

Dermato-Venereological Research at Karolinska Institutet, Stockholm

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Research at the Unit of Dermatology and Venereology, Karolinska Hospital

Dermatological research is facing similar challenges to those in other areas of biomedicine. While the genetic bases for several rare diseases have been unravelled in recent years, we still struggle to comprehend the basic biology and pathology of the common diseases. Increasing our understanding of underlying mechanisms will facilitate the development of more specific therapies and even cure, which is the ultimate goal of research. In recent years, we have experienced a promising development towards more powerful and targeted treatments in dermatology, as a result of a successful combination of basic and clinical research.

At the Karolinska Institutet, Dermatology and Venereology holds a solid position in both research and education. Large-scale genetic and epidemiological projects have been formed around chronic inflammatory skin diseases, and skin cancer is being studied in collaboration with international cancer networks. The department of dermatology provides substantial space for experimental research in a basic science building back-to-back with the clinical facilities, which enables close contact between hospital staff and scientists and facilitates working at both places and a translational scientific approach. Thus, there are presently two dermatology residents in our department who have 50% positions from Vetenskapsrådet, allowing them to develop their basic scientific career in parallel with clinical training. In the venereological field, research has in many clinics been focused on urethritis. *Mycoplasma genitalium* has been detected as an important bacterium but also other agents that may be of significance for non specific urethritis, have been studied. Research has also been conducted on viral infections, such as HPV and HSV. This will be further discussed in a forthcoming article in *Forum*.

Our ongoing projects are shown below:

Psoriasis: genetics, epidemiology and immunobiology (Mona Stähle)

This is a large, long-term study aimed at understanding the multiple facets of this complex disease. We are

engaged in elucidating the genetic background of psoriasis, and have recently completed a genome-wide association study in our patients. We are interested in long-term development in disease, and this year we have started a 10-year follow-up of patients captured at disease onset. Our aim is to identify biomarkers; genetic factors and others in serum, plasma and skin for different phenotypes; development of arthritis, overall disease severity, comorbidities. MicroRNAs (miRNAs) are recently-discovered molecules that regulate at least 60% of our genes and probably control functional pathways. We have identified differentially expressed miRNAs in psoriasis and are currently studying a subset of these functionally. miRNAs are also candidate biomarkers. The immunopathology of psoriasis is key to understanding the disease, and we have initiated a programme to characterize morphologically and functionally the cellular infiltrate in psoriasis skin during the different phases of disease activity. The development of systemic targeted treatments will contribute to our understanding of psoriasis. One important aim is to identify biomarkers to predict response to treatment, and during the past year we have established a research bio-bank, with samples from a majority of patients receiving systemic treatments in the region.

Immunobiology of psoriasis (Liv Eidsmo)

The current work aims at understanding mechanisms of T-cell inflammation in the skin during initiation, maintenance and recurrence of psoriatic skin inflammation. We propose that skin-resident T cells remain in healed skin and that recurrent disease is a result of local dendritic cell and T-cell interactions. We will investigate whether subclinical viral infections trigger and maintain chronic skin inflammation in psoriasis through local T-cell stimulation by infiltrating dendritic cells (DCs). This project utilizes the Stockholm Psoriasis bio-bank, which includes 800 patients to date. Through the cohort we have access to cryopreserved skin and serum from clinically well-characterized manifestations of psoriasis, and we can follow individual patients during different phases of the disease.



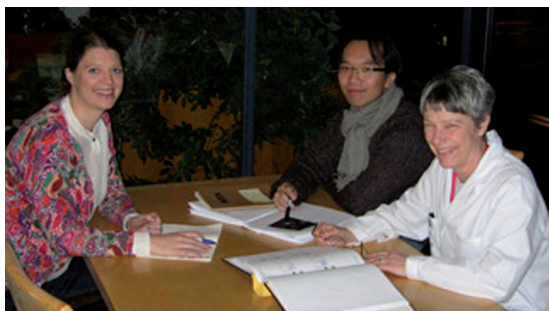
Prof. Mona Stähle, Head of the Unit of Dermatology and Venereology.



