

## HISTORICAL PERSPECTIVES

# Pioneers in Dermatology and Venereology: an interview with Professor Jens-Michael Schröder

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None Declared.

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None Declared.



## Curriculum vitae

Jens-M. Schröder was born in 1949 and graduated in chemistry. He received his diploma in chemistry in 1976. In 1980 he finished his Doctoral thesis in Organic Chemistry on constituents of *Hagenia abyssinica*, an Ethiopian anthelmintic drug. In 1979 Dr. Schröder joined the Dpt. of Dermatology at Kiel University to study on a grant of the German Research Foundation (DFG) in Prof. Enno Christophers' group, the role of neutrophils in psoriasis. In 1981 he became a research assistant and focused his research on neutrophil chemotaxis and chemotactic factors in lesional psoriatic scales. In 1984 he discovered in psoriatic scale extracts a novel chemotactic peptide, which he originally named ANAP, and later on, it was renamed NAP, Interleukin 8 or CXCL-8. With the discovery of IL-8 and other novel chemotactic cytokines, later termed 'chemokines', he focused on its role in cutaneous inflammation. With his work on the role of neutrophil-chemotactic cytokines in psoriasis he 'habilitated' in Experimental Dermatology and became *Privatdozent* at the Medical Faculty of the Kiel University in 1990. The high number of exciting findings on novel cytokines allowed him to apply for a DFG grant for a Clinical Research Unit on cutaneous inflammation, which was approved in 1991. In 1994 Dr. Schröder was appointed as a professor for the Biochemistry of Inflammation and became head of the Clinical Research Unit 'Cutaneous

inflammation' until his retirement in 2015. After the discovery of the first human inducible peptide antibiotic beta-defensin-2 in 1997, again from psoriatic scales, and the discovery of several other antimicrobial peptides from human skin, he recognized these host defence peptides as effectors of an epithelial defence system. As a founding member and speaker, Dr. Schröder created the interdisciplinary Collaborative Research Center (SFB 617) 'Mechanism of Epithelial Defense', which was approved by the DFG in 2002. In 2007 he was a co-founder of the Excellence Initiative 'Inflammation at Interfaces' at the Kiel University and acted on the steering committee until 2011. As vice-co-chair in 2009 and as co-chair in 2011, he organized two Gordon Research Conferences on Antimicrobial Peptides. In 2008 he received the prestigious high-risk Reinhart-Koselleck grant of the DFG to investigate 'resistance-avoiding antimicrobial principles of healthy human skin' and identified 'Cationic Intrinsically Disordered Antimicrobial Peptides, CIDAMPs' as natural disinfectants of healthy skin.

His scientific foci were on the role of neutrophils and eosinophils in cutaneous inflammation, mediators of inflammation, and the role of epithelial peptide antibiotics in epithelial defence and its regulation. He discovered or co-discovered several important molecules or their function, among them the chemokines IL-8, Gro-alpha, RANTES, eotaxin, the antimicrobial peptides hBD-2, hBD-3, RNase-7, Psoriasin, CIDAMPs like hornerin and filaggrin-2, the protease-inhibitors elafin, SPINK-9, SPINK-6 and others. He contributed to the understanding of the role of  $\beta$ -defensins as factors linking innate and adaptive immunity, as well as understanding the role of cathelicidin in psoriasis pathogenesis. Most of his discoveries originate from biochemical analyses of lesional psoriatic scales or stratum corneum.

Dr. Schröder published more than 413 original articles ([orcid.org/0000-0003-0682-6359](https://orcid.org/0000-0003-0682-6359)) and has been a member of the editorial or review board of several well-established journals. He received several prestigious national and international scientific

awards and became a 2016 honorary member of the European Society of Dermatological Research ESDR. Dr. Schröder is an elected member of the German National Academy of Science LEOPOLDINA.

### What brought you to work as a trained organic chemist in a dermatological clinic?

Just before finishing my Ph.D. thesis in Organic Chemistry, in 1979, I started looking for a job. I had heard that Prof. Enno Christophers was looking for a biochemist for his DFG project 'The role of granulocytes in psoriasis'. Although I am not a biochemist, I applied for this job and got it. I thought that this job was only until finishing my Ph.D. – also because there seemed to be no perspectives for a chemist working in a dermatology department. But Enno Christophers created conditions that allowed perspectives for me, as well as equipment within a small laboratory to perform biochemical and cell biological experiments.

### Your first research project was about neutrophil chemotaxis in psoriasis. This sounds very far away from a project for an organic chemist. Why did you have no fears of contact with this project?

