

Dermatological insight

Professor Martin Steinhoff has 20 years' experience in the field of dermatology. Here, he describes his expertise, research objectives and the truly translational nature of his work on skin disease



How has your background prepared you for your current positions as Professorial Chair of Dermatology and Director of the Charles Clinic and Institute of Dermatology at University College Dublin (UCD), Ireland?

I studied medicine and human biology in Marburg, Germany, followed by a residency in internal medicine and dermatology. In between, I did a postdoctoral fellowship at the University of California, San Francisco (UCSF) Medical Center, USA. At the University of Münster, Germany, where I finished my residency and became Assistant and later Associate Professor, I established the infrastructure for a functional day care unit and several outpatient clinics, and combined this with a basic science research group to form a

translational dermatology unit. This was an important experience for me and gave me the opportunity to combine patient care, basic research and clinical trials.

As Full Professor at UCSF, I continued to build a large clinical and translational infrastructure, establishing itch and rosacea clinics and a translational neuro-immunology research group. Within five years, my group was able to obtain funding of around US \$10 million to study how the immune and nervous systems communicate, and to test these mechanisms in animal disease models and human clinical trials. Now at UCD, the outstanding infrastructure, with large patient care clinics, clinical trial units and a new €20 million research centre for over 70 scientists provides an extraordinary opportunity to intensively study the pathophysiology of various skin diseases, hopefully leading to new and improved therapies.

What is your vision for the UCD Charles Clinic and Institute of Dermatology, and how will you achieve this?

My vision is not only for this Institute and Clinic, but for dermatology as a whole; to combine high-quality basic and clinical science, and to test novel therapies in clinical trials to improve patient wellbeing. This is attractive for research organisations, researchers, physician scientists, companies and patients alike. Indeed, we already have a

community of excellent researchers from many continents who want to conduct state-of-the-art dermatology research. In addition, we have established a sample bank for various diseases and, together with the Irish Skin Foundation, developed an infrastructure to showcase dermatology research and dermatological diseases to the public, patients and their families. The registration of various skin conditions in Ireland will be important for future research and clinical studies. This will facilitate future decisions about the health system and novel treatments in order to develop and provide the most effective drugs for therapy-resistant skin diseases.

Your clinical specialties are in the field of dermatology, but your wider research interests include neuroimmunology, itch and chronic inflammation. How do you combine these interests?

My clinical specialties are atopic dermatitis, pruritus (itch), eczema, psoriasis and rosacea, but my scientific approach comes primarily from a cell biology perspective. I am interested in the basic cellular mechanisms and pathways that lead to deregulation and thereby chronic diseases. We study these mechanisms in animal models and in human cells *in vitro*, starting from simple clinical observations that lead to mechanistic questions. Many fascinating questions remain unanswered, such as: how do the immune and nervous systems communicate, and which skin diseases are caused by the deregulation of this process?

Itching for a cure

The Charles Clinic and Institute of Dermatology at **University College Dublin**, Ireland, is advancing understanding of the mechanisms underlying skin disease to develop novel treatments and perform pioneering clinical trials for common conditions including eczema and itch

DISEASES OF THE skin are some of the most common and enduring, and can severely impact the confidence and quality of life of those affected. In fact, the British Skin Foundation estimates that in the UK alone there are 8 million people living with a skin disease, often without treatment.

Although symptomatically diverse, skin disorders may be linked by a common factor: neuro-immune interaction. For over 30 years, scientists have known that nerves communicate with the immune system, and that this process correlates with itch, pain, inflammation and cancer. First, neuroreceptors were discovered on immune cells. More recently, classical immune receptors have been identified on sensory neurons, leading to a surge of research into how the expression of neuronal immune receptors influences skin disorders.

Professor Martin Steinhoff has a longstanding interest in this interaction, having led research groups in Germany and the US dedicated to neuro-immune communication. Now, as Professorial Chair of Dermatology and Director of the University College Dublin (UCD) Charles Clinic and Institute for Dermatology – Ireland's only dermatology research institute – he is investigating how these systems communicate to maintain skin homeostasis and wellbeing, as well as

how and when deregulation of this interaction can cause sustained inflammation or chronic disease. A truly translational researcher, Steinhoff applies his findings to a number of clinical problems, including atopic dermatitis and itch, rosacea, acne, psoriasis and skin cancer.

