997-2001, Clinical Research Internship, Huddinge University Hospital; 2001-2004, Research group leader for Cellular and Molecular Immunology, Department of Medicine, Center for Molecular Medicine. During this period my salary was contributed by the Wenner-Gren Foundation and the Karolinska Institute "excellence program in biomedical research".

Maternity leave: 1999-2000, 16 months of maternity leave (75%); 2003-2004, 14 months of maternity leave (75%); and 2005-06, 14 months of maternity leave (75%).

Honors and Awards
The Inventors Stipend of Stockholm, the Capital of Sweden, 2006.
The Royal Swedish Academy of Sciences position in Medicine 2004,
The excellence position in biomedical research at the Karolinska Institutet 2001.
The Swedish Society of Medicine Award for young scientists, 2000 (100 000 SEK).
The Glaxo Wellcome Elion Young Investigators Award, 2000 (50 000 SEK).
The Söderquist Prize, 1999. Awarded by the Söderquist Foundation for outstanding scientific contribution in the field of infectious diseases in Sweden (180 000 SEK).
The Domagk Award, 1998. Awarded by the Swedish Society for Infectious Diseases and Bayer AB, Sweden for outstanding scientific contribution in the field of infectious diseases (25 000 SEK).
Knut and Alice Wallenberg Foundation: Stipend for an outstanding female researcher in Sweden, 1997 (200 000 SEK).

Supervision of PhD students (PhD students whom defended their thesis under my supervision (principal supervisor)): Jenny Odeberg (2002), Afsar Rahbar (2004), Sara Gredmark (2005), Stefania Varani (2005)

Supervision of post-doc:s: Jenny Odeberg, PhD**,** Petra Skarman, PhD**,** Piotr Religa. MD,PhD**,** Afsar Rahbar, PhD**,** Stefania Varani, MD,PhD**,** Sara Gredmark, MD, PhD (presently on a post-doctoral visit to Whitehead Institute, Cambridge, USA)**,** Rickard Glas, MD, PhD**,** and Hong Qui, PhD

Commissions of trust
- Member of the Strategic Research Committee, The Royal Academy of Sciences, 2005-
- Member of the Foundation for Virology Research at the Karolinska Institutet

- Member of the local organizing committee for the Herpes virus workshop, Åbo, 2005.
- Member of the Committee for Research and Education at the Karolinska Hospital, 2003-
- Member of the Committee for Research and Education at Karolinska University Hospital, 2004-
- Member of the steering committee for the Center for Molecular Medicine, 2004-
- Member of the steering committee for the Department of Medicine, 2003-
- Member of the committee for selection of students for the MD/PhD program at Karolinska Institute, 2004-
- Member of the International organizing committee for the Herpes virus workshop 2000 in Portland, and for the meeting in Madison, USA, 2003
- Member of the local organizing committee for the 5th International CMV Conference in Stockholm, May 1995

Regular reviewer for a number of international journals, including the Journal of Virology, Circulation, Blood, Journal of Immunology, Journal of Infectious Diseases, American Journal of Pathology, Scandinavian Journal of Infectious Diseases, Scandinavian Journal of Immunology, Transplantation, Arteriosclerosis, Thrombosis and Vascular Biology, Journal of Internal Medicine, and Trends in Microbiology, Acta Pediatrica, and PLOS Medicine.

- Reviewer for Grants applied for from the Knut and Alice Wallenberg Foundation
- Selection committee for Sven Gard Stipends, KI 2004-
- Selection committee for the best PhD thesis in Virology at KI 2004-
- Selection committee for Söderquist positions for researchers at the Center for Molecular Medicine, KI 2003

Patents

Owner of four patents concerning CMV pathogenesis and novel strategies for the prevention and treatment of CMV infections and long-term complications thereof, including vascular disease and chronic graft-versus-host disease in transplant patients.
Three other patent applications from my research group are pending.

Interactions with industry

Currently working closely with Roche to improve the awareness of the importance of CMV in many common diseases.

Curriculum Vitae for Marie Wahren-Herlenius

Website www.ki.se/medicin/medicine_ks/rheumatology_unit/research/maries_grupp.htm

Education and degrees

PhD 1994	Karolinska Institutet, Department of Cell and Molecular Biology
MD 1995	University Medical Degree, Karolinska Institutet
Docent 1999	Molecular Medicine, Karolinska Institutet
Licensed physician 2000	

Current position Professor of Experimental Rheumatology, Rheumatology Unit, Department of Medicine, Karolinska Institutet, 2006-present

Professional experience and previous appointments

Postdoc/ visiting scientist	1) University of Bergen, Norway with Prof Roland Jonsson 1994/1995 2) University of Tokyo, Japan with Prof Kioshi Takatsu 1998 3) Harvard Medical School, USA with Prof Vijay Kuchroo (visiting assistant professor 2001-2003)
Assistant professor	Karolinska Institutet, Dept of Medicine, Rheumatology Unit, 1999-2002 4-year position funded by the Swedish Research Council
Associate professor	Karolinska Institutet, Dept of Medicine, Rheumatology Unit, 2002-2005 6-year position with additional research grant, so-called "Excellence research position"
Associate professor	6-year senior research position in Molecular Autoimmunity Funded by the Swedish Research Council, 2005-present
Visiting professor	Harvard Medical School, USA, May 1 2007-April 30 2008

Supervision of graduate students

Supervised 8 graduate students to a PhD: Elisabet Welin Henriksson (1998, co-supervisor); Pia Tengnér (1999, main supervisor); Nader Pourmand (1999, main supervisor); Adla Bakhri Hassan (2002, co-supervisor); Stina Salomonsson (2004, main supervisor); Lars Ottosson (2005, main supervisor), Karin Popovic (2007, co-supervisor), Linn Strandberg (2007, main supervisor), supervised 2 students to a licentiate degree, and I am currently main supervisor for six students.

Supervision of postdoctoral fellows

Elisabet Welin Henriksson (1999-2000)
Monica Ek (2002-2005)
Lars Ottosson (2005-2006)
Wei Zhou (2004-2007)
Vijole Dzikaite (2006-present)
Stina Salomonsson (2007-present)

Honours and awards

1999 EULAR (European League Against Rheumatism), Young Investigator Award
1992 Odd-Fellow, Young Investigator Award
1999 EULAR (European Leaugue Against Rheumatism), Young Investigator Award (I)
1999 EULAR (European Leaugue Against Rheumatism), Young Investigator Award (II)
2003 Swedish Rheumatology Association Best Abstract of the Year Award (last author)
2005 INGVAR-award; The Swedish Foundation for Strategic Research
(one out of 6 awardees in life sciences among >400 applicants)
2005 Stina Salomonsson, who performed her PhD under my supervision, was awarded

Chorafa's prize for best thesis of the year (2004) at Karolinska Insitutet

2006 Scandinavian Journal of Rheumatology and Swedish Assoc of Rheumatology Award Prize for scientific achievement awarded a scientist not yet professor

2006 IMID-prize: Yearly award instituted 2006 by the Swedish Societies of Rheumatology, Dermatology and Gastroenterology together with Schering-Plough for outstanding research in Immune-Mediated Inflammatory Disorders

Selected commissions of trust

1991 President, PhD students' association, Karolinska Institutet
2001-2003 Research Secretary, Scandinavian Society for Immunology
2002-2004 Faculty Board, Karolinska Institutet (elected faculty representative)
2005-2007 Faculty Board, Karolinska Institutet (re-elected as faculty representative)
2002-2005 President, Junior faculty, Karolinska Institutet
2007- Swedish Research Council Medicine, Member of the board
2007- Associate Editor for the Scandinavian Journal of Immunology

Examination of PhD students

Faculty examiner on 5 occasions: Elwaleed Mustafa (2001, Huddinge Hospital, Sweden); 2002, Janne Bohnhorst (2002, Oslo University, Norway), Britt Nakken (2002, Bergen University, Norway), Filip Sköldberg (2003, Uppsala University, Sweden), Estelle Bajtner (2005, Lund University, Sweden)

Interaction with society and community outreach

- Regular lecturer at patient associations and have given several popular-scientific lectures at schools and for journalists
- Interviewed for Swedish TV and radio and broadcasted a number of times concerning both scientific findings and political issues of science
- Interviewed for Swedish popular science magazines a number of times concerning scientific findings (Sjögren's syndrome and congenital heart block)
- Published popular science articles on political issues of Swedish Governmental Funding policy (article from Junior Faculty published in Dagens Nyheter 2004)
- Participated in Children's show "Brainy" (Hjärnkontoret) as medical expert (6 programs)

Major grant support

Received first grant as principal investigator in 1997. Funded by Swedish Research Council since 1999, the Swedish Foundation for Strategic Research (INGVAR-grant and Canada Genome grant), the Heart-Lung Foundation, the King Gustaf V 80th birthday Foundation and the Swedish Rheumatism Association. EU funding for a project on Sjögren's syndrome 1998-2000 with ten participating European research groups. Received a 3-year Junior Individual Grant from the Strategic Research Foundation 1999-2001 and a 3-year grant within the Genome Canada call of the Strategic Foundation 2004. In 2005, received a 4+2 year "INGVAR"-grant from the Swedish Foundation for Strategic Research.

