Selected abstracts from the Dermatology Symposium

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WE'VE FOUND THE GENE – SO WHAT?

Professor Colin Munro, Consultant Dermatologist, Southern General Hospital, Glasgow, UK
Email colin.munro@clinmed.gla.ac.uk

In the past 20 years, the molecular aetiology of most common single gene disorders of the skin has been elucidated. For common complex traits, genome-wide linkage analysis has also identified many major loci. There has been a rich harvest in terms of our understanding of skin biology, but in many cases identification of molecular mechanisms has only emphasised the functional complexity of cutaneous biology.

What changes to clinical practice have resulted? Molecular diagnosis is still generally limited to severe neonatal presentations, where it has facilitated prenatal or preimplantation diagnosis. For other cutaneous disorders molecular diagnosis, where available, can be costly and rarely influences management. However, in single gene disorders which primarily present to dermatologists but predispose to systemic cancer, available molecular diagnosis to identify (or exclude) carrier status in relatives has implications for preventive screening.

Routine clinical care of single gene disorders has not yet been significantly affected by molecular understanding. In part this is because knowledge of specific gene defects may not fully explain how the clinical phenotype is produced. Novel non-genetic intervention still requires better understanding of pathogenic mechanisms.

Gene-based therapy, whether by replacement, correction or silencing of a defective gene, or by modulation of its expression, is the most intellectually satisfying approach to treatment. Several approaches show promise, but delivery to the skin remains a barrier to clinical application.

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BIOLOGICS AND PSORIASIS: A CHANGING SCENE

Professor Chris Griffiths, Professor of Dermatology, University of Manchester, UK
Email christopher.griffiths@manchester.ac.uk

The traditional approach to the management of psoriasis is algorithmic dividing psoriasis into mild or severe, dictated by the surface area involved. Mild disease is treated with topical therapies ranging from corticosteroids to vitamin D3 analogues and the more old-fashioned, and increasingly scarce, crude coal tar and anthralin therapies. More extensive disease is treated with either phototherapy (UVB or PUVA) or inpatient therapy moving to systemic therapies, including ciclosporin, methotrexate and acitretin, all of which have unpredictable outcome and side effects that may limit long-term use.

This approach is increasingly being superseded by the use of new targeted biologic therapies which have developed on the back of enhanced knowledge of immune mechanisms, both adaptive and innate, in the psoriatic process. Such mechanisms include the role of T cells, adhesion molecules and cytokines including TNF and interleukins 12 and 23. These new biologics offer the opportunity for long-term control of psoriasis.

Psoriasis should be regarded as a systemic disease no different from arthritis or inflammatory bowel disease. This approach implicates therapy with systemic drugs and moves away from the old-fashioned policy of rotational and/or intermittent therapies. With time it is hoped that early introduction of biologic therapies may be disease-modifying and that early reduction of inflammation may reduce comorbidities such as metabolic syndrome.

An important caveat to the use of biologic therapies for psoriasis is the need for long-term pharmacovigilance such as that instituted by the British Association of Dermatologists' Biologics Intervention Registry. The need for this was highlighted by the recent withdrawal of the T cell-targeted biologic efalizumab on account of cases of progressive multifocal leukoencephalopathy.

An increased knowledge of immune mechanisms may allow a non-Linnean classification of psoriasis using disease mechanisms, thereby promoting the role of pharmacogenomics in personalised therapy.

