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Progress Towards Treatment and Cure of Epidermolysis Bullosa: Summary of the DEBRA International Research Symposium EB2015

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Abstract

Epidermolysis bullosa (EB), a group of complex heritable blistering diseases, is the topic of triennial research meetings organized by DEBRA International, the umbrella of patient advocacy organizations. The DEBRA 2015 Research Conference, held in May 2015, brought together investigators and clinicians from around the world working at the forefront of EB research. Discussing the state-of-the-art approaches from a wide range of disciplines, there was a palpable excitement at this conference brought about by the optimism about applying new sequencing techniques, genome editing, protein replacement, autologous and allogeneic stem cell therapy, innovations in cancer biology, revertant mosaicism and iPSC techniques, all of which are aimed at developing new therapies for EB. Many in the field who have participated in EB research for many years were especially enthusiastic and felt that, possibly for the first time, the field seems uniquely poised to bring these new tools to effectively tackle EB using multiple complementary approaches towards improved quality of life and eventually a cure for patients suffering from EB, a currently intractable disease.

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Conflict of Interest

The authors state no conflict of interest.

Introduction

Epidermolysis bullosa (EB), a group of heritable blistering disorders, consists of four main subtypes of EB primarily distinguished by the level of blistering within the cutaneous basement membrane zone (Table 1). Each of these subtypes can display a spectrum of phenotypic severity reflecting the types and combinations of mutations in different genes, together with modifying environmental factors. The types of mutations also determine the mode of inheritance, either autosomal dominant or autosomal recessive. Currently 18 genes have been shown to be associated with the different subtypes of EB (Table 1).In spite of the tremendous progress made in understanding the molecular basis of different forms of EB, there is no cure for this disease.

DEBRA International, an organization advocating on behalf of the EB patients and their families, sponsors Triennial Research Conferences. The latest one in this series, organized by DEBRA of America in Braselton, Georgia in May 2015, was attended by over 100 researchers, physician scientists, trainees, and patient support group representatives (Figure 1). This Meeting Report summarizes the presentations and discussions that took place in this conference.

Animal Models for EB

In addition to many naturally occurring EB forms in animals reviewed previously (Bruckner-Tuderman *et al.*, 2010, 2013; Uitto *et al.*, 2010), a variety of model systems have been generated.

Novel murine models

Some recently developed animal models have revealed unexpected consequences and improved our understanding of phenotypic variability. For example, careful analysis of mouse models for junctional EB (JEB) identified the first major genetic modifier of JEB phenotype due to a laminin-γ2 mutation by collagen XVII, in particular molecular variations in its NC4-domain (Sproule *et al.*, 2014). Also, a recently reported knock in mouse model for JEB that displays alternative splicing of the *Lamb3* gene will aid in defining further genetic modifiers of JEB phenotypes (Hammersen *et al.*, 2015).

Another interesting finding relating to junctional skin blistering was revealed by the deletion of the linker extracellular domain of transmembrane collagen XVII in mice. This led to alternative shedding of the ectodomain, but not to JEB. Instead, induction of auto-immune blistering and itching were observed, and the phenotype of the mice mirrored signs of bullous pemphigoid, including perilesional eosinophilic infiltrations, blood eosinophilia and elevated serum IgE-levels (Hurskainen *et al.*, 2015). Future work will be aimed at discerning mutations and disease mechanisms predisposing to mechanobullous *vs.* inflammatory blistering phenotypes in both humans and mice.

Because of the multi-organ involvement, the severity of the phenotypes, and significant unmet medical need, the dystrophic forms of EB (DEB) has been the focus of many investigations often using previously developed collagen VII knock-out or hypomorphic

mice (Fritsch *et al.*, 2008; Heinonen *et al.*, 1999). In addition, a rat model for dominant DEB, which exhibits a gene dosage effect, offers a possibility to evaluate the influence of modifier genes on DEB phenotype (Nyström *et al.*, 2013).

