Progress in Epidermolysis Bullosa Research: Toward Treatment and Cure

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Epidermolysis bullosa (EB) is a clinically and genetically heterogeneous group of blistering disorders with considerable morbidity and mortality. Two decades ago, EB entered the molecular era with the identification of mutations in specific genes expressed within the cutaneous basement membrane zone; mutations in 14 genes have now been identified. This progress has now formed the basis for development of novel molecular therapies for this disease.

INTRODUCTION

New knowledge about the mutations that cause epidermolysis bullosa (EB) has had a major impact on its diagnosis and management (Table 1). First, identification of a mutation has been used to confirm EB diagnosis and to allow precise classification of patients in subcategories of EB. This knowledge has also been helpful in deciphering the mode of inheritance in instances where the family constellation did not readily lend itself to a definitive determination of autosomal dominant versus autosomal recessive inheritance. Finally, the identification of mutated genes and specific mutations has led to DNA-based prenatal testing and preimplantation genetic diagnosis in families at risk for recurrence of EB. In spite of this impressive progress, there is no specific or effective treatment for this group of currently intractable diseases.

EB 2009—THE STATE OF THE ART IN EB RESEARCH

EB 2009, recently held in Vienna, was organized by the EB patient support organization, DEBRA, with the following goals: (1) to review progress in and barriers to fundamental EB research, and the development of clinical solutions; (2) to consider research aspects of EB not addressed to date; (3) to identify unexplored opportunities and relevant research from complementary areas; and (4) to arrive at a community consensus on research and development priorities.

Attendance was by invitation and was limited to senior EB researchers and clinicians, with 20 invited speakers and 50 discussants. In addition, two DEBRA task forces convened separate meetings to address issues relating to research on the aggressive squamous cell carcinomas (SCCs) that develop primarily in patients with recessive dystrophic EB (RDEB), and the use of animal models as a tool for basic research and on preclinical testing of treatments for EB.

DEVELOPMENT OF MOLECULAR THERAPIES FOR EB

Recent excitement in EB research relates, in part, to the development of several approaches to address directly the molecular defects that lead to skin fragility, which manifests clinically as blisters and erosions. Complementary technologies, mostly in the advanced stages of preclinical research or already in early-stage clinical trials, have been reported (Table 2) (Tamai et al., 2009; Uitto, 2009).

Gene therapy

The first attempts to treat patients with EB by molecular approaches used an ex vivo strategy to correct the consequences of a genetic mutation for junctional EB (JEB) by introducing wild-type complementary DNA into the patient’s own skin-derived stem cells, which were then grown into epithelial sheets for grafting (Mavilio et al., 2006). Specifically, keratinocytes from the patient, with an identified mutation in the LAMB3 gene encoding one of the three subunit polypeptides of laminin 332, were cultured and transduced with the expression vector in cell culture. Corrected cell populations with stem cell characteristics were then expanded clonally and grown into epithelial sheets that were transplanted back to the patient’s skin in an area specifically prepared by laser ablation of the existing epidermis. At a 5-year follow-up, the graft revealed sustained phenotypic reversal of the blistering, and the persistent skin graft continued to express laminin 332 protein. This proof of principle for an ex-vivo gene therapy has encouraged the development of similar technologies to address the defective or absent COL7A1 gene that results in RDEB. Concerns...
over the risks associated with the use of retroviral vectors in gene therapy for other indications (notably development of leukemia in patients who have undergone treatment for severe combined immunodeficiency disease) have, particularly in Europe, led to a more stringent regulatory environment. Thus, technologies are being modified to address the theoretical risk of carcinogenesis due to the random integration of the transgene into the human genome. Several presentations at the conference focused on the development of "safer" vectors for EB gene therapy, either by targeting specific sites in the genome by self-inactivating viral vectors or through delivery mediated by transposons or zinc-finger nucleases. Alternative technologies such as spliceosome-mediated RNA trans-splicing have also shown promise in preclinical studies.

