



With her research, dermatologist Ulrike Raap aims to gain a better understanding of the cellular processes in skin diseases and combat the causes.

Layer by Layer, Cell by Cell

The skin, our largest sensory organ, is the subject of dermatologist Ulrike Raap's research and medical care. She describes it as an "architectural masterpiece" and hopes that by gaining a better understanding of its components she can pave the way for the development of novel treatment approaches

Shimmering soap bubbles float across the stage in the Experimental Auditorium on the University's Wechloy Campus, blown by the youngest members of the audience attending dermatologist Prof. Dr. Ulrike Raap's lecture "When the skin bubbles up" – her two sons. The 45-year-old has just held her inaugural lecture but she has long since settled in – in Oldenburg, at

the hospital where she is Director of the University Clinic for Dermatology and Allergology, and at the Medical Faculty with its international European Medical School Oldenburg-Groningen model degree programme.

The crowded auditorium was filled with new colleagues, students, and co-workers from the Medical Faculty and clinic as well as old friends and

colleagues. Raap, who moved to Oldenburg with her whole family just a month after accepting her post at the University, has been busy since she started here in autumn 2016. Her first joint publication with fellow dermatologist and head of the Groningen Department of Dermatology, Marcel Jonkman, has already been published and a joint project with Jonkman on

blistering skin diseases is due to begin in January. At her clinic, Raap has already changed several procedures and structures, had a bathroom converted into a patient reception area and switched to electronic patient records and chiefly paperless offices.

Hans Gerd Nothwang, Interim Dean of the School of Medicine and Health Sciences, describes Raap as a "power woman". "One can hardly imagine how much energy it takes for someone with two children to build a successful academic career in medicine and on top of that run marathons on the side," he comments. But Raap's main motivation, he concludes, has to be her fascination with the skin.

Dynamics and dramatic events in the skin

Ulrike Raap discovered her palpable enthusiasm for our largest sensory organ – and the close contact with patients it entails – in the first year of her medical studies, which she began in Lübeck and completed in her home city of Hanover. To finance her studies she started working as a hospital assistant and was soon on duty at the Department of Dermatology in Lübeck on a regular basis. "Even as an assistant I was allowed to dress complex wounds, and I really enjoyed it and had fun," she recalls. The team she worked with was always very friendly and relaxed, and this made a lasting impression on her. When her clinical clerkship ended her colleagues at the Hanover Medical School's Dermatology Department convinced her to do her doctorate there. This was followed by specialist training in dermatology.

Ever since, Raap's research has dug deeper and deeper, exploring the skin layer by layer, cell type by cell type, and after a one-year stay as a postdoctoral researcher at the Neuroimmunology Department in Marburg she is now also a proven expert in immunology. Not only has she analysed the molecular and cellular processes that take

place in the body when it detects and defends itself against (real or perceived) disruptive factors, she is also able to explain these processes in a way that people without any medical training can understand. When she describes the skin, she talks about motorways, filling stations, about bubbling cells and weapon arsenals – using these images to illustrate the dynamic and sometimes dramatic events that unfold beneath the surface.

Raap's vivid descriptions revolve around topics like the eosinophil granulocytes which, because of their double nuclei, "always look like they're wearing sunglasses" and were the subject of her doctoral thesis at the Hanover Medical School (MHH) in 1999. Eosinophils are mobile cells that develop in the bone marrow and mainly play a role in fighting parasites. "The eosinophils migrate to sites of inflammation, which is exactly where they are needed," Raap explains. "So if a person has a parasite in their intestine, for example, these guys receive a signal, march in, and start firing oxygen radicals and cytokines (a group of proteins) at the parasites. In the end the parasite is eliminated from the body full of holes."

But these parasite-fighters also play a role in quite a few skin diseases. "When someone comes to you with neurodermatitis and you see that eosinophil granulocytes – along with their weapons arsenal – have accumulated in the skin, you know why their skin is so inflamed." The dermatologist and her team discovered that, in patients with neurodermatitis, eosinophils can produce and release a nerve growth factor called BDNF. According to their research, the resulting "hyperactive" nerve cells are one reason why neurodermatitis patients frequently suffer from itchy skin.

Itching is another topic in Ulrike Raap's research portfolio. She discovered that levels of a protein called interleukin-31 (IL-31), that is known to cause itching and was first discovered in 2004 by American scientists, correlate with the severity of the disease in neu-

rodermatitis patients. "Putting this to the test was actually a very simple idea I came up with when I was changing my son's nappies," she recalls. "At the time my technical assistant and I would never have guessed that we would end up publishing this project in one of the biggest immunological journals."

This research led to another outstanding publication – which also won a lucrative prize – in which Raap, together with a colleague from Lübeck, studied interleukin-31 concentrations in mastocytosis patients. Mastocytosis leads to the accumulation of mast cells (or mastocytes) normally present in human skin, which can release histamine that triggers itching. This is a serious disorder, Raap explains: "When mast cells accumulate in the intestines patients may suffer from diarrhoea; when they accumulate in the bone marrow this can lead to osteoporosis." She and her colleague discovered that increased levels of interleukin-31 are also released in mastocytosis patients and that this correlates with the progression of the disease.

When the sticking power of chewing gum isn't enough

In the meantime, a direct link has also been established between the itch-producing protein IL-31 and eosinophil granulocytes – the blood cells that look like sunglasses under the microscope. This link is evident in bullous pemphigoid, an autoimmune blistering skin disorder. In this disease, the dermatologist explains, autoimmune antibodies "cause the skin cells that usually stick together like strips of chewing gum to separate, resulting in the formation of a blister." In such cases elevated levels of eosinophils are present not only in the skin and in the blood but also in extremely high concentrations in the blister fluid – "like little nuclear power plants". The eosinophils can release IL-31 and in turn be activated by it, resulting in a perpetual

motion machine. "It's all interconnected," Raap stresses.

