3 Murrell DF, Daniel BS, Joly P *et al.* Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. *J Am Acad Dermatol* 2012; **66**:479–85.
4 Masmoudi W, Vaillant M, Vassileva S *et al.* International validation of the Bullous Pemphigoid Disease Area Index severity score and calculation of cut-off values for defining mild, moderate and severe types of bullous pemphigoid. *Br J Dermatol* 2021; **184**:1106–12.
5 Wijayanti A, Zhao CY, Boettiger D *et al.* The reliability, validity and responsiveness of two disease scores (BPDAI and ABSIS) for bullous pemphigoid: which one to use? *Acta Derm Venereol* 2017; **97**:24–31.
6 Boulard C, Duvert Lehembre S, Picard-Dahan C *et al.* Calculation of cut-off values based on the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and Pemphigus Disease Area Index (PDAI) pemphigus scoring systems for defining moderate, significant and extensive types of pemphigus. *Br J Dermatol* 2016; **175**:142–9.

Advancing novel therapies for ichthyoses

DOI: 10.1111/bjd.19698

Linked Article: Valentin *et al.* Br J Dermatol 2021; **184**:1123–1131.

Sequencing technology increasingly allows for clarification of the genetic basis of disease pathogenesis in rare genodermatoses such as the ichthyoses. While there has been great progress in the discovery of genetic variations underlying ichthyoses and the elucidation of the pathomechanisms, therapeutic developments have been sparse. Too often, no therapeutic benefit follows from research advances in the field, and, to date, there are few examples for targeted therapy that address the molecular cause of the disease. Thus, patient options are still mostly limited to keratolytics, topical anti-inflammatory agents, rather unspecific emollient therapies, and topical and systemic retinoids.

However, it is likely that this will change. An increasing number of researchers are dedicated to devising new, targeted therapies based on progress in the understanding of disease pathogenesis, and powerful advances are being made in the area of genodermatoses. With regard to the ichthyoses, therapeutic intervention can take multiple and diverse forms. It remains unclear if a single one of the strategies will prevail. A competitive 'best athlete approach' is likely to yield optimal benefit for patients. Some examples of mechanism-targeted treatments currently being developed are listed in Table 1.

Table 1 Targeted therapies for ichthyoses

At the DNA level, mutations can be excised or corrected, or expression vectors can be introduced[3,4]
Small molecules modulate relevant signalling pathways, e.g. nitric oxide synthase inhibitors or Janus kinase inhibitors improve tissue models of harlequin ichthyosis[5]
Protease inhibitors are being developed to antagonize protease overactivity in Netherton syndrome[6]
Monoclonal antibodies neutralize mediators of skin inflammation in patients with ichthyosis[7,8]
Deficient lipid components that are essential for the epidermal barrier have been exogenously added and shown to improve the scaling phenotype in ichthyosis[9]
Decreased or absent proteins can be delivered to diseased skin grafts[2,10]

In 2010, Oji *et al.* reported that permeability barrier impairment in peeling skin syndrome 1 (PSS-1) is caused by corneodesmosin deficiency, resulting in a distinct ichthyosis phenotype, which includes decreased corneocyte coherence, food allergies and failure to thrive.[1] As in other related ichthyoses, this disease has a significant impact on patient quality of life and years lost due to disability, and there are no good therapies.

In this issue, Dr Oji's group presents compelling evidence of successful liposome-based delivery of recombinantly synthesized corneodesmosin to patient-derived PSS-1 keratinocytes both in monolayer and in three-dimensional (3D) cultures.[2] Aside from choosing protein supplementation as the method of disease modification, the efficient and precise delivery of the compounds to the crime scene – the tissue or the cell – represents a major hurdle. The carrier system used by Valentin *et al.* consists of 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine, mimicking cellular lipid membranes. Lamellar vesicles were optimized in size for efficient uptake of the corneodesmosin cargo, and for good penetration properties. Importantly, liposomes loaded with corneodesmosin and tagged with the lipopeptide P2K12 showed a localization at the plasma membrane of the keratinocytes. Consequently, corneodesmosin was successfully delivered to the cytoplasm of keratinocytes, and functional studies showed improvements of histopathological alterations and epidermal barrier function in 3D human skin equivalents.

As demonstrated, delivery remains a major hurdle to overcome when trying to deliver nucleic acids or peptides/proteins to viable epidermal cells. The skin barrier, as created by the stratum corneum, normally prevents large molecules from entering the body. Multiple strategies to penetrate the skin barrier for delivery of bioactive therapeutic molecules have shown promise. Other than the liposomes and cationic lipopeptide described here, additional carrier options include nanocarriers such as thermoresponsive nanogels or spherical nucleic nanoparticle conjugates. Also effective are disruptive biophysical interventions such as iontophoresis, sonophoresis, electroporation, laser abrasion, microneedles, high-velocity jets, intradermal injections and – most invasive – skin transplants. Optimization for enhanced

delivery must be carried out for each specific cargo and each specific entity.

Although liposome-based corneodesmosin delivery to PSS-1 skin appears highly attractive, the approach requires replication, refinement and *in vivo* confirmation. Nevertheless, the work is seminal and will be followed by more detailed descriptions of *in vivo* efficacy and potential adverse effects. This is a very exciting area of investigation, which opens up possibilities for treatment of PSS-1 and related disorders of cornification, i.e. ichthyoses.