Although I have been trained in chemistry, by heart I am a biologist. When I was young, I was interested in both, chemistry and biology, but decided to study chemistry because chemistry was expected to offer better chances for getting a job and my interest in biology served as a hobby. This interest and knowledge made it easier for me to work on the neutrophil chemotaxis project.

### You have not studied medicine. How did you manage to answer questions related to psoriasis pathogenesis?

In the beginning, it was really difficult. All things, including histological and immunological aspects of psoriasis, were foreign to me. I have read some textbooks and articles about immunology and immunohistochemistry in psoriasis and discussed every day about medical aspects with my mentor Enno Christophers. Further, I should say, I attended the weekly meeting where the most relevant patients and skin diseases were presented in a slide show. Although in the beginning, it was like *Böhmische Wälder*,<sup>1</sup> over time I understood the subject more and more. This was very helpful for me later on, to go deeper into the pathogenesis of psoriasis and generally to understand inflammation.

### Please list your 5 best publications

Schröder JM, Christophers E. Identification of C5ades arg and an anionic neutrophil-activating peptide (ANAP) in psoriatic scales. *J Invest Dermatol* 1986; 87, 53–58.

<sup>1</sup>Bohemian forests

Discovery of interleukin 8, isolated from psoriatic scale extracts.

Harder J, Bartels J, Christophers E, Schröder JM. A peptide antibiotic from human skin. *Nature* 1997; 387861.

Discovery of human  $\beta$ -Defensin-2, isolated from psoriatic scales.

Yang D, Chertov O, Bykovskaia SN, Chen Q, Buffo MJ, Shogan J, Anderson M, Schröder JM, Wang JM, Howard OM, Oppenheim JJ. Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science* 1999; 286:525–528.

Discovery of Beta-defensins as innate and adaptive immunity-linking factors.

Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, Cao W, Wang YH, Su B, Nestle FO, Zal T, Mellman I, Schröder JM, Liu YJ, Gilliet M. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* 2007; 449, 564–569.

Identification of the antimicrobial peptide LL-37, complexed with DNA, in psoriatic scale extracts as plasmacytoid dendritic cell self-DNA-sensing agent.

Latendorf T, Gerstel U, Wu Z, Bartels J, Becker A, Tholey A, Schröder JM. Cationic Intrinsically Disordered Antimicrobial Peptides (CIDAMPs) Represent a New Paradigm of Innate Defence with a Potential for Novel Anti-Infectives. *Sci Rep*. 2019; Mar 4;9:3331. doi: 10.1038/s41598-019-39 219-w.

Discovery of an overlooked innate defence system of body surfaces with CIDAMPs as common natural disinfectants.

### Your curriculum of research reveals the discovery of a huge number of novel molecules, mainly from psoriatic scales and stratum corneum. What is the key to your success?

As an analytical chemist, I got lots of experience in chemical structure-based research questions. A key was the use of different physicochemical methods to get physicochemical data together with bioassay data and a plausibility test to confirm or refute a proposed structure. Further, I have always looked after unexpected findings, which sometimes led to completely new projects, that is the discovery of the protease inhibitor elafin or the discovery of the inducible beta-defensin hBD-2 in psoriatic scales. Another important aspect was detective work (I was trained to be a detective before I began my study of chemistry). For example, a striking finding was the discovery that only bacterial biofilms induce hBD-2: My PhD-student investigated, whether culture filtrates of bacteria can induce hBD-2. He always failed to see an effect, except one morning. I asked him, whether he had changed the protocol, but he said, nothing was changed. So, detective work was necessary and finally, it came out that the shaker did not work. The consequence of this initially ignored fact has been that bacteria were grown as biofilm-forming static cultures, which release inducers of antimicrobial peptides.

### Have you ever been president or in the leadership of an academic society or scientific organization?

I was elected to be president of the German 'Arbeitsgemeinschaft Dermatologische Forschung, ADF' in 1990 – without having studied medicine. Further, with the discovery of several antimicrobial peptides (AMPs) in the skin and other epithelia, I speculated that AMPs could be the effector molecules of an epithelial defence system also in other human epithelia as well as in animals and plants, and created in 2001, a DFG-supported interdisciplinary collaborative research centre 'Molecular Mechanisms of Epithelial Defense' with myself as speaker. In 2011 I was co-chair and organizer of the Gordon Research Conference on Antimicrobial Peptides.

