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Dermato-Venereological Research at Helsinki University

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The Department of Dermatology and Allergology (including venereology) is among the oldest clinical departments at Helsinki University Hospital and trains specialists in skin and allergic diseases. The multidisciplinary composition of the department is unique at the European level. Translational research, starting from research targets identified at the bedside, which are brought to the laboratory and returned to the clinic for diagnostics or therapy, are central to our research. The research group shares a research lab at Biomedicum Helsinki with the Department of Oncology. This has eased cell culture, molecular biology, and transfection and new, more sophisticated research activities.

Currently, our research focuses on the following main interconnected areas: skin cancer, inflammation and immunity. Studies on the genetics and pathomechanisms of multifactorial diseases, especially psoriasis, lupus erythematosus and autoinflammatory diseases, performed in collaboration with international genetics groups – notably Prof. Juha Kere's group at Karolinska Institutet – and centres of excellence, are also an important part of the research. Other important interests include clinical investigator-initiated research projects and participation in long-term EU-funded projects like the EPIDERM project and the Microbes in Allergy and Autoimmunity Research Study started in 2011.

A brief description of some of our ongoing research projects is given below.

Inflammation and cancer translational research group

In the clinic, we are facing the need for personalised medicine for diagnostics and treatment to enable the identification of patient subgroups suitable for a given type of therapy. Biomarkers for identifying such patients in advance are lacking in most instances. Our research will take advantage of novel cancer-associated gene aberrations and pathways, identified by Prof. Annamari Ranki's group, that link inflammation and cancer. A key finding for this project was our recent identification of two central signalling pathways affected by the newly discovered cancer-associated gene NAV3. We have found NAV3 copy number changes in cutaneous T-cell lymphomas (CTCL), as well as other malignancies such as brain tumours (unpublished observation), melanoma (unpublished observation) and colorectal cancer (CRC). Among the genes up-regulated by NAV3 in at least two different target cell types, we identified two central receptor molecules of two important pathways, namely the GnRH pathway and the Jak/Stat pathway. Both these pathways are known to be involved in as well oncogenic processes as in inflammation. Thus, for the first time, we have identified a definite gene product and signalling pathway linking cancer to "smouldering" inflammation in the tumour microenvironment. We are further studying these pathways in the context of oncogenic changes that induce an inflammatory microenvironment and thereby confer upon transformed cells a growth advantage. Our research on NF-κB signalling defects associated with natural TNFRSF1A mutations and TRAPS provides additional information. Our collaborative study with the Institute of Virology, Helmholtz Zentrum München on the role of human endogenous retroviruses (HERV) cloned from the chromosomal loci aberrated in CTCL, will further identify gene products activated by HERV and contributing to tumorigenesis. We perform translational clinical studies on patient-derived tissue samples (gene expression profiling and array comparative genomic hybridization), functional studies in vitro using receptor ligands and siRNA technology, expression arrays, in situ PLA, coimmunoprecipitation and fluorescence in situ hybridization-based technologies, and mouse xenotransplant model studies. We aim to identify novel common gene pathways and biomarkers in the genesis and/or progression of lymphomas, epithelial cancers and melanoma. We have protected our discoveries by patenting, and one diagnostic product is currently being commercialised by a Finnish biotechnology company. Clinical and molecular studies on the mechanism of early atopic sensitisation and on AIRE gene-associated peripheral tolerance are also being carried out.

Identification of prognostic factors for melanoma dissemination

It is well known that the presence of melanoma micrometastases inside the sentinel nodes correlates with the development of a disseminated disease. An important question which Olli Saksela's group will attempt to answer by analysing the antigenic and

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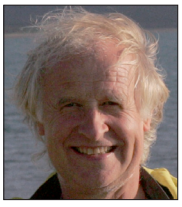
Olli Saksela, Associate Professor of Dermatology.



Sakari Reitamo, Acting Professor of Dermatology.

Sari Suomela, PhD, Department of Dermatology.