A NEUROIMMUNOENDOCRINE ORGAN

In recent years, a raft of research has come together to identify a network between sensory nerves, the neuroendocrine axis and the immune system. Sensory nerves interact with hormones and immune factors to influence vital functions in the body, including inflammation, itch, tumour development, skin ageing and wound healing. Working together, multidirectional interactions between neuromediators, immune mediators, their receptors and regulatory protein-degrading enzymes (proteases) maintain tissue integrity and regulate inflammatory responses in skin.

Steinhoff is interested in gaining further insight into neuro-immune communication – how two of the most important systems in the body interact with each other in a variety of disease types, from inflammation and infection to ageing and cancer. His team is currently working to describe the role of immune receptors on sensory nerves, using this to develop and test novel therapeutics for skin diseases currently resistant to therapy.

RECEPTOR ACTIVATION

A major focus of Steinhoff's work are proteases and protease-activated receptors (PARs), which have roles in skin inflammation, itch and immunity. Studying these receptors led Steinhoff to what he considers his most significant finding, published in 2000 in *Nature Medicine*.

Working independently, his group discovered that proteases can directly activate a receptor found on sensory nerves, called PAR-2, in turn regulating inflammation. This revolutionised understanding of how proteases, generated by immune cells, can communicate with nerves to cause skin diseases. "This had direct therapeutic impact, as protease inhibitors or PAR antagonists may be beneficial for the treatment of atopic dermatitis, other eczemas or itch," Steinhoff enthuses. Since its publication, the article has been cited over 500 times, and accelerated research in dermatology.

A NOVEL NERVE PROTEIN TARGET

Itch is a prevalent but poorly understood symptom of numerous skin and systemic diseases, and a frustration with which many patients can identify. Although antihistamines can relieve chronic itch for some, they fail to suppress the symptom in over half of skin disease patients. Consequently, as the underlying pathways largely remain a mystery, there are no entirely effective treatments available to alleviate this affliction.

Could you discuss your recently published work in the *Journal of Clinical Investigation* on a nerve protein target for chronic itch?

We uncovered that endothelin is not only an important histamine-independent itch mediator in mice, but also in human chronic itch. Moreover, endothelin-converting enzyme-1 (ECE-1), which normally regulates endothelin activation, seems to block endothelin-induced itch, making it an endogenous anti-pruritic molecule that controls itch. Finally, we provided evidence that endothelin-A receptor antagonists may be beneficial for treatment of recalcitrant chronic itch, where endothelin plays a role as a transmitter.

To what extent has collaboration been important to your work?

Collaborations have always been important to me. In my experience, the brains of two or three scientists can produce better and faster results than one; especially in interdisciplinary fields that require both basic scientific and clinical knowledge. If I have a scientific question, I look for the best people in the field and discuss the problem or hypothesis with them; it is more fun, speeds up learning processes and minimises mistakes. Working with outstanding scientists has been critical for my success in describing new mechanisms in skin diseases.



INTELLIGENCE

UCD CHARLES CLINIC AND INSTITUTE FOR TRANSLATIONAL DERMATOLOGY

OBJECTIVES

To understand nervous and immune system interactions, the mechanisms responsible for skin homeostasis and, if dysregulated, how this results in sustained inflammation or tumourigenesis.

KEY COLLABORATORS

Dr Nigel Bunnett, Monash University, Australia • **Dr Earl Carstens**, University of California, Davis, USA • **Dr Richard Gallo**, University of California, San Diego, USA • **Dr Bernhard Homey**, University of Düsseldorf, Germany • **Dr Hasabe KO**, Toray Cooperation, Japan • **Dr David Julius**, University of California, San Francisco, USA • **Professor Steven McMahon**, King's College London, UK

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MARTIN STEINHOFF received his MD, MSc and PhD from the University of Marburg, Germany. In 2002, he became Assistant Professor of Dermatology at the University of Münster, rising from Assistant Professor to Full Professor in only six years. He has board certifications in dermatology, venereology, phlebology and allergy from Germany, and in dermatology from the California Medical Board. Steinhoff has also received several prestigious scientific awards for his research in Germany and the US. To date, his group has published more than 200 articles, reviews and book chapters spanning basic science and clinical dermatology. Steinhoff was appointed to the Professorial Chair of Dermatology and Director of Charles Clinic and Institute of Dermatology at University College Dublin in January 2014. He joins UCD from the University of California, San Francisco, where he held the position of Professor-in-Residence in the Departments of Dermatology and Surgery from 2009-14.



