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

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Background
- Psoriasis (PsO) is an auto-immune disease, characterized by inflammation and flares, production of red, itchy, and scaly skin.
- Wnt signaling plays an important role in the pathology of PsO by regulating inflammation, keratinocyte proliferation, and dermal fibrosis.1,2
- Treatment of mild to moderate PsO (<10% BSA) with safe and effective topical agents is a medical need.
- SM04755, a novel, small-molecule Wnt pathway inhibitor previously demonstrated inhibition of inflammation and keratinocyte proliferation in vitro and in an imiquimod-induced mouse PsO model.3

Hypothesis:
- SM04755 treatment inhibits cytokine production in vitro.
- SM04755 treatment results in decreased inflammation and improved skin health in a mouse model with reconstitution of ICR scid mice with minor histocompatibility mismatched naïve CD4+ T lymphocytes, which closely resembles human PsO pathophysiology.

Methods
- Immunoreconstituted model: FR4 (FVB N, IL-6-/-) and C3H/HeN (IL-12-/-) mice were treated topically with SM04755 or vehicle (n=10/group).
- ELISA: IL-1β, IL-6, TNF-α, and IFN-γ were measured in serum, plasma, and ear tissue.
- Histology: Skin biopsies were evaluated for epidermal thickness and dermal inflammation.
- Immunofluorescence: CD4+ T cells were evaluated for nuclear factor κB (NF-κB) activation.

Results
- SM04755 dose-dependently inhibited pro-inflammatory cytokine secretion in primary human PBMCs stimulated with CD8+ T cells.
- SM04755 inhibited IL-1β, IL-6, and TNF-α production in vivo.
- SM04755 reduced levels of inflammatory cytokines in the ears, skin, and plasma of mice treated with SM04755.

Conclusions
- SM04755 treatment decreased ear thickness and spliced weight compared with vehicle treatment at multiple time points (mean ± SD, n=5, p<0.01).
- Mouse weights and ear spliced weight were observed following 7 weeks of treatment of SM04755 treatment.

References:

Figure 1. Schematic for reconstitution of ICR scid mice with MHA mismatched CD4+ T lymphocytes model of psoriasis.

Figure 2. Dose-dependent inhibition of pro-inflammatory cytokine secretion by SM04755 in primary human PBMCs stimulated with CD8+ T cells receptor dependent responses (n=3, mean ± SD, p<0.05, ***p<0.001).

Figure 3. Dose-dependent inhibition of pro-inflammatory cytokine secretion by SM04755 in primary human PBMCs stimulated with PMA.

Figure 4. Measurement of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in mouse ears, skin, and plasma, following 7 weeks of treatment with either vehicle or SM04755 (n=5 per group, mean ± SD, p<0.05 vs vehicle).

Figure 5. SM04755 reduced epidermal thickness and inflammation in a mouse psoriasis model.

Figure 6. Vehicle- or SM04755- treated mice following 3 weeks and 7 weeks of topical treatment.

Figure 7. (a) Ear thickness from naive vehicle- or SM04755- treated mice. SM04755 treatment decreased ear thickness compared with vehicle at multiple time points (mean ± SD, n=5, p<0.01).

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