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TOPICAL DRUG PENETRATION: A COLOURFUL APPROACH

Professor Eugene Healy, Professor of Dermatology, University of Southampton, UK
Email ehealy@southampton.ac.uk

There are many advantages to treating skin disease with topical rather than systemic agents, including direct targeting of the affected tissue and less potential for systemic adverse effects. The number of topical preparations for skin disorders is limited, primarily because most agents fail to penetrate through the stratum corneum into the epidermis and dermis. A number of cell-penetrable peptides have been used to transport a variety of molecules into cells, but less work has been carried out to examine the ability of cell-penetrable peptides to deliver compounds into skin. We have developed a new carrier molecule (PPL), and have investigated whether PPL can transport a 13 amino acid peptide (alpha-melanocyte stimulating hormone, αMSH) and an antisense peptide nucleic acid targeting the tyrosinase gene (antiTyr-PNA) into cells and skin. The results suggest that PPL can carry these cargo molecules into cells in vitro and into skin ex vivo, and suggest that PPL might have potential for future use in topical drug delivery.

Declaration of interests A patent application has been applied for on this technology by the University of Southampton; WO 2007/113531 A2.

FILAGGRIN STORY AND ATOPIC DERMATITIS

Professor WH Irwin McLean, Head of Human Genetics, Ninewells Hospital & Medical School, Dundee, UK
Email w.h.i.mclean@dundee.ac.uk

Atopic dermatitis ('eczema') is a common complex disease in which a combination of strong genetic predisposing factors combine with appropriate environmental stimuli and lead to inflammatory skin disease. In 2006, my research group identified the first mutations in the filaggrin gene as the cause of the common dry, flaky skin condition, ichthyosis vulgaris. Profilaggrin is the main protein component of keratohyalin granules in the epidermis and its processed product, filaggrin, is involved in the biogenesis and subsequent hydration of the stratum corneum. The nonsense or frameshift mutations identified in the filaggrin gene lead to complete loss of profilaggrin/filaggrin protein production in the epidermis. Surprisingly, these mutations are very common in the population and are carried by 5–14% of people of white European ancestry.

Since many individuals with ichthyosis vulgaris also have eczema and associated allergies, and the filaggrin gene is located within a known eczema susceptibility locus, we went on to investigate these mutations in atopic disease. This revealed that filaggrin loss-of-function mutations are a major risk factor for atopic eczema and associated allergic conditions, importantly including atopic asthma and allergic rhinitis. These studies have been very widely replicated, including in non-white populations. In light of recent genome-wide association analysis, filaggrin is now recognised as the major gene for eczema.

Recently, we have reported a mouse mutant that is deficient in filaggrin expression due to a frameshift mutation highly analogous to the common human mutations. These mice have allowed us to prove experimentally that filaggrin deficiency causes enhanced percutaneous antigen transfer, leading to an allergic immune response, i.e. this confirms the hypothesis that filaggrin is essential for normal skin barrier function and that disruption of the skin barrier is a major pathomechanism underlying atopic eczema. We are currently pursuing small molecule drug discovery aimed at restoring or enhancing filaggrin expression in the skin. These mice, in which we have identified a range of clinically relevant biomarkers, will be instrumental in validating new therapeutic approaches for atopic eczema that target the skin barrier rather than treating the subsequent allergic immune response.

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PATHOPHYSIOLOGY OF THE INHERITED BLISTERING DISEASES

Professor Leena Bruckner-Tuderman, University Medical Centre, Albert-Ludwigs University of Freiburg, Germany
Email bruckner-tuderman@uniklinik-freiburg.de

The major role of the skin is to separate and protect the inner environment of the organism from the external milieu and its physical, chemical and biological insults. To achieve these complex functions, numerous structural proteins and molecular networks in the epidermis corroborate to assure the mutual cohesion of keratinocytes and their adhesion to the basement membrane. Multi-protein complexes, e.g. the hemidesmosomes, the focal contacts or the anchoring fibrils, play an important role in keratinocyte-basement membrane-dermal adhesion. Genetic diseases with skin fragility are caused by mutations in genes encoding different protein components of these structures.

Epidermolysis bullosa (EB), the prototype of the skin fragility syndromes, represents a clinically and genetically heterogeneous group of diseases characterised by skin blistering after minor trauma. In the different EB forms, the phenotypes range from very mild symptoms to extensive muco-cutaneous blistering and multiorgan disease. Mutations in 13 distinct genes are responsible for the different subtypes, including genes for keratins, integrins, basement membrane collagens and laminins.

