Göteborg Science Centre for Molecular Skin Research

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Ann-Therese Karlberg is Professor in Dermatochemistry and Skin Allergy at the University of Gothenburg since 2002. During the years, her main research interest has been to answer the question: What makes a molecule an allergen? Compounds that are not sensitizers themselves, but are activated either in the skin by bioactivation or outside the body by autoxidation are in focus in her research. Below she gives a description on the recently developed platform for molecular skin research.

Göteborg Science Centre for Molecular Skin Research was established in 2006 as an interdisciplinary research platform within the Departments of Chemistry and Physics at the Faculty of Science, University of Gothenburg. Following international evaluation, and in competition with other applications from interdisciplinary constellations within the Faculty, skin research at the molecular level was considered so interesting that direct sponsorship from the Faculty of Science was provided. Close collaboration with dermatologists in the Faculty of Medicine and the Sahlgrenska University Hospital was a prerequisite for the establishment. This skin research platform board therefore includes two well-known dermatologists from Gothenburg: Professor Jan Faergemann and Associate Professor Ann-Marie Wennberg, Head of the Dermatology Clinic, Sahlgrenska University Hospital.

The objective of Göteborg Science Centre for Molecular Skin Research is to create a fundamental understanding of the molecular processes involved in the interaction between chemicals or ultraviolet-visible spectroscopy (UV-VIS) radiation and the skin. The intention is to improve the existing methods for prevention, diagnosis and treatment of allergic contact dermatitis and skin cancer. A goal is that the knowledge obtained will lead to improvements in the effects of topical drugs and the use of transdermal drug delivery (TDD).

The competence within the platform is unique due to its extensive collaboration within the fields of dermatochemistry, dermatology, medicinal chemistry, nanotechnology, biophysics, physical chemistry, organic chemistry, surface chemistry and pharmaceutics at the University of Gothenburg, Sahlgrenska University Hospital, and Chalmers University of Technology. The creation of the platform has engaged seven young scientists within the Departments of Physics and Chemistry, of whom five are women. They are starting to develop their own research groups, working in interdisciplinary projects and jointly supervising PhD students. Thus, the platform has evolved into a hothouse for young female scientists at those departments where female researchers above the PhD level are very few. During 2009 six PhD dissertations will be finalized within the research area of the skin research platform. Of these PhD students, two are dermatologists with tutors from both dermatology and science (chemistry and physics).

The number of publications related to the platform has increased over the years as a result of increased collaboration among the researchers (Fig. 1). Meetings are arranged regularly (twice every semester) in which senior researchers, PhD students and students studying for a master degree participate. The meetings are intended to bring together all researchers to discuss research results and other important issues. External

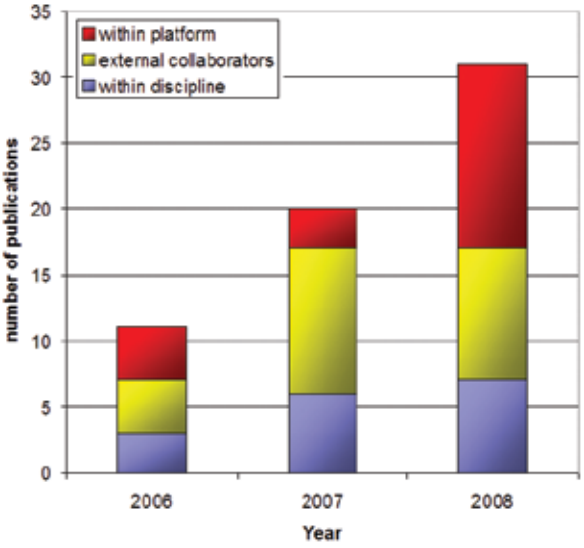

Fig. 1. Number of publications within the area of molecular skin research.

scientists are invited either to give scientific presentations or for discussion of more general topics.

The work within the platform consists of research projects with various profiles, in which the skills of researchers with different backgrounds are of utmost importance. Some examples are given below.

Bioimaging techniques are valuable tools used to investigate what is happening in the skin. Research within the fields of skin cancers and precancers is prominent at the Sahlgrenska University Hospital, and this is one of the core research activities within the platform. For many years skin cancers have been investigated using bioimaging in collaboration between researchers at the Department of Physics and dermatologists at the Sahlgrenska University Hospital. Visualization using two-photon microscopy (TPM) has been established for investigations of skin cancers. Since near-infrared light is used, histopathological information on the cellular level can be obtained on intact skin. Thus, TPM has the potential to become a non-invasive tumour diagnostic technique. A clinical study has been performed, in which the potential of TPM to diagnose basal cell carcinoma and squamous cell carcinoma has been demonstrated.

Bioimaging techniques can also be used to study the transport of xenobiotics, e.g. contact allergens, in the skin. TPM has been established for investigations of the localization and distribution of fluorescent compounds in human skin based on visualization. One important aspect of studying the transport of xenobiotics in tissue is to be able to visualize the processes in real time. This will be done using a real-time imaging diffusion chamber. Preliminary results have been obtained demonstrating the use of a method for on-line visualization of the skin during exposure to fluorescent compounds using TPM. Once the method has been validated, various xenobiotics and delivery systems will be explored using the technique. The work will also involve measurements of optical point-spread-function within human skin, and theoretical modelling of light propagation when applying two-photon excitation in skin. The development of theoretical models is being carried out in collaboration with Stefan Andersson-Engels, of the Department of Physics, Lund University.

