

# EB2017—Progress in Epidermolysis Bullosa Research toward Treatment and Cure

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Epidermolysis bullosa, a group of heritable blistering disorders, shows extensive phenotypic variability due to mutations in as many as 20 distinct genes. There is no cure for this devastating group of disorders; however, a number of preclinical developments show promise, and some approaches have already reached the stage of early clinical trials. Dystrophic Epidermolysis Bullosa Research Association (DEBRA) International, a global coalition of national patient organizations advocating on behalf of the patients and families with epidermolysis bullosa, supports research and organizes periodic scientific and clinical meetings on this disease. The most recent meeting, EB2017, was held in Salzburg in September 2017. This report summarizes some of the recent research and clinical developments that have identified promising avenues toward treatment and perhaps eventual cure, with improved quality of life for patients with epidermolysis bullosa.

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## Introduction

Epidermolysis bullosa (EB) is a highly heterogeneous group of skin fragility disorders with extensive phenotypic variability and diverse clinical outcomes (for review, see [Fine et al., 2014](#)). The diagnostic hallmark of this group of diseases is blistering of the skin as a result of minor trauma, leading to erosions and nonhealing ulcers. In certain subtypes, these findings are associated with mutilating scarring and early development of aggressive squamous cell carcinomas. Despite tremendous progress made over the last quarter century in understanding the molecular genetics and the pathomechanistic pathways in this group of disorders, there is no cure as yet.

Dystrophic Epidermolysis Bullosa Research Association (DEBRA) International, a coalition of national patient organizations, funds research and advocates on behalf of the patients and families with EB. Toward this goal, DEBRA International organizes periodic research and clinical meetings for

investigators working on EB and in related fields to allow review of the state of the art and to provide a platform for exchange of ideas for research prioritization ([Bruckner-Tuderman et al., 2013](#); [Uitto et al., 2010, 2016](#)). To reflect the accelerating translation of research into clinical application, DEBRA International organized its latest research conference, EB2017, for the first time in conjunction with the annual clinical conference of EB-CLINET (a worldwide clinical network of EB centers and experts; [www.eb-clinet.org](http://www.eb-clinet.org)) in Salzburg, Austria (September 24–27, 2017). This meeting was attended by more than 250 scientists and clinicians ([Figure 1](#)). This synopsis summarizes some of the findings reported at this conference.

## Identification of Novel Genes and Mutant Alleles with Clinical Implications

The heritable forms of EB were initially divided into three broad categories based on the level of blistering within the skin as visualized by transmission

electron microscopy, namely, the epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), and dystrophic epidermolysis bullosa (DEB) subtypes ([Fine et al., 2014](#)). Although this early classification was somewhat helpful for prognostication, it was clear that each of these three categories represents a spectrum of severity and outcome. This phenotypic variability was shown to reflect mutations in 10 distinct genes expressed within the cutaneous basement membrane zone. Subsequently, Kindler syndrome was proposed to be the fourth subtype of EB, and demonstration of mutations in *FERMT1* brought the number of mutated genes to 11 ([Jobard et al., 2003](#); [Siegel et al., 2003](#)). More recently, a number of genes, primarily expressed within the epidermis and largely associated with EBS, brought the total number of mutant genes to 18 ([Table 1](#)). At the end of 2016, several investigators independently identified mutations in a novel gene, *KLHL24*, in a significant number

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Abbreviations: BMT, bone marrow transplantation; DEB, dystrophic epidermolysis bullosa; DEBRA, Dystrophic Epidermolysis Bullosa Research Association; EB, epidermolysis bullosa; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; PTC, premature termination codon; RDEB, autosomal recessive dystrophic epidermolysis bullosa

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**Figure 1.** Some of the participants in the joint DEBRA International EB2017 Research Symposium and EB-CLINET Clinical Conference held in Salzburg, September 24–27, 2017. (Photo courtesy of Rudolf Hametner).

of patients with EBS (He et al., 2016; Lee et al., 2017; Lin et al., 2016). Finally, quite recently, a patient with a Kindler syndrome-like clinical presentation, including early blistering that subsided with age, and nephropathy, was found to harbor a homozygous splicing mutation in *CD151*, encoding a tetraspanin (TM4) that is expressed at the cutaneous basement membrane zone (Vahidnezhad et al., 2017a). These observations, together with previously published cases with similar clinical presentations, suggested that the total number of genes harboring mutations in different subtypes of EB is at least 20 (Table 1).

