



Stefanie and Kilian Eyerich record several hundred attributes for each patient – an extract of the database is listed above. By analyzing this data, the researchers hope to improve the diagnosis and treatment of individual skin complaints.

The Right Treatment for Every Skin Type

Two scientists with one objective: Stefanie and Kilian Eyerich want to understand how inflammatory skin diseases occur and why they become chronic for some people. They are using the most advanced methods available and one of the world's most comprehensive dermatology databases.

Claudia Doyle

Für jede Haut das Richtige

Chronisch-entzündliche Hautkrankheiten wie zum Beispiel Neurodermitis (atopisches Ekzem) oder Schuppenflechte (Psoriasis) plagen immer mehr Menschen. Die Haut rötet und schuppt sich, oft kommt noch unerträglicher Juckreiz dazu. Neurodermitis tritt meist schon bei Kleinkindern auf, oft ohne erkennbaren Grund. Zwischen 15 und 20 Prozent aller Kinder leiden daran, Tendenz steigend. Schuppenflechte manifestiert sich meist erst später im Leben. Auch bei dieser Krankheit ist die genaue Ursache unklar.

Der Mediziner Kilian Eyerich ist Professor für Experimentelle Dermato-Immunologie an der Technischen Universität München (TUM). Stefanie Eyerich ist Biologin und leitet eine Forschungsgruppe am Zentrum Allergie und Umwelt der TUM und des Helmholtz Zentrums München. Gemeinsam haben sie sich das Ziel gesetzt, die Diagnose von Hautkrankheiten mithilfe von molekularen Markern zu verbessern und dem Patienten eine Prognose über den Verlauf seiner Erkrankung zu geben. In ihrem neuen Projekt erheben sie umfassende Daten von 400 Patienten, die entweder Schuppenflechte oder Neurodermitis haben. Von den Betroffenen entnehmen sie je eine gesunde und eine geschädigte Hautprobe. Zudem erfassen sie Werte wie Alter, familiäre Vorbelastung und Zeitpunkt des Krankheitsausbruchs. Sie analysieren die Blutwerte, die Bakterienpopulationen der Haut und die RNA-Sequenzdaten aus den Hautbiopsien. Dann suchen sie nach Gemeinsamkeiten zwischen den Fällen. Bioinformatiker helfen dabei, die Datenmengen in beherrschbare Häppchen zu zerlegen. Sobald ein Gen identifiziert ist, das bei vielen Patienten einen Einfluss auf die Hautgesundheit zu haben scheint, geht es zurück ins Labor. Dort testen die Biologin und der Mediziner, was passiert, wenn Hautzellen zu viel oder zu wenig von diesem Gen exprimieren. Sie nutzen für ihre Experimente dreidimensionale Zellkulturmodelle, also Hautzellen, die in Petrischalen speziell für diese Versuche gezüchtet werden. Diese reagieren relativ ähnlich wie echte Haut, die Ergebnisse lassen sich also gut aus dem Labor in die Klinik übertragen. Bisher verlassen sich Dermatologen bei der Diagnose von Hautkrankheiten vor allem auf ihre Augen. Bald sollen sie zuverlässigere Methoden zur Hand haben. □

Kilian Eyerich's group "Experimental Dermato-Immunology"
www.derma-allergie.med.tum.de/forschung/experimentelle-dermato-immunologie.html

Stefanie Eyerich's group "Skin Immunology and Allergy"
www.zaum-online.de/research/lab-eyerich

One day a young patient came to the clinic to see Prof. Kilian Eyerich. Since earliest childhood, the teenager had suffered from atopic eczema, also known as neurodermatitis. This skin condition often makes its first appearance when the patient is still a child. For reasons that are not understood, the number of cases is steadily increasing. Today about 15 to 20 percent of all children suffer from the condition, which is accompanied by a red rash and sometimes itchy or oozing sores. The eczema generally comes and goes for no apparent reason. That was also true for this patient.

In puberty the atopic eczema suddenly vanished, but now he was plagued by scaly patches of skin: a condition known as psoriasis. This skin condition, which is to some extent hereditary, affects at least 100 million individuals worldwide.

Psoriasis and atopic eczema: two illnesses characterized by red, scaly and itchy skin. However, it is practically unknown for one patient to have both. For Stefanie and Kilian Eyerich, this patient was the starting point for a major insight into the contribution of different T helper cells to disease pathology.