Klas Nordlind, Professor of Dermatology and Venereology.



Carl-Fredrik Wahlgren, Professor of Dermatology and Venereology.



A research meeting: Liv Eidsmo, Stanley Cheuk and Kerstin Bergh.

miRNA research (Andor Pivarcsi and Enikő Pibarcsi)

Our primary interest is the role of miRNAs in the pathogenesis of chronic skin inflammation. miRNAs are a recently discovered class of post-transcriptional regulators of gene expression with critical functions in health and disease. Atopic eczema is one of the most common chronic inflammatory skin diseases, particularly in industrialized societies, with a current lifetime prevalence of 10–20%. Until recently, very little was known about their expression and function in human skin and inflammatory diseases. We recently performed the first global analysis of miRNA expression profile in healthy skin, atopic eczema and psoriasis skin and identified a set of miRNAs that may play important roles in skin inflammation. We are using miRNA-specific quantitative real-time polymerase chain reaction (PCR) and *in situ* hybridization to analyse miRNA expression in healthy or inflamed skin samples. *In vitro* models are being used to study the function of miRNAs, using miRNA precursors to overexpress them or inhibitors to interfere with them. We predict miRNA target genes using computational approaches and verify them with 3'UTR Luciferase reporter assays. To explore the function of selected miRNAs in the skin under healthy and pathological conditions, we are systematically investigating their role in the pathogenesis of disease and *in vitro* and *in vivo* disease models using global approaches, such as miRNA expression profiling.

Atopic eczema: studies of genetic and environmental factors, clinical manifestations, co-morbidity and prognosis (Carl-Fredrik Wahlgren)

Atopic eczema (AE) is a pruritic, chronically relapsing, inflammatory skin disease that affects ~20% of Swedish children and a proportion of adults. Its prevalence in children has doubled since the 1970s. The reason for this is unclear. AE is a multifactorial disease caused by a combined influence of genetic and environmental factors. The present project aims at identifying genetic and environmental factors of importance for AE: onset, clinical manifestations, quality of life, co-morbidity and persistence. The study is based on a birth cohort of children born in Stockholm, the BAMSE cohort, as well as more than 500 families with at least two siblings affected by AE. The work is interdisciplinary, comprising collaboration with many research groups, national and international. The genetic studies are

supervised by Maria Bradley, and one focus here is to unravel the different flaggrin mutations in different populations and in relation to phenotypes of AE.

Hereditary angioedema in Sweden (Sweha; Carl-Fredrik Wahlgren)

Hereditary angioedema is a very rare autosomal-dominant disease caused by quantitative or qualitative C1-inhibitor deficiency and the generation of vasoactive inflammatory mediators, especially bradykinin. It presents with recurrent attacks of swelling of the skin and of the mucous membranes in the gastrointestinal tract and airways. Abdominal pain is a frequent and disabling symptom. Angioedema of the larynx can be life-threatening. The diagnosis is established with laboratory tests. Several treatments are currently available. The aim of the study is to set up a Swedish population-based registry (Sweha-Reg) with data on heredity, morbidity, mortality and treatment, and a bio-bank (Sweha-Bank) for biochemical and genetic analyses. The project is executed at the Karolinska Institutet and led by Carl-Fredrik Wahlgren with a network of Swedish physicians.

Wound healing (Mona Stähle)

Wound healing is a fundamental biological process that entails a complex coordination of inflammation, cell migration, proliferation and tissue remodelling. How this physiological process is controlled and executed is insufficiently understood, and mechanisms leading to impaired wound healing and chronic ulcers even less so. For the past few years we have focused on the role of the human cathelicidin protein, hCAP18/LL-37 in this process. We have shown that hCAP18/LL-37 is lacking in chronic ulcers and is upregulated during normal physiological wound healing. The project is, at present, focused on studying molecular pathways involved in hCAP18 signalling and its role in cell migration and proliferation. One aim of this project is to develop treatments for impaired wound healing.