Identification of mutations in candidate genes in different families with EB was originally based on PCR amplification of exons and flanking intronic sequences, followed by Sanger sequencing. Considering the large number of candidate genes in EB and the fact that many of these genes are large and multi-exonic, this approach has proven to be labor intensive, time consuming, and expensive. More recently, a number of next-generation sequencing panels encompassing EB-related genes have been developed, and this relatively inexpensive approach has markedly facilitated and streamlined mutation detection in families (Tenedini et al., 2015; Vahidnezhad et al., 2017b, 2017c). These panels have been supplemented with next-generation sequencing approaches, including whole-exome and whole-genome sequencing,

combined with homozygosity mapping in consanguineous families. These approaches have allowed rapid expansion of the mutation databases and provided tools to identify family-specific mutations for confirmation of the diagnosis with subcategorization and prognostication.

#### Refined Phenotype-Genotype Correlations

Examination of mutation databases in the context of clinical presentations has allowed development of phenotype-genotype correlations, which now form the basis of prognostication, in general terms, based on mutations in newborns before phenotypic development is apparent. Advanced mutation detection strategies have also identified a number of unusual genetic constellations in patients with complex phenotypes, many of which were reported in the EB2017 meeting. For example, EBS with mottled pigmentation, which has previously been shown to result from a specific mutation (p.Pro25Leu) in *KRT5*, is now shown to also result from mutations in the *EXPH5* gene (Turcan et al., 2016a). Mutations in *BPAG1-e* can cause an unusual EBS of an intermediate generalized phenotype with prurigo papules (Turcan et al., 2017). Large intragenic *KRT5* deletions have also been shown to account for some unsolved cases of EBS (Has et al., 2017). Mutations in the *ITGB4* gene, frequently associated with an autosomal recessive form of JEB, can also result in an autosomal dominant form

of EB (Turcan et al., 2016b). Unusual genetic alterations in *COL7A1* have also been linked to unusual phenotypes; for example, large deletions targeting the triple helical domain of type VII collagen can cause acral dominant dystrophic EB (Chmel et al., 2017). Also, a patient initially diagnosed with Shabbir syndrome was found not to have mutations in *LAMA3A* but in *LAMB3* instead (Vahidnezhad et al., 2018).

#### Preclinical Development of Treatment Strategies

A spectrum of preclinical approaches has been used to develop treatment strategies for EB. Therapy approaches aimed at correcting the primary genetic defect at the DNA, mRNA, or protein levels extend from induced pluripotent stem (iPS) cells or fibroblast-/keratinocyte-based gene correction and protein therapies to antisense oligonucleotides and premature termination codon (PTC) read-through drugs. Another line of treatment strategies includes disease-modifying, symptom-relief therapies, which address inflammatory and fibrotic processes that modify specific EB phenotypes.

#### Preclinical development of iPS cell-based technologies

At the EB2017 meeting, several investigators reported that iPS cells can be derived from EB fibroblasts or EB keratinocytes which, in turn, can be redifferentiated after gene correction into keratinocytes and fibroblasts.