Faszination Forschung: Professor Eyerich, Dr. Eyerich, how were you able to help this patient?

Kilian Eyerich: We treated his psoriasis and the therapy proved very effective.

Stefanie Eyerich: But the more the psoriasis improved, the faster the atopic eczema returned.

So as soon as you fought against one illness, the other flared up again?

K.E.: That's what happened, and we had never seen that before. We do have a few patients who suffer from atopic eczema as children and later develop psoriasis. In those cases, however, the atopic eczema disappears entirely. This interaction is very rare. We found only a few such patients in all of Europe.

Did that arouse your curiosity as a researcher?

S.E.: Yes, because we couldn't explain it. So we started looking at which kind of immune cells play a dominant role in the two skin conditions.

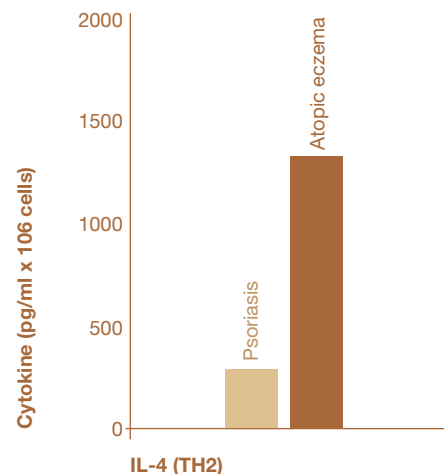
K.E.: And it is indeed two different types of T helper cells, present at the same time, that can trigger an entirely different skin reaction.

T helper cells (Th) are a group of white blood cells that form part of the adaptive immune system. They recognize hostile intruders such as viruses and bacteria on the basis of certain protein structures on their surfaces and then trigger an immune response. For a long time, only two types of T helper cells were known: Th1 and Th2. It was only 10 years ago when a third type was discovered: Th17.

The role of Th17 lymphocytes is to maintain homeostasis in tissues, for example when wounds are healing: In case of skin wounds, the body has two tasks. First, it has to close the



With large numbers of the population suffering from chronic inflammatory skin diseases, Stefanie and Kilian Eyerich want to gain a better understanding of these conditions through personalized medicine.

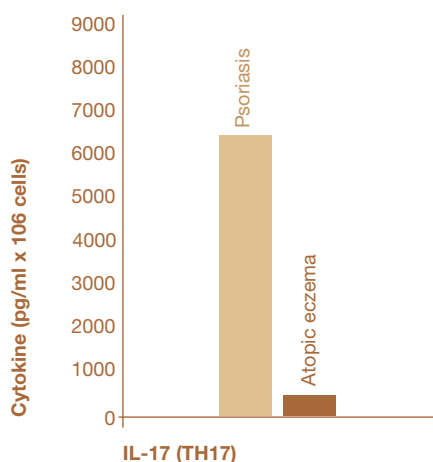


In atopic eczema, the Th2 lymphocytes are dominant. These damage the skin barrier and prevent wounds from healing. The skin becomes dry and prone to weeping at the same time.

Atopic eczema

- // Affected areas not clearly defined
- // Over 20 million adult sufferers in Europe
- // Red, scaly, itchy skin
- // Skin is both dry and prone to weeping; formation of blisters
- // Occurrence: Crook of the arm, back of the knee, face

Graphics: edlundsepp (source Eyerich); Picture credit: Magdalena Jooss/TUM



In psoriasis, Th17 lymphocytes dominate. They instruct the skin cells to divide, but if this happens at an accelerated rate, the characteristic scales will form.

Psoriasis

// Affected areas clearly defined

// 20 million sufferers in Europe

// Red, scaly, itchy skin

// Skin forms silvery-white scales which fall off easily

// Occurrence: Elbow, knee, scalp

wound. It does this by instructing the skin cells to divide and to migrate. Second, it has to prevent pathogens from invading the tissue. It is exactly these two tasks that the Th17 lymphocytes perform. They not only trigger growth in the skin cells, but also the production of antimicrobial substances.

In a patient with psoriasis, this program takes place although there is no wound. The cells multiply wildly at breakneck speed, resulting in flaking of the skin.

How can this insight be used in treatment?

K.E.: The most effective therapy for psoriasis today is to block interleukin 17, the messenger substance sent out by the Th17 cells. That is now the gold standard.

