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The long and winding road that leads to advanced therapies for rare diseases

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Cultures of human epithelial stem cells can be used to regenerate several squamous epithelia. For instance, limbal stem cell cultures allow corneal regeneration and visual restoration in patients with massive ocular chemical burns. Cultures of transgenic epidermal stem can restore a normal epidermis in patients suffering from devastating genetic skin diseases as Junctional Epidermolysis Bullosa (JEB). We report life-saving regeneration of the entire epidermis on a seven-year-old JEB child suffering from a devastating form of LAMB3-dependent JEB. The regenerated transgenic epidermis remained stable throughout the entire 9-year follow-up period and did not form blisters, even upon shear force. The proviral integration pattern was maintained in vivo and epidermal renewal did not cause any clonal selection. Clonal tracing showed that the human epidermis is sustained by a limited number of long-lived stem cells, detected as holoclones, that can extensively self-renew and produce short-lived progenitors that replenish terminally differentiated keratinocytes.

In studying the different behavior of JEB and COL7A1-dependent generalized Dystrophic EB (RDEB) cultures we discovered a pivotal role of YAP in sustaining human epidermal stem cells, which explains the progressive stem cell loss observed in JEB. Epidermal stem cell depletion of primary JEB keratinocytes is due to perturbation of the YAP/TAZ pathway and consequent alteration of the expression of FOXM1. This pathway is not altered in RDEB, explaining the different behavior of transgenic RDEB cells vs transgenic JEB cells. This notion imposes the development of a different gene correction strategy to successfully tackle RDEB.