Zebrafish and drosophila

Interesting alternative animal models to study EB have recently been reported, including zebrafish and *drosophila*. Several of the EB-relevant genes are expressed in zebrafish, and therefore, this model system has been used to generate skin blistering phenotypes reflecting features of EB, such as morpholino-mediated knock-down of collagen XVII gene-expression (Kim *et al.*, 2010; Li and Uitto, 2014). Recent work has used the keratin-free tissue environment in *drosophila* to investigate the formation of keratin networks and to define mechanisms by which mutated keratins cause cellular pathology (Bohnekamp *et al.*, 2015). Human keratins 5 and 14, when expressed in *drosophila* epithelia, formed well-organized keratin networks thus validating the fly as a novel genetic model system for keratin physiology and pathology. Inclusion of a mutated keratin 14 in the networks caused semi-lethality, wing blisters and perturbed cellular integrity. This drosophila model of EBS will be valuable for further investigation of the effects of different keratin mutations, their cellular consequences, and possibilities for therapeutic interventions.

Organotypic cultures

Yet another model to investigate disease mechanisms and test therapeutic approaches are the 3D skin equivalent organotypic cultures. One study treated grafted human RDEB equivalents topically with recombinant human collagen VII and showed that the therapeutic collagen restored anchoring fibrils and promoted dermal-epidermal adhesion (Wang *et al.*, 2013). Another investigation combined gene corrected epithelial stem cell clones for the epidermal compartment and fibroblasts in the dermal compartment and used the equivalents to test the structure and stability of the corrected skin (Duarte *et al.*, 2014).

Squamous Cell Carcinoma in RDEB

Clinical challenge

Squamous cell carcinoma (SCC) remains the biggest cause of mortality in RDEB patients with >80% succumbing by age 55 years (Fine *et al.*, 2009). These tumors, while histologically often well differentiated, demonstrate aggressively invasive behavior with development of multifocal lesions and rapid metastasis. Clinically, there is still no consensus on the best way to tackle this formidable clinical problem, and new and effective therapies are in urgent need (Mellerio *et al.*, 2015).

Therapy development

It is clear that lack of type VII collagen in RDEB has significant impact on overall dermal architecture (Küttner *et al.*, 2013; Nyström *et al.*, 2013) which has been shown to promote tumor progression (Ng *et al.*, 2012). One plausible strategy for therapy would be to target this altered, fibrotic microenvironment. For example, targeting the cancer associated fibroblasts with the JAK inhibitor Ruxolitinib has been shown to prevent *in vitro* invasion of SCC tumors driven by the contractility of activated, surrounding fibroblasts (Albrengues *et*

al., 2014). Given the demonstrable role of fibroblasts in RDEB associated SCC (Ng *et al.*, 2012), this small molecular inhibitor may well provide a viable SCC treatment option. With respect to targeting the tumor keratinocytes, screening of polo-like kinase inhibitors has identified a lead compound that showed good preclinical data in targeting tumor over normal cells, and this compound is currently in phase II/III trial for other malignancies. As such, there is hope that direct translation of this screen will be possible within a short timeframe.

SCC genomics

Genetically, RDEB associated SCCs remain poorly characterized. Although a high burden of driver mutations has been highlighted in a handful of RDEB tumors as compared to UV-induced SSCs by traditional Sanger sequencing (Arbiser *et al.*, 2004; Pourreyron *et al.*, 2007; Wang *et al.*, 2011), comprehensive analysis of all protein coding genes, overall understanding of tumor burden and spectrum of mutations in these tumors are lacking. In the light of a recent demonstration that non-RDEB UV exposed skin harbors a huge burden of mutations (Martincorena *et al.*, 2015), one might speculate that the altered microenvironment in RDEB is unable to suppress alterations in proliferation and differentiation as a result of mutations in genes such as *TP53* or *NOTCH1*. Efforts to collect and sequence RDEB associated SCCs are in progress (Ray Cho, personal communication).

Roles of infection and inflammation—Recent work has identified a possible link with microbial infection, inflammation and tumor development in RDEB (Hoste *et al.*, 2015). Although inflammation has long been suspected to play a major role in tumor development in RDEB, documented evidence is lacking. Recent work using a mouse model has shown that tumors formed after wounding are accelerated by the addition of bacterial flagellin. Antibiotic administration reduced tumor burden, and tumor formation in this model was dependent on leukocytes, Myd88, and TLR5 driven NFκB signaling (Hoste *et al.*, 2015). This evidence raises the possibility that a preventative measure might be to reduce bacterial load in RDEB skin.

THERAPY DEVELOPMENT

A number of novel approaches towards treatment of EB have been recently developed, and in particular, significant progress has been made in cell-based therapies, in gene replacement and repair technologies, and in direct protein replacement therapy (Table 2). Many of these approaches have reached a milestone that allows them to move to early clinical trials; the currently approved clinical trials on EB are listed in supplemental Table S1.