Curriculum Vitae for Birgitta Agerberth

PhD, Department of Biochemistry II, Karolinska Institutet, 1993

Post-doc, Department of Microbiology, University of Stockholm, 1993-1995

Docent (Associate Professor) in Medical Biochemistry, Karolinska Institutet 1998

Current position: Senior scientist (forskare) at the Department of Biochemistry and Biophysics, Karolinska Institutet, since 2002-01-01

Previous positions: 1970-09-01-1988-10-17, technician at the Department of Biochemistry II, Karolinska Institutet; 1988-10-18-1993-09-02, PhD student at the Department of Biochemistry II, Karolinska Institutet; 1993-1995, post-doc (see above); 1995-12-01-1997-12-31, position as researcher at the Department of Medical Biochemistry and Biophysics, Karolinska Institutet; 1998-01-01-2001-12-31, research position (forskarassistent) awarded by the Medical Research Council at the Department of Medical Biochemistry and Biophysics, Karolinska Institutet;

Scientific merits On 18 occasions I have been an invited speaker at different conferences both nationally and internationally, the most prestigious ones being two Gordon Conferences on Antimicrobial peptides, Ventura, CA USA (Invited lecturer and discussion leader, March 2001; invited speaker, March 2005; discussion leader, April 2007). Elected to organize the Gordon Conference on Antimicrobial Peptides in Italy 2011.

Supervision of graduate students
Current PhD students: Ylva Kai-Larsen, Biomedical program, Karolinska Institutet. Registration May 2005, Half-time September 2007; Andreas Cederlund, Civil engineer, Molecular Biotechnics, Uppsala University. Registration Jan. 2007; Protim Sarker, Master degree in Microbiology, University of Dhaka, Bangladesh. Sarker has received a scholarship from the Swedish Institute working in the fruitful collaboration with Dr. Rubhana Raqib, ICDDR,B, Dhaka, Bangladesh. Planned registration in 2008.
Previous students: Maria Tollin, PhD April 2005. "Antimicrobial peptides and proteins in innate immunity. Emphasis on isolation, characterization and gene regulation.", Main supervisor; Peter Bergman, MD 2001, PhD Sept. 2005. "Antimicrobial peptides and pathogenic Neisseria. Experimental studies in mouse, man and rat.", Main supervisor; Gudmundur Bergsson, PhD Dec. 2005. "Antimicrobial polypeptides and lipids as a part of innate defense mechanism of fish and human fetus.", Main supervisor; Yuqin Wang, PhD March 2001. "Protein and lipid interactions of mammalian antibacterial polypeptides" Supervisor together with Prof. Jan Johansson at that time at MBB; Stefan Termén, PhD Dec. 2004. "Expression of cathelicidin antimicrobial peptides in man and rat" Supervisor together with Prof. Gudmundur H. Gudmundsson, University of Iceland.

Faculty opponent Oslo University, Norway, 2004, "Identification and Biochemical characterization of Antimicrobial Peptides in Fish" by Gunn Alice Birkemo; University of Lund, Department of Clinical Sciences, Section for Dermatology and Venereology, 2007, "Antimicrobial Activities of Histidine-Rich Glycoprotein and Cationic Peptides" by Victoria Rydengård.

Referee for scientific journals On 41 occasions I have been referee for different scientific journals.

Thesis committees On seven occasions member of thesis committees (1 University of Stockholm, 6 Karolinska Insitutet) and on nine occasions in the committee of half-time seminars (all Karolinska Institutet)

Administrative tasks Organiser of the 2nd MBB Conference, Södertälje, Sweden, 2004; Organiser of a Nobel minisymposium on "Pattern Recognition and Effectors in Innate Immunity", Stockholm, Sweden, 2002; One of four members of the organising committee for the 11th Congress on Genes, Gene Families and Isozymes, Stockholm, Sweden, 2001.

Pedagogical merits

Pedagogic activities - undergraduate teaching: Teaching duties in Medical and Biomedical Chemistry at Karolinska Institutet, since 1990. The subjects taught include protein structure and function, intermediary metabolism and biochemistry. The duties have included lectures, seminars, exams and practical laboratory work, and have consisted of about five weeks teaching per semester. At present the teaching is in the medical, dental and biomedical programs.

Pedagogic activities - graduate teaching

EMBO course in "Protein purification and structure analysis", 1993

Graduate courses: Invited lecture at eight different occasions, Karolinska Institutet.

Responsible for a course in "Medical Biochemistry" including a written exam (2 points) for graduate students (17 students) at the Department of Medical Biochemistry and Biophysics, 2002.

Curriculum Vitae for Anders Hamsten

Professional preparation	Karolinska Institutet, MB	1975
	Karolinska Institutet, MD	1978
PhD	Karolinska Institutet, Medicine	1986
Post-doc	Karolinska Institutet, Atherosclerosis Research Unit, Department of Medicine, position endowed by the MRC	1987-1990
Docent	Karolinska Institutet (Medicine)	1990
Accreditation	Board certified specialist in internal medicine and cardiology	1986
Current position	Professor of Cardiovascular Diseases, Karolinska Institutet	1999-
	Head, Atherosclerosis Research Unit, Dept. Medicine, Karolinska Institutet	1993-
	Honorary consultant cardiologist, Karolinska University Hospital	1991-
Previous positions	Houseman, Department of Medicine, Serafimer Hospital	1978-1980
	Registrar/Senior registrar, Dept. Medicine, Danderyd Hospital,	1980-1986
	Junior investigator of the Swedish Medical Research Council	1987-1990
	Senior registrar, Cardiovascular Medicine, Karolinska Hospital	1987-1991
	Senior Investigator of the Swedish Heart-Lung Foundation (position at the KI endowed and supported by the Swedish Heart-Lung Foundation)	1991-1997
	Reader in Cardiovascular Research, Karolinska Institutet	April-June1997
	Professor of Cardiovascular Research, Karolinska Institutet	1997-1998
Distinctions	1st price for best original article from Scandinavian Society of Atherosclerosis	1986
	The Friedrich Merz price from the Johann Wolfgang Goethe-Universität, Frankfurt	1997
	Fellow of the Royal College of Physicians (FRCP); elected according to bye-law 39b (scientific excellence)	2002
PhD theses	Principal supervisor for 7 PhD students and co-supervisor for 17 PhD students who have completed their thesis Principal supervisor for (+ year of PhD): Fredrik Karpe (1992), Per Tornvall (1993), Peter Båvenholm (1995), Elisabeth Moor (1996), Johan Björkegren (1998), Ferdinand van't Hooft (1999) and Susanna Boquist (2000) Co-supervisor for (+ year of PhD): Jan Johansson (1991), Anette Asplund-Carlson (1994), Kamaran Fatah (1998), Lennart Nilsson (1999), Wolfgang Dichtl (2000), Pia Lundman (2001), Sofia Jormsjö (2002), Camilla Skoglund Andersson (2003), Tiina Skoog (2003), Josefin Skogsberg (2003), Majid Kalani (2003), Karl Gertow (2004), Katja Kannisto (2004), Maria Mannila (2006), Ann Samnegård (2006), Per Sjögren (2006) and Alexander Kovacs (2007)	
Post-doc:s	Supervisor for 21 post-doctoral fellows and scientists Fredrik Karpe MD PhD 1992-1999; Per Eriksson PhD 1992-; Angela Silveira PhD 1992-; Ewa Ehrenborg MD PhD 1997-; Beth Allison PhD 1998-2000; Francesca Ragogna PhD 1998; Giacomo Ruotolo MD PhD 1996-1998; Rachel Fisher PhD 1998-; Eric Gagne PhD 1998; Ferdinand	

	van't Hooft MD PhD 1999-; Danilo Norata PhD 2000-2001; Carl Whatling PhD 2000-2002; Jacob Lagrercrantz MD PhD 2002-2006; Johan Björkegren MD PhD 2002-; Josefin Skogsberg PhD 2003-; Dick Wågsäter PhD 2005-; Jacob Odeberg MD PhD 2006-; Vincent Fontaine PhD 2006-; Anders Mälarstig PhD 2006-; Maria Nastase Mannila 2006-; Maria Jesús Iglesias PhD 2007-	
Commissions of trust	Member of the Nobel Assembly for Medicine and Physiology	2004-
	Member of the Nobel Committee for Medicine and Physiology	2004
	Vice-Chairman of Medicine, Karolinska Institutet	1996-1999
	Chairman of Medicine, Karolinska Institutet	1999-2004 2005-2007
	Academic Chairman, Division of Cardiovascular and Respiratory Diseases, Karolinska University Hospital	2004-2007
	Member of the Research Committee of the Karolinska Hospital	2002-2007
	-:-	1992-1996
	International Evaluator of British Heart Foundation chairs	1996, 2000, 2006
	Faculty examiner of 12 PhD theses at Swedish, Finnish and British universities	1990-
Structure of research group	15 full-time researchers (3 full professors, 5 associate professors (docenter), 5 post-doctoral fellows and 2 visiting scientists), 5 clinical fellows with a PhD, 6 PhD students, 8 technical and administrative staff and 2 research nurses	
Publications	Author of 278 published original articles, 24 review articles and editorials published in peer-reviewed journals, and 28 review articles published in journal supplements or book chapters; 304 items listed in PubMed (on 18 Sept 2007)	
Networks	Prof Hugh Watkins, Wellcome Trust Centre for Human Genetics, University of Oxford, UK (e-mail: hugh.watkins@cardiovascular-medicine.oxford.ac.uk) Prof Steve Humphries, Department of Cardiovascular Genetics, University College London, UK (e-mail:rmhaseh@ucl.ac.uk) Prof Elena Tremoli, Institute of Pharmacological Sciences, University of Milan, Italy (e-mail: elena.tremoli@unimi.it) Prof Jan Nilsson, Wallenberg Laboratory, University of Lund, Malmö, Sweden (e-mail: Jan.Nilsson@med.lu.se Prof Ann-Christine Syvänen, Molecular Medicine Unit, Department of Medical Sciences, Uppsala University (e-mail: ann-christine.syvanen@medsci.uu.se)	
International leadership	Co-ordinator of the HIFMECH study, a European Concerted Action supported by the European Commission on the molecular genetics of haemostatic function in relation to coronary heart disease. PI of the PROCARDIS study, a European Concerted Action supported by the European Commission on the genome-wide search for new genes underlying coronary artery disease.	