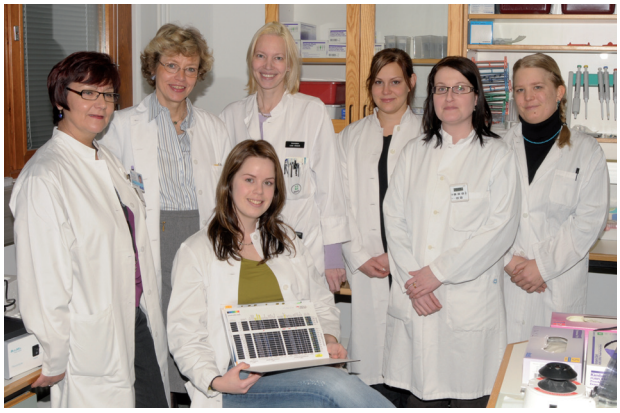


Fig. 1. The inflammation and cancer translational research group. *From left:* Kaija Järvinen, Annamari Ranki, Liisa Väkevä, Jonna Varis, Kirsi Niiranen, Emilia Carlsson and Pilvi Maliniemi (sitting).

genetic properties of micrometastatic nodal cells is whether patients with positive sentinel nodes can further be divided into low- and high-risk patients. This is a crucial question since the requirement for complete evacuation of the nodal basin after positive sentinel node detection is a matter of extensive debate, and means for determining the potential for aggressive growth and the spread of melanoma cells to non-sentinel nodes are needed. Although the growth of micrometastases to macrometastases is known to be the rate-limiting step in metastatic progression and the main determinant of cancer fatality, the molecular mechanisms involved have been little studied. We recently succeeded in identifying several genes that are consistently upregulated, and one signalling pathway that is consistently overactive, in macrometastases. Our aim now is to determine whether these changes are absolutely required for metastatic growth. We will further study by global gene expression analysis an important practical question: whether the behaviour of melanoma cells and patient outcome could be predicted using the results of genetic or proteomic analyses of primary melanomas. It is now clear that tumour progression is not just dependent on cancer cells, but on the intricate interplay between cancer cells and stromal cells (fibroblasts, inflammatory cells, endothelial cells). Therefore, we will study tumours as one complex unit. The project is expected to provide the foundation for the rational design of targeted therapies for the prevention and management of metastatic melanoma, and is thus of high clinical relevance and practical applicability.

Atopic dermatitis: Clinical studies and long-term outcomes

Long-term clinical studies of atopic dermatitis (AD) have been the main research interest for Sakari Reitamo and his co-workers for many years. Although AD is a chronic disease, long-term studies and long-term treatment plans for patients have been lacking.

Our studies of topical calcineurin inhibitors have not revealed any long-term adverse events or harmful effects on the skin barrier. Treatment with tacrolimus ointment for one year increased collagen synthesis in the skin, in contrast to topical corticosteroids, which reduce both skin thickness and collagen synthesis. These effects are the main limiting factors for long-term topical corticosteroid treatment of moderate-to-severe AD. Our patients needed treatment for 9 out of 10 days during a one-year study to control their disease. Effective topical treatment seems to modify the disease: our long-term studies with tacrolimus ointment and topical corticosteroids revealed that effective treatment of skin inflammation can not only reduce disease severity, but also improve cell-mediated immunity in the skin, which indicates reversal of the skin's Th2 polarisation. Improvements in the Th2/Th1 balance and skin barrier function are also suggested by the results of long-term studies which show that effective treatment with tacrolimus ointment results in the elimination of Staphylococci and reductions of infection with other microbes, including herpes simplex virus. Recent studies in adults suggest that effective, long-term treatment of AD may also improve respiratory symptoms.

Maintenance treatment of AD has greatly improved the long-term outcome, especially in the more severe forms of the disease. Studies on this treatment modality have been performed with topical corticosteroids (for up to 24 weeks) and topical calcineurin inhibitors (TCIs) (for up to one year). Long-term maintenance treatment better suits topical calcineurin inhibitors than topical corticosteroids, as there are no long-term harmful effects on the skin barrier. The ultimate goal of treatment should be complete control of AD. In the future, the role of corticosteroids will mainly be the short-term control of disease flares. Systemic treatment and UV treatments will be used less in future years.

When topical calcineurin inhibitors are used, monotherapy without corticosteroids should be used whenever possible as long-term outcome may be worsened by mixing these compounds. Some body regions, such as the hands, feet and the scalp, will need additional corticosteroid treatment. Long-term treatment results are greatly influenced by patient compliance, and better information to the patients will improve compliance. The long-term outcome for individual patients can usually be estimated after one year of treatment. Patients with good compliance can expect improvement of all atopic symptoms over time. In the future, we will perform studies from early infancy after the initial appearance of AD with the aim of preventing atopic airway symptoms.

Keratinocyte biology and disease – In search of psoriasis effector genes

The pathways leading to altered keratinocyte proliferation and differentiation in psoriasis are still not fully understood. Aberrant keratinocyte metabolism as a primary cause is suggested by the observations that keratinocyte proliferation is increased, and keratin expression profiles altered, in psoriatic lesions.

