TRIDs4DEB collaboration: Identification of novel drug discovery starting points for the treatment of recessive dystrophic epidermolysis bullosa

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Abstract

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic disease caused by a deficiency in collagen VII (C7) due to mutations in the COL7A1 gene. This disrupts skin and mucosa architecture, resulting in blistering, chronic wounds, inflammation, and increased skin cancer risk among other symptoms. RDEB patients have an extremely poor quality of life and often die at young age. One class of mutations in RDEB are premature termination codons (PTC). Using patient-derived keratinocytes and a library of 8,273 small molecules and 20,160 microbial extracts evaluated in a phenotypic screen interrogating C7 levels, we identified three active chemical series. Two showed PTC readthrough activity, and one upregulated truncated C7 expression, showing synergistic activity when combined with the reference readthrough aminoglycoside gentamicin. These compounds represent potential starting points for novel systemic therapies that could complement topical based treatments for RDEB. This project was a collaboration with UC3M (Madrid) and Fundación MEDINA (Granada) with partial financial support from the Spanish Ministry of Science.