Curriculum Vitae for Rikard Holmdahl

Doctorate exams: PhD 1985, MD 1987

Postdoctoral training
1986-1987 Assistant professor (Uppsala University, lab research periods one month each in Weizman Institute (Israel), Gainsville University (Florida) and Mt Sinai Medical School (NY),
1988-1989 Clinical residency training, University Hospital, Uppsala
1990-1993 Research fellow, Medical Research Council in Sweden

Docent (Associate Professor): 1987

Present employment
Professor in Medical Inflammation Research, Lund University, 50% (all research) (100% from March 1994-2006, 50% from January 2007)
Professor in the Finnish Distinguished Professor program of the Finnish Academy, Turku University, 50% (all research) (50% from January 2007 to January 2012)
Professor at the Karolinska Institutet from 1 January 2008

Previous employments/educations
1971-1976 industrial employments (Nymans/Uppsala/, Alfa Laval /Tumba/, Sandvik Coromant /Stockholm/).
1976-1977 Biochemistry 1 year (Stockholm/Uppsala University),
1977-1985 Medical education 5.5 years (Uppsala University),
1986-1987 Assistant professor, Swedish Medical Research Council
1988-1989 Clinical residency training ("forskar-AT"), University Hospital, Uppsala
1990-1993 Research fellow, Swedish Medical Research Council

Paternal leave, military service
1975 Military service (4 months); 1983 Paternal leave (6 months); 1985 Paternal leave (4 months)

Supervision of PhD students
Main supervisor (year of completion of PhD):
1) Mikael Andersson (90) 2) Tom Goldschmidt (91), 3) Listelotte Jansson (94), 4) John Mo (94), 5) Erik Michaëlsson (96), 6) Vivianne Malmström (97), 7) Carina Vingsbo-Lundberg (97), 8) Ulrica Brunsberg (98), 9) Peter Kjellen (99), 10) Alexandre Corthay (00), 11) Johan Jirholt (00), 12) MIkael Vestberg (01), 13) Ann-Sofie Hansson (01), 14) Åsa Johansson (01), 15) Shemin Lu (02), 16) Lars Svensson (02), 17) Johan Bäcklund (02), 18) Patrik Wernhoff (02), 19) Peter Olofsson (03), 20) Jens Holmberg (04), 21) Martina Johannesson (05), 22) Robert Bockermann (05) 22) Estelle Bajtner (05) 23) Stefan Carlsen (05), 24) Kutty Selva Nandakumar (06). 25) Lina Olsson (07), 26) Emma Ahlqvist (07), 27) Malin Hultqvist (07)
Co-supervisor:
Per Larsson (89), Inga Hansson (93), Ingrid Teige (04), Jinan Li (04), Meirav Holmdahl (05), Jenny Karlsson (05), Alexandra Treschow (05).

Supervision of post-doc:s (present position in parenthesis):
Stefan Persson, 94-96 (research director Resistentia AB , Uppsala), Liselotte Jansson 95-00 (section head, Astrazeneca Göteborg), John A Mo 95-98 (scientist Astrazeneca Lund), Aiping Lu 95-96 (professor Univ of Traditional Medicine, Beijing), Anna Mikulowska 96-97 (scientist, California), Andrew Cook, 96-99 (senior lecturer, Melbourne), Kristin Bergsteinsdottir, 96-00 (scientist company Rejkjavik), Shohreh Issazadeh-Navikas 98-05 (professor Copenhagen

University), Åsa Andersson 98-05 (senior lecturer Copenhagen University), Ragnar Mattsson 98-99 (professor Lund University), Anna Karin Lindqvist, 01-04 (CRO Cartela AB, Lund), Hisakata Yamada, 01-03 (senior lecturer, Fukukou University), Shemin Lu, 02-04 (Professor and Head of Immunology, Xian University), Balik Dzambazhov 02-04, 05- (senior lecturer, Plovdic University), Kang Feng 03-04 (assistant professor, New York), Ming Zhao, 03-04 (assistant professor, S:t Louis), Lena Wester-Rosenlöf, 04-06 (postdoc, Rostock University), Kyra Gelderman, 04-06 (scientist Amsterdam Univ), Ivanka Teneva 05-, Duoija Cao 05-, Kristin Bauer 06-

Commision of trust and awards

1993- Head of the Medical Inflammation Research Laboratory
1996- Member of the editorial board of Scandinavian Journal of Immunology
1997- Member of the editorial board of European Journal of Immunology
1998-2001 Member of the advisory board of the medical faculty, Lund University
1999- Associated editor for Arthritis Research
1999- Member of the international advisory board of Modern Rheumatology
2001-2005 Member of the medical faculty board, Lund University
2002-2006 Member of the editorial board of Journal of Autoimmunity
2002- Member of the editorial board for the Journal of Experimental Animal Science
2003- Member of the scientific evaluation committee for the King Gustaf V 80th birthday foundation
2003-2009 Member of the scientific advisory board of the German Center for Rheumatology Research in Berlin
2003- Member of the Executive Committee of European Journal of Immunology
2004- Board member of Scandinavian Foundation for Immunology
2004- Member of the editorial board and section editor for the journal Drug Discovery and Therapy
2004- Member of the editorial board for Current Rheumatology Reviews
2004-2006 Member of Faculty 1000 in Medicine
2004- Director of the programme area “Chronic Inflammation Research programme” in Lund University
2006-2009 Guest professor at Xian Jaio Tong University
2007-2011 Guest professor Finnish Academy/Turku University (50%)

Organized several large meetings and courses. Some recent examples are the Scandinavian society for immunology, Lund 99; Fernström Jubileum symposia; Functional genomics of inflammation, Lund 03, Member of the scientific committee for the European Rheumatology Congress (EULAR) in Europe for 2004, 2005 and 2006, Responsible organizer of the “Neuropromise course for genetic and bioinformatics analysis” in Lund with 30 participants from all over Europe during one week, including both theoretical and practical training; Coordinator Baltic Summer School 4-21 Sept 2007 with 100 participants
Research prizes: Craaford 1989, Fernström 1992, Gustafsson 1994, European Descartes price 2002, and Salus Ansvar 2003
The Medical Inflammation Research group was selected as an Excellence center for rheumatology research by EULAR (the European Rehumatolgy Association)

Faculty examiner for PhD theses: Åsa Andersson (Umeå 93), Anna Ridderrstad (Sthlm 94), Xue-Feng Bai (Sthlm-KI 98), Johnny Lorentzen (Sthlm-KI, 98), Kristina Bartnes (Tromsö 98), Oyvind Molberg (oslo 98), Mitchell Korgsgaard (Copenhagen 99), Teis Jensen (Copenahgen 00), Olof Hultgren (Göteborg 00), Ling Yun Xu (Sthlm-KI 00), Molly Vernersson (Uppsala 02), Helle Jacobsen (Copenhagen 04), Max Benner (New York 06), Ulrika Islander (Göteborg 07)

Curriculum Vitae for Jesper Z. Haeggström

Professional Preparation
Swedish Military School for Interpreters (Tolkskolan), Uppsala, 1974.
University of Uppsala, *Chemistry, Philosophy, Russian, Medicine*, B.A. 1980, M.D. 1981.
University of Miami, *Educational Commision for Foreign Medical Graduates*, 1982.
Karolinska Institutet, *lipid biochemistry*, Ph.D. 1988.
Karolinska Institutet, Post-doc, *protein chemistry and molecular biology*, 1988-1991.

Appointments
Research associate (FoAss) at the Dept. of Physiol. Chem., KI, 1988-1992.
Assistant professor (Docent) in *Medical & Physiological Chemistry*, KI, 1991.
Assoc. prof. Dept. of Med. Biochem. Biophys. (MBB), KI, 1992-1998.
Position as "*Karolinska Institutet Senior Investigator*", 1999-2003.
Professor, Head of Division, Physiol. Chemistry 2, (MBB), KI, 2000-present
Deputy Chairman, Dept. Med. Biochem. Biophys. (MBB), KI, 2000-present

Commissions of trust
SAB of *Bert L. and Nathalie K. Vallee Foundation*, Harvard, Boston, 1996-present
Member of the Faculty Board of Postgraduate Education, KI, 1999-2001.
Vice Chairman of the working group on "*Organisation*" within KI-05, 2004.
Member of the Faculty Board of Research, KI, 2002 - present.

Management/Networks
Vice coordinaor, EU 4th FP, "*Biochemistry of leukotrienes, inflammatory and allergic mediators in the arachidonic acid cascade*", (5 teams) 1995-1998.
Coordinator (Swe), Eur. PhD. Prog., "*Roles of Eicosanoids in Biol. and Med.*", 2001-present
Coordinator, post-graduate program in *Nanobiology and Biophysics*, KI/KTH, 2004-present
Coordinator, EU 5th FP, LEUCHRON (4 teams), 2001-2004
Coordinator, EU 6th FP, EICOSANOX (19 teams), 2004-2009

Participation/organization of scientific symposia
Invited lecturer and/or conference chairman 29 times since 1993.
Co-organizer and session chairman of "*Leukotrienes as targets for treatment of asthma and other diseases: Current basic and clinical research*", KI, Sthlm, Nov. 1998.
Organizer and chairman "*The Eicosanoids*", Stockholm, Oct. 2002.
Co-organizer and session chairman "*The Eicosanoid Challenge in Drug Development*", Stockholm April 2003.
Organizer and chairman of the *Berzelius Lecture* on *Cyclooxygenases*, Stockholm, Oct. 2004.
Co-organizer of a Nobel Symposium in Nanobiology, "*Controlled Nanoscale Motions in Biological and Artificial Systems*", June 13-17, 2005.
Chairman and general secretary of the 2006 *Days of Molecular Medicine* symposium (DMM2006) on *Inflammation in Chronic Diseases*, Stockholm, May 24-27, 2006. Jointly organized between KI, Massachussets General Hospital, Boston, and Nature Medicine.
Co-organizer of the 2007 *Days of Molecular Medicine* symposium on "*Emerging Technologies and Cancer Biology"*, Boston, May 22-24, 2007.

