

Dermato-Venereological Research at Bispebjerg hospital

ROBERT GNIADDECKI

Department of Dermatology and Venereology, Bispebjerg Hospital, Copenhagen, Denmark. E-mail: rg01@bbh.regionh.dk

The University Department of Dermatology at Bispebjerg Hospital Denmark has a long and complicated history; its roots can be traced back to the first Danish department of dermatology established in 1911 at Rigshospital. Since then the department has undergone multiple rounds of mergers; first with the dermatology department at Finsen Institute, and subsequently with the existing clinic at Bispebjerg Hospital (in 1996). Now, our department, together with the dermatology clinic at Gentofte hospital, serves a population of over 1.6 million in The Capital Region of Denmark, and provides teledermatology consultations to Greenland.

The Department of Dermatology at Bispebjerg Hospital is among the largest dermatological departments in Scandinavia, and has a very high level of clinical and scientific activity. It is housed in three interconnecting buildings; the in-patient department, the outpatient clinic and the research unit.

Organization

The department comprises a large outpatient clinic (>90,000 consultations per year), inpatient clinic (30 beds), a separate interdisciplinary centre for wound management, and an open venereology clinic. The department's areas of special interest are skin cancer and psoriasis. These patients are primarily treated in the specialized clinics (pigmented lesion clinic, cutaneous lymphoma clinic, cancer clinic for immunosuppressed patients) and in the specialized therapeutic units (radiotherapy facility delivering orthovoltage X-ray treatment, photodynamic therapy unit, lasers, extracorporeal photopheresis facility, phototherapy unit). Research facilities in the department are integrated, and comprise a dedicated research laboratory with facilities for cell culture, molecular biology and photobiology, and a GCP (Good Clinical Practice) clinical trials unit. The senior staff of the department comprise: two clinical professors (one ordinary clinical professor and one research clinical professor with specialty in skin cancer) and nine consultants.

Areas of special expertise

Patients are referred from dermatology specialists in private practice, with conditions that comprise all aspects of skin diseases and problem wounds. The areas of special clinical expertise are: skin cancer (pigmented tumours, cutaneous lymphoma, non-melanoma skin cancer), psoriasis and biologic treatment, treatment of cutaneous manifestations of graft-versus-host disease, diagnosis and treatment of photodermatosis, lymphoedema and autoimmune bullous diseases. Our success within these areas is the result of the long-term commitment of two generations of dermatologists working in the department, which has led to the publication of numerous highly cited papers in top-ranking journals,

such as Nature, Lancet, N Engl J Med, Blood, and J Invest Dermatol. The department strongly encourages translational research activities.

Cutaneous lymphomas

Patients with cutaneous lymphomas are managed in the specialized lymphoma clinic, which cares for >100 patients with this diagnosis. We have initiated a multidisciplinary team ("Copenhagen Cutaneous Lymphoma Group") comprising interested dermatologists, haematologists, clinical immunologists, oncologists and pathologists for consultation on difficult cases. To enhance research and information exchange we have recently established a dedicated clinical database, which is now also being implemented in other countries (Sweden, Poland and Hungary). The therapies are delivered primarily in our department (phototherapy and other skin-directed therapies, superficial radiotherapy, biologic therapy, photopheresis) or in cooperation with the Radiotherapy Clinic and the Department of Haematology and Oncology (Rigshospitalet, Copenhagen) for electron beam radiation, polychemotherapy and bone marrow transplantation. Clinical development comprises active research on radiotherapy of cutaneous lymphomas, where we have successfully established a low-dose irradiation protocol (in a phase IB/II clinical development), and in cooperation with the European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force in novel chemotherapies of T-cell lymphomas and mini-bone-marrow transplantation for advanced disease. We work actively on the refinement of staging procedures in cutaneous lymphomas, especially evaluating the usefulness of positron emission tomography-computed tomography (PET-CT) technology and molecular techniques. The major achievements within the translational research are the identification of new therapeutic targets comprising receptor Notch1- and p53-blocking agents, and we plan to progress to a phase I clinical trial with the Notch inhibitors for advanced patients with mycosis fungoides. We also perform research in molecular therapy of lymphoma using the microRNA paradigm to design novel therapeutics.

Non-melanoma skin cancer

Non-melanoma skin cancer is the most prevalent malignancy in humans and this is an area of active research. With many simple cases being treated in specialist practices, we focus on high-need patient comprising organ transplant recipients and patients with multiple



Prof Robert Gniadecki, Department of Dermatology and Venereology.