**Table 1. Classification, phenotypic spectrum, and molecular heterogeneity of EB**

Type of EB	Mutated Genes	Chromosomal Location	Protein	Inheritance	Number of Reported Mutations <sup>1</sup>	Associated Phenotypes and Other Comments
EBS	<i>DSP</i>	6p24.3	Desmoplakin	AR	265 <sup>2</sup>	EB, lethal acantholytic
	<i>PKP1</i>	1q32.1	Plakophilin1	AR	16	Ectodermal dysplasia/skin fragility syndrome
	<i>JUP</i>	17q21.2	Plakoglobin	AR	40 <sup>3</sup>	Skin fragility, palmoplantar keratoderma, and woolly hair, with or without cardiomyopathy
	<i>KRT5</i>	12q13.13	Keratin 5	AD	151 <sup>4</sup>	75% of all EBS cases; 14 cases of AR EBS-K14 have been reported
	<i>KRT14</i>	17q21.2	Keratin 14	AD, AR	114 <sup>5</sup>	
	<i>PLEC</i>	8q24.3	Plectin	AR (AD)	92	Form of EBS; EB with pyloric atresia, EB with muscular dystrophy; rare AD EBS-Ogna type
	<i>DST</i>	6p12.1	BPAG1	AR	6	
	<i>EXPH5</i>	17q25.1	Exophilin 5	AR	8	
	<i>TGM5</i>	10q24.3–q25.1	Transglutaminase 5	AR	26	Acral peeling skin syndrome
	<i>KLHL24</i>	3q27.1	Kelch-like protein 24	AD	5	EBS, generalized, with scarring and hair loss
JEB	<i>LAMA3</i>	18q11.2	Laminin-332	AR	48	9% of all JEB cases
	<i>LAMB3</i>	1q32.2		AR	112	70% of all JEB cases
	<i>LAMC2</i>	1q25.3		AR	39	9% of all JEB cases
	<i>COL17A1</i>	10q24.3–q25.1	Collagen XVII	AR	99 <sup>6</sup>	12% of all JEB cases
	<i>ITGA6</i>	2q31.1	$\alpha$ 6 $\beta$ 4 integrin	AR	8	A few reported cases
	<i>ITGB4</i>	17q25.1		AR (AD)	95	AD mode of inheritance reported in one study
	<i>ITGA3</i>	17q21.33	Integrin $\alpha$ 3 subunit	AR	11	EB is reported in association with congenital nephrotic syndrome and interstitial lung disease
DEB	<i>COL7A1</i>	3p21.31	Collagen VII	AR, AD	773	100% of all DEB cases
KS	<i>FERMT1</i>	20p12.3	Kindlin-1	AR	78	100% of all KS cases
KS-like	<i>CD151</i>	11p15.5	Tetraspanin CD151	AR	2	EB with nephropathy

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; K14, keratin 14; KS, Kindler syndrome.

<sup>1</sup>The numbers represent the total number of distinct disease-associated mutations according to The Human Gene Mutation Database ([www.hgmd.cf.ac.uk](http://www.hgmd.cf.ac.uk)) as of November 22, 2017. Mutations in *KLHL24*, not yet available on this database, were gathered from the three existing reports of *KLHL24*-associated EB, as summarized by Has (2017).

<sup>2</sup>In addition to EBS, mutations in *DSP* are related to following diseases: arrhythmogenic right ventricular dysplasia 8 (OMIM:607450); cardiomyopathy, dilated, with woolly hair and keratoderma (OMIM:605676); dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis (OMIM: 615821); EB, lethal acantholytic (OMIM:609638); keratosis palmoplantaris striata II (OMIM:612908); skin fragility-woolly hair syndrome (OMIM:607655).

<sup>3</sup>*JUP* mutations can cause AR Naxos disease (OMIM:601214); AD mutations can lead to arrhythmogenic right ventricular dysplasia 12 (OMIM:611525).

<sup>4</sup>*KRT5* mutations are related to EBS and Dowling-Degos disease (OMIM:179850).

<sup>5</sup>Mutations in *KRT14* cause different types of EBS (including with mottled pigmentation), as well as dermatopathia pigmentosa reticularis (OMIM:125595) and Naegeli-Franceschetti-Jadassohn syndrome (OMIM:161000).

<sup>6</sup>Mutations in *COL17A1* cause JEB and inherited epithelial recurrent erosion dystrophy-like disease with eye manifestations only (OMIM:122400).