Skin barrier (Lars Norlén)

Our research group is focused on the biophysical understanding of the human skin barrier and its fundamental role in skin disease. Ongoing projects are addressing the structural organization and function of the stratum corneum extracellular lipid matrix, membrane transformations involved in skin barrier formation, desmosomal reorganization during epidermal differentiation, stratum corneum cohesion and desquamation, and keratin intermediate filament structural organization and reorganization during epidermal differentiation. At present, our main experimental techniques are cryo-electron microscopy (CEMOVIS) and tomography (TOVIS) on vitreous skin sections.

Skin cancer (Bernt Lindelöf)

There are numerous studies of these forms of skin cancer. One group of patients who have an extremely high risk of getting skin cancer is organ-transplant recipients. This group of patients have, for example, a 100-fold (10,000%) increased risk of developing squamous cell carcinoma compared with the normal

population. The Swedish transplant cohort, at present comprising approximately 7,000 patients, is the base for several of our studies. The immune system is suppressed by medication in these patients in order to prevent rejection of new organs. The effect of this immunomodulation on carcinogenesis is being studied, together with co-factors, such as virus infections (human papilloma virus and cytomegalovirus). In addition, genetic studies on cancers are being performed. Basal cell carcinoma of the skin, the most common form of cancer, all organs included, is presently being investigated in a large epidemiological study. Approximately 100,000 patients from the Swedish Cancer Registry with basal cell carcinoma are included. Having a basal cell carcinoma is an indirect sign of having been exposed to the sun a lot in the past. Sun exposure is necessary to produce vitamin D in the body, and recent research has indicated that vitamin D is protective against cancer and certain other diseases and conditions. Thus, the risk of having other forms of cancers before the basal cell carcinoma is calculated in order to provide some new information on the importance of sun exposure. Lentigo maligna is malignant melanoma *in situ*. Grenz ray therapy (ultra soft X-rays) is used to treat these lesions with good therapeutic and cosmetic results. Up to 300 patients have been treated and will undergo long-term follow-up.

Neurocutaneous science (Klas Nordlind group)

The skin may be considered as a mirror of the soul. Light from the outside world passes through the layers of epidermal cells, the first line of immune defence, and then interacts with the neuroendocrine system. The dynamic interactions between these two extensive systems involve many molecules, among which serotonin (5-hydroxytryptamine; 5-HT) and the tachykinin family may be of major importance. Our research is focused on studying the expression of these ligands and their receptors in the most common chronic inflammatory skin diseases, atopic eczema, allergic contact eczema and psoriasis, as well as in sensitive skin and pruritus. The research is focused on patients at our Neurocutaneous Reception. In addition, murine models with induced allergic contact eczema (Balb/C) and atopic dermatitis (NC/Nga), are being used. In these models the brain is also studied.

Hidradenitis suppurativa and impedance (Lennart Emtestam)

In skin, as in other tissues, pathophysiological changes are related to changes in electrical impedance. In collaboration with Stig Ollmar, the group uses different types of experimental skin reactions as models for the studies. The aim is to determine whether impedance methods can function as diagnostic tools. Furthermore, the focus is on skin cancer, and multi-centre studies on malignant melanoma are on-going. Hidradenitis suppurativa is a relapsing disease of apocrine gland-bearing areas, affecting 2–4% of all fertile women. Under the supervision of Jan Lapins, the group focuses on studies of aetiopathogenesis, new treatment modalities and better classification of the disease. In 2010, Karin Sartorius defended her thesis “Hidradenitis suppurativa – clinical studies with focus on evaluation”.

Research at the Unit for Dermatology, Institution for Clinical Science, Karolinska Institutet Danderyd Hospital (in cooperation with Centre for Molecular Medicine and Unit for Epidemiology, Karolinska Institutet, Solna)

Epidemiology, co-morbidity and pathomechanisms of cutaneous lupus erythematosus (Ass Prof Filippa Nyberg)

Lupus erythematosus (LE) is an autoimmune disease with a wide range of clinical manifestations. Sun exposure is an evident exogenous trigger of both cutaneous (CLE) and systemic LE (SLE), and CLE resembling skin lesions can be induced experimentally for research or clinical purposes using artificial ultraviolet radiation (UVR) sources.

