Most of us take healthy skin for granted. It is our generally durable and self-repairing physical border with the external world. Rich with nerve endings in its protective layers, it provides constant feedback about our environment while keeping moisture in and harmful germs out. However, for patients with epidermolysis bullosa, a skin-fragility disorder in which mucocutaneous membranes blister and shear away in response to the normal mechanical stresses of daily life, few, if any, of these benefits exist.

In normal skin, three molecules of type VII collagen (C7) polymerize, interact with dermal and epidermal proteins, and form the main component of anchoring fibrils. As a biologic Velcro, anchoring fibrils connect the layers of skin by extending from the cutaneous basement-membrane zone and hooking into the interstitial collagen fibers of the papillary dermis. In recessive dystrophic epidermolysis bullosa (RDEB), biallelic loss-of-function mutations in the gene encoding C7 (COL7A1) result in severely diminished or absent C7. Without anchoring fibrils at the dermal–epidermal junction, patients with RDEB have severe skin blistering, alopecia, nail dystrophy, corneal erosions, and mucosal wounds.1 This skin damage is extremely painful, with exquisite sensitivity to pressure and to hot and cold, loss of fluids, and increased risk of local and systemic infection. Compromised integrity of the upper part of the esophagus leads to strictures, chronic blood loss, and failure to thrive. Frequent skin injury and aberrant tissue repair cause mutilating scarring and mit- ten deformities of the fingers and toes. Persistent wounds that never heal leave children, some as young as 6 years of age, with a high predilection for aggressive squamous-cell carcinomas.

The extreme suffering and diverse effects of this disorder have motivated research teams to seek therapies for RDEB from many directions, using gene-based, protein-based, or cell-based approaches. The failure to obtain a total cure has fueled greater efforts toward finding one.

One such effort was recently described by Sebastiano et al.2 First, the investigators created patient-specific induced pluripotent stem cells from fibroblasts and keratinocytes; they then genetically corrected the COL7A1 mutation in these cells, using a highly recombinogenic species of adeno-associated virus for mediating homology-driven repair (so-called gene editing). Second, they used the combined power of genome sequencing and bioinformatics to characterize genome alterations in RDEB gene-edited stem cells, including changes in genes known to be involved in the pathogenesis of squamous-cell carcinoma. This allowed them to select corrected cells and still minimize the potential risks of gene therapy as much as possible.

Third, they derived sheets of keratinocytes from the induced pluripotent stem cells and used skin grafting to demonstrate conclusively that functional C7 was expressed in cells relevant to the pathologic features of RDEB in both in vitro and in vivo models. In short, by building on and extending the work of others,3,4 Sebastiano et al. have established a new and refined standard for generating autologous skin grafts to treat the skin wounds that typify RDEB and have begun to establish cell-manufacturing standards in anticipation of future clinical trials.

Although this substantive advance gives hope that the most painful and bothersome skin lesions can be healed, it may not resolve other clinical manifestations, because wounds can occur anywhere on the skin surface at any time, and grafting them all may not be possible. Also, wound biofilms will be a major challenge to successful grafting. Furthermore, RDEB is a systemic disease that often leads to injury of the
Figure 1. Combination Therapy for Epidermolysis Bullosa.

Many different therapeutic approaches are possible for epidermolysis bullosa, although none have been completely successful. Local therapies include intradermal injection, use of microneedles, and skin grafts, such as that proposed by Sebastiano et al.2 These methods are proving effective in healing surface wounds but do not reach all the physical manifestations of epidermolysis bullosa. The potential for a cure most likely lies in a combined approach of both local and systemic therapies, individualized to the specific patient.
oral and upper esophageal mucosa, cornea, and kidney, where grafting cannot reach. Finally, the risk of squamous-cell carcinoma, typically aggressive, metastatic, and lethal, may persist as long as any wounds frequently recur.

Therefore, a systemic approach is needed, which led to our own attempt to modify the course of RDEB using hematopoietic-cell populations that can circulate throughout all tissues of the body throughout life. The key is a broader platform of combination therapy for these patients, brought about by the collective intelligence and collaborative work of investigators in epidermolysis bullosa research (Fig. 1). In this scenario of the future, additions or corrections to COL7A1, the replacement of C7 protein, and cellular therapy would be applied locally or systematically, once or serially, alone or in combination, with other interventions that cooperatively establish a portfolio of options enabling truly personalized and clinically meaningful changes in the practice of medicine for children and adults with RDEB.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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