A great advantage of iPS cell-based treatment approaches lies in the autologous nature of the cells that are generated and in the lack of immune reactions to corresponding tissue grafts. Significant technical advances in production, gene correction/gene editing, and safety of good manufacturing practice-quality iPS cells have been reported (Bilousova and Roop, 2014; Sebastiano et al., 2014), and examples of quality criteria include minimal cellular heterogeneity and high level of production of the corrected protein, for example, keratins 5 and 14 in cases of EBS and collagen VII in DEB. Furthermore, to improve graft quality, refinement of three-dimensional organotypic cultures with iPS cell-derived keratinocytes and fibroblasts is being pursued

(Shinkuma et al., 2016). Finally, inducible pluripotent stem cells have been established from revertant keratinocytes (Tolar et al., 2014; Umegaki-Arao et al., 2014), although clinical translation involving these cells has yet to be accomplished.

#### Protein and mRNA-based approaches

Prospects of protein therapy using recombinant human collagen VII have been investigated in the past few years. Initial observations in a preclinical mouse model suggested that intravenously administered collagen VII could reverse the disease phenotype in autosomal recessive DEB (RDEB) (Hou et al., 2015), leading to the hypothesis that—analogueous to enzyme deficiencies that can be treated by

infusions of recombinant enzymes— injections of good manufacturing practice-quality collagen VII might provide a useful therapeutic option for individuals with DEB. However, the development of the therapy turned out to be more challenging than anticipated, and this project has been taken over by industry partners (most recently, <http://phoenixtissuerepair.com>). It remains to be seen whether this line of treatment option can be successfully adapted from mouse models to humans. As an alternative, a planned early-stage trial of intradermal injection of recombinant human collagen VII, produced following optimization of posttranslational modifying enzymes (prolyl-4-hydroxylase, C-proteinase) to maximize stability and solubility, may



offer a future option for localized therapy (P. Marinkovich, personal communication).

Therapeutic approaches targeting gene transcription have been tested mainly with *COL7A1* as a model. In vitro antisense oligonucleotide treatment of cells with mutant *COL7A1* genes can lead to skipping of specific exons at the RNA level, which when in frame, restores synthesis of essentially normal, although slightly shortened, collagen VII (Bremer et al., 2016; Turczynski et al., 2016). Preclinical in vivo testing has shown that antisense oligonucleotide-based exon skipping can promote skin stability by partially functional collagen VII in DEB mice (Bornert et al., 2016).

Another approach targeting gene transcription is based on read-through of PTCs. The premise of this approach is that about 10% of genetic diseases are caused by nonsense mutations that introduce PTC and nonsense-mediated mRNA decay (Mort et al., 2008). Aminoglycoside antibiotics, such as gentamicins, can induce PTC read-through. Gentamicins were first tested for their efficacy to induce PTC readthrough for *COL7A1* in vitro, but their effects depend on the local nucleotide micro-environment of the mutations, and not all nonsense mutations are amenable to this kind of correction (Baradaran-Heravi et al., 2017; Cogan et al., 2014). In addition, the renal and ototoxicities of aminoglycosides may prevent widespread clinical implementation. Nevertheless, a pilot trial assessed topical administration and intradermal injection of gentamicin to the skin of five patients with RDEB and showed enhanced collagen VII synthesis, suggesting that local application may offer a therapeutic option with reduced systemic toxicity of gentamicin (Woodley et al., 2017). Gentamicin preparations are mixtures of related molecules, and a minor gentamicin component, gentamicin B1, seems promising because of its potency as an inducer of the PTC read-through and its low toxicity (Baradaran-Heravi et al., 2017). Another interesting compound is amlexanox, which induces PTC read-through and is thought to inhibit nonsense mediated mRNA decay. Amlexanox has been shown to increase mRNA expression and synthesis of

full-length collagen VII in RDEB fibroblasts and keratinocytes with nonsense mutations (Atanasova et al., 2017). This drug is approved by the US Food and Drug Administration for other clinical indications, and its toxicity profile and pharmacokinetics have been established, thus facilitating its translation to clinical trials.