**Protein replacement therapy**

An alternative to gene delivery may be protein therapy, whereby purified wild-type protein is administered to the skin by topical application or local injection. In animal models, some success has been achieved by systemic delivery through intravenous injection. The feasibility of recombinant protein therapy has been suggested by recent observations that injection of human type VII collagen into collagen VII-deficient "knock-out" mice can reverse the blistering phenotype (Remington et al., 2009). Specifically, the untreated Col7a1−/− mice, which recapitulate the clinical, genetic, histopathological, and ultrastructural features of recessively inherited dystrophic forms of EB, usually die within the first week of life due to extreme fragility of the skin and mucous membranes (Heinonen et al., 1999). Intradermal injections of recombinant type VII collagen extended the life span of these mice, and some survived as long as 20–25 weeks. Immunofluorescence analysis of the treated mice, which were initially completely devoid of type VII collagen, revealed that the injected collagen homed to the cutaneous basement membrane zone, eliciting repair, with formation of anchoring fibrils and resulting in reduced blistering (Remington et al., 2009). Based on these and other observations, clinical trials for phase I/II studies will commence, once the necessary quantities of GMP-purified human type VII collagen are secured and regulatory authority approval is obtained.

Protein replacement is attractive because no viruses or living cells are involved in its delivery. In addition, dermatologists are familiar with the intracutaneous injection of extracellular matrix components, including collagen-containing preparations. Although similar pre-clinical studies use the delivery of laminin 332 for patients with JEB, the

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**Table 1. Clinical and genetic heterogeneity of epidermolysis bullosa**

<table>
<thead>
<tr>
<th>EB variant</th>
<th>Inheritance</th>
<th>Location of blisters</th>
<th>Mutated genes</th>
<th>Altered or missing proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBS</td>
<td>AD (AR)</td>
<td>Basal layer of the epidermis</td>
<td>KRT5, KRT14, PLEC1</td>
<td>Basal keratins</td>
</tr>
<tr>
<td>EB-MD</td>
<td>AR</td>
<td>Basal layer of the epidermis</td>
<td>PLEC1</td>
<td>Plectin</td>
</tr>
<tr>
<td>Junctional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JEB-H, JEB-nH</td>
<td>AR</td>
<td>LL</td>
<td>LAMA3, LAMB3, LAMC2, COL17A1</td>
<td>Laminin 332, type XVII collagen</td>
</tr>
<tr>
<td>EB-PA</td>
<td>AR</td>
<td>Basal layer-LL interface</td>
<td>ITGA6, ITGB4, PLEC1</td>
<td>α6β4 Integrin, plectin</td>
</tr>
<tr>
<td>Dystrophic</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DDEB, RDEB</td>
<td>AD, AR</td>
<td>Sub-lamina densa</td>
<td>COL7A1</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>Other2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethal Acantholytic</td>
<td>AR</td>
<td>Suprabasal layers of the epidermis</td>
<td>DSP</td>
<td>Desmoplakin</td>
</tr>
<tr>
<td>Kindler syndrome</td>
<td>AR</td>
<td>Mixed</td>
<td>KIND1/FERMT1</td>
<td>Kindlin1</td>
</tr>
<tr>
<td>Ectodermal dysplasia/</td>
<td>AR</td>
<td>Suprabasal layer of the epidermis</td>
<td>PKP1</td>
<td>Plakophilin1</td>
</tr>
<tr>
<td>skin fragility syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBS, other3</td>
<td>AR</td>
<td>Basal keratinocytes with lack of hemidesmosomal inner plaque</td>
<td>DST</td>
<td>BPAG1 (epithelial isoform)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EB-MD, epidermolysis bullosa with muscular dystrophy; EB-PA, epidermolysis bullosa with pyloric atresia; EDS, ectodermal dysplasia syndrome; JEB-H, JEB Herlitz; JEB-nH, JEB non-Herlitz variant; LL, lamina lucida; RDEB and DDEB, recessive and dominant dystrophic forms of EB.

1 This classification highlights the most common subtypes of EB, i.e., simplex (EBS), junctional (JEB), and dystrophic (DEB), which are differentiated by the location of blister formation within the cutaneous basement membrane zone, as determined by ultrastructural analysis and/or immuno-epitope mapping.

2 Rare, phenotypes with superficial or mixed locations of blistering have been proposed to belong to the spectrum of EB phenotypes (Fine et al., 2008).