But the Th17 lymphocytes do not play any role in atopic eczema?

K.E.: In atopic eczema, it is the Th2 lymphocytes that are the dominant factor.

S.E.: Th2 lymphocytes are known as a driving force behind allergies. In the skin they can also become part of a misguided immune response: They damage the skin barrier and thus interfere with the healing of wounds by preventing strong connections from forming between the new skin cells. This allows moisture to escape, resulting in extremely dry skin. At the same time, micro-organisms such as bacteria or fungi can colonize the area, sometimes even penetrating down to the deeper skin layers.

K.E.: Th2 lymphocytes have the exact opposite effect of Th17 lymphocytes. And it was ultimately this patient who showed us this. He had either atopic eczema or psoriasis lesions, but never both at once.

In 2015 Kilian Eyerich was awarded a Starting Grant by the European Research Council (ERC). The goal of the project is to improve diagnostics for skin diseases. Today dermatologists rely above all on their eyes when diagnosing illnesses. A look at the patient followed by a look at the skin cells under the microscope: in most cases, this makes it possible for clinicians to make a reliable distinction between atopic eczema and psoriasis. In most cases.

There are patients where it is not clear which of the two conditions is present. Especially when the changes in the skin occur in the hands, it can be quite difficult to tell the difference between atopic eczema and psoriasis.

It has also proved impossible until now to make accurate prognoses on the future course of these conditions. There is still no way of predicting whether a patient will develop asthma from their atopic eczema or arthritis from psoriasis. Stefanie and Kilian Eyerich have therefore made it their goal to improve the diagnosis of skin diseases with the help of molecular markers and provide patients with a prognosis on how their condition will develop over time. ▶



Picture credit: Magdalena Jooss/TUM

“Our goal is personalized medicine for chronic inflammatory skin diseases.”

Kilian Eyerich

Today dermatologists have to rely on their eyes alone to arrive at a diagnosis. What are the advantages of molecular markers such as genes or proteins?

K.E.: A molecular diagnosis is more specific, which means that treatments can be targeted more precisely. When a drug costs 25,000 euros per year, it should go to a patient who will presumably benefit from it. There is enormous variation in eczema conditions, and we still know very little about them. Our goal is personalized medicine for chronic inflammatory skin diseases.

How do you aim to achieve that?

S.E.: By collecting highly detailed patient data and comparing it with the RNA sequencing data from the skin biopsies.

K.E.: In our database there are around 400 patients who either have psoriasis or atopic eczema. And we have characterized every one of them on the basis of hundreds of attributes.

Which ones?

K.E.: For example, which area of the skin is affected? Is there any family history? Are there other accompanying conditions? When did the condition occur for the first time? You can't seriously compare a six-month-old infant with an 80-year-old adult. But that is still happening today.

And you also include biological parameters?

K.E.: Of course. We look at the immune cells, blood vessels, endothelial cells, blood results, the bacterial populations on the skin. And then we look for common factors linking the patients.

S.E.: For that we need bioinformatics experts who break down the data into smaller packages.

K.E.: It takes an interdisciplinary approach.

The scientists have been working on the project since July 2016. From each patient they took samples of both healthy and damaged skin and sequenced the RNA. Whereas the DNA in all cells is identical, the RNA profile reveals which genes are expressed in the individual cells. An RNA analysis therefore provides information on what is currently happening in the cell. Now the analysis is being carried out.

When a gene is identified that may have an effect on the skin health of many patients, the laboratory work begins again. Stefanie Eyerich tests what happens when skin cells express too much or too little of the gene in question. For her experiments she uses three-dimensional cell culture models, specially grown in Petri dishes for this purpose. Their responses are quite similar to those of real skin, so that it is relatively easy to transfer the results from the laboratory to a clinical setting. ▶

Dr. Stefanie Eyerich and Prof. Kilian Eyerich

Better Together

In search of an area for her doctoral research at TUM, biologist Stefanie Eyerich (39) knew she wanted a subject in the field of medicine. She found dermatology – and her husband. She took on a topic that the medical student Kilian Eyerich (38) had examined in his own doctoral research.

After completing her thesis, Stefanie Eyerich went to pursue her studies in London. And Kilian Eyerich went to Rome where he worked as a postdoctoral researcher.