Intracellular signalling molecules in basal keratinocytes are able to induce skin inflammation similar to that observed in psoriasis. In collaboration with Assistant Professor Jyrki Vuola at the Department of Plastic Surgery and Assistant Professor Esko Kankuri at the Institute of Biomedicine, Dr Sari Suomela, together with Professor Juha Kere's and Associate Professor Outi Elomaa's psoriasis team at the Research Program's Unit aim to identify effector molecules behind psoriasis by large scale transcriptome and proteome approaches. We aim to compare expression profiles of normal and psoriatic samples by using deep sequencing which allows detections of novel transcripts, low-expressed genes and micro RNAs as well. The second line of research is the function of the psoriasis susceptibility gene CCHCR1. We have performed pioneering work in the identification of CCHCR1 as a psoriasis susceptibility gene and in collecting a large number of patient DNA samples for genetic studies. The function of CCHCR1 remained largely unknown until recently, when we demonstrated that it has an antiproliferative effect on mouse keratinocytes (Tiala et al., 2008). Our current hypothesis is that the aberrant function of CCHCR1 may lead to abnormal keratinocyte proliferation. We continue to study the function, regulation and localisation of CCHCR1 in normal and psoriatic keratinocytes. With a focus on the functional biological properties of keratinocytes, our project not only seeks to identify differences between normal and psoriatic skin, but also to elucidate the biology – differentiation and stress responses – of normal keratinocytes. The identification of susceptibility proteins and genes will provide insights into the precise biochemical pathways that control psoriasis, enabling the development of safer and more specific drugs with fewer side effects and the identification of clinical patient subgroups. By detecting aberrations in gene regulation leading to psoriatic skin changes, we can interrupt the process more effectively and earlier and understand the natural course and triggering factors of the disease. Furthermore, our findings have relevance for other T-cell-mediated autoimmune diseases, including rheumatoid arthritis, multiple sclerosis and Crohn's disease.

Lupus susceptibility genes: Functional pathways and roles in Related autoimmune diseases

While the genetic background of systemic lupus erythematosus (SLE) has been extensively studied, comprehensive studies of cutaneous lupus erythematosus (CLE) genetics are still lacking (Kuhn et al. 2005). The late Professor Ulpu Saarialho-Kere's group recently showed that the verified SLE risk genes *IRF5*, *TYK2*, *CTLA4* and *STAT4* are also associated with CLE, and that their expression is up-regulated in the dermal inflammatory infiltrate of CLE skin. Our novel results demonstrate that the *ITGAM* gene is even more strongly associated with DLE than with SLE in Finnish patients.

The special interest of Dr Sari Koskenmies, Assistant Professor Jaana Panelius and their collaborators is to study the expression patterns of the above candidate proteins (encoded by functional candidate genes or candidate genes identified by genome-wide association studies) in response to ultraviolet radiation (UVA and UVB) exposure, and to relate the expression levels to identified disease risk-mediating haplotypes. It is generally known that ultraviolet radiation is a triggering factor for lupus and lupus-related skin manifestations. However, the pathogenetic and immunological mechanisms behind this are unknown. Based on our own data and published data on SLE susceptibility genes, we aim to study gene polymorphisms, phenotype–genotype correlations and the tissue expression of proteins encoded by known SLE susceptibility genes and novel putative susceptibility genes. Since some of the disease-associated genes are likely to interact, we intend to perform gene and protein interaction studies for genes showing associations with LE to study how disease-associated transcripts and proteins relate to each other in affected tissues.

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Facts

Founded in 1640 in Turku, Helsinki University is one of the oldest universities in Europe. (It relocated to Helsinki in 1828.) It is ranked among the 100 best universities in the world and has approximately 8,100 employees, of whom 3,900 are researchers and lecturers, and a total of 35,000 students. Helsinki University has 11 faculties. The Unit of Dermatology and Venereology within the Faculty of Medicine appointed their first professor in 1874.

The group of researchers at the Department of Dermatology and Allergology in Helsinki consists of:

2 professors (one part-time) + 2 clinical instructors (one part-time)
11 senior researchers, of whom 9 are MDs and one a molecular biologist
7 registered PhD students

The Department has published some 400 original articles during the past 5 years (approximately 50% of these have been published by dermatologists).
During the last 5 years, 9 doctoral theses have been produced.