### What was your greatest achievement in your professional life?

For a scientist, it is always a dream to follow an idea without having financial limits and without bureaucratic obstacles. In 2008, the German Research Foundation (DFG) created the so-called Reinhart Koselleck Projects, which enable outstanding researchers with a proven scientific track record to pursue exceptionally innovative, higher-risk research. In 2008 I submitted a grant application (only 5 pages!) with a crazy idea (I proposed three hypotheses, which could explain, why healthy skin is healthy and not always infected). One of these hypotheses was part of a rejected grant application, where the referees did not believe my ideas. Exactly on my birthday, I got the information, that I had won this prestigious grant, which gave me 1.5-million euros and allowed me to freely follow my ideas for 5 years – exactly until my retirement in 2015! At that time, I had been the first scientist in medicine, who earned such a high-risk grant. With one of the hypotheses (which had been rejected in a previous grant application!), I was right and described a yet unknown general disinfection system of healthy human skin and in general body surfaces in animals and plants. This system is based on so-called Cationic Intrinsically Disordered Antimicrobial Peptides (CIDAMPs).

### What was the greatest disappointment in your professional life?

When you perform hypothesis-driven research, there is a high risk that your hypothesis is wrong. Since I like very much this type of always challenging research, I always had to be aware that this could happen to me. In the proposal of my high-risk Reinhart Koselleck-Project I had three hypotheses. One hypothesis (originally my favourite!) was about the structural identification of the most potent and efficient antimicrobial of healthy human skin. Upon HPLC analyses of healthy human skin washing fluids, I reproducibly found very low amounts of an activity peak. So, I pooled the fractions with this activity for the past 10 (!) years. With modern methods, I was able

to get some, but peculiar data. Based on these data I created the hypothesis that this novel skin-derived antibiotic has a unique, not yet described structure. To make the long story short, I identified it as chlorhexidine. This was very disappointing for me and my team because we had spent lots of effort and money. But why did we identify chlorhexidine? The explanation was: we used handwashing fluids obtained from clinical personnel, which always used a disinfectant after handwashing! This persisted at the skin surface. Fortunately, I had two other hypotheses, and the discovery of CIDAMPs later on compensated for our frustration.

### Which was your most challenging discovery and have you had also some funny experiences with it?

My most challenging discovery was the novel neutrophil-chemotactic factor ANAP (later renamed IL-8), isolated from psoriatic scales. In the early 80s, it was proposed that complement split products are causing neutrophil accumulation in psoriasis. My problem with this hypothesis was the known pan-leukotactic activities of C5a. Why do we see only neutrophils, but no other leukocytes in the epidermis? I proposed the existence of a neutrophil-selective or –specific chemotactic factor. To address this question directly, I tried to isolate biochemically neutrophil chemoattractants from lesional psoriatic scales and found, besides the complement fragment, yet unknown activity we termed 'anionic neutrophil-activating peptide' (ANAP). When this finding was presented at different conferences, I got lots of sceptical commentaries including 'what do you think, is that pharmacological garbage, what you are investigating?' Nevertheless, I continued to characterize this ANAP and found that the same peptide was produced by monocytes, keratinocytes, fibroblasts, lymphocytes and endothelial cells. It was then purified from litres of LPS-challenged monocyte supernatants. Fortunately, we got an offer from Harry Gregory, ICI, to get an amino acid sequence of the isolated material. The finding that ANAP-like activity was produced by nearly all cells, we suggested renaming this ubiquitously produced peptide to ubiquitin. Later on, we got a phone call from Harry Gregory, who told us that he got the sequence of ubiquitin. We were astonished that he was able to read minds! Then we recognized that a peptide with the name 'ubiquitin' already exists. We were very much disappointed that ubiquitin lacked neutrophil-chemotactic activity and suggested that it was co-purified with the novel chemotaxin. Harry Gregory told us, that 98% of the sample was ubiquitin, and thus a maximum of 2% belongs to the unknown chemotactic factor. This was a challenge to separate 2% peptide from 98% co-purifying contaminant! But I have been successful using a special technique, which allowed enough material for new sequence analysis. This made us optimistic to get soon the data, but then Harry Gregory gave us a phone call telling us: 'When shit can happen, it happens'! After having the first amino acid identified, the lamp of the sequencer died and no more sequence data were

available! This was the first time in Harry's professional life that this happened. So, we had to produce again many litres of culture supernatants, which then allowed us to get the sequence of this neutrophil-selective chemotactic peptide, which was then renamed first as Neutrophil-activating Peptide (NAP) and then as Interleukin-8 (IL-8) or more recently CXCL8.

### **Apart from dermatologic research, what is your major interest?**

Although I am trained as a chemist, by heart I am a biologist. Since my youth, I am birding, interested in botany and gardening. After being in retirement, I intensified ornithology research, in particular helping to get answers, to why the common starling became today so rare. Further, I am gardening, where I prefer culturing difficult plants, as well as culturing regional-threatened plants on the red list for distribution in suitable habitats to increase the local biodiversity of plants and insects.

