Human COL7A1-corrected induced pluripotent stem cells for the treatment of recessive dystrophic epidermolysis bullosa.

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Public Summary:
Epidermolysis bullosa (EB) is a family of inherited genetic blistering skin diseases. Children with one subtype lack a specific gene, called type VII collagen, develop a severe, scarring EB subtype, recessive dystrophic epidermolysis bullosa (RDEB). The lack of collagen VII results in the upper layers of the skin being only very loosely attached to the deeper layers of the skin resulting in painful blisters and wounds that cannot heal. The children typically die in their teens from infection, organ failure or skin cancer in the setting of these never-healing wounds. Patients with RDEB and other EB subtypes have been extensively diagnosed and treated here at Stanford for the past quarter century and, despite all efforts, current therapy for RDEB is limited to palliative wound care. In this paper we describe a novel approach to treat this devastating disease. We have shown that human induced pluripotent stem cells can be derived from EB patients, they can be gene-corrected in the culture dish, and subsequently turned into healthy skin cells. These genetically repaired, but still patient-derived skin cells can be grown into sheets of skin that we have shown can be transplanted onto the skin of immune-compromized mice. These human skin grafts showed long-term survival and restoration of the collagen VII. This work is a proof-of-principle that iPS cell reprogramming is a viable approach for clinical application

Scientific Abstract:
Patients with recessive dystrophic epidermolysis bullosa (RDEB) lack functional type VII collagen owing to mutations in the gene COL7A1 and suffer severe blistering and chronic wounds that ultimately lead to infection and development of lethal squamous cell carcinoma. The discovery of induced pluripotent stem cells (iPSCs) and the ability to edit the genome bring the possibility to provide definitive genetic therapy through corrected autologous tissues. We generated patient-derived COL7A1-corrected epithelial keratinocyte sheets for autologous grafting. We demonstrate the utility of sequential reprogramming and adenovirus-associated viral genome editing to generate corrected iPSC banks. iPSC-derived keratinocytes were produced with minimal heterogeneity, and these cells secreted wild-type type VII collagen, resulting in stratified epidermis in vitro in organotypic cultures and in vivo in mice. Sequencing of corrected cell lines before tissue formation revealed heterogeneity of cancer-predisposing mutations, allowing us to select COL7A1-corrected banks with minimal mutational burden for downstream epidermis production. Our results provide a clinical platform to use iPSCs in the treatment of debilitating genodermatoses, such as RDEB.