Ph.D. students as main supervisor: Juan F. Medina, 1992. Sen. Invest., Head of Lab. Mol. Gen., School of Med., Univ. Navarra, SP. **Anders Wetterholm,** 1993. Sen. Res. KI. **Martina Andberg**, 1997. Sen. Res., VTT Biotech., Espoo, FI. **Martin J. Mueller**, 2001. Prof., Head of Dept. Pharm. Biol., Julius von Sachs-Institute, Würtzburg, GE. **Filippa Strömberg**, 2001. Sci. Secr. WCN, CMM, KI. **Mattias Sjöström**, 2003. Post-doc, Dept. Med., KI, **Peter Rudberg**,

Nov. 2004. AT-läk, **Fredrik Tholander**, 1/12 2006, **Hong Qiu**, 22/1, 2007, **Oliver Schroeder**, 30/3, 2007.

Supervisor of post-docs: *Luigi Macchia*, University of Bari, 1990-1994; *Takashi Watanabe*, Tottory Univ., Japan, 1992-1993; *Carol Ng*, New York Med. Coll., USA, 1993-1995; *Martin J. Mueller,* Univ. of Munich, Germany, 1993-1995; *Luigi Macchia*, Univ. of Bari, Italy, 1993-1996, presently collaborator; *Ceil Herman*, New Mexico State Univ., USA, 1995-1996; *Per-Johan Jakobsson*, KI, 1997-1999, presently collaborator; *Martina Andberg*, KI, 1997-1999; *Anuradha Desai*, Univ. of Hyderabad, India, 1998-1999; *Oliver Schröder*, Univ. of Frankfurt, Germany, 1999-2001; *Tove Hammarberg*, SU, 2004-; *Alan Sabirsh*, Univ. of Lund, 2004-2006; *Ulrike Haas*, University of Frankfurt, 2005-present; *Antonio DiGennaro*, University of Milan, 2006-present, *Alicia Hidalgo*, University of Madrid, 2006-present. Craig Wheelock, Univ. California Davies, 2007-present.

Entrepreneurial activities

1. Patents. Haeggström, J.Z., et al. "*Drug-design based on the structure of LTA4 hydrolase*",(granted EP 1157101 and US prov. appl. 60/122, 110). Haeggström, J.Z. "*Methods and compositions for modulating x*", (pat. appl. No PA2001 00020), Haeggström, J.Z., et al.. "*Drug-design based on the three dimensional structure of LTC4 synthase*",. Provisional Application (EPC ref BIOBY/P38046US).

2. Licensing and/or collaborations with industry. *Schering AG*, 2001-. *Biolipox AB*, 2003-, *Johnson & Johnson*, 2004-

3. Companies. Co-founder of *Pyrinox AB* (2001) and *Cardoz AB (2006)*.

Scientific awards/fellowships

Fellowship from Procordia research foundations, 1992-1994.
Recipient of the 1998 "*Ulf Widengren research fellowship*" (ASTRA).
Recipient of a 2-year "*Individual Junior Grant*" SSF, 1998-2000.
Awarded the "*Bert L. Valle Visiting Professorship"*, Harvard Medical School, Boston, 2007.

Miscellaneous

Appointed reviewer for research foundations: STINT, The Wellcome Trust, Human Frontier Science Program, EU BIOMED2 programme, Italian University Grant System (MURST).
Member of the Ediorial Boards of: *J. Biol. Chem*., 2002 – present
Prostagl. Leukotr. & Ess. Fatty Acids, 2004 - present

Scientific production: > 130 scientific publications in the field of eicosanoids.

Curriculum Vitae for Lars Klareskog

Education and university positions
MD, Uppsala University 1974
PhD, Uppsala University 1978 (Medical and Physiological Chemistry; On the structure and function of MHC class II transplantation antigens; Supervisors Per A Peterson and Lars Rask).
Research fellow in experimental Rheumatology (Swedish Medical Research Council) 1979-82
Associate professor in Immunology, Uppsala University 1982-83
Clinical fellow in Rheumatology and Internal Medicine (and part-time research), Uppsala University Hospital 1983-1990
Professor and Chairman, Clinical Immunology, Uppsala Universitet 1990-93
Professor and Chairman, Rheumatology Clinic and Rheumatology Research Unit, Karolinska Institutet and Karolinska Hospital 1993- present
Visiting scientist, Harvard Medical School, February-May 2004

Additional positions (elected)
Chairman, Department of Medicine, Karolinska Institutet/Karolinska Hospital 1993-1999; Member Nobel Assembly at Karolinska Institutet 1995 – present; Member Nobel Committee at Karolinska Institutet 1995-97; President, Annual European Congress of Rheumatology, Stockholm, 2002; Member Scientific Committee EULAR 2001-2003; Co-chairman of the committee for infrastructure in clinical research at Karolinska University Hospital 2004 –; Chairman European League Against Rheumatism committee on Investigative Rheumatology (from 2006)

Recent distinctions
Jaan van Bremer medal 2004, the Dutch Rheumatology Society International Prize for Rheumatology research; Hasinger prize/lecture, German Rheumatism Center 2004; Wyeth Rheumatology Prize 2004; and The Rheumatology Unit at Karolinska
was recently officially recognised by the European Rheumatology Society as one of six European Rheumatology Centers of Excellence.

Editorial Boards
Arthritis & Rheumatism; Annals of Rheumatic Diseases; Arthritis Research and Therapy; Current Opinion in Rheumatology; Rheumatology; Nature Rev Rheumatology;

Networks in academia and society
Chairman, Scientific Board of the Swedish Rheumatism Association (patient organisation), 1997- present; Scientific advisor, Swedish Medical Products Agency 2000-present; Co-chairman EULAR Committe for European Registries for Biologics in arthritis 2001-present; Scientific advisor/Member International Advisory Boards of several pharmaceutical and biotech companies; Main coordinator EU Integrated project AutoCure (11MEuro over 5 years, involving 21 leading research groups in Europe); Co-Pi of NIH genetics grants for RA; Chairman of FOCIS Center of Excellence at Karolinska Institutet 2005- (FOCIS = Federation of Clinical Immunology Societies)

Supervision of PhD students
Main supervisor for 21 (co-supervisor for 18) PhD students (year of disputation; then present position): **Rikard Holmdahl**, 1985, prof medical inflammation research, Lund;, **Per Larsson** 1989, ass prof, senior physician rheumatology Karolinska;; **Cecilia Nordling** 1991, adm head Royal Acad Sci; **Sveinn Gudmundsson**, 1993, head Blood Bank, Reykjavik; **Sandra Kleinau** 1993, ass prof Uppsala; **Anders Bucht**, 1995, ass prof, head inflammation research National Defence Lab Umeå; **Helena Erlandsson Harris** 1997, Ass prof (VR-position), Karolinska;

Johnny Lorentzen 1997, ass prof Karolinska, **Johan Rönnelid**, (head clinical autoimmunity lab, Uppsala); **Tony Hansson**, 1999, research group leader, Pharmacia Diagnostics; **Lars Mattsson**, 1999, scientist Pharmacia Diagnostics; **Ann-Kristin Ulfgren**, 2000, ass prof Karolinska; **Louise Berg**, 2000, scientist (VR-position) immunology, KI; **Lena Svelander** 2003; scientist biotech company; **Jon Lampa**, **Iva Gunnarsson**, **Lena Björnådal**, **Esbjörn Larsson** 2002-2004– all senior phycisians/clinical scientists Karolinska, **Patrik Stolt** senior physician, Västerås, Sweden, **Anca Catrina**, rheumatologist (Bukarest/Stockholm); **Erik af Klint** 2006**,** rheumatologist, Stockholm

Postdoctoral fellows
Alvin Wells, US; **Alkvin Wanders**, Germany; **Johan Frostegård** Sweden; **Ulf Nyman**, Sweden; **Anders Eriksson**, Sweden; **Marina Korotkova**, Russia; **Marina Smolnikova**, Russia; **Marius Wick**, Austria; **Monica Hermansson**, UK/Sweden; **Mona Widhe**, Sweden, **Sukanyia Raghawan**, India

Published papers
Around 340

Curriculum Vitae for Tomas Olsson

PhD exam: M.D., 1977, and Ph.D,1980 in Medical Sciences (Pathology), University of Linköping, Sweden

Postdoctoral training: 1980-1984 Postdoctoral Training in Neuroimmunology, Dept Neurol Linköping University; 1984 Specialist in Clinical Neurology

Docent/associate professor 1985 in Neurology, Karolinska Institutet

Present appointment:1995- Professor in Molecular Medicine, 1995- Senior staff physician in Neurology, Karolinska University Hospital. Around 70 % of time for research.