3 A single patient with skin blistering, together with late-onset neurological abnormalities, has been described (Groves et al., 2010). Assessment of the genotype/phenotype correlation is, however, complicated by the presence of CADASIL (cerebral arteriopathy, autosomal dominant, with subcortical infarcts and leukoencephalopathy) due to a separately inherited heterozygous mutation in NOTCH3.
success of this approach with any particular protein will depend on the nature of the protein and the rate of its turnover in skin. The half-lives of these molecules in human skin have not yet been determined, but recent studies in mice have suggested that type VII collagen has a long half-life, owing to the newly synthesized protein being relatively stable and persistent (Fritsch et al., 2009).

Cell-based therapies

Cell-based therapeutic approaches (focused primarily on two cell types) have been tested recently in patients with EB. First, direct injection of either autologous or allogeneic fibroblasts intradermally around the area of blistering has been tested in patients with reduced or absent expression of type VII collagen (Wong et al., 2008). As expected, the autologous fibroblasts did not cause major adverse effects, and the allogeneic fibroblasts elicited only a minor inflammatory reaction. Interestingly, the injected cells did not appear to persist in the skin beyond a few weeks; yet, the benefits, in terms of reduced blistering tendency and improved wound healing, were sustained for several months. In addition, patients who lacked type VII collagen expression completely seemed to benefit little from the intradermal fibroblast injection, whereas those showing significant, yet reduced, baseline expression of COL7A1 showed definite improvement. The mechanism for improvement in the latter patients was suggested to be, at least in part, sustained cytokine-mediated upregulation of the expression of the mutant type VII collagen gene product in the resident cells (both fibroblasts and keratinocytes) of patients who showed residual levels of synthetic activity from their mutant allele. These patients, therefore, synthesize mutant type VII collagen, which is partially functional and forms functional anchoring fibrils. It appears, therefore, that injection of cultured fibroblasts from unrelated donors might be useful in a select subgroup of patients with RDEB.

Cell-based therapies for RDEB have been extended more recently to the use of stem cells for RDEB. These clinical trials were predicated upon preclinical animal studies that used a type VII collagen “knock-out” mouse model as a target for bone marrow-derived cell transfer (Chino et al., 2008; Tolar et al., 2009). In these studies, green fluorescent protein (GFP)-expressing mice were used as donors of bone marrow cells, enabling the investigators to trace donor cells in the recipients. In one study, a specific subpopulation of bone marrow-derived cells, positive for the signaling lymphocytic activation molecule family receptor (CD150+/CD48−), extended the survival of some animals when transferred to Col7a1−/− mice, which usually die within the first week of life (Tolar et al., 2009). The surviving animals showed evidence of engraftment of GFP-positive donor cells in the skin, production of type VII collagen, and healing of skin blisters. Another study showed successful engraftment of GFP-positive bone marrow cells in the skin after embryonic bone marrow cell transfer, and the recipient mice showed significantly reduced blistering after birth and an extended survival of up to several weeks (Chino et al., 2008). Examination of the recipient mice showed evidence of differentiation of bone marrow-derived cells toward fibroblastic phenotypes and expression of type VII collagen. In the latter studies, intriguingly, mice subjected to embryonic bone marrow cell transfer became tolerant to GFP, and subsequent grafting of GFP-expressing skin did not induce the production of antibodies against GFP (Chino et al., 2008). Collectively, these studies attest to the possibility that stem cells can be a source of dermal cells, such as fibroblasts, for regeneration of damaged skin in heritable skin diseases, such as EB.