The study of the biological consequences of gene mutations is useful for understanding molecular disease mechanisms and for planning biologically valid therapeutic strategies. Equally importantly, it generates new indirect information on the normal functions of the affected proteins. This talk summarises the current knowledge of the molecular and functional characteristics and pathological alterations of proteins involved in adhesion and stability of the epidermal basement membrane zone in the skin.

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MANAGEMENT OF ATOPIC DERMATITIS

Professor Nick Reynolds, Professor of Dermatology, University of Newcastle upon Tyne, UK
Email n.j.reynolds@ncl.ac.uk

Severe eczema can be devastating and may affect the quality of life of families/carers as well as the patient themselves. The effects of severe itch can be underestimated, particularly by non-dermatologists. Moreover, recent studies have highlighted that the recurrent, partial sleep disturbance which often occurs in patients with severe atopic eczema can result in significant neuro-cognitive impairment. The psychological disturbance caused by eczema is increasingly recognised: teasing (for example about possible contagion) can lead to social exclusion and result in negative effects on self-image and self-esteem. Patients with chronic skin diseases including eczema show significant dissatisfaction with current treatments and are disillusioned with their care.

Eczema runs a fluctuating course and the optimal management of severe eczema depends on many factors including acute or chronic presentation and the presence of complications such as secondary infection, such that each patient presents an individual problem. A multi-disciplinary and 'educational' approach is increasingly being employed (with important input from specialist nurses). There is a good evidence base to support the use of topical steroids and second-line treatments such as topical calcineurin inhibitors or phototherapy. However, rather surprisingly the evidence base is lacking for a number of treatments used routinely in clinical practice, including emollients, bandages and interventions to reduce *Staphylococcus aureus* skin colonisation and secondary infection.

Progression to systemic therapy depends in part on severity and failure/relapse/contraindications to second-line therapies such as topical calcineurin inhibitors or phototherapy. The need for randomised controlled trials to evaluate systemic treatments is underscored by (a) the fluctuating course and (b) a significant placebo response. However, clinical trials do not always define factors such as whether eczema is acute or chronic which clearly impact on decision making in the clinical setting.

The evidence base and the pros and cons for ciclosporin, azathioprine and methotrexate will be presented. Alternative options include mycophenolate mofetil or intravenous immune globulin.

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DIAGNOSIS AND TREATMENT OF ACUTE SKIN INFECTIONS FOR THE INTERNAL PHYSICIAN

Dr Neil Cox, Consultant Dermatologist, Cumberland Infirmary, Carlisle, UK
Email neil.cox@ncumbria-acute.nhs.uk

General physicians and GPs see many skin infections, varying from trivial athlete's foot through to life-threatening necrotising fasciitis. This talk concentrates on those that cause diagnostic or therapeutic problems, or that are serious, in a largely visual format.

Examples of potentially severe but relatively common skin infections include streptococcal cellulitis and herpes zoster. Some of these have systemic manifestations, such as streptococcal toxic shock syndrome. Distinguishing cellulitis from chronic oedema causes diagnostic difficulty; home treatment of cellulitis is an emerging therapeutic option, but the same condition may be a precursor of necrotising fasciitis and death – warning signs such as 'crescendo pain' are highlighted.

At the other end of the spectrum of severity, fungal infections of the skin and nails are common and often chronic, but are often incorrectly diagnosed and treated. Likewise, the failure to recognise and treat scabies appropriately is relatively common but important as this infestation can cause great problems, especially in nursing home and hospital settings.

A few less common diagnoses that may present acutely and that cause diagnostic problems (such as cutaneous larva migrans, infections in immunosuppressed subjects, and orf) are also demonstrated.

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DRUG REACTIONS IN THE SKIN: WHAT IS NEW?

