J Biotechnol Biomater 2016, 6:1(Suppl)
http://dx.doi.org/10.4172/2155-952X.C1.050

OMICS International
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Annual Conference and Expo on
Biomaterials

March 14-16, 2016 London, UK

An efficient, simple to apply non-viral gene therapy for recessive dystrophic epidermolysis bullosa

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Recessive dystrophic epidermolysis bullosa (RDEB) has been defined as severe chronic skin fragility and caused by mutations in *COL7A1*, which encodes for the elastic structural protein type VII collagen (C7). The 8.9 Kb *COL7A1* transcript is particularly a large sequence with many repeating units which makes it difficult to manipulate and package into viral systems. Therefore, the minicircle system is ideal for use with *COL7A1*, firstly to minimize the overall DNA construct size while secondly increasing the safety profile of the gene therapy. We successfully inserted *COL7A1* into the parental plasmid MN512A1 and combined it with our highly efficient a non-viral vector (HPAE). HPAE-MC-COL7A1 polyplexes successfully produced significant levels of recombinant C7 with negligible cytotoxicity in RDEB-TA4 keratinocytes. Minimal effect was seen on primary keratinocyte metabolic health, even after multiple applications of HPAE polyplexes. Furthermore, *in vivo* transfection studies revealed that HPAE carrying MC-COL7A1 restores the expression of C7 along the basement membrane zone in a human RDEB graft mouse model after intradermal injection and topical application. Of the 7 animals treated, 5 were positive for recombinant C7, with all animals receiving 2 or more applications having strong positive signal. While further assessment is required to prove this approach is safe and well tolerated in the long term, HPAE-MC-COL7A1 polyplexes showed great promise as a potential therapeutic for RDEB.

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