Cell Therapy

Fibroblasts—Therapeutic application of autologous or allogeneic cells is now being explored in clinical trials in different forms of EB. Two proof-of-concept studies in RDEB subjects demonstrated that a single intradermal injection of allogeneic fibroblasts increased *COL7A1* gene expression in most individuals (Nagy *et al.*, 2011; Wong *et al.*, 2008). These trials also demonstrated the low immunogenicity of allogeneic fibroblasts and lack of host response. Two subsequent randomized double-blind studies then assessed the impact of allogeneic fibroblasts on wound healing in RDEB: one found no differences in the extent or

rate of re-epithelization of chronic erosions (Venugopal *et al.*, 2013), whereas the other showed that a single injection could speed up wound healing for up to 28 days compared to vehicle (Petrof *et al.*, 2013b).

Mesenchymal stromal/stem cells—The use of intradermal mesenchymal stromal cell (MSC) therapy was first reported in two patients with RDEB in 2010, and recently clinical trials using intravenous BM-derived MSCs from unrelated donors into subjects with RDEB have been performed; clinical improvements in wound healing were observed in most subjects for 4-6 months (Conget *et al.*, 2010; El Darouti *et al.*, 2015). Furthermore, an early phase clinical trial of intravenously administered allogeneic MSCs in 10 children with RDEB has recently been published (Petrof *et al.*, 2015). In the latter study, while no significant safety concerns were raised, skin biopsies did not reveal increase in collagen VII or new anchoring fibrils. There was, however, indications of reduced skin inflammation and better wound healing, as well as less skin pain and itching. Thus, although further assessment, including placebo-controlled studies, will be necessary, the anti-inflammatory effects of allogeneic MSCs appear to offer a rationale for their use in clinical care (Petrof *et al.*, 2015).

A clinical trial of intradermal MSCs to improve wound healing in adults with RDEB is also currently being conducted in Japan (Katsuto Tamai, personal communication, June 2015), with preliminary evidence for improved and sustained wound healing for more than 12 months following a single injection of MSCs into wound margins. Additional studies have demonstrated that pre-conditioning of MSCs with growth factors or cytokines to augment collagen VII production might have clinical relevance (Perdoni *et al.*, 2014).

Bone marrow transplantation—Results of an early clinical trial of whole BM transplantation (BMT) in children with RDEB has been reported (Wagner *et al.*, 2010). In this study, seven patients entered the initial trial and six underwent BMT. All individuals had some clinical improvement and five of the six showed increased collagen VII at the DEJ. No individual has been cured following BMT, but several have shown a marked reduction in blister formation and major improvement in quality of life (Jakub Tolar, personal communication). Nevertheless, toxicity relating to complete myeloablation has been a concern, especially since two of the seven patients enrolled in the initial study died from complications of this procedure. Consequently, BMT protocols have been refined to introduce reduced intensity conditioning with decreasing mortality rates while maintaining clinical improvement. Specifically, to overcome the challenges of complete myeloablation, several studies are underway using non-myeloablative conditioning to determine the safety and efficacy of this approach using a less toxic conditioning regimen, with early results being reported as having reduced complications and mortality ((Geyer *et al.*, 2015); Jakub Tolar, personal communication).

Mechanisms of BMT—To explore possible mechanisms of BMT a mouse model was used to demonstrate that BM-derived keratinocytes represent a specific subpopulation of Lineage-negative, Platelet-derived growth factor receptor alpha-positive ($Lin^{-}/PDGFR\alpha^{+}$) cells, still a somewhat heterogeneous collection of cells(Tamai *et al.*, 2011). The study proposed that skin grafts (and blister roofs in RDEB) act as hypoxic bioreactors, rapidly

releasing HMGB1. Following skin grafting, HMGB1 levels in serum increased and HMGB1 was shown to mobilize the $Lin^{-}/PDGFR\alpha^{+}$ cells from the BM and recruit these cells along a concentration gradient to the area of hypoxic keratinocytes. Differentiation of these cells into keratinocytes and the capacity to generate new collagen VII in the skin was clearly demonstrated (Tamai *et al.*, 2011). Subsequent work has identified the importance of a stromal derived factor 1-alpha (SDF1a) – C-X-C chemokine receptor type 4 (CXCR-4) signaling pathway in the recruitment of the key regenerative cells (Iinuma *et al.*, 2015). These data pave the way for clinical translation, with recombinant HMBG1 peptides to mobilize BM progenitors and cell therapy approaches using specific sub-populations of MSCs likely to enter clinical trials in the near future.