Previous appointments

1999-2003	Vice head, Department of Medicine Karolinska Hospital
2003-present	Head of section for CNS research, Karolinska Hospital.
1986-1988	Research position, Swedish Medical Research Council (MFR).
1988-1994	Deputy chair, department of Neurology Huddinge University Hospital
1989-1994	Half time research position (MFR)
1980-1984	Resident in Clinical Neurology, University Hospital, Linköping
1984-1994	Senior Staff Physician, Huddinge Hospital, Karolinska Institutet.
1978-1980	Resident in internal medicine, surgery, psychiatry, Linköping.
1973-1978	Instructor in Pathology, medical studies Linköping University
1972-1973	Instructor in Anatomy Uppsala University

Awards Erik K Fernström prize for medical research, Karolinska institute, 1994

Supervision of graduate students (Ph.D. if not otherwise indicated)
Main supervisor*:* 1.Ernerudh J: 1987-Professor in clinical Immunology, Linköping 2. Strigård K: 1989.-Senior staff surgeon Huddinge Hospital 3. Bakhiet M:1993-Professor in molecular medicine Bahrein 4.Link J. 1994. Neurologist in USA. 5. Mustafa, M.I. 1994-Clinical Immunologist in UAE. 6. Mix E. 1994- associate professor, researcher, Germany.7.Issazadeh S.1996- now professor in Denmark. 8. Weissert R 1999-Associate professor, researcher Tuebingen, Germany . 9. Dahlman, I.1999-Researcher and resident Huddinge Hospital. 10. Wallström E. 2000-resident in neurology-now forms his own group. 11. Lundberg, C. 2000. Employed in the pharmaceutical Industry. 12. de Graaf, K. Stockholm 2001-researcher in Tuebingen Germany. 13. Muhallab, Saad. 2002- started clinical training. 14. Becanovic, K.2003-on post doc abroad. 15. Jagodic M. 2004 (still post doc in my lab) 16. Sheng, J . 2004 (licenciate) 17. Rita Nohra 2006 (licenciate).18. Sana Eltayeb june 2007. 19. Monica Marta sept 2007.

Postdoctoral fellows: Moiz Bakhiet 1996-1998, Bob Harris 1996-2004, Magnus Andersson 1996-2004, Agneta Levinovitz 1996-1999, Anders Svenningsson 1997-2001, Fredrik Piehl 1998-2004, Anna Lobell 2000-2004, Erik Wallström 2000-2004, Lou Brundin 1999-2003, Kristina Becanovic 2004-2005, Margarita Diez 2004-, Olle Lidman 2004-, Maja Jagodic 2005-.

Commissions of trust
Reviewer of Research grants: Wellcome trust (UK), Inserm and ARSEP (France), British and Australian MS foundations, Austrian government, Dutch research council, Italian MS foundation, EU Biomed 2, Swedish foundation for Neurologically disabled, King Gustav V foundation, Swedish foundation for rheumatism. Swedish Research council (Chairman for Neuroscience committe´)
Reviewer of academic positions: Stanford, Harvard, Scripps Clinic, Inserm, Karolinska Institutet, Umeå and Göteborg Universities
Editorial boards: European Journal of Neurology, Scandinavian Journal of Immunology, co-editor in Current Opinion of Immunology

Scientific journal reviewing: PNAS, J. Immunol, J. Neuroimmunol, Scand J Immunol., Eur.J.Neurosci , Brain, Annals of Neurology, Immunology Letters, Neuroscience Letters, Arthritis and Rhematism, Annals of Neurology
Opponent/doctoral thesis scrutiny: Once or twice yearly, so far about 10 times also internationally such as: Bergen and Oslo Norway, Turku and Tampere Finland, Aarhus Denmark, Leuven and Brussels Belgium.

Other activities in academia, society and industry
Academia: 1) Member of the Nobel assembly. 2) Chairman for the Swedish expert committee for MS, 1997-2002, now member of the board of the Swedish MS society and heading the section for the use of disease modifying drugs. 3) Member of the international MS societies. 4) Co-founder of the European school of Neuroimmunology (ESNI), and now member of its scientific and organizational board. 5) Member of the international scientific board of the international congress of Neuroimmunology (ISNI). 6) Member of the international scientific board of the European committee for the treatment of MS. 7) Previous partner in two different EU supported concerted actions on multiple sclerosis with Otto Hommes (Netherlands) and Marco Londei (UK) as coordinators. In addition, I have recently co-ordinated one EU supported concerted action with Hans Lassmann (Vienna) and Christopher Linington (Max Planck, Martinsried) as partners. This program resulted in over 50 publications. I am now partner in two recently funded EC programs; Neuropromise (Francesca Aloisi, Rome, co-ordinator) and EURATools (Tim Aitman UK, co-ordinator).
Invited lectures approximately 30 times.

Society: I frequently give interviews to the public press and media (three- four times a year) on neuroinflammatory diseases such as multiple sclerosis and the post polio syndrome. I or my associated collegues interact frequently with patient organisations for Neurological disease such as Neurologiskt Handikappades Riksförbund and lecture for patients and their spouses/relatives.

Industry: 1) I was scientific consultant for Pharmacia a year period during the 90 ies 2) I was consultant for Astra Södertälje during a 5 year period -1996-2001, during their start up of drug finding studies for MS. 3) I have been ad Hoc consultant/advisor for several companies related to MS treatment: Active Biotech, Teva, Aventis, BMS, Serono, Biogen, Schering, 4) I am presently in the scientific steering board for the testing of a new MS drug in MS for Aventis.5) I have been PI in several phase I, II and III clinical trials of new drugs in MS. I am presently PI for three such studies.

Curriculum Vitae for Mona Ståhle

PhD: Karolinska Institutet, 1989

Post–doc: Washington University, St Louis, USA, 1989-1991

Docent (Associate Professor): Karolinska Institutet, 1994

Current positions: Professor of Dermatology, Karolinska institutet, and senior consultant in dermatology at the Karolinska University Hospital, 1999-

Previous position: resident, junior consultant and senior consultant in dermatology at the Karolinska University Hospital, 1979-

Distinctions: E and I Janzon Prize, for studies on the role of matrix metalloproteinases in skin biology, 1995

Supervision of graduate students (year of completion of PhD)
Anne Birgitte Undén PhD 1997
Margareta Frohm PhD 2000
Lotus Mallbris PhD 2005
Johan Heilborn PhD 2005
Sofia Holm PhD 2005

Supervision of post-doc:s

Mitsuse Inoue	1991-1993
Kevin O´Brien	1999-2001
Fabio Sanchez	2001-
Enikö Sonkoly	2006 -
Gunther Weber	2003 -2006
Lotus Mallbris	2005-
Angela Garcia	2006-2007
Andor Pivarsci	2007-

Boards and Committees

Board of Acta Dermato-Venereologica
Board of Clinical and Experimental Dermatology
Chair Welander – Finsen Foundation
Board of GRAPPA (Group for Research on Psoriasis and Psoriatic Arthritis)
Scientific Chair for World congress on Psoriasis and Psoriatic Arthritis 2009
Medical advisor, Swedish Psoriasis Association

Entrepreneurial activities
Founder of Lipopeptide AB, start-up company in the Karolinska Development portfolio
Inventor in 9 patent applications, 5 of which are in PCT-phase and 3 in a national phase

Appendix C

List of publications

Göran Hansson

Publications 2003-2007

A. Original papers

Caligiuri G, Rudling M, Ollivier V, Jacob M-P, Michel J-B, **Hansson GK**, Nicoletti A: Interleukin-10 deficiency increases atherosclerosis, thrombosis, and low-density lipoproteins in apolipoprotein E knockout mice. ***Mol Med*** 9:10-17, 2003.

Elhage R, Jawien J, Rudling M, Ljunggren HG, Takeda K, Akira S, Bayard F, **Hansson GK**: Reduced atherosclerosis in interleukin-18 deficient apolipoprotein E-knockout mice. ***Cardiovasc Res*** 59:234,240, 2003.

Erl W, Hristov M, Neureuter M, Yan ZQ, **Hansson GK**, Weber PC: HMGCoA reductase inhibitors induce apoptosis in neointima-derived vascular smooth muscle cells. ***Atherosclerosis*** 169:251-258, 2003.

Robertson AKL, Rudling M, Zhou X, Gorelik L, Flavell RA, **Hansson GK**: Disruption of TGF-β signalling in T cells accelerates atherosclerosis. ***J Clin Invest*** 112:1342-1350, 2003.

Tupin E, Nicoletti A, Elhage R, Rudling M, Ljunggren HG, **Hansson GK**, Paulsson Berne G: CD1d-dependent activation of NKT cells aggravates atherosclerosis***. J Exp Med***, 2004;199:417-422.

Robertson AK, Zhou X, Strandvik B, **Hansson GK**: Th2 shift in severe hypercholesterolemia leads to strong IgE responses to an exogenous antigen. ***Scand J Immunol*** 2004; 59:285-293.

Wuttge DM, Zhou X, Sheikine Y, Wågsäter D, Stemme V, Hedin U, Stemme S, **Hansson GK**, Sirsjö A: CXCL16/SR-PSOX is an interferon-γ regulated chemokine and scavenger receptor expressed in atherosclerotic lesions. ***Arterioscl Thromb Vasc Biol*** 2004; 24:750-755.

Hemdahl AL, Falk E, Thorén P, **Hansson GK**: Thrombin inhibitor reduces myocardial infarction in apoE$^{-/-}$ x LDLR$^{-/-}$ mice. ***Am J Physiol*** 2004;287:H872-877.

Persson L, Boren J, Robertson AK, Wallenius V, **Hansson GK**, Pekna M. Lack of Complement Factor C3, but Not Factor B, Increases Hyperlipidemia and Atherosclerosis in Apolipoprotein E-/- Low-Density Lipoprotein Receptor-/- Mice. ***Arterioscler Thromb Vasc Biol.*** 2004, 24:1062-1067.

Zhou X, **Hansson GK**: Effect of sex and age on serum biochemical reference ranges in C57BL/6J mice. ***Comp Med***. 2004;54:176-8.

Edfeldt K, Bennet AM, Eriksson P, Frostegard J, Wiman B, Hamsten A, **Hansson GK**, de Faire U, Yan ZQ: Association of hypo-responsive toll-like receptor 4 variants with risk of myocardial infarction. ***Eur Heart J***. 2004;25:1447-53.

Chen F, Eriksson P, **Hansson GK**, Herzfeld I, Klein M, Hansson LO, Valen G. Expression of matrix metalloproteinase 9 and its regulators in the unstable coronary atherosclerotic plaque. ***Int J Mol Med***. 2005 Jan;15(1):57-65.