Prof Hans Christian Wulf, Department of Dermatology and Venereology.



Tommy Karlsmark, Associate Professor and Head of the Department of Dermatology and Venereology.



Fig. 1. Therapy of extensive actinic keratoses with photodynamic therapy.



Fig. 2. Treatment with extracorporeal photopheresis in the inpatient unit.



Fig. 3. Treatment of a tumour of cutaneous lymphoma with orthovoltage radiotherapy.

neoplasias. These patients are treated in a specialized cancer clinic, the important part of which is the early detection and prevention of skin cancer. Long-term interest in photobiology and non-surgical treatment techniques has been useful in this respect. Research in the department has enlarged our knowledge of personal exposure to carcinogenic ultraviolet radiation, which helps in developing preventive strategies for patients. The department also made important contributions to photodynamic therapy, which is now in development as a method for early debulking of high-risk patients from thin carcinomas and pre-malignant lesions. The major achievement is the development of solar photodynamic therapy, which would increase the accessibility of the treatment. An important part of the treatment is radiotherapy; orthovoltage therapy is available in our department (the only centre in Denmark) and provides cost-effective, safe therapy of carcinomas in elderly patients. Another area of interest is the development of clinical databases for long-term follow-up and further optimization of photodynamic therapy (laser-assisted delivery of photosensitizers into the tumour mass).

Laboratory research on non-melanoma skin cancer comprises investigations on the mechanisms of photocarcinogenesis. Our laboratory has developed a novel polymerase chain reaction (PCR)-based method for DNA damage quantification and set up a facility for free radical measurements in the skin by photon counting. The department has a fully equipped photobiology laboratory with established techniques for measurement of skin pigmentation, exposure, and light sources, and an animal facility with an established mouse carcinogenesis model.

Malignant melanoma

Malignant melanoma is a potentially lethal cancer with a steadily increasing incidence. The major role of dermatology in melanoma is in prevention and early detection. We have established a dedicated pigmented lesion clinic and adopted digital dermoscopy as a standard of care for high-risk patients with melanocytic skin lesions. We are currently establishing a digital photography database of all patients with pigmented lesions seen in our department. This database will enable more efficient follow-up and future studies on the role of genetic background in the risk assessment of patients with malignant melanoma. This database will also enable better risk assessment of patients by cross-correlation of clinical data with the

personal ultraviolet exposure data generated in the individual dosimetry project. We are also working with novel diagnostic techniques. We have successfully adopted Raman spectroscopy for *in vitro* investigation of the skin, and we have published preliminary data suggesting the usefulness of this technique for objective and automated diagnosis of pigmented lesions.

Basic research in malignant melanoma is a relatively new area in our department. We focus on laboratory research on the early stages of melanoma development. Experience from cutaneous lymphomas with microRNA technology has been transferred to melanoma research. We have also adopted the microdissection technique, which has enabled purification of a melanoma cell population directly from paraffin-embedded biopsies. We have identified a group of microRNA species that seem to modulate early carcinogenesis in melanoma and sentinel node metastasis (e.g. miR-125b, let-7c). Future research will be aimed at employing these findings for the assessment of survival prognosis in patients with early cutaneous malignant melanoma.

Other areas of interest

Psoriasis has developed as an active area of research following the introduction of biologic therapy. We have established a large outpatient clinic for biological therapy, which currently provides care for >300 patients with psoriasis and psoriasis arthritis. Our department plays an active role in the national psoriasis database DERMBIO, and conducts active clinical research focused on life-quality measurements in psoriasis, drug compliance and cost-effectiveness of the biologics. A new, developing field is the assessment of cardiovascular risk factors in patients with psoria-



Fig. 4. Checking the narrow-band UVB apparatus.



Fig. 5. Outpatient consultation in the pigmented lesion clinic.

sis. We have established a prospective programme for psoriasis patients on systemic therapy, including body fat measurements, insulin resistance assessment and other relevant cardiovascular parameters. In the future this will enable better understanding of the increased cardiovascular morbidity in psoriasis and assess whether it is modulated by psoriasis therapy.

Bullous diseases have a long research tradition in our department. As the only department in Denmark we provide an in-house immunofluorescence service employing modern techniques, such as overlay confocal microscopy, split skin and basal membrane wave-pattern analysis. We were the first to describe apoptosis in pemphigus, which contributed to a new view on the mechanism of acantholysis.