#### Preclinical development of symptom relief therapies

Symptom relief therapies are the current focus of EB research with the aim of counteracting subjective clinical findings, such as pain and itch, as well as skin fibrosis, which greatly impair the quality of life of EB patients. Molecular mechanisms responsible for secondary processes are now being defined. In EBS, in addition to providing keratinocytes with structural stability against mechanical stress, keratin intermediate filaments regulate immune responses by controlling expression of IL-1, IL-18, and other cytokines. For example, the cytokine thymic stromal lymphopoietin is highly up-regulated in EBS and mediates itch in mice and patients with keratin mutations (Kumar et al., 2016). Keratins and other cytoskeleton-associated proteins also contribute to epidermal cell-cell adhesion via spatially and temporally controlled stabilization of desmogleins and their suprastructures, desmosomes (Vielmuth et al., 2017). Several other molecules have recently been identified that are altered upon breach of epidermal integrity and induce proinflammatory signaling (T. Magin, personal communication). Such molecules may become therapeutic targets in EBS, and perhaps in other forms of EB.

One of the most debilitating features of RDEB is progressive soft tissue fibrosis, which causes joint contractures, deformities of the extremities, and strictures at mucosal surfaces, particularly in the esophagus. The molecular and cellular mechanisms leading to these complications include inflammation and excessive TGF- $\beta$  signaling (canonical and noncanonical). Limiting these processes could substantially improve functionality and quality of life of the affected individuals. Losartan, a drug approved by the US Food and Drug Administration and European Medicines Agency, is

known to inhibit excessive TGF- $\beta$  signaling in some, but not all, fibrotic diseases. In RDEB mice, it efficiently reduced inflammation, TGF- $\beta$  activity, extracellular matrix accumulation, and progression of fibrosis (Nyström et al., 2015). Recent investigations showed that a parallel pathway involving signaling through the anti-fibrotic AT-2 and MAS receptors (Passos-Silva et al., 2015) can be a target in RDEB. Toward this end, a phase 2 investigator-initiated clinical trial (Reflect study, EudraCT no. 2015-003670-32) explores safety and tolerability of losartan in children with moderate to severe RDEB and collects information on its efficacy (D. Kiritsi, personal communication).

Another approach to diminishing systemic inflammation and fibrosis focuses on HMGB1-derived peptides as a potential drug. The HMGB1 factor is released from necrotic epithelial cells in RDEB and signals to bone marrow-derived mesenchymal stem cells, leading to their migration to circulation and homing to damaged skin (Aikawa et al., 2015). In RDEB mice, the HMGB1-derived peptide prevented both skin fibrosis and gastrointestinal tract strictures and, importantly, extended the lifespan of the mice significantly (K. Tamai, personal communication).

Collectively, preclinical development of biologically valid treatments shows encouraging promise for future therapies. In particular, remodeling of the dermal matrix by fibroblasts in the absence of collagen VII in RDEB results in key changes in gene expression profiles, and there is increasing evidence that this drives the development of aggressive squamous cell carcinoma (Martins et al., 2016). Stromal modulators of TGF- $\beta$  activity that, in turn, drive metastasis, angiogenesis, and activation of fibroblasts (Costanza et al., 2017) are likely targets for drug development to combat squamous cell carcinoma in EB.

#### Early Clinical Trials in EB

Based on the progress made in understanding the genetic basis and pathomechanistic details of EB leading to skin fragility and extensive exploration of treatment opportunities at the preclinical level, the pipeline for clinical trials in EB has opened. In fact, 61 clinical trials involving EB patients are

currently registered in [clinicaltrials.gov](https://clinicaltrials.gov) (USA), and 16 of these were registered in 2016–2017, reflecting acceleration of clinical trial activity in this disease (H. Rischel, personal communication). Additional clinical trials and observational studies registered in the European Union may be found at EudraCT register (<https://eudract.ema.europa.eu/results-web/>) and worldwide at the World Health Organization register (<http://www.who.int/ictrp/en>). Thus, diverse approaches to developing treatments that improve quality of life and provide eventual cures for EB patients are being pursued.