They both returned to Munich in 2009. She went to the Center of Allergy and Environment (ZAUM), a joint research institution of TUM and Helmholtz Zentrum München (HMGU). He began his residency as a dermatologist. During that time, Kilian Eyerich also intensified his research activities and completed his Ph.D. That meant days in the clinic and evenings in the laboratory. At that time, financial support – or role models – for this career path were virtually non-existent. Although the structures have improved since then, many young doctors are still hesitant to take on that kind of double workload.

In 2012 Kilian Eyerich became a senior physician at the Department of Dermatology and Allergy of TUM's university hospital. In 2014 he was appointed to a Heisenberg Professorship at TUM, funded by the German Research Foundation (DFG).

Stefanie Eyerich was appointed head of a joint junior research group at ZAUM and HMGU in 2013.

Despite the many projects they carry out together and their shared laboratories, the two scientists see very little of each other in a normal workday. After his morning in the clinic, Kilian Eyerich pops into the shared office before lunch. Afterwards they go their separate ways again. One of them has to leave to pick up their children from school.

Fortunately their working hours are flexible – above all in Stefanie Eyerich’s case – and their superiors are understanding. That was especially important when the children were small and daycare places hard to come by. If both of them want to attend a congress, the grandparents step in to help.

S.E.: We don’t see much of each other at work, but on the scientific level our work is very much interconnected.

K.E.: You’re right up to date with the latest methods ...

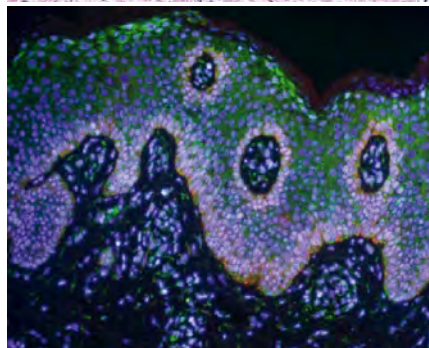
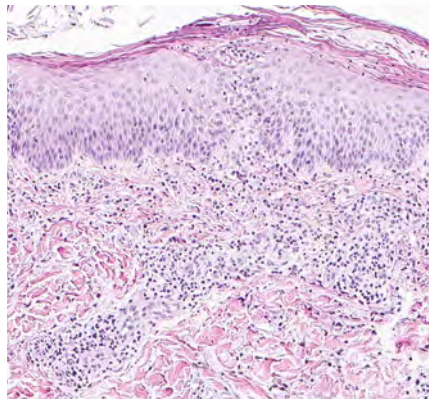
S.E.: ... and you contribute the patient data from the clinic.

K.E.: Each half perfectly complements the other.

Claudia Doyle

Atopic eczema

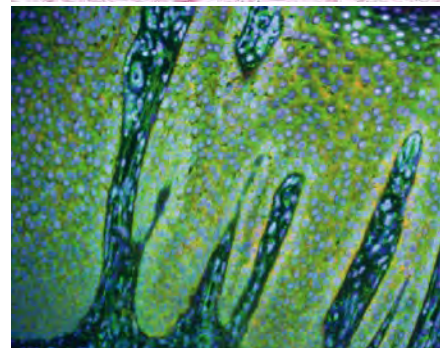
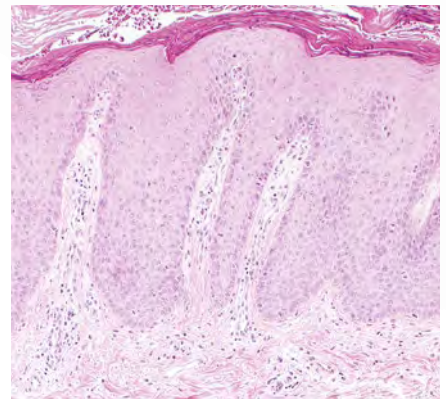
// Top: Light microscopy
// Bottom: Fluorescence microscopy



In atopic eczema, the connections between the epidermis and skin cells (keratinocytes) are damaged. The skin cells create more of a semiochemical called CCL27 (red staining in lower picture).

Psoriasis

// Top: Light microscopy
// Bottom: Fluorescence microscopy



In psoriasis, the epidermis becomes thicker. The skin cells form more of the enzyme iNOS (green staining in lower picture), which plays an important role in the immune system.

“We need bio-informatics experts who break down the data into smaller packages.”

Stefanie Eyerich