The first allogeneic bone marrow cell transfer trial on patients with RDEB was initiated in 2007, and at the time of this Conference (September, 2009), five individuals had been transplanted (Wagner et al., 2009). Histopathological examination suggested chimerism with donor-derived cells in the skin varying from 11 to 38%, the donor cells being largely perivascular. These cells also showed a tendency to migrate to the cutaneous basement membrane zone, with ultrastructural evidence of synthesis of anchoring fibrils. On an optimistic note, these early observations suggest that bone-marrow cell transfer could provide a means to correct the
basement membrane defect in patients with RDEB. While these trials were being conducted in a multi-disciplinary environment consisting of pediatric oncologists, dermatologists, gastroenterologists, anesthesiologists, and other specialists, together with nursing staff specializing in the care of bone marrow transplant patients, two out of the five patients entered in the study had died from complications of the conditioning for bone marrow transfer or of consequences of immunological mismatch. With this perspective, new trials in different academic institutions have been initiated with a reduced-intensity conditioning regimen (Christiano et al., 2009). The rationale for the reduced-intensity conditioning is that, instead of complete myeloablation of the recipient’s own immune system, the patient initially becomes chimeric, with subsequent and gradual replacement of the immune system (Satwani et al., 2008). This approach is expected to have lower morbidity, and even mortality, as it may avoid the susceptibility to infection and cytokine storm associated with the aggressive conditioning regimen. It was pointed out, however, that even the milder conditioning does not avoid the complications related to mismatch of the graft with the recipient’s immune system, which may lead to graft-versus-host disease. It should be emphasized that these studies are at the early stages of development and a full refinement in experimental settings in specialized centers is required before these modalities can be recommended for EB patient populations in general. The critical questions relating to bone marrow-derived cell transfer pertain to the specific identity of the cells, the mechanisms by which they home from bone marrow to the circulation and eventually to areas in need of repair, their ultimate differentiated phenotype, location, and persistence, as well as the roles they have in improved skin structural integrity.

PREVENTION AND TREATMENT OF COMPLICATIONS IN EB
Compromised wound healing and tissue fibrosis

The major consequences of recurrent blistering of the skin in patients with EB are the development of erosions and ulcers with compromised wound healing, while patients with certain subtypes of EB, especially the dystrophic variants, show extensive scarring that can lead to mutilation, particularly of the hands and feet (Fine and Mellerio, 2009a).

Although the primary molecular pathology underlying blister formation in the major forms of EB has been characterized with the delineation of mutations in 14 genes encoding skin structural proteins, it is the downstream consequences of these mutations that have the greatest impact on disease morbidity and mortality (Fine et al., 2008). For example, although skin fragility in dystrophic EB is caused by disruption of the anchoring fibril protein, type VII collagen (Chung and Uitto, 2010), the major disease burden results from “frustrated” attempts at tissue repair, in which the normal processes of granulation tissue formation, re-epithelialization, and extracellular matrix remodeling are compromised; this leads to delayed wound healing, chronic inflammation, fibrosis, scarring, and an increased risk of developing SCCs (Fine and Mellerio, 2009b). Understanding the precise biology and pathology of the abnormal tissue environment is clearly germane to developing new strategies to counter these downstream events and effectively manage patients. This topic was addressed in detail.

It is evident that the investigators have not yet established a full understanding of the dystrophic or junctional EB “wound expression profiles”, data that are seemingly fundamental for developing rational therapies (Wessagowit et al., 2004). Surprisingly perhaps, to date there have been only limited numbers of studies (or, in some instances, no data) on measurements of oxidative stress, pro-inflammatory cytokines, growth factors, T-cell subsets, toll-like receptor function, epithelial/mesenchymal signaling pathways, or fibroblast/myofibroblast biology in EB tissue (Tyring et al., 1989; Chopra et al., 1992). Indeed, despite recent data implicating certain T-cell-associated cytokines as contributors to the chronic inflammation that is linked to malignancy (Langowski et al., 2006; Wang et al., 2009), this topic has not yet been explored in the setting of EB. With regard to pro-inflammatory cytokines, for example, the last few years have seen the introduction of a number of recombinant proteins that target specific cytokines or their receptors, e.g. IL-1, tumor necrosis factor-α, and T-cell-associated cytokines such as IL-17 and IL-23 (Fitch et al., 2007; Mössner et al., 2008; Neven et al., 2008; Zhu et al., 2009), but we do not yet know whether these or related therapies might have clinical relevance to individuals living with EB. Transforming growth factor-β has been implicated as important for the excessive fibrosis found in non-EB diseases (Sargent et al., 2010) and in mouse models, but it is not known whether countering the effects of this cytokine, for example, by using neutralizing antibodies to transforming growth factor-β1 or by increasing the expression of the anti-scarring alternative isoform transforming growth factor-β3, might reduce scarring and contractures in patients with EB (Young et al., 2009). Nor has a scientific rationale been defined for possible trials of recombinant growth factors such as platelet-derived growth factor, basic fibroblast growth factor, or granulocyte macrophage colony-stimulating factor in EB (Barrientos et al., 2008). One innovation, the use of topical inhibitors of NF-κB, such as ethyl pyruvate, was thought to have therapeutic potential, notwithstanding that NF-κB signaling has not been fully evaluated in EB skin.

