Modulatory Effects of Novel Epoxy-Tiglianes on Dermal Fibroblast-Myofibroblast Wound Healing Responses Mediate Their Enhanced Anti-Scarring Properties

**Introduction**

- The novel epoxy-tiglianes, 12-tigloyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigilane-3-one (EBC-46) and a less active related compound, 12-tigloyl-13-(2-methylbutanoyl)-5,6-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigilane-3-one (EBC-211), occur within seeds of the Fontainea Bluethorn Tree, indigenous to Queensland’s tropical rainforest.

- EBC-46 is currently being developed as an anti-cancer agent by Australian biotechnology company, Qbiotics (www.qbiotics.com), for the intra-tumoral treatment of cutaneous & sub-cutaneous tumours in humans & animals.

- In veterinary clinical trials, exceptional dermal wound healing responses, characterised by accelerated re-epithelialisation, closure & reduced scarring, have been consistently observed following tumour ablation by EBC-46.

- This suggests that EBC-46 & EBC-211 could offer treatments that abrogate normal & excessive dermal scarring (fibrosis), evident during clinical situations such as burn injuries, surgical / non-surgical lacerations & hypertrophic / keloid scarring.

- Indeed, as existing clinical therapies are acknowledged to be unsatisfactory for use in the prevention or attenuation of excessive scar formation, there is a huge clinical need to develop effective therapies which arrest or prevent fibrosis.

**Alims & Objectives**

As fibroblasts are pivotal to dermal healing responses, wound closure & scarring, fibroblasts & the scar-forming myofibroblasts represent viable targets for the anti-fibrotic properties of epoxy-tiglianes. Therefore, this study examined the effects of EBC-46 & the lesser active analogue (EBC-211), on fibroblast proliferation, migration & transforming growth factor-β (TGF-β), driven fibroblast-myofibroblast-differentiation in vitro.

**Materials & Methods**

- **Primary Dermal Fibroblasts**
  - Serum-starvation (24h)
  - DEME, antibiotics, L-glutamine (2mM)
  - EBC-46
  - EBC-211

- **MTT Assay** (24 – 168h)
- **Flow Cytometry** (0 – 24h)
- **Cell Cycle Analysis**
- **e-SMMA gene expression at 0.1 µg/mL & 10 µg/mL, respectively.

- **EBC-46 & EBC-211 significantly inhibited e-SMA gene expression at 0.1 µg/mL & 10 µg/mL, respectively.

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**Conclusions**

- Both EBC-46 & EBC-211 significantly inhibit fibroblast proliferative responses & TGF-β₁, driven, fibroblast-myofibroblast-differentiation in vitro.

- EBC-46 & EBC-211 have no significant effects on scratch wound repopulation.

- Therefore, findings suggest that epoxy-tiglianes primarily induce anti-scarring responses by attenuating fibroblast proliferation & TGF-β₁-driven, myofibroblast-differentiation; & highlight the potential of epoxy-tiglianes as novel therapeutics for excessive dermal scarring & fibrosis.

- Further studies are elucidating the mechanisms by which epoxy-tiglianes mediate these anti-scarring effects.

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