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Use of Zikani's Ribosome Modulating Agents for Treating Recessive Dystrophic & Junctional Epidermolysis Bullosa with Nonsense Mutations

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Abstract : Background: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a genetic skin condition characterized by skin tearing and unremitting blistering upon minimal trauma. Repeated blistering, fibrosis, and scarring lead to aggressive squamous cell carcinoma later in life. RDEB is caused by mutations in the COL7A1 gene encoding collagen type VII (C7), the major component of anchoring fibrils mediating epidermis-dermis adherence. Nonsense mutations in the COL7A1 gene of a subset of RDEB patients leads to premature termination codons (PTC). Similarly, most Junctional Epidermolysis Bullosa (JEB) cases are caused by nonsense mutations in the LAMB3 gene encoding the β3 subunit of laminin 332. Currently, there is an unmet need for the treatment of RDEB and JEB. Zikani Therapeutics has discovered an array of macrocyclic compounds with ring structures similar to macrolide antibiotics that can facilitate readthrough activity of nonsense mutations in the COL7A1 and LAMB3 genes by acting as Ribosome Modulating Agents (RMAs). The medicinal chemistry synthetic advancements of these macrocyclic compounds have allowed targeting the human ribosome while preserving the structural elements responsible for the safety and pharmacokinetic profile of clinically used macrolide antibiotics. Methods: C7 expression was used as a measure of readthrough activity by immunoblot assays in two primary human fibroblasts from RDEB patients (R578X/R578X and R163X/R1683X-COL7A1). Similarly, immunoblot assays in C325X/c.629-12T > A-LAMB3 keratinocytes were used to measure readthrough activity for JEB. The relative readthrough activity of each compound was measured relative to Gentamicin. An imaging-based fibroblast migration assay was used as an assessment of C7 functionality in RDEB-fibroblasts over 16-20 hrs. The incubation period for the above experiments was 48 hrs for RDEB fibroblasts and 72 hours for JEB keratinocytes. Results: 9 RMAs demonstrated increased protein expression in both patient RDEB fibroblasts. The highest readthrough activity at tested concentrations without cytotoxicities increased protein expression up to 179% of Gentamicin (400 µg/ml), with favored readthrough activity in R163X/R1683X-COL7A1 fibroblasts. Concurrent with protein expression, fibroblast hypermotility phenotype observed in RDEB was rescued by reducing motility by ~35% to WT levels (the same level as 690 µM Gentamicin treated cells). Laminin β3 expression was also shown to be increased by 6 RMAs in keratinocytes to 33-83% of (400 µg/ml) Gentamicin. Conclusions: To date, 9 RMAs have been identified that enhance the expression of functional C7 in a mutation-dependent manner in two different RDEB patient fibroblast backgrounds (R578X/R578X and R163X/R1683X-COL7A1). A further 6 RMAs have been identified that enhance the readthrough of C325X-LAMB3 in JEB patient keratinocytes. Based on the clinical trial conducted by us with topical gentamycin in 2017, Zikani's RMAs achieve clinically significant levels of read-through for the treatment of recessive dystrophic and Junctional Epidermolysis Bullosa.

Keywords : epidermolysis bullosa, nonsense mutation, readthrough, ribosome modulation
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