During the years 2003–2011, three PhD studies with their clinical platform at Department of Dermatology, Danderyd Hospital have focused on epidemiology and pathogenesis of CLE.

Our research network has formed around translational research on CLE. Our set-up allows swift movement from the patient to the laboratory, as well as to patient registries, including the newly established open-care registry of Sweden.

The incidence of CLE in Sweden has recently been shown by us to be 4.0/100,000, with a female:male ratio of 3:1. CLE can be further subdivided into acute CLE, subacute CLE and chronic CLE. From registry studies, we estimated the incidence of SCLE in Sweden to be 1:100,000. In a clinical follow-up of these patients, drug-induced SCLE was found in a few patients who were Ro/SSA-positive but otherwise healthy at baseline. Clinical and epidemiological studies in recent years have suggested that malignancy is strongly associated with chronic inflammation. Among 3,663 patients diagnosed with CLE in our Swedish, population-based registry studies, an increased incidence of various cancers including non-melanoma skin cancer was found.

Different aspects of the molecular regulation of cutaneous inflammation in CLE, cytokines and Ro52 auto-antigen have been studied in biopsies from experimentally UV-induced and spontaneous CLE lesions. We demonstrated that HMGB1, an alarmin with cytokine functions, is upregulated in UVR-induced CLE lesions, and its highest expression coincided with the peak of clinical activity of the lesions. Ro52 and iNOS were observed in the epidermis of CLE skin lesions. Our results of *in vitro* experiments indicate that UVR and NO can influence expression and subcellular localization of Ro52 in keratinocytes. In a Scandinavian co-operation, the *ITGAM* gene was shown to be overrepresented in patients with DLE.

It is very important that the not so uncommon patient group with CLE is identified to be able to improve patient information and treatment guidelines in this group.

Research at the Unit of Occupational and Environmental Dermatology, Karolinska Institutet

CAROLA LIDÉN

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Prof Carola Lidén, Head of the Unit of Occupational and Environmental Dermatology.

The Unit of Occupational and Environmental Dermatology is part of the Institute of Environmental Medicine in Karolinska Institutet. The outpatient clinic is part of the Department of Community Medicine, Karolinska University Hospital. The group is multidisciplinary, with dermatologists, epidemiologists, occupational hygienists, chemists and toxicologists working in close cooperation. The overall aim of the research is prevention of occupational and environmental skin disease, focusing on the most important chemical risk factors causing contact dermatitis in workers and consumers. Our research, which uses clinical, epidemiological and experimental methodology, is aimed at increasing knowledge of hazardous skin exposure and risk reduction. Our research on skin sensitizing metals has been of vital importance in reducing nickel allergy risk, and our research on assessment of skin exposure to sensitizers is in the international frontline. We are active in risk assessment and risk management on the regional, national and international level, and national and international research cooperation is ongoing.

Current research projects are described here:

Hazardous skin exposure (Carola Lidén)

Our aims are to develop, improve and apply methods for skin exposure assessment and absorption, focusing on new exposures; to draw attention to the need for, and possibility of, reducing hazardous skin exposure; and to establish a centre of excellence concerning hazardous skin exposure, risk assessment and risk management.

Epidemiology of hand eczema (Birgitta Meding)

Hand eczema affects approximately 10% of the population of working age. Exogenous factors, such as wet work and contact allergens, and endogenous factors both contribute to the condition. Hand eczema has consequences for the individual and society in terms of healthcare consumption, sick leave, change of work, and an often protracted disease course. Occurrence of hand eczema in the general population and in high-risk groups is being studied in several projects. Risk factors, harmful exposures, prognosis, consequences, and quality of life are all being studied, providing us with knowledge of importance for preventive strategies.

