

**Fig 1.** A possible model for the effects of altered tryptophan metabolism in basal cell carcinoma (BCC). The BCC expresses increased levels of tryptophan 2,3-dioxygenase (TDO), which increases kynurenine levels in the tissue, this has two effects. It blocks the function of tumour-reactive T cells, which reduces tumour immune surveillance. Also, through increased neutral amino acid uptake it can reduce apoptosis and increase proliferation in the BCC itself. SLC, solute carrier.

reduces proliferation and migration of keratinocytes in wounds, and hair growth was significantly reduced.<sup>6</sup>

The role of metabolic changes in keratinocyte cancers such as BCC and squamous cell carcinoma, in addition to associated precursor lesions, are not well characterized. To address this deficiency, and to understand which is the predominant enzyme in tryptophan catabolism in BCC, Tina and coworkers compared BCC biopsies and gluteal control skin using microarray analysis to see if there was any evidence of upregulated amino acid transporters and breakdown genes. They found overexpression of SLC7A5, SLC7A7, SLC7A8 and TDO.<sup>1</sup> They then confirmed the increase of SLC7A5 and, for the first time in BCC, showed an increase in SLC7A8 and TDO. This is likely to improve tumour persistence (Fig. 1).

Although the clinical trial and drug discovery landscape for TDO is far less advanced than for IDO1 and IDO2,<sup>2</sup> there is now an argument to investigate inhibition of tryptophan catabolism as a therapeutic avenue to treat not only BCC but potentially keratinocyte cancer in general.

## Acknowledgments

I thank Catherine Harwood and Rebecca Porter for critical reading of this commentary.

## Conflicts of interest

None to declare.

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## Therapies for epidermolysis bullosa: delivery is key

DOI: 10.1111/bjd.17324

Linked Article: Peking et al. *Br J Dermatol* 2019; **180**:141–148.

Variants in the KRT14 gene that encodes keratin 14, are responsible for approximately 37% of all cases of epidermolysis bullosa simplex (EBS).<sup>1</sup> EBS is characterized by skin fragility and blistering upon minor friction. Currently, treatment of the disease is merely symptomatic and, therefore, research into therapeutic approaches is of great interest. Over recent years, several therapeutic approaches have been explored, among which are RNA-based approaches,<sup>2</sup> such as trans-splicing.

The study by Peking and colleagues, in this issue of the *BJD*,<sup>3</sup> aimed to correct a mutation in exon 1 of KRT14 by using a previously reported 5'-trans-splicing module that replaces exons 1–7 of the KRT14 mRNA.<sup>4</sup> The current study aims to elaborate on the molecular integrity of trans-splicing corrected keratinocytes. Accordingly, the RNA trans-splicing module was stably transduced into an EBS patient-derived keratinocyte cell line. Subsequently, skin equivalents were generated out of these corrected cells and grafted onto the backs of mice. These skin equivalents revealed a stable, well-differentiated epidermis

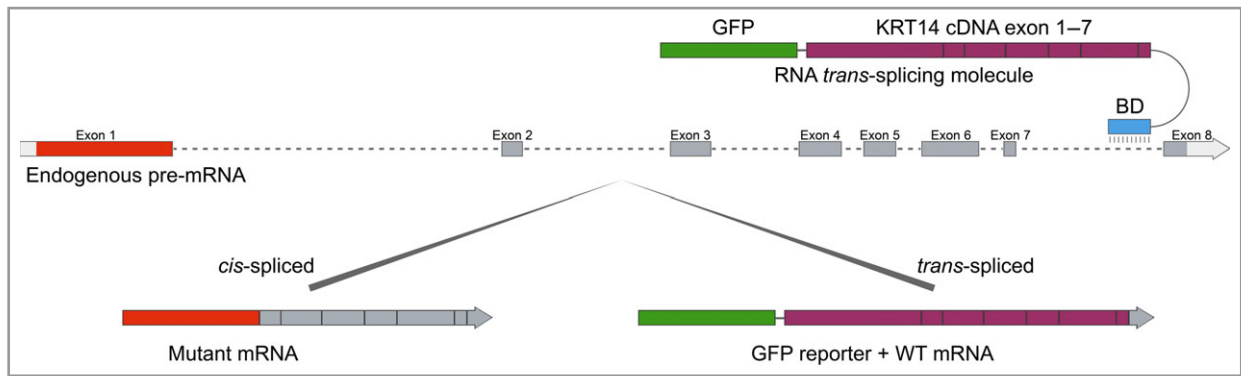


Fig 1. Schematic overview of trans-splicing in the KRT14 gene. The RNA trans-splicing molecule (RTM) RTM163 comprises three major elements: (i) a green fluorescent protein (GFP) reporter; (ii) the wild-type (WT) KRT14 cDNA exon 1–7 (purple); and (iii) an intronic binding domain (BD) that binds to intron 7 (blue). Binding of the RTM to the endogenous pre-mRNA (grey) results into two mRNAs: the cis-spliced mutant KRT14 mRNA and the trans-spliced WT mRNA. In this example, exon 1, a hotspot for pathogenic variants, is shown in red. In theory, pathogenic variants located anywhere in exon 1–7 could be corrected by RTM163. In a clinical setting the GFP reporter would be removed resulting in WT KRT14 mRNA only. In contrast to the trans-splicing approach, which is capable of correcting all variants in exon 1–7, other approaches would most likely need the design and optimization of numerous molecules as more than 60 variants in the KRT14 have been described as causing epidermolysis bullosa.

showing the great potential of trans-splicing as a therapeutic approach for EBS.