Zhou X, Robertson AK, Rudling M, Parini P, **Hansson GK**. Lesion development and response to immunization reveal a complex role for CD4 in atherosclerosis. ***Circ Res*** 2005;96:427-34.

Olofsson PS, Jatta K, Wågsäter D, Gredmark S, Hedin U, Paulsson-Berne G, Söderberg-Nauclér C, **Hansson GK**, Sirsjö A. The antiviral cytomegalovirus-inducible gene 5/viperin is

expressed in atherosclerosis and regulated by proinflammatory agents. ***Arterioscler Thromb Vasc Biol 2005***; 25:e113-6.

Lundberg GA, Kellin A, Samnegård A, Lundman P, Tornvall P, Dimmeler S, Zeiher AM, Hamsten A, **Hansson GK**, Eriksson P. Severity of coronary artery stenosis is associated with a polymorphism in the CXCL16/SR-PSOX gene. ***J Intern Med*** 2005;415-22.

Hemdahl AL, Caligiuri G, **Hansson GK**, Thoren P. Electrocardiographic characterization of stress-induced myocardial infarction in atherosclerotic mice. ***Acta Physiol Scand*** 2005;184:87-94.

Elhage R, Gourdy P, Jawien J, Brouchet L, Castano C, Fievet C, **Hansson GK**, Arnal JF, Bayard F. The Atheroprotective Effect of 17β-Estradiol Depends on Complex Interactions in Adaptive Immunity. ***Am J Pathol*** 2005;167:267-74.

de Graaf KL, Berne GP, Herrmann MM, **Hansson GK**, Olsson T, Weissert R. CDR3 sequence preference of TCRBV8S2(+) T cells within the CNS does not reflect single amino acid dependent avidity expansion. ***J Neuroimmunol*** 2005;166:47-54.

Pekna M, Persson L, Boren J, Nicoletti A, **Hansson GK**. Immunoglobulin treatment reduces atherosclerosis in apoE-/- LDLR-/- mice via the complement system. ***Clin Exp Immunol*** 2005;142:441-5.

Hemdahl AL, Gabrielsen A, Zhu C, Eriksson P, Hedin U, Kastrup J, Thoren P, **Hansson GK**. Expression of Neutrophil Gelatinase-Associated Lipocalin in Atherosclerosis and Myocardial Infarction. ***Arterioscler Thromb Vasc Biol*** 2006;26:136-142.

Bäck M, Bu DX, Bränström R, Sheikine Y, Yan ZQ, **Hansson GK**. Leukotriene B4 signaling by means of NF-kB-dependent BLT1 receptors on vascular smooth muscle cells in atherosclerosis and intimal hyperplasia. ***Proc Natl Acad Sci USA*** 2005; 102:17501-6.

Sandberg WJ, Yndestad A, Oie E, Smith C, Ueland T, Ovchinnikova O, Robertson AK, Muller F, Semb AG, Scholz H, Andreassen AK, Gullestad L, Damas JK, Froland SS, **Hansson GK**, Halvorsen B, Aukrust P. Enhanced T-cell expression of RANK ligand in acute coronary syndrome. Possible role in plaque destabilization. ***Arterioscler Throm Vasc Biol***. 2006;26:857-63.

Zhou X, Robertson AK, Hjerpe C**, Hansson GK**. Adoptive transfer of CD4+ T cells reactive to modified low-density lipoprotein aggravates atherosclerosis. ***Arterioscl Thromb Vasc Biol*** 2006;26:864-70.

Wang Y, Gabrielsen A, Lawler PR, Paulsson-Berne G, Steinbruchel DA, **Hansson GK**, Kastrup J: Myocardial gene expression of angiogenic factors in human chronic ischemic myocardium: influence of acute ischemia/cardioplegia and reperfusion. ***Microcirculation***. 2006;13:187-97.

Tran PK, Agardh HE, Tran-Lundmark K, Ekstrand J, Roy J, Henderson B, Gabrielsen A, **Hansson GK**, Swedenborg J, Paulsson-Berne G, Hedin U. Reduced perlecan expression and accumulation in human carotid atherosclerotic lesions. ***Atherosclerosis***. 2007: 190:264-70

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(Discovery that regulatory T cells inhibit atherosclerosis and act via TGF-b; cited 30 times).

Cecilia Söderberg-Nauclér

Publications 1999-2007*
(three more years have been added to the list due to maternity leave with three children)

A. Original papers

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Marie Wahren-Herlenius

Publications 2003-2007

A. Original papers

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VETENSKAPSRÅDET
THE SWEDISH RESEARCH COUNCIL

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2007-11299-54784-39

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Appendix U

Requirements for implementation

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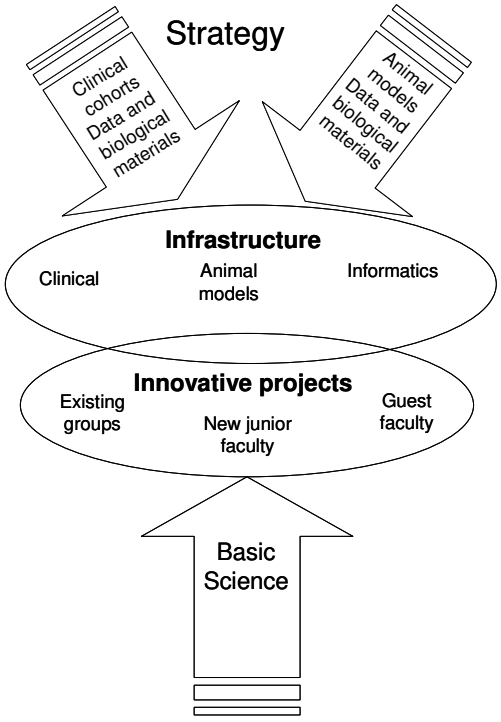
Appendix U - CERIC

Organisation and implementation of the research plan

The organisation of CERIC is designed to fit the specific aims of the program, i.e. to combine the availability of extensive clinical materials and data with an expanding excellent experimental environment. We have been convinced that experimentalists wanting to understand the molecular pathogenesis of a complex disease, in our case the inflammatory component of cardiovascular diseases (CVD), must have access to an extensive and well characterised population of patients and "pre-patients". Our consortium has access to unique, large longitudinally followed patient cohorts, in which epidemiological tools can be used to determine genetic, environmental and immunologic determinants of disease. Unique biobanks containing human pathological tissue (surgical specimens) that are linked to clinical databases have also been generated by consortium members and will be made available within CERIC. The organisation of the CERIC center is aimed to make these cohorts and the data attached to them, as well as appropriate animal models, available for research on the molecular pathogenesis of cardiovascular disease and inflammation. The combined environment will be designed to offer these opportunities for existing groups and their junior faculty, for new junior faculty recruited into the program, and for guest faculty that can utilise the access to clinical materials and data, and provide new ideas and molecular technologies to our environment.

Illustration of the interactions between existing and novel components of the environment



The presently available structure including investments from KI and major funds: Research on the role of inflammation in CVD is mainly located at two physical KI units, (1) at the Centre for Molecular Medicine embedded in the Karolinska University Hospital Solna and (2) in the Department of Medical Biochemistry and Biophysics (MBB) at the campus of

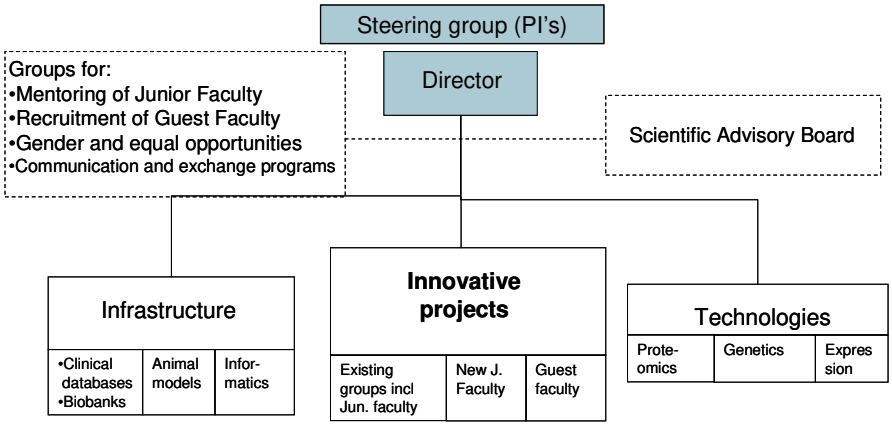
KI (some 500 meters from CMM). Groups working at CMM are strongly affiliated with clinics with responsibility for cardiovascular and inflammatory diseases (cardiology, vascular surgery, rheumatology, dermatology, neurology). The clinical investigators (5 of the CERIC PIs) in these units are also responsible for national networks that collect clinical information and biobanks from individuals with cardiovascular and inflammatory diseases. Substantial KI as well as external funding is presently invested in making the patient information available (KI Health informatics centre), providing high quality biobanking (KI Biobank), and constructing national network (coordinated from KI) for large patient cohorts (Combine consortium, funded by VINNOVA and others). Groups working at MBB and CMM have built units for experimental models of cardiovascular and inflammatory diseases, and a new animal facility (investment 100 MSEK by KI) has recently been started at MBB and will serve as the main physical location for the new central facility for mouse models of CID and CVD.

The infrastructure of the new centre (CERIC) will be organised to make optimal use of the two major resources of our consortium, i.e. the clinical cohorts/genetic epidemiology and the rodent models. New investment will be made in informatics in order to create systems where information of genotypes, phenotypes and immunity in different CID and CVD can be compared between different human diseases and relevant rodent models. A logistics system linked to the new informatics systems will be designed to enable retrieval of appropriate biological materials in biobanks as well as in clinics and animal facilities.