Alternative sources of stem cells—Cord blood and other compartments of the umbilical cord, such as Wharton's jelly or tissues associated with the placenta, are rich sources of stem cells. In addition to hematopoietic stem cells, cord blood is an important source of other progenitor cells, as well as MSCs, very small embryonic/epiblast I-like stem cells and unrestricted somatic stem cells, which may have individual or collective value in regenerative medicine. Nevertheless, comparison of umbilical cord cells versus BM stem cells in individuals with RDEB has shown better skin engraftment with a BM-derived population (Tolar *et al.*, 2012), and therefore, the clinical utility of cord cells in EB or other skin disorders remains to be determined in future clinical trials. Other populations, such as human cord blood-derived unrestricted somatic stem cells, are also being explored, in the EB mouse models, in preparation for clinical application (Liao *et al.*, 2014; Liao *et al.*, 2015).

Revertant Mosaicism and Inducible Pluripotent Stem Cells

One striking observation in EB patients' skin is that some patches of skin can undergo spontaneous correction of the genetic defect, a phenomenon known as revertant mosaicism or "natural gene therapy" (Jonkman *et al.*, 1997). The predominant mechanisms of gene correction include back mutation, gene conversion, intragenic recombination and second-site mutation (Kiritsi *et al.*, 2014; Pasmooij *et al.*, 2012). The genetic correction appears to be limited to keratinocytes but the opportunity to expand keratinocytes derived from a patch of revertant mosaicism in culture, followed by application of a graft to the affected skin, creates a translational opportunity for personalized revertant cell therapy. The first attempt at revertant cell therapy was reported in an individual with generalized intermediate junctional EB yielded inconclusive results because the revertant keratinocyte population dropped from 30% to 3% in culture and no clinical benefits were noted after grafting (Gostynski *et al.*, 2009). An alternative approach using pinch/punch grafting of skin from the revertant patches, however, has been used successfully to heal chronic erosions in a patient with a similar form of EB with mutations in *LAMB3* (Gostynski *et al.*, 2014).

One potentially exciting future therapeutic approach may be to combine the natural phenomenon of revertant mosaicism with recent stem cell biology techniques, specifically in creating inducible pluripotent stem cells (iPSCs). Spontaneously corrected cells for iPSC generation that are derived from revertant keratinocytes would avoid the need for further genetic correction or gene editing. With regards to skin, iPSCs have recently been generated

from keratinocytes and fibroblasts derived from individuals with EB (Sebastiano *et al.*, 2014; Wenzel *et al.*, 2014) and also from revertant keratinocytes (Tolar *et al.*, 2014; Umegaki-Arao *et al.*, 2014). While no therapeutic use of iPSCs in dermatology has been achieved yet, it is clearly poised to undergo rapid translation in the future as the entire iPSC field moves into clinical applications.

Gene Correction Technologies

Over the years, EB investigators' efforts have revolved around gene replacement, and indeed, several clinical trials are now in progress based mainly on *ex vivo* culture of EB keratinocytes, transduction with viral vectors containing genes of interest, and re-grafting back onto patient's skin (for active clinical trials in EB, see Table S1). Other innovative genome editing techniques are emerging, including antisense-mediated exon skipping to restore the open reading frame of nonsense-bearing mRNA transcripts, spliceosome-mediated RNA *trans*-splicing, and premature termination codon (PTC) read-through coupled with antagonists of nonsense mediated mRNA decay (Bidou *et al.*, 2012; Koller *et al.*, 2015; Turczynski *et al.*, 2012). Finally, the advent of CRISPR/cas gene editing techniques is also poised to transform the combined approach of mutation correction with iPSC technologies.

Protein Replacement Therapy

The consequences of mutations in different genes in EB are varied, but in some cases, such as nonsense and PTC mutations, there is complete absence of the corresponding protein. The potential for protein replacement by introduction of recombinant type VII collagen was initially tested in wound healing models in wild-type or *Col7a1* knock-out mice. Recombinant type VII collagen, when injected intradermally to the mice or applied topically, incorporated into the dermal-epidermal junction followed by formation of anchoring fibrils with correction of the EB phenotype, as demonstrated by decreased skin fragility, reduced new blister formation and markedly prolonged survival (Hou *et al.*, 2015; Remington *et al.*, 2009; Woodley *et al.*, 2013).

