Phase I/IIa clinical trial for Recessive Dystrophic Epidermolysis Bullosa using genetically corrected autologous keratinocytes

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Recessive Dystrophic Epidermolysis Bullosa (RDEB) is an inherited genetic skin disorder caused by mutations in the *COL7A1* gene encoding type VII collagen (C7). Current therapy is limited to supportive palliation. We report the results of the on going Phase I/IIa clinical trial of ex vivo gene therapy for the treatment of severe RDEB. 6 adult RDEB subjects (mean age 26) enrolled in this trial carried various heterozygous *COL7A1* mutations resulting in expression of only truncated C7 protein undetectable by C7 NC2 antibodies and displayed absent/sparse anchoring fibrils (AF) by EM. Autologous RDEB keratinocytes isolated from skin biopsies were transduced with GMP grade retrovirus carrying full-length *COL7A1*. 6 ~35cm^2 autologous epidermal sheets were grafted onto chronic wounds that were unhealed for a mean of 8.5 years. The primary endpoint of the Phase I/IIA trial is to evaluate wound healing compared to untreated baseline wound. Secondary endpoints included expression of full-length C7 and restoration of AF at 3 and 6 months. No serious adverse events were reported, and no replication competent virus has been detected for up to 3 years. At 3 months, 94% (27/36 grafts), at 6 months, 67% (16/24 grafts) and at 12 months 50% (12/24 grafts) showed significant wound healing as defined as > 75% healing compared with baseline. C7 expression and morphologically normal NC2 reactive AF were demonstrated at the basement membrane of graft biopsies for up to 2 years however expression gradually diminished over time. These data demonstrate that *COL7A1* ex-vivo gene transfer has a favorable safety profile, as well as wound healing efficacy which correlates with molecular correction. Together these findings highlight the potential of cell based therapy in RDEB patients.