Small Molecule Wnt Pathway Inhibitor (SM04755) as a Potential Topical Psoriasis Treatment

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Aim

SM04755, a novel, topical, small-molecule Wnt pathway inhibitor was evaluated in preclinical studies for potential to inhibit inflammation, keratinocyte proliferation and dermal fibrosis in psoriasis (PSO).

Methods

Wnt pathway inhibition was measured with a cell-based reporter assay. Anti-inflammatory activity in lipopolysaccharide (LPS) stimulated monocytes and anti-CD3/anti-CD28 stimulated PBMCs was measured by ELISA for pro-inflammatory cytokines. Cytokine induced keratinocyte proliferation was measured in HaCat cells by an EdU incorporation assay. Fibrosis in TGFβ stimulated human dermal fibroblasts (HDFs) was measured by smooth muscle actin (αSMA), plasminogen activator inhibitor (PAI-1), connective tissue growth factor (CTGF) and collagen expression by qPCR. *In vivo* efficacy was evaluated in an Imiquimod-induced mouse PSO model by measures of skin and ear thicknesses, visual skin health scores, spleen weight, *ex vivo* T cell activation and cytokine plasma levels.

Results

SM04755 was a potent (EC_{50} =152nM) and selective inhibitor of Wnt signaling and LPS, anti-CD3/anti-CD28 induced cytokine secretion (EC_{50} = 500nM) in monocytes and PBMCs, and cytokine induced keratinocyte proliferation (EC_{50} = 900nM). SM04755 inhibited TGFβ stimulated fibrosis with decreased gene expression ($p<0.05$) of αSMA (EC_{50} = 400nM), PAI-1, CTGF and collagen in HDFs. In a Imiquimod-induced mouse PSO model, topical SM04755 (400$\mu g/cm^2$) decreased skin and ear thicknesses ($p<0.01$), improved skin visual skin health scores and reduced spleen weight ($p<0.01$) as compared to vehicle. Clobetasol, a positive control, decreased skin thickness ($p<0.001$) below that of normal skin (a known adverse effect of steroid treatment). SM04755 inhibited *ex vivo* T cell activation and cytokine secretion compared to vehicle.

Conclusion

SM04755 inhibited inflammation, keratinocyte proliferation and fibrosis *in vitro*. In a PSO mouse model, topical SM04755 inhibited inflammation and improved skin health compared to vehicle. SM04755 has potential as a topical therapy for psoriasis.