Birding and gardening helped me very much during my professional life to compensate for the frustration that came up due to setbacks in science, rejected grants and manuscripts and also to have resilience in the face of challenging projects. It was my personal experience that gardening difficult plants is a good training for cultivating resilience in challenging projects.

### **Finally, what message would you give to young dermatologists?**

It is a dream of every young scientist to discover something exciting! This message shall give you some suggestions on what in my mind was important in my professional life to have had success in science and discover so many novel molecules of relevance in dermatology and epithelial defence.

Experimental dermatological research can be fascinating, challenging, boring and frustrating! It depends on the chosen topics and you.

During routine experiments in research, sometimes you are confronted with an unexpected observation. In most cases, you think you have made a mistake or there has been something wrong with the reagents, machines or with you ('I have had a bad day today'). Unexpected findings are mostly ignored because the reasons for mistaken results seem to be obvious. In some cases, however, a finding makes you curious, but you think you cannot follow it because it would be beyond your original scientific question. In other cases, you think, it might be out of interest for you or your mentor or you lack the expertise to follow the scientific question. Also, lack of financial support is an often-heard argument. Then you might think that you have no time to perform key experiments to follow an unexpected and interesting observation further.

I have to say from my personal experience that many of the scientific findings I made during my professional life were not expected! Most of my initial key experiments did not require

much time, not much money, and no expensive and yet unavailable laboratory equipment. If you are today in a similar situation, you have many more possibilities to let perform such key experiments, for example by services. Thus, an important point for you would be, to have support from your mentor to follow your interesting observation. I am thankful to my previous mentor Prof. Enno Christophers, who gave me in the 80s the freedom to follow the ideas I had, when I was a research assistant in his laboratory, together with equipment and financial support for initial experiments. This support allowed me to generate preliminary results, which were in many cases the basis of a grant application!

Unexpected findings could come up in different situations: I discovered the neutrophil attractant IL-8 (originally named 'ANAP') in psoriatic scale extracts because the expected complement fragment C5a showed a curious double peak-forming dose-response curve. The only plausible explanation was the existence of another factor apart from C5a – and that was ANAP!

In another case, we attempted to reproduce published results that an eosinophil chemoattract is produced by lymphocytes. We unexpectedly found by careful cell separation experiments that lymphocytes do not produce eosinophil attractants, but platelets, which are contaminants in lymphocyte preparations. These secrete the eosinophil-chemotactic chemokine RANTES. This example shows that unrelated cellular contamination could be responsible for effects attributed to the dominating cell type.

Also, the discovery of the elastase-inhibitor elafin came from an unexpected absence of elastase activity in a neutrophil-enzyme-release assay. Here we suggested in the beginning that it was an artefact. But further experiments showed that the enzyme inhibition was reproducible! Another example is the discovery of the antimicrobial peptide human  $\beta$ -defensin-2. In the very beginning, we constantly found it in psoriatic scale extracts during the purification of IL-8 as an unknown contaminant. Although it lacked chemotactic activity, it made me curious and I wanted to know what always co-purifies with IL-8! Amino acid sequencing then revealed a sequence similar to beta-defensins, which have been that time only described in cattle! This finding stimulated speculation and let me create a new hypothesis that this molecule is part of an unknown skin defence system. The consequence has been the beginning of a new area of research on epithelial defence and led to several new grants in my laboratory. This is another example, where a finding beyond our original scientific question resulted not only in a new protein but opened the door to a new field.

Hypothesis-driven research, as I have mostly done in my professional life, also can have a high potential for frustration: It starts with the grant application. There sometimes referees may ask for results, which you do not have but want to generate with the grant money. Another source of frustration could be the rejection of the grant application because referees see too much

speculation or a crazy hypothesis! There is also some personal experience: In the early 90s, we found in stratum corneum a highly abundant, but unknown protein. This could be identified as hornerin when data bank analyses were available more than 10 years later. In 2007 we found sometimes antimicrobial activity in hornerin preparations, but not always! Further, its biochemical data were found to be very strange. With these data, a grant application, which contained dogma challenging, crazy hypotheses, was rejected. However, these crazy hypotheses led to funding by the prestigious high-risk Reinhart-Koselleck project of the German Research Council (DFG). This grant type supports projects, which need to be so risky that support from other grant types is not possible! In this case, the frustration upon early rejection was overcompensated by winning a prestigious high-risk grant.

Finally, I would like to let you know what in my mind is important for success in experimental dermatological research: Be unbiased and open to all of your findings, even when they may challenge a dogma! Be much more critical of your findings than a referee! If you have found something very exciting, try to confirm the result using a completely different approach. Do not give up too early! Increase your resilience! Establish your method to compensate for frustration!

\*Note: The *Pioneers in Dermatology and Venereology* interview was conceived and conducted by Johannes Ring.

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