M. Schmuth, J. Reichelt and R. Gruber

Department of Dermatology, Venereology and Allergy, Medical University of Innsbruck, Innsbruck, Austria
Email: matthias.schmuth@i-med.ac.at

Conflicts of interest M.S. has received research grants from ExpanScience; has participated as a Principal Investigator in trials sponsored by Roche, Amgen, MSD, GSK, Eli Lilly, AbbVie, and Orfagen; and has received travel funds from Nogra Pharma. M.S. has not accepted any honoraria from industry for advisory boards or speakers' bureau participation, and does not own pharma stocks, equity or patent licenses.

References

1 Oji V, Eckl KM, Aufenvenne K *et al.* Loss of corneodesmosin leads to severe skin barrier defect, pruritus, and atopy: unraveling the peeling skin disease. *Am J Hum Genet* 2010; **87**:274–81.
2 Valentin F, Wiegmann H, Tarinski T *et al.* Development of a pathogenesis-based therapy for peeling skin syndrome type 1. *Br J Dermatol* 2021; **184**:1123–31.
3 March OP, Lettner T, Klausegger A *et al.* Gene editing-mediated disruption of epidermolytic ichthyosis-associated KRT10 alleles restores filament stability in keratinocytes. *J Invest Dermatol* 2019; **139**:1699–710.
4 Freedman JC, Parry TJ, Zhang P *et al.* Preclinical evaluation of a modified HSV-1 vector encoding human TGM1 for the treatment of autosomal recessive congenital ichthyosis (ARCI). *J Invest Dermatol* 2020; https://doi.org/10.1016/j.jid.2020.07.035.
5 Enjalbert F, Dewan P, Caley MP *et al.* 3D model of harlequin ichthyosis reveals inflammatory therapeutic targets. *J Clin Invest* 2020; **130**:4798–810.
6 Walker AL, Denis A, Bingham RP *et al.* Design and development of a series of borocycles as selective, covalent kallikrein 5 inhibitors. *Bioorg Med Chem Lett* 2019; **29**:126675.
7 Haiges D, Fischer J, Hörer S *et al.* Biologic therapy targeting IL-17 ameliorates a case of congenital ichthyosiform cornification disorder. *J Dtsch Dermatol Ges* 2019; **17**:70–2.
8 Steuer AB, Cohen DE. Treatment of Netherton syndrome with dupilumab. *JAMA Dermatol* 2020; **156**:350–1.
9 Paller AC, van Steensel MAM, Rodriguez-Martín M *et al.* Pathogenesis-based therapy reverses cutaneous abnormalities in an inherited disorder of distal cholesterol metabolism. *J Invest Dermatol* 2011; **131**:2242–8.
10 Plank R, Yealland G, Miceli E *et al.* Transglutaminase 1 replacement therapy successfully mitigates the autosomal recessive congenital ichthyosis phenotype in full-thickness skin disease equivalents. *J Invest Dermatol* 2019; **139**:1191–5.

Regulatory noncoding RNAs help protect keratinocytes from ultraviolet-mediated damage in vitiligo

DOI: 10.1111/bjd.19827

Linked Article: Brahmbhatt *et al.* *Br J Dermatol* 2021; **184**: 1132–1142.

Nonsegmental vitiligo (NSV) is an autoimmune skin disorder associated with the absence of protective melanin in keratinocytes.[1] Recent observational studies have paradoxically shown that patients with NSV have a decreased lifetime risk of developing both melanoma and keratinocytic skin cancers (KSCs).[2] In this issue of the *BJD*, Brahmbhatt *et al.* reveal a molecular mechanism in lesional vitiligo keratinocytes that may account for this observation, which protects keratinocytes from ultraviolet (UV)-induced DNA damage.[3]

The authors studied RNA in lesional and nonlesional epidermal vitiligo skin biopsies in five patients. They focused on two classes of noncoding RNAs (ncRNA) that play important roles in the regulation of gene expression in cells:[4] microRNAs (miRNAs), which interact with binding sites on target mRNAs and repress their expression; and long ncRNAs (lncRNAs), which are frequently involved in epigenetic gene regulation. lncRNAs can function as guides, scaffolds or decoys for proteins and other cellular molecules.

The authors found that the most significantly downregulated miRNA molecule in lesional vitiligo was miR-211, and that Sirtuin1 (SIRT1), a direct target of miR-211, was upregulated. SIRT1 is a nicotine adenine dinucleotide-dependent deacetylase, important in DNA damage repair. The authors then showed in keratinocyte cell cultures that the addition of miR-211 increased sensitivity to UV-induced DNA damage, which was rescued, in part, by the addition of the SIRT1 activator resveratrol, supporting the role of SIRT1 in a protective mechanism against UV-induced DNA damage.

miR-211 itself is regulated by a lncRNA, called metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). MALAT1 was overexpressed in lesional epidermis, and the authors demonstrated experimentally that MALAT1 negatively regulated miR-211, which, in turn, led to overexpression of SIRT1. The authors concluded that the MALAT1–miR-211–SIRT1 axis contributes to protection from UV-mediated DNA damage in NSV keratinocytes.

miR-211 is known to be downregulated in vitiligo melanocytes,[5] where it regulates cellular metabolism.[6] The findings of Brahmbhatt *et al.* shift the focus to NSV keratinocytes and DNA