It is likely that many of the aberrant cellular processes in wound healing that lead to delayed tissue repair and fibrosis overlap with cancer-associated inflammation in EB, and that an improved understanding of the skin “ecosystem”, for example, in terms of chemokines, growth factors, and remodeling enzymes, is pivotal in driving translational research on this disorder.

SCC in EB

One of the devastating consequences of recurrent blistering, particularly in RDEB, is the development of SCCs (Mallipedi et al., 2004a, b; Fine et al., 2009). These tumors occur in the vast majority of patients with RDEB in their third or fourth decade, primarily on the hands and feet. In contrast to SCCs in the general population, RDEB-associated malignancies are
aggressive, with a high propensity for metastatic spread. Few therapeutic options exist, except for surgical removal (often necessitating amputation of the affected limbs, with uncertain effects on the overall survival). In addition to their relentless malignant behavior, these tumors appear to be multifocal and icnclonal, as suggested by observations of several primary tumors coexisting in the same patient (Tomita et al., 2003). Furthermore, distinguishing malignant foci in chronically disrupted epidermis is a significant diagnostic challenge.

Taken together, these grim characteristics call for a concerted effort to improve the diagnosis, staging, and treatment of these tumors. In recognition of the significance of this problem, a task force was established 3 years ago by DEBRA to develop new diagnostic and therapeutic approaches to skin cancer in EB. Systematic investigations into the pathomechanisms that distinguish RDEB-associated SCC from other SCCs have yet to be carried out. Such studies would be of value in identifying potential biomarkers for this malignancy; these are sorely needed due to the difficulties associated with the clinical diagnosis of RDEB-associated SCC. In addition, such studies may lead to previously unreported therapeutic targets. At present, it is unknown whether RDEB-SCC represents a distinct neoplastic entity with a unique assortment of pathway activations, leading to its clinically aggressive behavior, or whether it is indistinguishable from rare aggressive SCCs in patients without RDEB. Several groups have recently performed comparatively small-scale microarray cell and tissue analyses to address this question (Arbiser et al., 2004; Mallipeddi et al., 2004b; Kivisaari et al., 2008), but progress has been hampered by the apparent lack of sufficient material for molecular analysis. Although DEBRA has supported the early-stage development of an EB SCC Bank (http://www.netzwerk-eb.de/e439/e480/inhaltSS9/RequestformSCCTissuebank_ger.pdf? preview=preview), hosting tissue samples and a limited number of derived cell lines, it is necessary to supplement these resources by collecting clinical samples to make the most of the limited material available in laboratories around the world. It should be noted that SCC samples from EB patients are usually of poor quality, with high microbial loads; understandably, a surgeon’s priority is the patient, not the sample. A major obstacle is stable funding to maintain and administer centralized tissue banks for this purpose.

It seems likely that the continuous tissue reorganization associated with chronic inflammatory processes distinguishes RDEB-SCC from sporadic SCC. But why are these tumors so aggressive? Comparing the molecular footprints of RDEB-SCC with those of related tumors in non-RDEB patients from the skin and oral mucosa (head and neck SCCs), for which ample datasets have already been assembled (Dong et al., 2001; Chung et al., 2004), represents one useful approach to this question. Others address how molecular events related to continuous tissue remodeling support the malignant traits of keratinocytes, including the investigation of proteolytically generated fragments of extracellular matrix components, such as laminin 332 and perlecan, as well as the expression and function of integrin subunits upregulated in skin cancer, inflammation, and regeneration. Largely, these studies are in the preclinical phases and address the molecular mechanisms shared by malignant and regenerating tissues.

