Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04755) as a Potential Topical Treatment for Scleroderma

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Background
- Scleroderma is an autoimmune fibrotic disease which can present with skin manifestations amongst other signs and symptoms.
- The Wnt pathway plays an important role in inflammation, skin fibrosis, and vasculopathy, and is upregulated in scleroderma.
- Topical and systemic treatments for scleroderma are limited and not all patients respond.
- The Wnt pathway promotes fibroblast activation, myofibroblast differentiation, and extracellular matrix (ECM) deposition.

Methods
- To identify small molecule Wnt signaling inhibitors, a small molecule chemical library was screened in a cellular Wnt pathway-based assay using a β-galactosin TF/β-responsive reporter in SW480 colon cancer cells. Wnt pathway inhibition was further confirmed by qRT-PCR for Wnt target genes (Axin2, TCF4, CTGF, and LIF). In addition, SM04755 is stable in plasma and is not metabolized in vivo.
- Anti-inflammatory activity was evaluated by measuring IL-6 and TNF-α secretion using ELISA in lipopolysaccharides (LPS)-stimulated THP-1 cells treated with SM04755 for 24hrs. In vivo pharmacokinetics were evaluated following topical application in rats by qRT-PCR based expression of Wnt signaling and fibrotic markers.
- In vivo efficacy was evaluated in a subcutaneous bleomycin model of scleroderma by histological assessment of the thickness of the layers of skin. CD31 immunohistochemistry for vasculopathy, and qRT-PCR expression of Wnt signaling and fibrotic markers.

Results
- SM04755 inhibited inflammatory cytokine secretion in vitro and prevented fibrosis in vivo.
- SM04755 reduced dermal & deep fascia thicknesses and increased adipose tissue thickness in a mouse bleomycin scleroderma model.
- SM04755 reduced vasculopathy in a mouse bleomycin scleroderma model.

Discussion
- SM04755, a potent and specific inhibitor of Wnt signaling, inhibited inflammation and reversed dermal fibrosis in vivo.
- SM04755 could be a potential topical therapy for scleroderma.

References