Innovative projects: A number of separate projects will be carried out with the aim of addressing the common goals of the centre while making efficient use of its infrastructure. Laboratory space will be made available at CMM and MBB for newly recruited junior faculty as well as for guest scientists, who will be able to utilise the combined human and rodent materials as well as the collaborative networks. We will start a special program for mentoring junior faculty towards research leadership. We will also create a special program for visiting scientists, who may stay from weeks to years, in order to address scientific problems within CID and CVD, by using our unique cohorts, biomaterials and network. These guest scientists will in turn, be able to add ideas and methods to the CERIC environment.

Management structure: The management of the centre will be designed to allow efficacy in building the infrastructure in collaboration with several existing initiatives, and help identifying and recruiting junior faculty members and guest faculty able to perform innovative projects. The 10 PIs will constitute a steering committee that will take the major decisions on funding of specific projects and on strategic investment in infrastructure.

Outline of the management structure:



Budget

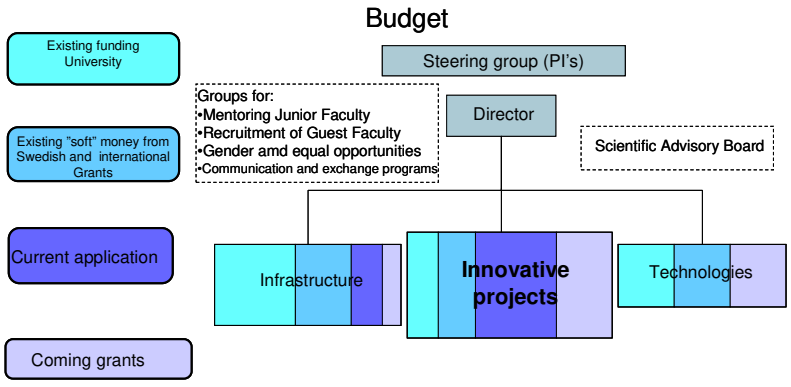
Funding will be used for two major purposes:

1) Investments in our infrastructure, in order to optimize availability of patient materials and mouse models for hypothesis driven research in inflammation and CVD. Thus, an informatics system will be built which allows identification of common genes and molecular pathways between different CID, CVD and relevant rodent models of these diseases. Strategic investments will also be made for genotyping and biomarker studies of patient cohorts, and for creating mouse models of inflammation-dependent CVD, by breeding strains such as the *Apoe* $^{-/-}$ mouse onto various CID models.

2) Resources will be allocated for specific support, for salaries as well as laboratory costs, within the various innovative projects. These funds will be used mainly for junior faculty members and postdocs. A budget will also be available to help recruiting guest scientists, mainly to support laboratory costs (salaries will normally be covered from home institutions).

The budget is constructed to give maximum leverage from the Linnaeus center investment, making use of existing investments (from KI and from Foundations), and enhancing further investments, once the Linnaeus grant is provided. One major source of such additional contributions would be grants to enhance and enable recruitment of guest scientists to our special ”guest scientist facility”.

Schematic budget overview



More precise budget:

For the first three years **(all sums valid on annual basis)**

A. From the current application for the Linnaeus grant (the infrastructure and co-funding from KI for whole period):

- **Infrastructure**
- Coordination of clinical databases and biobanks: 0.3 MSEK
- New rodent models combining CID and CVD mouse models: 1.4 MSEK
- Informatics combining information from human disease and rodent models: 0.5 MSEK

Innovative projects:

- Salaries and research support for junior faculty and postdoctoral fellows: 6.0 MSEK

- Support for guest faculty: 0.4 MSEK

Seminars and mentoring program:

- Seminars and annual meetings for the consortium: 0.2 MSEK
- Mentoring program 0.2 MSEK

All sums include 18% overhead.

B. From previously existing grants:
B1. Karolinska Institutet (specific co-funding)

Infrastructure

- Coordination of clinical databases and biobanks: KI Biobank: 4.0 MSEK (specifically for CID and CVD)
- New rodent models combining CID and CVD mouse models: Mouse facility (at MBB): 4.0 MSEK (specifically for this project)
- Informatics combining information from human disease and rodent models: KI Health Informatics Centre (specifically for CID and CVD): 2.0 MSEK

Innovative projects

- Recruitment package for Rikard Holmdahl and collaborators (specifically for this project): 5.0 MSEK
- Faculty positions – 3.0 MSEK

In addition, the projct will benefit from KI's investments in:

- Proteomics center: 1.0 MSEK
- MAF (mutation analyses facility): 1.0 MSEK
- Expression array facility: 0.5 MSEK

B2. Existing VR grants (for PI:s and junior faculty associated with PI:s today)

Göran Hansson – 1700 kSEK/år
VR grants for faculty associated with the Hansson Group:
Gabrielle Berne – 250 kSEK/year
Z-Q Yan – 250 kSEK/year
Total Göran Hansson group: 2200 kSEK

Anders Hamsten – 900 kSEK/år
VR grants for faculty associated with the Hamsten Group: 1530 kSEK/år
Total Anders Hamsten group: 2430 kSEK/year

Lars Klareskog – 650 kSEK/year
VR grants for faculty associated with the Klareskog Group:
Helena Erlandsson Harris – 300 kSEK/year
Ingrid Lundberg – 674 kSEK/year
Per-Johan Jakobsson – 250 kSEK/year
Vivianne Malmström – 275 kSEK/year
Johan Askling – 275 kSEK/year
Johnny Lorentzen – 345 kSEK/year

Leonid Padyukov – 300 kSEK/year
Total Lars Klareskog group: 3069 kSEK/år

Jesper Hæggström – 700 tkr/year
Olof Rådmark – 650 tkr/year
Total Jesper Haeggström group 1350 tkr/year

Tomas Olsson – 1600 kSEK/year
VR grants for faculty associated with the Olsson Group:
Fredrik Piehl- half time research position 410 tkr
Fredrik Piehl 225 tkr
Robert Harris 460 tkr
Erik Wallström 50 tkr)
Total VR-grants Tomas Olsson group: 2845 tkr/year

Cecilia Söderberg Nauclér - 550kSEK/year
Marie Wahren Herlenius – 1047 kSEK/year research position + 600 kSEK/year
Birgitta Agerberth – 275 kSEK/year
Rikard Holmdahl - 1260 kSEK/year
Mona Ståhle – 350 kSEK/year

Total VR-grants within the consortium: 14 081 kSEK/år

B3. Major grants from other Foundations (Swedish and International):

- **Combine** (grant from VINNOVA, Swedish Foundation for Strategic Research and 4 other Swedish governmental agencies and foundations) on a national program on chronic inflammatory diseases, aimed at also creating and coordinating national clinical databases and biobanks for CID, and in particular rheumatic diseases. PI Lars Klareskog: 12 MSEK annually for 5 years (from 2008)
- **Chronic inflammation. CIDaT** (grant from the same group of foundation) for research on new diagnostic tools and targets for drug development against inflammatory diseases (PI Jesper Haeggström) 2 MKr annually for 5 years (from 2008)
- **European Commission FP6 grants** (to end of 2008):
- European Vasc Genomics Network, G K Hansson partner, 0.4 MSEK.
- EICOSANOX integrated project on autacoids in cardiovascular and pulmonary disease, JZ Haeggström coordinator, GK Hansson partner; 3.9 MSEK annually 2008-9.
- PROCARDIS, A Hamsten partner, 3.5 MSEK annually 2007-2011.
- **European Commission FP7 grants** (starting 2008)
- AtheroRemo collaborative project approved, contract not yet signed. If budget approved, KI partners Hansson and Haeggström will receive 3 MSEK annually 2008-12.
- **Leducq Transatlantic Network of Excellence on Atherothrombosis** (2006-2010) KI partners Hansson and Hamsten receive 1.2 MSEK annually.
- **AutoCure FP6 grant for postgenomic research in Rheumatology** (2006-2011); European coordinator;: Lars Klareskog (total 11MEuro; KI part 1.5 MSEK yearly)
- **Imagen (NIH) (2006-2009); Studies on MHC genes in RA and other inflammatory diseases:** Co-pi: Lars Klareskog; 0.7 MKr yearly

C. Expected funding if the Linnaeus grant for CERIC is approved:
Guest scientist resources from other universities: (4 MSEK annually estimation)
Technology investments – from collaborations with several different national and international institutions

- Genome Institute of Singapore (for large scale genotyping of RA, IBD and psoriasis cohorts) 10 MSEK annually (estimation)
- Human Proteome Resources (KTH), Increased utilisation of existing resouces that receive large scale funding from the Wallenberg Foundation.
- Proteomics (MS facility) supported by KI/SLL (4 MSEK annually)

Appendix U - commitment by the university						N.B. All financial figures should be expressed in million SEK					
	2008*	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018*
1. Grant applied for	5	10	10	10	10	10	10	10	10	10	5
Commitment by the University											
Infrastructure											
Clinical databases and biobank	2	4	4	4	4	4	4	4	4	4	4
Rodent models	2	4	4	4	4	4	4	4	4	4	4
Informatics	1,2	2,4	2,4	2,4	2,4	2,4	2,4	2,4	2,4	2,4	2,4
Recruitment package	5	5	5	5	5	0	0	0	0	0	0
Faculty positions	3	3	3	3	3	3	3	3	3	3	3
Total University commitment	13,2	18,4	18,4	18,4	18,4	13,4	13,4	13,4	13,4	13,4	13,4
University commitment as a percentage of grant applied for											
In addition, the Centre will benefit from KI:s investments in the core facilities listed below											
	Annual investment by KI (million SEK)										
Proteomics center	1	2	2	2	2	2	2	2	2	2	2,0
MAF (mutation analyses facility)	1	2	2	2	2	2	2	2	2	2	2,0
Expression array facility	0.5	1	1	1	1	1	1	1	1	1	1,0

Explanations
1. Linné grant per year.
2. Existing faculty positions funded by KI. Persons entering pension have been taken into account.
3. Strategic elite researcher positions and other strategic funds from Karolinska Institutet as well as ALF funds.
4. Premises, based on the area utilised by research groups within the centre.