As a result, Steinhoff has dedicated significant research efforts to understanding this enigmatic symptom. He made important progress in the field earlier this year when he revealed a key regulator of itch. Based on the knowledge that the majority of patients do not find their symptoms relieved by antihistamines, Steinhoff hypothesised that histamine must not be the only itch mediator in humans. Though existing research characterised the protein endothelin as a potent mediator of itch in animals, its role in humans was previously unknown.

In a paper published in the *Journal of Clinical Investigation*, Steinhoff confirmed that the same was true in humans, and furthermore, that it could be inhibited pharmacologically. His team identified endothelin-converting enzyme-1 (ECE-1) as a modulator of endothelin-1 (ET-1). He also found that, by modulating ET-1, ECE-1 activates the kinases ERK1/2 – inducing itch in a histamine-independent manner.

In mouse models of itch, inhibiting ECE-1 increased scratching behaviour, while inhibiting ERK1/2 had the opposite effect, suggesting itch was ameliorated. Moreover, the ECE-1/ER-1/ERK1/2 pathway was found to be more active in human patients with prurigo nodularis – a skin disease characterised by intensely itchy nodules.

Together, these findings strongly suggest that the ET-1/EATR/ECE-1 axis could be a potential route out of itch for certain patients. Blocking ET-1 or activating ECE-1 could suppress the itch process, aiding a subset of those patients who cannot be treated with antihistamines.

ITCH INVESTIGATIONS

Building on this, the team described another previously hidden mechanism of itch. In research published in the *Journal of Allergy and Clinical Immunology*, they described the cellular mechanism that enables a cytokine, which traditionally regulates communication between immune cells, to induce itch. The Steinhoff group and collaborators discovered how interleukin-31 (IL-31) can cause itch by activating its receptor on sensory nerves: IL-31 receptor alpha (IL-31RA).

Although IL-31 had previously been linked to itch, the cellular basis for this was unknown. Utilising *in vivo* behavioural techniques, neurophysiology, immunohistochemistry, biochemical, fluorescence activated cell sorting and polymerase chain reaction, the team determined enhanced IL-31 levels in T cells of both mice and humans with atopic dermatitis and prurigo, and characterised how this cytokine receptor modulates neuronal function.

Their findings demonstrated that functional IL-31RA is expressed by a subpopulation of neurons, representing a critical link between T cells and sensory nerves. "This explains how cytokines can communicate directly with sensory nerves to regulate itch, and supports recent findings that immune cells can signal nerves to induce itch," Steinhoff explains. It also provides a new therapeutic mechanism; targeting IL-31 released by TH2 cells or the neuronal IL-31RA could be an effective means of managing T cell-mediated itch,

which includes atopic dermatitis, prurigo and cutaneous T cell lymphoma.

CHANGING PERCEPTIONS

Steinhoff is making great strides to improve research and awareness of itch, not only a dermatological symptom, but also a common problem in systemic diseases and even some cancers. Ultimately, he hopes to change views on itch, in turn improving patient care. "Everyone who has experienced the devastating effects of chronic itch will agree that relieving a patient is as important as treating the underlying cause. Chronic recalcitrant itch should be acknowledged as an urgent medical need – similar to migraine or chronic pain," he comments.

Over the years, Steinhoff has made several seminal discoveries, both in Germany and the US. Now at the UCD Charles Clinic and Institute of Dermatology, he plans to apply a groundbreaking systems biology approach. "We can learn a lot by utilising bioinformatics and biostatistics to understand the different complex pathways that control skin diseases," he expounds. Working with the Systems Biology Institute at UCD, his team is already utilising proteomics and genomics methods, along with immune techniques, to study signal transduction pathways in a number of skin diseases. He plans to utilise the first class translational infrastructure at UCD to take these findings into human clinical studies, revolutionising treatment for skin diseases.

Skin conditions under study

Atopic dermatitis is the most common form of eczema. Although it primarily affects children, in many cases it can persist into, or even begin in, adulthood. It is a chronic condition, characterised by itchy, red, dry and cracked skin, and its complex cause remains poorly understood.

Rosacea is a prevalent chronic skin condition primarily affecting the face. Characterised by facial redness and often pimples, rosacea can lead to skin pain and even disfigurement. It mainly affects middle-aged and fair-skinned individuals. Left untreated, the condition deteriorates, and its effects on personal appearance can cause significant psychological and social problems.

Pruritus or itch is tolerable when mild, but can become severe and extremely frustrating, potentially resulting in aggressiveness, depression or even suicide. It is a typical but extremely unpleasant symptom of skin conditions, from which millions of people suffer worldwide. Due to a lack of understanding of its complex mechanistic basis, there are very few existing treatments for itch thus far.