Gaining a better understanding of the cellular processes in skin diseases in order to combat them more effectively is the main goal of Raap's research. Among other things, she leads a sub-project in a clinical research group funded by the German Research Foundation (DFG) on bullous pemphigoid. In this project, in addition to eosinophils, she is also studying basophil granulocytes, which play a role in allergic – and acute and potentially life-threatening – inflammation. She is also involved in a project led by a colleague in Münster on the topic of itching. And in January the project funded by the Oldenburg faculty of medicine begins in which Raap and her Groningen colleague Jonkman

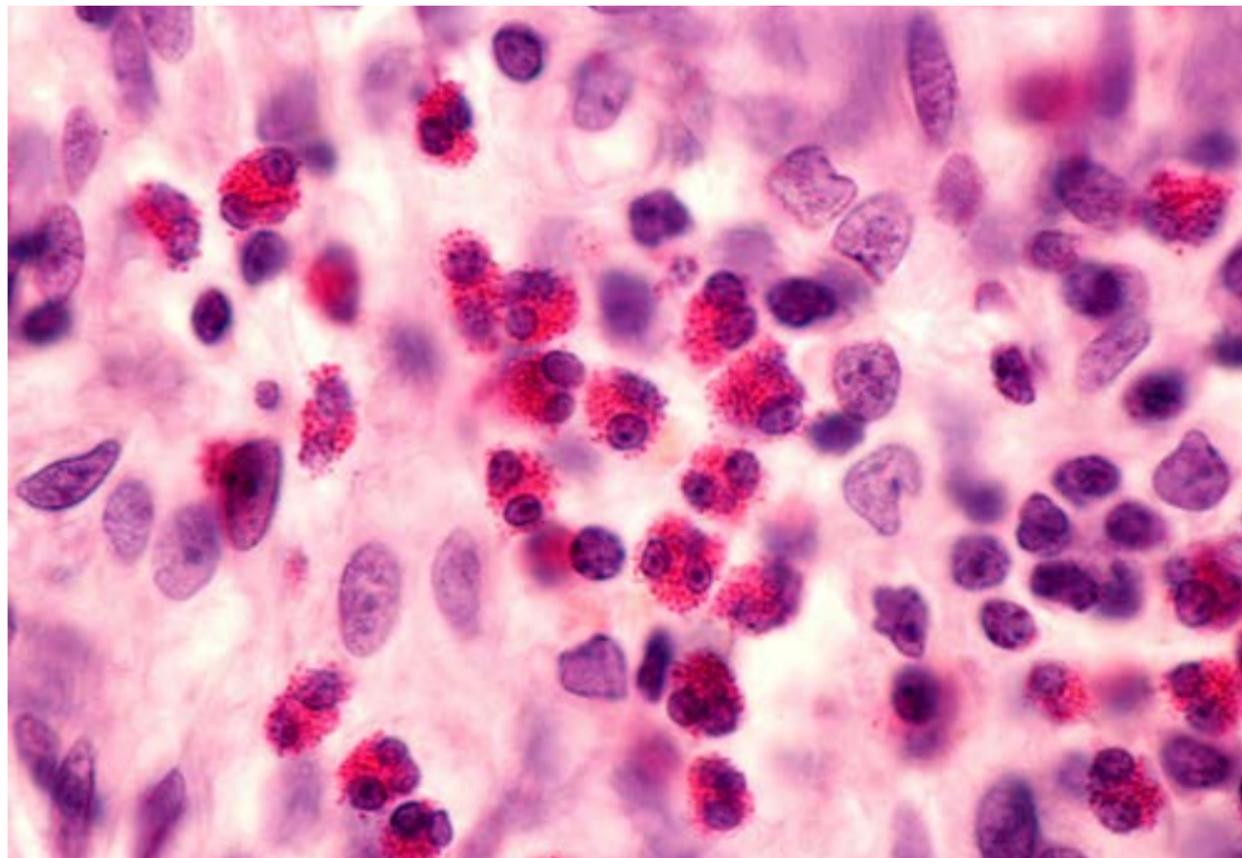
aim to establish a special skin model for blistering autoimmune disorders.

Detective work in cases of unexpected allergic reactions

Raap not only combines her research, for example the weekly meetings with Bernhard Gibbs, her Head of Research at the Wechloy Campus, with her post as Director of the dermatology clinic and its private and outpatient services, she also teaches at the "European Medical School". She enjoys "showing young people all the great things we are doing in dermatology", she says. Treating sexually transmitted diseases

at the clinic, doing detective work in unexpected cases of contact dermatitis, dealing with serious autoimmune disorders or operating on sebaceous cysts or skin cancers: the broad spectrum of activities her field offers is "a dream come true" for Raap.

In her research and teaching as well as at the clinic, the patients' well-being is always her top priority. "We work on the patient and with the patient, and our goal here is to develop new treatment options for the patients," Raap stresses. To this end her team deals with the "full spectrum" of immunological research: "No cell is safe when we're around," she jokes. All with the goal of ensuring that – contrary to the title of her inaugural lecture – the skin doesn't "bubble up". (ds)



Eosinophile granulocytes: because of their double nuclei they "look like they're wearing sunglasses". Since Ulrike Raap earned her doctorate in 1999 her research has repeatedly focussed on these mobile cells that migrate to sites of inflammation and have been linked among other things to itching.