Karolinska Institutet's processes for support and follow-up of the centre's management
The processes for support and follow-up involve direct monitoring by the KI Board of Research and monitoring by an external scientific advisory board (SAB).

The KI Board of Research will establish a plan for the annual follow-up of the centre's activities. The Board will require that the centre submits an annual report within a fixed period after the end of each 12-month term. The report will include an internal assessment of scientific achievements with a publication (papers, seminars and conferences) list, milestones and deliverables achieved, a report on the dissemination plan, a gender equality report, an updated risk/contingency plan, and the centre's financial status including all sources of internal and external funding. The annual report will also include revised scientific and financial plans for the following period.

In addition, the SAB will submit, on an annual basis, a report of their assessment of the scientific progress of the centre, including suggestions that the SAB believes valuable or necessary. The report will be submitted both to the management of the centre and to the KI Board of Research.

Furthermore, the KI Board of Research will support and supervise hearings and workshops with the centre every three. The aim of these hearings and workshops is to harmonise and develop joint strategic goals.

Prioritisation of inflammation and cardiovascular research from Karolinska Institutet, and specific support for the CERIC application

Inflammatory diseases, including those specifically addressed in the CERIC application, are included in the highly prioritised "inflammation" area in KI. This area is one of the prime priorities at KI, both regarding basic and clinical research. Karolinska has a strong tradition in the field, represented both by research in the prostanoid field, in immunology and in translational research related to inflammatory and cardiovascular diseases. Through a series of strategic recruitments over several years, including the recent recruitment of professor Rikard Holmdahl from Lund, the area has been made even stronger. The CERIC application represents a major milestone from KI in this respect as this application represents the major lines of excellent research on inflammation at KI. Thus, it is of major and strategic interest for KI to support research described in CERIC. KI has already undertaken such support by the substantial support to Rikard Holmdahl and his group, and KI is also committed to continue and extend this support to all fields described in CERIC. Of particular importance will be the support to the recently inaugurated animal facility (investment 100MSEK), the KI biobank, and the genetic and expression array facilities at KI.

The research groups in CERIC are already co-localised in the two major centres for inflammation research at KI, i.e. at the Center for Molecular Medicine, and at the Department for Medical Biochemistry and Biophysics. The work in these two locations is already well coordinated, with biochemical and mouse work centered around MBB, and translational and clinical science excellently located at the CMM with a very close relationship to patient care and access to patient-derived materials and clinical scientists. The steering board of CERIC will, together with KI, develop a close collaboration between these two hubs for translational and basic science further.

The groups in CERIC already harbour a substantial number of junior faculty, with existing VR grants and potentials for further growth into excellent international science leaders. We will develop an extensive program for the development of scientific and leaderships skills for this existing young faculty as well as for junior faculty that will be recruited to CERIC from the international scene; We are convinced that it will be possible to recruit very excellent young scientists to the environment where we both have access to unique patient materials and animal models and to an inspiring mix of already collaborating senior scientists.

In addition, we intend to create a special laboratory facility for "guest faculty". The idea behind this, is that we want to use the unique potentials for focused research on disease mechanisms, that are provided from our patient cohorts, and create a laboratory where the guest scientists have easy access to these materials as well as to relevant animal models. Here these scientists will be able to work for shorter or longer times (weeks to years) and bring with them ideas and technologies for dissemination to our faculty. We believe that we will be in a position to recruit extremely excellent international faculty to this laboratory and to the general KI environment, where CERIC and KI will provide laboratory facilities and access to patients and mouse models, but where we expect salaries for faculty to come from their home institutions (sabbaticals etc).

Finally, the CERIC investigators will work together with KI and use the existing excellent climate and tradition of collaboration between the CERIC group members, and create an even more efficient management structure. This will ensure that projects are evaluated, that communication works properly in the consortium, and most of all that a creative culture is being maintained and developed so that junior and senior faculty can get the most from the unique setting for translational research in inflammation that is offered at Karolinska Institutet and the Karolinska University Hospital.

VETENSKAPSRÅDET
THE SWEDISH RESEARCH COUNCIL

Kod
2007-11299-54784-39

Name of applicant
Wallberg Henriksson, Harriet

Date of birth
560525-1924

Title of research programme

Appendix V

Other information

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Strategy and action plan for Equal Opportunities within CERIC

CERIC Equal Opportunities Strategy

In seeking to provide equal opportunities, CERIC is concerned with the issues of equality and gender, ethnic and religious diversity, accessibility and participation for persons with disabilities, and equal rights for individuals with different sexual orientations.

An active endeavour to bring about equal opportunities enhances awareness in the organisation, and increases the quality of activities. Equal opportunities help make the scientific environment an attractive and conducive work setting. This is crucial to recruit and keep innovative and creative people, and to promote an environment that transcends conventional boundaries.

Commitment from the leadership of an organisation is essential to the success of positive action initiatives aimed at creating and maintaining equal opportunities in areas of employment (1). The CERIC steering group encompassing the ten PIs of this application will be responsible for and actively support the programs which will ensure that actions, norms and routines reflect an attitude characterised by respect for individuals and their varying circumstances.

Vision and Goals

- CERIC aims at creating a working environment that makes full use of the resources contributed from internal and external funding sources, by students, scientists and employees with different backgrounds, life situations and skills.

- Recruitment and advancement processes should be non-discriminatory.

- New employees should be received in such a way that they all feel welcome.

- Programs within CERIC should formally offer equal opportunities and be characterized by accessibility, preparedness and consideration for the needs of various participants.

- Equal opportunities should prevail in terms of employees' working conditions, salaries, influence, career prospects and scope for combining a professional career with responsibility for the home and family.

Current situation within CERIC

A specified goal within the Karolinska Institute is to obtain a 60/40 balance between genders at the different academic levels. The current representation of men and women at different academic levels within CERIC is a result of long term visionary programs and active efforts from leading scientists within the CERIC consortium to promote equal opportunities (2-4), and is close

to those set goals at all levels (**Table 1**). A further verification of the ability of PIs within CERIC to create an environment characterized by equal rights is the **Stockholm County Equal Opportunities Award 2006** given to the Rheumatology Unit headed by Lars Klareskog.

Table 1. Number and distribution according to sex among scientists at different academic levels within CERIC.

Academic position	Total no in CERIC	women	men
Professor	11	36%	64%
Assoc professor	27	48%	52%
Junior scientist/ postdoc	61	59%	41%

CERIC offers an international environment, and with a proven track record of fair and just evaluation of the individual, in addition to being a leading environment for research on CVD and CID, has attracted many non-Swedish scientists and clinicians. Nationalities currently represented among scientists within CERIC Denmark, Germany, United Kingdom, The Netherlands, Russia, Rumania, Lithuania, Serbia, China, India, Iran and Iceland. These scientists and clinician-scientists are found at both junior scientist/postdoc levels and in tenured positions.

The Equal Opportunities Action Plan

To maintain and continue to develop an environment that provides equal opportunities as described in our vision and goals, CERIC will establish an Equal Opportunities Program. Projecting a positive image and highlighting successful examples as well as mentorship have been identified as important means to encourage under-represented groups in pursuing a scientific career (5,6). The program will therefore contain the following such components and other points of action:

- A bi-annual, all personnel inclusive questionnaire to identify barriers to equal opportunities experienced in the environment. This questionnaire will also contain questions on initiatives aimed at promoting equal opportunities and serve as the follow-up and evaluation instrument of the initiatives.

- A formalized mentorship and career support program aimed at the junior scientists within the environment. The program will run annually and each round last one year. The program will include both mentor-mentee interactions, as well as interaction with the whole group admitted to the program that particular year.

- A seminar series with highly successful international scientists from groups traditionally under-represented at the senior scientific level. The scientists will be invited both for a

traditional seminar on their studies, but also for round-table discussions with the junior faculty on what obstacles they experienced in their careers, and how they handled them.

- Development of effective publicity material describing the work of the scientists within CERIC, including scientists of under-represented groups, to be used for mounting exhibitions and on the CERIC webpage.

- Education of recruiting and seminar committees on equal opportunities. Education will be provided in the form of open lectures given by invited speakers, eg the Equal Opportunities co-ordinator at KI

- Open and widespread advertisement of all positions and funding announced by CERIC

- Adding a welcoming positive action statement to under-represented groups in advertisement of positions and funding with CERIC

Responsibility and Organisation
An executive organization to handle seminars, mentor program and education will be built, but decision making and policy questions will be handled directly in the CERIC steering committee to emphasis the importance of these matters in the organisation. Marie Wahren-Herlenius, vice-coordinator of CERIC, who has experience of developing similar programs within the Junior Faculty organisation of the Karolinska Institute will be the chair of the Equal Opportunities Executive Program of CERIC.

Evaluation

A continuous in-built evaluation of the program will be provided by the bi-annual questionnaire described above. The results will be compiled and presented to the CERIC steering committee, which will decide on further actions or development of the program based on the questionnaire results to achieve the set goals for equal opportunities. Creative strategies to achieve these goals are also welcomed from all CERIC staff.

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Dnr
2007 -

Co-ordinator/Repr.of University
Wallberg Henriksson, Harriet

Date of birth
560525-1924

Reg date
2007-11-06 12:58:21

Title of research programme

VR

VR-M

*Linnéstöd och Berzelius Center
*Medicin
Karolinska Institutet
2008-07-01 -- 2018-06-30

Appendix S

Signatures

2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
4500	9000	9000	9000	9000	9000	9000	9000	9000	9000	4500

Repr.of University

Date

Clarifi cation of signature

Telephone

Vetenskapsrådets noteringar
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