Treating RDEB-associated SCC by surgical means is primarily palliative. Although targeted agents currently being tested in sporadic SCC (e.g., EGFR inhibitors) were considered for RDEB-associated SCC, these interventions are not likely to be curative due to the aggressive nature of RDEB-associated SCCs. In addition, their multifocal nature—consistent with distinct molecular events and pathways driving different tumors in the same patient—and their putative genetic instability could contribute to treatment resistance. A different approach would be ‘chemopreventive’: using topically formulated antiinflammatory drugs to reduce the tumor initiation and progression driven by continuous chronic inflammation and excessive regenerative processes. However, the negative consequences of this approach, related to undue interference with wound healing and the difficulty of defining suitable end points and time frames in which to evaluate the efficacy of specific regimens, must be considered. Instead, it may be worthwhile to use the existing animal models for preclinical testing of these types of approaches.

THE ROLE OF PATIENT ADVOCACY ORGANIZATIONS—THE PARADIGM OF DEBRA INTERNATIONAL

Increasingly, patient advocacy organizations are becoming partners in the research process, not only providing research funding and access to patients, but also helping to identify research priorities, lobbying governments for funding and equitable access to healthcare, and promoting industrial collaboration (Terry et al., 2007). Nowhere is this more important than in orphan disease fields, where patients, clinicians, and investigators face the challenges of a rare but disabling and life-limiting condition, largely neglected by ‘big pharma’ because of niche market size.

DEBRA International is the primary charitable patient-support organization working on behalf of patients with EB and their families. It is a network of approximately 30 autonomous national DEBRA organizations, working together on areas of mutual interest, including lobbying nationally and internationally for political and funding recognition, support for research, and provision of support services, including social welfare, information on EB, and, in some countries, a specialist EB nursing service. DEBRA International has, as its mission, ‘working for a life free of pain’; this mission embraces not only research into the causes and possible treatments for EB, but also delivery of care. At the same time, DEBRA manages the expectations of patients who hear too often the promises of ‘major research breakthroughs’, for whom only a cure represents exactly that, while giving those patients a public voice. The activities of patient advocacy organizations, such as DEBRA International, are critical for our progress.

EB 2009—SUMMARY AND CONCLUSIONS

EB 2009 was highly successful in assessing the current state of EB research and in advancing the agenda. This meeting reflected the progress made in research, particularly in
molecular therapies, toward treatment, and perhaps cure of EB. The areas of active investigation include gene therapy, protein replacement approaches, and cell-based (particularly stem-cell and fibroblast) therapies, and some of these approaches are already entering the clinical arena. It is clear, however, that these approaches are at the early stages of investigation, and there are a number of uncertainties, even controversies, surrounding them. For example, are the gene therapy approaches, which currently concentrate on the development of safer and more efficient vectors for the delivery of genes to the skin, so as to avoid the potential of tumorigenesis due to random integration of the DNA into the recipient genome, the “holy grail” for EB treatment? Are they going to be successful in eliciting permanent correction of the primary gene defect? Is the protein replacement approach, which is likely to elicit a transient effect, a primary treatment modality requiring multiple treatments or could it serve as a complementary approach to other modalities, such as gene therapy, which might provide a permanent cure? The bone marrow transplantation approach, which has been reported to be preliminarily successful in some individuals, has also resulted in considerable morbidity and even mortality associated with the aggressive recipient conditioning of the traditional bone marrow transfer protocols. New clinical trials adopting modified, perhaps less aggressive, conditioning approaches are being initiated. Are these approaches effective in reversing the blistering phenotype, and what are the overall risk/benefit ratios? Yet further approaches, which are yet to be reported, combine a better understanding of both EB and advanced technologies—notably variations of stem-cell technologies (including induced pluripotent stem cells)—both as research tools and, ultimately, possible therapies. These, to our knowledge previously unreported, approaches bring with them still more questions and both technical and regulatory challenges in establishing their efficacy and safety. Collectively, it is hoped that perhaps not in too distant future, we may have treatments, either in the form of a combination of therapies or in a single modality approach, to help patients suffering from EB.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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