Professor Jean-Claude Roujeau, Professor of Dermatology, University of Paris, France
Email jean-claude.roujeau@hmn.aphp.fr

Adverse drug reactions affecting the skin are frequent. Most are benign; life-threatening ones are very rare but have a strong impact on the benefit/risk evaluation of medicines. The aim of this presentation is to provide an 'expert' overview on the epidemiology, diagnosis and management of Severe Cutaneous Adverse Reactions to drugs (SCAR).

Since 2003 the RegiSCAR study has enrolled more than 500 European patients with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), a prospective cohort permitting better evaluation of prognosis and sequelae.

Clinical definitions proposed in 1993 for SJS, TEN and erythema multiforme (EM) majus were validated as well as diagnosis scores used for SJS/TEN, drug rash with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP). The cohort study demonstrated that the risk of dying from SJS or TEN was even higher than previously suspected and followed by a high prevalence (>80%) of more or less invalidating sequelae.

Allopurinol is nowadays the principal cause of SCAR in Europe. Sixty-one percent of 31 European patients with allopurinol-induced SJS/TEN carried the HLA-B*5801 allele (OR =61 [32–118], p <10–8) as previously observed among Han Chinese in Taiwan. An analysis of treatments did not demonstrate a benefit from intravenous immune globulin in SJS/TEN but suggested that further studies of corticosteroids could be worthwhile.

Earlier recognition and referral to reference centres and better understanding of the mechanisms of acute lesions and sequelae should soon lead to improved management of SCAR.

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AUTOMATED DIAGNOSTIC SYSTEMS FOR SKIN DISEASE

Professor Jonathan Rees, Professor of Dermatology, University of Edinburgh, UK
Email jonathan.rees@ed.ac.uk

A major skill of the dermatologist is attaching semantics to images. To what extent is it possible to imagine machines taking on this role?

Doctors no longer pretend they can estimate blood pressure based on examination of the pulse, nor is urine tasted to distinguish the different types of diabetes. The use of machines offers a number of potential advantages including a reduction in cost, higher accuracy and ease of audit.

Dermatology is a highly visual subject with endpoints that are, in comparison with much of medicine, soft or complex. It is widely assumed by clinicians that automated methods of diagnosis relying on computer vision are unlikely to influence clinical practice. I argue otherwise and review the current state of automated visual diagnosis, making the following arguments:

- Clinicians usually overestimate their diagnostic ability.
- Clinicians may have less insight into how they diagnose than they imagine.
- Automated methods, given their relatively young age, are promising in comparison with other experimental areas of medical research.
- Technology growth across many domains may be relevant to the tractability of attaching semantics to images in cutaneous medicine.

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DO WE REALLY UNDERSTAND ATOPIC DERMATITIS?

Dr Mike Ardern-Jones, Senior Lecturer in Dermatology, University of Southampton, UK
Email m.aj@soton.ac.uk

Atopic dermatitis (AD) has had at least 20 synonyms over the past century. The need to redefine such a common disease probably reflects the complex phenotype and suggests that AD individuals are actually a pathogenically heterogeneous population. AD is an important disease as it now affects 20–30% of schoolchildren.

Advances in our understanding of the genetics of AD have demonstrated the important role of the skin barrier in the disease process. As well as having dry skin and increased transepidermal water loss, individuals with AD also suffer increased skin infections and allergies. Recent work suggests that the barrier is not purely a structural entity, but also an immunological and chemical one. These functions are likely to be determined by genetic factors which modulate the risk of developing AD. It is well recognised that the disease's prevalence has increased significantly over the past 40–50 years. Also, approximately 50% of children 'grow out' of AD. These epidemiological statistics are difficult to explain on the basis of genetic factors alone and it is likely that the environment also plays a major role in pathogenesis.

For any individual with AD, the goal should be to identify and reverse the causative factors as far as possible. Therefore to completely understand AD it is necessary to develop a model which encompasses all of the aspects discussed above.

Declaration of interests None declared.