Novel Treatments in the Pipeline

Treatment of Itch—It has become increasingly clear that there is an immediate demand for so-called symptom-relief therapies to ameliorate the disease symptoms with improved quality of life for the patients. Recent surveys of patients with EB have identified intractable itch and pain as one of the main issues for the daily management from the patient's perspective. In this regard, investigators with extensive background knowledge on itch have now initiated programs to address itch and its mechanisms in EB, with the hope that it can be effectively counteracted by pharmacological means. Critical for this is understanding of the similarities and differences that itch in EB patients may have in comparison to itch mechanisms as previously delineated in other dermatologic conditions.

Anti-fibrotic therapies—One of the major complications of EB, particularly the RDEB subtype, is extensive scarring and fibrosis which can result in functional limitations of movement when affecting the joints, and in extensive fusion of the digits in the hands leading to mitten deformities with compromised dexterity. Animal studies using the

hypomorphic mouse model have suggested that the fibrosis is driven by TGF-β, as reflected by transition of dermal fibroblasts to myofibroblasts with capacity for extensive extracellular matrix production. Losartan, an angiotensin II type 1 receptor antagonist, that is FDA/EMA approved for hypertension, has been shown to reduce TGF-β-mediated fibrosis in some connective tissue disorders although its effects are context and disease specific (Nyström *et al.*, 2015). Treatment of hypomorphic DEB mice with Losartan clearly ameliorated disease signs by reducing fibrosis and inflammation, counteracting formation of mitten deformities (Nyström *et al.*, 2015). These observations suggest that clinical trials of Losartan in patients with RDEB are indicated.

Other examples of repurposing FDA/EMA-approved drugs is Ruxolitinib known to reduce JAK/STAT-mediated fibrosis (Albrengues *et al.*, 2014). Other potential FDA approved drugs for counteracting interstitial fibrosis, pirfenidone and nintedanib, could be repurposed for EB-associated fibrosis. Finally, 4-phenylbutyrate, a molecule known to untangle pathological protein aggregates, has been tested in plectin deficient mice (Winter *et al.*, 2014).

Anti-inflammatory therapies—Some of the new pharmacologic approaches attempt to target the inflammatory phenotype of EB. One such study has utilized topical application of Diacerein, a prodrug of the IL-1 converting enzyme inhibitor, rhein, which has been approved for systemic treatment of osteoarthritis (Wally *et al.*, 2013). Topical application of this molecule in EBS patients reduced blistering which remained significantly below the initial level following randomized withdrawal. The application of Diacerein was found to be safe, and it apparently prevents blistering by down regulating the activated stress-signal cascade, including IL-1β induced JNK-pathway.

Enhanced wound healing—One of the major goals in EB is to enhance wound healing processes, and a novel therapeutic approach has been suggested to be the use of antimicrobial peptides that control pathogenic infections and activate the adaptive immune system. One of such peptides is cathelicidin which not only has the capability of augmenting host defense but also appears to play a role in tissue repair and wound closure. Preliminary studies have indicated low expression levels of cathelicidin mRNA in RDEB keratinocyte cultures, suggesting that upregulation of cathelicidin could improve wound healing in RDEB. In this regard, vitamin D3 analog calcipotriol was shown to upregulate cathelicidin expression in a dose-dependent manner (Hüttner *et al.*, 2012; Moniaga *et al.*, 2013).

Patient Perspectives and the Role of Advocacy Organizations

The ultimate beneficiaries of the ongoing research will be people with EB. It is, therefore, critical to involve the patients and their advocacy organizations, such as DEBRA International, in the process of identifying the most important issues presented by this disease, as perceived by the patients themselves. In this regard, it has become increasingly evident that problems such as intractable itch and excruciating pain need to be addressed to improve quality of life for these patients. To this aim, DEBRA International has initiated the creation of clinical best practice guidelines for major aspects of EB care, including oral healthcare, wound care, and pain management, which are already freely available to

clinicians (www.debra-international.org/med-professionals/clinical-practice-guidelines-cpgs/forEB.htlm); other guidelines on cancer management and nutrition are under development. In addition, while DEBRA International provides a route for coordinating information to patients and clinicians about research and clinical trials on EB, it conversely provides information about EB patients and their priorities to those planning clinical trials. In this meeting, a presentation by DEBRA Ireland noted the importance of investing time in informing patients, and considering patients as participants in the process, and not just as trial subjects. Thus, it is critically important to solicit the patients' participation with meaningful involvement, and to inform the patient community of clinical trial outcomes.