Patients with *chronic wounds and lymphoedema* are treated in a Center for Wound Healing and Lymphoedema Clinic. The latter is the only centre in Denmark providing clinical care for lymphoedema patients. The Wound Healing Center is staffed by a multidisciplinary team comprising vascular and orthopaedic surgeons and dermatologists. The focus is on diabetic foot ulcers and immunological wounds.

Research groups

Professor Robert Gniadecki, MD. Clinical research: Radiotherapy and cutaneous malignancies, imaging methods for staging of cutaneous lymphomas, co-morbidities in psoriasis, life quality in psoriasis, clinical trials in psoriasis, photopheresis for graft-versus-host disease and cutaneous lymphomas. *Laboratory research:* Therapeutic targets in cutaneous lymphoma, microRNA regulation of cutaneous lymphomas and malignant melanoma. *Publications 2006–2010.* 64 publications, 277 citations.

Professor Hans Christian Wulf, MD. Clinical research: Porphyrrias, phototherapy of inflammatory skin diseases, photodynamic therapy. *Laboratory research:* Personal exposure to ultraviolet radiation (the EU research grant), mutagenic effect of ultraviolet radiation, and photosynthesis of vitamin D. *Publications 2006–2010.* 69 publications, 606 citations.

Merete Høedersdal, MD. Use of lasers for percutaneous drug delivery, side-effects of laser treatment. *Publications 2006–2010.* 45 publications, 205 citations.

Tove Agner, MD. Contact dermatitis, skin barrier. *Publications 2006–2010.* 39 publications, 312 citations.

Tommy Karlsmark, MD. Lymphoedema and wound healing. *Publications 2006–2010.* 26 publications, 28 citations.

Network and international collaboration

On the international level our department belongs to the leading institutions within dermatology. Fellows and scholars regularly visit the department, which testifies to its international interest. The department has a tradition of hosting foreign PhD students (from China, Italy, Belgium and Poland). The department's faculty are members of the international dermatological societies (American Academy of Dermatology (AAD), European Organization for Research and Treatment of Cancer (EORTC), European Academy of Dermatology and Venereology (EADV), Society of Investigative Dermatology (SID), European Society of Dermatological Research (ESDR), and European Wound Management Association (EWMA)) and the department is represented in the boards of important organizations (EORTC CLTF (EORTC's Cutaneous Lymphoma Task Force), EADV, ESDR, European Society of Contact Dermatitis (ESCD) and ISCL (International Society for Cutaneous Lymphomas)).

The department has organized and hosted several important international events, such as the EORTC CLTF Meeting in 2008 and an EADV Course on Cutaneous Lymphomas (in 2009).

On the institutional level we have formalized collaboration with Harvard University (Boston, MA, USA) on the development of laser-assisted drug delivery technology. We cooperate with several leading institutions, such as King's College London (UK), Karolinska Institutet (Sweden), Center for Research on Environmental Epidemiology (Spain), Departments of Dermatology at Ninewells Hospital (Dundee, UK), Zurich (Switzerland), Leiden (Holland), Göteborg and Uppsala (Sweden) and Stavanger (Norway). Moreover, the Department is actively involved in commercial multicenter clinical trials in the areas of psoriasis, skin cancer, cutaneous lymphomas and autoimmune diseases, and cooperates with Danish and foreign companies with drug development in these areas.

The international visibility of the department is underscored by the fact that it serves as an international teaching centre of excellence in the fields of biologic treatment of psoriasis, cutaneous lymphoma, photodynamic therapy and wound healing.

The beautiful building of the dermatology outpatient department at Bispebjerg Hospital.



Facts

The faculty at the Department of Dermatology and Venereology at Bispebjerg University hospital consists of:

- 2 professors
- 9 consultants
- 14 junior physicians

Clinical activities:

- 30 in-patient beds/2,000 hospitalizations/year
- 95,000 outpatient consultations/year

Specialized outpatient clinics and units

- Psoriasis clinic; Skin cancer clinic for immunosuppressed patients; Pigmented lesion clinic; Eczema clinic; Clinic for connective tissue diseases; Laser clinic; Cutaneous lymphoma clinic; Venereology; Photodermatology and phototherapy.

Specialized treatments:

- Radiotherapy; Extracorporeal photopheresis.
- Research activity 2006–2010:* The group has published 221 original articles and 17 theses.