

Interviews

EMJ is pleased to present three compelling interviews with leading dermatologists, offering a glimpse into the future of inflammatory skin disease management. Sara J. Brown discusses her cutting-edge research using a human skin organoid model to map the complex interplay of genetics and environmental factors in eczema. Martin Metz sheds light on the serious systemic burden of chronic spontaneous urticaria, advocating for more effective treatment to address comorbidities like suicide risk. Finally, Astrid Haaskjold Lossius highlights the importance of consistency in care, detailing her work on harmonised treatment guidelines for childhood atopic dermatitis and discussing overcoming psychological barriers such as steroid phobia.

Featuring: Sara J. Brown, Martin Metz, and Astrid Haaskjold Lossius



Sara J. Brown

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Q1 Your research uses a human skin organoid model to investigate genetic and environmental interactions in eczema. Can you explain the advantages of this model over traditional methods, and how it's helping you pinpoint why the prevalence of eczema has increased?

The organoid model that we use is a very simplified form of human skin, but the advantage it brings is that we can isolate the specific aspects of eczema risk that we are interested in, and control these very precisely.

We know that eczema is partly a genetic disease, because it runs in families with other atopic conditions, but the fact that eczema has increased in prevalence over recent decades shows the importance of environmental factors as drivers for this disease. In human

population studies, we are limited to data that can be collected in observational epidemiology, and in clinical trials, we are obviously limited by ethical constraints over what environmental exposures can be manipulated. In the skin organoid, we can specifically alter the expression of selected genes and expose the model skin to controlled environmental effects, such as pet or food allergens, cigarette smoke, or cleansing products. We can then monitor the response using a range of functional measurements (e.g., transepidermal water loss) and molecular measurements (including gene expression, and protein and lipid levels).

We are still a long way from answering the question 'Why has the prevalence of eczema increased?', but in using the skin organoid, we have made a start in unpicking the complexity.

“In the skin organoid, we can specifically alter the expression of selected genes”

Q2 You have a background in both genetics and clinical dermatology. How does this unique combination of expertise directly influence the way you approach research questions and the design of your studies?

I love genetics because it allows us to get to the root cause, the earliest initiating mechanisms in disease. And I love clinical work because our patients are so inspiring. Patients suffer with skin disease, and clinical work raises important questions: this is what influences my approach to research. 'Why do some patients get mild or severe eczema?', 'Why do some people not respond to treatment?', 'Why don't we have better treatments?' I design my studies around these big questions from the clinic and use human skin cells and human data wherever possible to address these, so the path back to the clinic is at least theoretically possible.

My approach to therapy development also brings together genetics and clinical observation, focusing on methods to improve skin barrier function to complement our current success in treating atopic inflammation.

Q3 Your recent study on gene–environment interactions in atopic eczema showed that early-life dog exposure might modify a genetic risk factor. How do you plan to build on this finding, and what are the broader implications of these gene–environment interactions for eczema prevention and treatment?

In collaboration with a group of colleagues worldwide, we analysed data from large population studies and showed that early-life dog exposure (in utero or up to 2 years of age) can reduce the risk of eczema. This is a statistical association and was most significant in a subset of the population who

carry a specific genetic risk for eczema. So, we went on to test the association using human skin cells (keratinocytes) in the lab, with genetic analysis, modulation of gene expression, and exposure of the cells to dog allergen. We showed that a dampening-down of atopic inflammation when cells are exposed to dog allergen appears to occur via the IL-7 receptor, consistent with the genetic effect. This is preliminary evidence that the IL-7 pathway may modulate the risk of eczema, but a lot more work will be needed before this can be used as a treatment or as a preventative strategy. I do love dogs, but our work does not mean that everyone who is worried about eczema should have a pet dog!

We plan to build on this work by testing further environmental effects and their interaction with other genetic risk mechanisms, because we know that different people (with a different genetic background) respond differently



to environmental factors. This may elucidate mechanisms or pathways that could be targeted to treat, or preferably prevent, eczema in the future.

Q4 You have a strong focus on drug screening using human cells to define molecular targets. How close is this work to identifying a truly novel drug or prevention strategy for eczema that goes beyond existing treatments?

The pathway to therapy development is very challenging and prone to failure at every step, so I am cautious not to over-promise. But we have made substantial progress in understanding genetic mechanisms controlling skin barrier formation and function that can be targeted by small molecules. We have identified such molecules and are working with medicinal chemists to optimise these now. This progress offers real hope for novel therapy and preventative strategies.

Q5 You have written about the need for more rigorous research into topical steroid withdrawal (TSW). What are the key unanswered questions about TSW's molecular mechanisms, and what specific research designs would you advocate for to address them?