The participants of the EB2015 included not only researchers but also patients and their family members. In fact, the President of DEBRA International, Rainer Riedl, and the Director of DebRA of America, Brett Kopelan, are also fathers of RDEB children. In the closing, they shared the impressions of the patients and the advocacy organizations that EB research is speeding up dramatically and that a striking number of new clinical trials and new medical products can be expected in the very near future. In this regard, this meeting has provided inspiration not only to those working on understanding the disease and developing novel treatments, but also to the patients and the parents whose perspective has been increasingly heard.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EB	epidermolysis bullosa
JEB	junctional EB
DEB	dystrophic EB
RDEB	recessive DEB
iPS	induced pluripotent stem cells
SCC	squamous cell carcinoma
MSC	mesenchymal stromal cell
BM	bone marrow
BMT	bone marrow transplantation
NGS	next generation sequencing

WES whole exome sequencing

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Figure 1.
Participants in the EB2015 Research Symposium held in Braselton, GA, in May 2015.

Table 1

Molecular Heterogeneity of Different Forms of EB

Disease	Gene	Cytogenetic Location	Inheritance	Proportion of EB Attributed to Mutations in this Gene
Simplex Epidermolysis Bullosa (EBS)	*KRT5*	12q13.13	AD	75% of EBS-AD cases;
	KRT14	17q21.2	AR, AD	15 cases of EBS-AR Have been reported with KRT14 mutations
	TGM5	15q15.2	AR	
	DSP	6p24.3	AR	
	PKP1	1q32.1	AR	
	JUP	17q21.2	AR, AD	
	PLEC	8q24.3	AR	
	DST	6p12.1	AR	
	ITGB4	17q25.1	AR	
	COL17A1	10q24.3-q25.1	AR	
Junctional Epidermolysis Bullosa (JEB)	*LAMA3*	18q11.2	AR	9% of all JEB cases; specific mutations in the LOC (Shabir) syndrome
	LAMB3	1q32.2	AR	70% of all JEB cases
	LAMC2	1q25.3	AR	9% of all JEB cases
	COL17A1	10q24.3-q25.1	AR	10% of all JEB cases
	ITGA6	2q31.1	AR	A few cases reported
	ITGB4	17q25.1	AR	Many cases reported
	ITGA3	17q21.33	AR	A few cases reported
Dystrophic Epidermolysis Bullosa (DEB)	*COL7A1*	3p21.31	AR, AD	100% of all DEB cases
Kindler Syndrome (KS)	*FERMT1*	20p12.3	AR	100% of all KS cases

AR, autosomal recessive; AD, autosomal dominant

Table 2

Molecular and Pharmacological Approaches for the Treatment of EB*

Approach	Strategies	Current Status+
Cell-based therapies	• Injection of allogeneic fibroblasts	CT
	• Systemic or perilesional administration of mesenchymal stem cells	CT
	• Autologous application of revertant mosaic cells	CT
	• Use of cord blood stem cells	PC
Bone marrow transplantation	• BMT following complete myeloablation	CT
	• Non-myeloablative conditioning	CT
	• Autologous induced pluripotent stem cells	PC
Gene therapy/mRNA editing	• *Ex vivo* keratinocyte therapy	CT
	• CRISPR/cas editing	PC
	• RNA *trans*-splicing	PC
	• PTC read-through and NMD antagonists	PC
Protein replacement therapy	• Delivery of recombinant type VII collagen in RDEB	PC
Novel and repurposed drug treatments	• Anti-itch medications	PS
	• Anti-fibrotic molecules (Losartan and Ruxolitinib)	PC
	• Anti-inflammatory therapies	PS
	• Enhanced wound healing (cathelicidin, Zorblisa, Keragel™)	PS

*CT, clinical trials initiated, ongoing or recently completed; PC, these approaches are tested in preclinical studies, often utilizing appropriate mouse models of EB; PS, testing of these drugs is at the planning stages; BMT, bone marrow transplantation; PTC, premature termination codon; NMD, nonsense-mediated mRNA decay.

+For details on ongoing clinical trials; see Supplemental Figure S1.