Topical photodynamic therapy (PDT) has been shown to be an excellent treatment for superficial skin cancers and precancers, such as basal cell carcinoma and actinic keratosis. However, the treatment has several limitations, i.e. poor drug penetration and experience of pain during treatment. One project in co-operation with Sven Engström, Pharmaceutical Technology, Chalmers University of Technology, involves the design of new drug delivery systems for PDT, based on cubic lipid systems. The possibilities for improving the photodynamic effect using nanoparticles are being investigated and experimental studies have been initiated in which gold nanoparticles and nanorods are produced and functionalized.

Nanotechnology is an emerging technique used in the cosmetics and pharmaceutical industry. The impact of nanotechnology on allergic contact dermatitis is being investigated in co-operation with Klaus E. Andersen and Jakob Torp Madsen at the Department of Dermatology, Odense University Hospital, University of Southern Denmark. The encapsulation of known allergens in liposomes and polycapronelactam nanoparticles is investigated in Odense, where a possible difference in sensitizing capacity is studied in mice and in patch-test studies in volunteer patients with known contact allergy to the actual haptens. In Gothenburg, in-depth investigations are performed using TPM of the distribution of fluorescent haptens encapsulated in liposomes and polycapronelactam when administered to human skin.

Göteborg Science Centre for Molecular Skin Research has become one of the major centres in Europe for research on contact allergy at the molecular level. The foundation for this was when the experimental work on occupational dermatology at the National Institute of Working Life (ALI) in Stockholm was localized to the University of Gothenburg in 2002. Being head of the Department of Occupational Dermatology at ALI, I became professor of dermatochemistry and allergy research at the Department of Chemistry in Gothenburg and, together with four other members of the team at ALI, started to build up the dermatochemistry research, involving not only chemistry but also predictive testing in mice and patch-testing, in close collaboration with the dermatologists at Sahlgrenska University Hospital.

Activation of non-allergenic compounds into potent contact allergens by oxidation in the air (autoxidation) has been my major research interest for many years. Unsaturated hydrocarbons, which are not allergenic themselves, can be activated outside the body by autoxidation to form a mixture of oxidation products, some of which are potent skin sensitizers. Monoterpenes, which are used as fragrance components, belong to this group and, currently, several new identified allergenic compounds are being used for screening among consecutive dermatitis patients at the Department of Dermatology, Sahlgrenska University Hospital, to study the clinical relevance and appropriate diagnostic test concentrations. A new position involving both clinical investigations of the exposure to allergens of contact dermatitis patients, and research in collaboration with researchers in the platform has been advertised at the Department of Dermatology. The clinical

research is performed in collaboration with Magnus Bruze and co-workers at the Department of Occupational and Environmental Dermatology at Malmö University Hospital.

The impact of "free radicals" on our health has been debated. Investigations of a radical mechanism involved in the formation of immunogenic hapten-protein complexes by hydroperoxides, the most important haptens formed by autoxidation, have been performed. For the first time we have demonstrated that radicals form specific immunogens causing contact allergy.

A major area of work within the research into contact allergy is the study of the structure-activity relationship (SAR) using series of compounds modelled from one original allergenic hapten. The chemical reactivity of the model compounds with peptides and proteins, as well as their sensitizing capacity, are investigated in order to elucidate what structural alerts make the molecules allergenic. Investigations aiming to increase our understanding of the SARs for metabolic activation of various groups of prohaptens are also of major interest within the platform. Collaborations have started with Hans Merk and his research group at the Interdisciplinary Centre for Clinical Research, (IZKF) BIOMAT, RWTH, Aachen, Germany. The group in Aachen has specific knowledge of skin metabolism and experience from work with in vitro experiments using dendritic cells. A skin-like cytochrome P450 enzyme mixture (CYP cocktail) consisting of human isoenzymes has been developed that also allows the investigation of compounds that are not allergenic themselves but need CYP-mediated metabolic activation to become sensitizers.

In 2007 a successful conference "Looking Skin Deep" was organized by the platform. It gathered a large number of international and national researchers within science and dermatology. During the conference several workshops were held within the field of skin imaging.

Continuing Medical Education

CME MCQ – Biologic Era:

The following questions are based on the Educational Review in Forum No. 3:
Ståhle M. Systemic Treatment for Psoriasis – a New Biologic Era. Forum for Nordic Dermato-Venereology 2008; 13: 69–73

1. Which of the following registered drugs, and drugs in the pipeline, inhibits tumour necrosis factor alpha (TNF-α) signalling?
   A. Infliximab
   B. Efaluzimab
   C. Adalimumab
   D. Ustekinumab
   E. Eternacept
   F. ABT-874

2. Combine the correct suffix with the correct class of biologic agent:
   1. ximab; 2. umab; 3. zumab; 4. cept
   A. Human monoclonal antibody
   B. Chimeric monoclonal antibody
   C. Receptor-antibody fusion protein
   D. Humanized monoclonal antibody

3. Novel regulatory mechanisms important for skin biology are being explored and one of the more exciting fields currently evolving is the role of small endogenous RNAs (micro RNAs). Which of the following (A-E) relates to this potential therapeutic target?
   A. DNA
   B. mithochondria
   C. miR-203
   D. FK-506
   E. TNF blockage

Recommended answers:
1. A + C + E
2. 1-B; 2-A; 3-D; 4-C
3. C