### Bone marrow transplantation

In 2010, the results of an early clinical trial of whole bone marrow transplantation (BMT) in six children with RDEB were reported (Wagner et al., 2010). That study described clinical improvements in all subjects, and five of the six showed increased collagen VII deposition at the dermal-epidermal junction. No individual was cured after BMT, but several showed a marked reduction in blister formation and substantial improvement in quality of life. However, toxicity relating to myeloablative conditioning was a concern because of high morbidity and mortality. Seven years later, this meeting provided an opportunity to reflect on the BMT experience and its value for clinical application in EB. Globally, but mainly because of the considerable experience from the University of Minnesota, more than 40 children with either RDEB or JEB have now undergone BMT. Although detailed results of the clinical experiences of the subsequent clinical trials have yet to be published, a number of lessons are emerging: (i) beneficial and sustained clinical responses, but not cures, continue to be noted in some, but not all, children with RDEB undergoing BMT; (ii) mortality rates with revised conditioning protocols have decreased and are now approximately 15%; (iii) some RDEB children show positive clinical improvement even in the absence of an increase in collagen VII in their skin; and (iv) experience of BMT in JEB is limited, but with occasional exceptions, BMT does not appear to have therapeutic benefit in this type of EB (Hammersen et al., 2016; Hook et al., 2017).

For families with children who have RDEB, many personal dilemmas remain: BMT is an experimental therapy and is being performed as part of a number of clinical trials; it should not be considered an approved therapy. The mortality risk and the uncertainty of the degree and mechanism of clinical response need to be weighed against the present status of translational research in RDEB, which is that BMT is currently the only treatment approach that has shown a systemic impact on what is a systemic disease. There is clearly a need for the data from the extended clinical trials to be published as soon as possible, with a view to developing recommendations and caveats for use of BMT for EB.

### Cell therapy

Previously, randomized, double-blind clinical trials of intradermal injections of allogeneic fibroblasts into RDEB skin showed varying results on the extent or rate of re-epithelization of chronic erosions (Petrof et al., 2013; Venugopal et al., 2013). Nevertheless, a universal adverse finding was the considerable pain that results from injecting cells into often scarred skin. This type of local cell therapy has, therefore, now focused on delivering *COL7A1* gene therapy in autologous fibroblasts to both intact skin and RDEB wounds ([clinicaltrials.gov](https://clinicaltrials.gov) identifiers NCT02493816 and NCT02810951). In contrast, allogeneic cell therapy has progressed to systemic testing. An early phase clinical trial of intravenously administered allogeneic mesenchymal stromal cells in 10 children with RDEB showed improvements in wound healing, reduction in pain and itch, and a positive impact on quality of life (Petrof et al., 2015). A similar study in 10 adults with RDEB is currently being evaluated for safety and early efficacy ([clinicaltrials.gov](https://clinicaltrials.gov) identifier NCT02323789). Clinical benefits appear to be sustained for up to 9 months, with further improvements after additional cell infusions, raising the possibility of repeated infusions of this form of mesenchymal stromal cell therapy having potential clinical utility. The likely benefits relate to the anti-inflammatory effects of the cells, because skin biopsy studies have not

shown any increase in collagen VII or new anchoring fibrils in the treated patients' skin. Indeed, additional pre-clinical work has shown that this type of systemic delivery cannot deliver adequate cell numbers needed to restore collagen VII expression at the cutaneous basement membrane zone (Kuhl et al., 2015).