The major advantage of trans-splicing over many other approaches is that one RNA trans-splicing module can be employed to correct multiple variants in several exons, eliminating the need for designing patient-specific or variant-specific therapies (Fig. 1). However, this comes at a price, as it requires relatively large trans-splicing modules to be delivered into the target cells.<sup>5</sup> And this could pose a problem. Viral delivery into cultured keratinocyte stem cells, followed by fluorescence activated cell sorting, subsequent generation of skin equivalents and, finally, transplantation back into the patient does not seem a viable approach for routine clinical application. No doubt the preclinical results with trans-splicing have been absolutely encouraging so far; however, the crucial factor to determine whether or not it will eventually earn a place on the list of genetic therapies for genetic skin conditions is whether it will be possible to deliver the trans-splicing module into the target cells in situ safely and efficiently. Unfortunately, this is true for other approaches as well, and not only RNA-based ones.<sup>6,7</sup> But there is hope, as methods to deliver nucleic acids such as trans-splicing modules into cells are rapidly improving and becoming safer.<sup>8</sup>

There are high hopes of a future in which most genetic diseases will be curable by virally delivered gene-editing tools such as CRISPR (clustered regularly interspaced short palindromic repeats)-guided endonucleases. CRISPR has already proven its value in the generation of numerous disease models and correction of diseases in vitro.<sup>9</sup> However, it is still of great importance that other strategies, such as trans-splicing and other RNA-targeting therapies, are not pushed aside for this gene-editing-future. The magic bullet of gene-editing is still far off and complications of viral delivery, viral tropism, off-target effects and unforeseen carcinogenicity of the CRISPR approach and viral delivery, make RNA-based and RNA-

targeting therapeutics highly relevant. At least, for a period of time, until gene-editing can be safely employed as it should. Therefore, it is of great importance that reports like the one by Peking and colleagues are published in journals like the *BJD*.<sup>3</sup> Thus, bringing to the attention of a broader range of researchers and clinicians the numerous other therapeutic approaches in the pipeline for genodermatoses, rather than waiting for the magic bullet. For the heterogeneous group of patients with epidermolysis bullosa, for whom one therapy will not cure all, having options is good.

## Conflicts of interest

None to declare.

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## What lessons can we learn from an apparent decrease in the use of topical drugs for psoriasis?

DOI: 10.1111/bjd.17315

Linked Article: Svendsen et al. *Br J Dermatol* 2019; **180**:157–164.

This issue of the *BJD* includes an important study from Denmark by Svendsen and colleagues concerning the use of topical antipsoriatic drugs derived from a health registry.<sup>1</sup> Information from 7743 patients during 2005–2015 revealed that topical antipsoriatic drugs were included in 59 575 prescriptions: 31% were for topical corticosteroids combined with calcipotriol; 6.5% for calcipotriol alone; 24% for very potent topical corticosteroids; 30% for potent topical corticosteroids; and 7.2% for moderately potent topical corticosteroids; finally, 1.6% were for topical corticosteroids combined with antimicrobials.<sup>1</sup> The authors found a 19% reduction in the overall prescribing of these drugs during the 10-year study period.<sup>1</sup>

Of interest, was that a minority of these Danish patients, just 25%, accounted for 70% of the total amount of topical antipsoriatic drugs prescribed. Additionally, biological drugs were used in just 6% of the patients.<sup>1</sup> The authors speculated that the decrease in the use of topical drugs may reflect an increase in the use of methotrexate to control the disease.<sup>1</sup> They also wondered if the reduced use of topical corticosteroids might be explained by increasing corticosteroid phobia or even a reduction in adherence to prescribed treatment.<sup>1</sup>

In another population-based survey on topical treatments for psoriasis, Lebwohl et al. found that most patients were undertreated.<sup>2</sup> Furthermore, 57% who received oral therapy and 45% who received biological therapy discontinued topical treatment, citing safety and/or tolerability concerns and a lack of, or loss, of efficacy.<sup>2</sup> This high dropout rate for topical therapies was even more striking than in the current study by Svendsen et al.<sup>1</sup>

Patient adherence to topical psoriasis therapy is generally low.<sup>3</sup> The high burden of treatment and the substantial effort required to maintain ongoing therapy frequently lead to treatment fatigue.<sup>3</sup> Thus, the decrease in the use of topical agents reported by Svendsen et al.<sup>1</sup> might have other, simpler explanations.<sup>3–5</sup> Furthermore, for topical dermatological products, patients prefer and tend to be more adherent to, certain topical vehicles based on convenience and cosmetic acceptability.<sup>3,6</sup>

Finally, Wolf et al.<sup>7</sup> conducted a quality of life study among Austrian patients with psoriasis: there were 1184 participants,

of whom 42.1% reported that at least 11.2% of body surface area was affected. The authors observed that 97.2% had used topical therapies since disease onset, but over the final 4 weeks of the study, only 88.2% were still using topical agents.<sup>7</sup> Overall, the data from these three distinct studies suggests that adherence to topical therapies is complex, and is influenced by several factors. It is apparent from the study by Svendsen and colleagues that the rapidly changing profile of systemic treatments for psoriasis is having an impact on patient's use of the most standard and traditional antipsoriasis treatments, namely topical therapies.

## Funding Sources

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

## Conflicts of interest

P.R.C. has no current or past affiliations or other involvement in any organization or entity with an interest in this commentary and has not been involved in any study included in this article; however, in the last 4 years, P.R.C. has received sponsorship for attending scientific meetings or congresses from Eucerin, Novartis, ISDIN and Pfizer. Also, P.R.C. is a speaker for Takeda, Leo-Pharma and Novartis laboratories.

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