We still have a lot to learn about the molecular mechanisms leading to TSW and a major challenge is that TSW is a very diverse condition, with changes within the skin as well as systemic features. So, the first step is for us to learn from people with lived experience of TSW, to define core features which we can use to request specific samples for molecular analysis. A powerful research design would include longitudinal sampling of skin, blood, and saliva, to track the condition from its onset to the acute, severe stage, through the longer-term effects. In some patients, these can last months or years, before full resolution. The matching of samples from

skin, blood, and saliva would allow a comprehensive analysis of mechanisms that we wish to investigate (e.g., skin or systemic steroid insufficiency) as well as 'hypothesis-free' multi-omic analyses. I have started this work, but it will take time and more grant funding to complete this to a high standard. Convincing our research funding bodies that TSW is an important condition, worthy of research, is therefore an essential next step.

Q6 As a clinical academic, you care for patients of all ages with a wide range of skin diseases. How does your work with patients directly inform your research questions, and what have you learned from patient and public engagement that has shaped your research priorities?

I listen to my patients in clinic, but the public engagement arena allows more open, frank discussion, and children are especially good at very honest dialogue! Probably the most



important but heart-breaking message that I have heard from patients outside the clinic is that many doctors dismiss their condition as 'only' skin or 'only' eczema. The impact on the whole of life is not fully recognised, and that is frustrating. Another learning point is the discomfort caused by many of our topical treatments, and the battles that can develop in families between children and their parents/carers. So, I have changed my practice, now recommending much simpler regimes for eczema care. I focus on pre-bedtime as an opportunity for treatment to give the best chance of sleep during the night, whilst relieving families of the burden of time-consuming and complex regimes. I have learnt that some patients prefer topical treatments, whilst others strongly prefer oral or injected systemic treatments. From a research perspective, the different modes of delivery require different pharmacokinetic characteristics of the drug compounds, and this is an important consideration for our therapy development work.

Q7 Given your expertise in both eczema and ichthyoses, how does your research on genetic predispositions to dry skin conditions provide insights into other inflammatory or allergic skin diseases?

I began my research looking at the skin barrier protein filaggrin, and the genetic condition ichthyosis vulgaris, caused by loss-of-function mutations in the gene *FLG*. That was nearly 20 years ago; work from my group and many others over these 2 decades has shown a role for *FLG* in predisposition to multiple atopic disorders, indicating that primary skin barrier dysfunction can lead to multi-system disease.

“**The development of global dermatology is a driver for innovation**”

Many questions remain about exactly how filaggrin plays this role in disease predisposition, not least because more severe skin barrier defects, for example epidermolysis bullosa, do not lead to allergic or atopic disease. There is something special about the barrier defect and immune dysregulation that occurs when filaggrin is missing from the skin. There is also a damaging feed-forward loop where filaggrin expression is downregulated by atopic inflammation, further worsening the skin barrier dysfunction.

Filaggrin/*FLG* have proven difficult to target directly and, this is where an understanding of genetic mechanisms upstream of *FLG* may be useful in designing treatments. Similarly, it is difficult to know where to start in modifying the vast array of environmental factors in modern life, but we know that *FLG* affects the skin's response to allergens and irritants, so if we can understand these interactions then we may be able to intervene.

Q8 Looking at the future of dermatology, what do you see as the most significant breakthrough we can expect in the next 5–10 years, and how might that innovation impact the way inflammatory skin conditions are managed?

Many researchers, myself included, are working towards personalised medicine as an ideal

for the future, but I don't think this will be achieved in the next 5–10 years because of the great complexity and diversity of many skin conditions.

What I do see as an exciting opportunity is to bring together the detailed understanding that we now have of molecular mechanisms, with treatments to target multiple aspects of a complex disease simultaneously. Examples include normalising keratinocyte differentiation as well as reducing inflammation (in eczema), enhancing innate immunity as well as reducing scarring (in hidradenitis suppurativa), or targeting both active inflammation and tissue resident inflammatory memory (in psoriasis).

We are also seeing a growing number of patients who do not experience benefit, or who develop worsening skin inflammation despite novel therapies. I am hopeful that our understanding of genetic predisposition might inform treatment decision-making to rebalance the skin to a state of homeostasis for these patients.

Finally, recent progress in treating patients with inflammatory skin conditions has been exciting and rewarding, but this sadly excludes those who cannot access treatment for economic or sociopolitical reasons. The development of global dermatology is a driver for innovation to reduce cost and to combat the practical challenges of service delivery towards equitable provision of care. Success in this would represent a very significant breakthrough.