Ryan Moseley et al., J Tissue Sci Eng 2017, 8:5(Suppl)
DOI: 10.4172/2157-7552-C1-042



# REPURPOSING INGENOL MEBUTATE AS A NOVEL PHARMACEUTICAL THERAPY FOR NORMAL AND PATHOLOGICAL DERMAL FIBROSIS

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Excessive dermal scarring/fibrosis possess major challenges to Healthcare Services worldwide. This is confounded by existing therapies being unsatisfactory at preventing or arresting fibrosis. Therefore, there is significant need for novel anti-fibrotic therapies with improved efficacy. The anti-cancer drug, ingenol mebutate (IngM), is licensed for actinic keratosis and non-melanoma skin cancers. IngM also stimulates exceptional healing and reduced scarring in treated skin, implying IngM possesses potent anti-fibrotic properties. As transforming growth factor-β1 (TGF-β1)-driven, dermal fibroblast-myofibroblast differentiation is pivotal to scarring outcomes, fibroblasts and myofibroblasts represent viable IngM targets. This work evaluated IngM efficacy against normal (dermal) and pathological (keloid) fibroblasts/myofibroblasts; and its mechanisms of action. Human dermal and keloid fibroblasts were treated with IngM (0-10μg/mL) and rhTGF-β1 (10ng/mL); and assessed for myofibroblast differentiation by immunocytochemistry/QRT-PCR for -smooth muscle actin (α-SMA) expression/stress fibre formation; QRT-PCR/Western blotting of other myofibroblast-/extracellular matrix (ECM)-related genes/proteins; hyaluronan synthesis/assembly (ELISA, hyaluronan synthase QRT-PCR, pericellular localization); and Microarrays/protein validation analysis. Although IngM does not inhibit dermal fibroblast-myofibroblast differentiation, IngM alters myofibroblast pro-fibrotic ECM deposition due to enhanced degradation of type I collagen by up-regulated matrix metalloproteinases (MMP-1, MMP-9). IngM also increases myofibroblast hyaluronan synthesis by hyaluronan synthase-2. Although reduced MMPs and hyaluronan are hallmarks of keloid scars, increased MMP/hyaluronan levels were also identified in IngM-treated keloid fibroblasts; in addition to reversed keloid fibroblast-myofibroblast formation and reduced type I collagen expression. Therefore, IngM modulates dermal/keloid fibroblast differentiation and behaviour, inducing scar tissue resolution. Such findings support IngM development/repurposing as a novel anti-fibrotic therapeutic against normal and pathological dermal scarring.

## Biography

Ryan Moseley graduated from Swansea University with a BSc (Honours) Degree in Biochemistry. Later, he obtained his PhD from the School of Dentistry, University of Wales College of Medicine, examining the role of oxidative stress in periodontal disease. Dr Moseley continues his research at Cardiff University, where he is currently a Reader in Tissue Repair and Director of the CITER MSc Programme in Tissue Engineering. Dr. Moseley's research focusses on the mechanisms underlying dermal and oral wound healing during health and disease; and the development of stem cell-, biomaterial- and pharmaceutical-based strategies to address impaired healing in these tissues.

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