### Gene therapy

Since the initial report of successful gene therapy based on grafting of ex vivo corrected keratinocytes to a patient's skin in an individual with JEB, published in 2006 (Mavilio et al., 2006), there have been few public reports of progress using this treatment for EB. In November 2016, however, the results of a single center clinical trial of ex vivo cultures of RDEB keratinocytes, transduced with a retroviral vector containing full-length *COL7A1* cDNA, and regrafted back onto the patient's wounds as epidermal sheets, were reported (Siprashvili et al., 2016). There was evidence of wound healing and collagen VII expression in most samples, although the clinical response was variable and generally declined over the following 12 months. However, the procedure was deemed safe, and the data have provided a basis for expansion of this approach to further trials in more people with RDEB. A similar approach has been taken to correct the defect in a JEB patient with chronic nonhealing ulcers in which grafting of the gene-corrected keratinocytes showed remarkable healing (Bauer et al., 2017). One potential criticism of ex vivo/keratinocyte gene therapy approaches has often been that they can be applied to only limited areas of skin, and thus it would be unlikely to have much impact on overall health and quality of life. However, this notion has recently been dispelled in an extraordinary account of the use of ex vivo holoclone stem cell-derived keratinocyte gene therapy to replace over 80% of the skin of a 7-year-old boy with generalized intermediate JEB caused by *LAMB3* mutations (Hirsch et al., 2017). The cost and general applicability of the approach remain controversial, but there can be no denying the incredible transformation in the life of the boy who was treated.

### Novel topical treatments

Topical therapies, with easy applicability and low toxicity, remain an attractive avenue of translational research in EB, even if the therapeutic mechanisms underpinning such treatments are not fully known. A number of products have been, or are being, tested in proof-of-concept or later-phase early clinical trials. For example, a betulin-rich triterpene extract from birch bark (Oleogel-S10, Birken AG, Niefern-Oeschelbronn, Germany) has been assessed in an open, blindly evaluated, controlled, prospective phase 2 pilot trial in wounds in individuals with DEB (EudraCT no. 2010-019945-24). In evaluating 12 wound pairs in 10 subjects, there was a trend toward accelerated wound healing with the intervention, but statistical significance was not demonstrable (Schwieger-Briel et al., 2017). A larger study to assess the reproducibility of these preliminary observations is ongoing (J. Kern, personal communication).

The importance of controlled clinical trials in developing topical treatments for EB is emphasized by recent studies attempting to develop 6% allantoin as a new drug enhancing wound healing in EB (SD101; Amicus Therapeutics, Cranbury, NJ). Allantoin has been previously shown to enhance epidermal wound healing in model systems, and early observations in a limited number of EB patients suggested beneficial effects. A large clinical trial involving 169 patients with different forms of EB indeed showed improvement in the treated patients; however, the vehicle-treated controls did equally well, probably reflecting the meticulous daily care of the patients enrolled in the trial. Thus, the study failed to show definitive improvement attributable to allantoin, and no further clinical trials of SD-101 in EB are planned. However, Amicus Therapeutics remains committed to share its valuable learnings with the EB community with the hope that it will guide the development of better clinical trials (J. Wisk, personal communication).

### DEBRA as Research Advocate

DEBRA has, as a patient organization, supported EB research for over 30 years, from studies into the underlying pathology of EB through to proof-of-

principle therapeutic concept studies and early stage clinical trials. More recently, DEBRA has initiated studies, such as Prospective Epidermolysis Bullosa Longitudinal Evaluation Study (PEBLES), to document the natural history of RDEB toward identification and validation of clinically appropriate parameters against which therapies may be evaluated in clinical trials. In recognition of the essential role of the biopharma industry as partners in developing therapies, DEBRA International organized an 'Industry Partnering Panel' workshop at EB2017, to consider how DEBRA can assist in overcoming common barriers faced by companies engaging in EB clinical trials. A consortium approach, engaging with industry and other stakeholders, is now in development to address these challenges, and to expedite creation and delivery of clinical treatments.

### CONFLICT OF INTEREST

JU is the Chair of the DEBRA of America Medical and Scientific Panel. LBT has received research support from Tarix Orphan Ltd., Cambridge, MA. RR and CR are the President of DEBRA Austria and the Head of Research of DEBRA International, respectively.

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### SUPPLEMENTARY MATERIAL

A brief video is available as Supplementary Material to this article online at [www.jidonline.org](http://www.jidonline.org), and at <https://doi.org/10.1016/j.jid.2017.12.016>. For the full video, go to <https://www.youtube.com/watch?v=ic6V5vbnfids>.

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