Skin toxicology and the skin barrier function (Anders Boman)

Based on our experience of skin sensitization and absorption, predictive test methods, and permeation through protective gloves, we are engaged in risk assessment for occupational

health services and authorities. Knowledge is limited as to how the skin barrier varies over time in occupations with wear, and on how preventive measures affect the normal barrier and development of hand eczema.

Hairdressers exposure to permanent hair dyes (Marie-Louise Lind)

A postdoctoral project is studying skin exposure to permanent hair dyes in hairdressers. Exposure is assessed by hand rinse sampling, analysis of extracts of hair cuttings from newly dyed hair, surface sampling in hairdressing salons and permeation through protective gloves.

Consumer exposure to reactive chemicals (Carola Lidén and Mihaly Matura)

The composition of products is assessed. An important finding was that more than 90% of hair dye products contain several strong sensitizers, posing large risks to consumers and hairdressers. Ingredient labels are difficult to understand. We aim to provide a basis for more user-friendly labelling. Studies have been performed on the role of air-oxidation of some fragrance substances producing strong sensitizers.

Contact allergy to metals: skin exposure and prevention (Carola Lidén)

A method for assessment of skin exposure to metals has been developed (acid wipe sampling) and is now used in several studies. Metal release from various alloys and patch test reactivity is assessed. The suitability of spot tests for nickel (dimethylglyoxime (DMG) test) and cobalt to assess skin exposure is being studied.

Metal exposure in recycling of electronic waste (Anneli Julander)

Electric and electronic equipment are recycled by a rapidly growing industry. Several metals are toxic, some are allergenic, and they may cause risks to workers. This postdoctoral project concerns exposure to metals and dust in electronic recycling facilities. The levels of several metals in air and dust, on skin, in blood and urine is being studied.

Metal allergy with a surface and material perspective (Klara Misdander)

To reduce the risk of allergy and contact dermatitis to metals, it is necessary to increase our understanding of metal release mechanisms and corrosion. In this postdoctoral project, metal

release will be studied in relation to skin deposition by short-term skin contact. The focus is on alloys and coated materials used in objects such as keys, handles, tools and coins.

Effects of mineral wool on human skin (Lennart Lundgren)

Man-made vitreous fibres, e.g. mineral wool, are used for insulation and as reinforcement in many materials. It is well-known to cause skin irritation, especially in atopic eczema. A survey of skin effects among insulators, and studies in a human whole-body exposure chamber will be carried out.

Epoxy allergy in workers re-lining pipes (Ingegård Anveden Berglind)

Epoxy resin systems are important and potent occupational skin sensitizers, particularly in the building industry. Re-lining of

pipes is a new application with high risks, which was first noted in our out-patient clinic. This research project will study the knowledge, attitudes, techniques and skin exposure in workers who re-line pipes.

Hand eczema, contact allergy and career in a birth cohort (BAMSE) (Carola Lidén)

Hand eczema, contact allergy and choice of education and career are topics that will be studied within the follow-up of the BAMSE birth cohort at the age of 16 years. A web-based questionnaire, clinical examination, and patch testing for allergy are used. The project will increase knowledge of the prevalence in young people of hand eczema, contact allergy and genetic risk factors for hand eczema.

Karolinska Institutet

White arrow indicates the location of the Unit of Dermato-Venereology and the yellow arrow indicates the location of the Unit of Occupational and Environmental Dermatology.



Facts

Karolinska Institutet was founded 200 years ago. Today, the university employs over 4,400 people and is attended by approximately 6,000 students. The Unit of Dermatology and Venereology within the Faculty of Medicine appointed their first professor in 1948.

The Unit of Dermatology and Venereology at Karolinska Institutet:

- 3 Professors
- 2 Adjunct Professors
- 7 Assistant Professors
- 6 PhD researchers
- 3 doctoral students

The group publishes approximately 30 original articles per year. During the last 3 years seven doctoral thesis have been produced.

The Unit of Occupational and Environmental Dermatology at Karolinska Institutet:

- 1 Professor
- 2 Assistant Professors
- 8 PhD researchers
- 2 doctoral students

The group publishes approximately 12 original articles per year. During the last 3 years three doctoral theses have been produced.