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

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#7541

Introduction

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

Hypothesis:

- SM04755 treatment results in decreased inflammation, improved skin health in a mouse model with reconstitution of ICR scid mice with minor histocompatibility antigen (MHA) mismatched naïve CD4+ T lymphocytes, which closely resembles human PSO pathophysiology.[3]
- SM04755 treatment inhibits cytokine production *in vitro*.

Methods

- Immune reconstitution model:[3] **(Figure 1)**: PBMCs were isolated from F2 (BALB/c x 129/SvJ) mice and analyzed by flow cytometry to identify H-2d haplotype donor mice. CD4+/CD45RB^{Hi} cells from donor mice spleens were purified and injected intravenously into CB17/ICR-Tac Prkdc/scid (ICR scid) mice (5x10^5 cells/mouse).
- Skin appearance and ear thickness were evaluated weekly. At the first signs of PSO (lesions and increased thickness; week 6), psoriatic mice were randomized and treated with daily topical SM04755 (400 µg/cm^2) or vehicle from week 7 until week 14.
- After 7 weeks of treatment, body and spleen weights were measured, and inflammation was evaluated by measuring cytokines (IL-1β, TNF-α, IL-6) in tissues from skin, ears, spleen and plasma using ELISA. Epidermal thickness and infiltrating cells in the skin were histologically evaluated.
- *In vitro* cytokine assay: A panel of pro- and anti-inflammatory cytokines (IL-1β, IL-6, IL-8, IL-17A, IL-17F, IL-12, IL-23, IFN-γ, TNF-α) were evaluated in peripheral blood mononuclear cells (PBMCs) stimulated with CD3/CD28 or Phorbol 12-myristate 13-acetate (PMA) and treated with SM04755 or vehicle, using a multiplex immunoassay platform (Meso Scale Discovery).

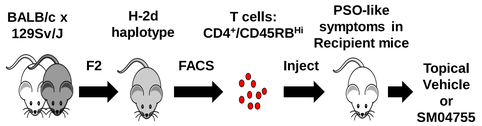

Figure 1. Schematic for reconstitution of ICR scid mice with MHA mismatched CD4+ T lymphocytes model of Psoriasis.

Results

SM04755 decreased skin lesions and improved skin appearance in a mouse model of psoriasis

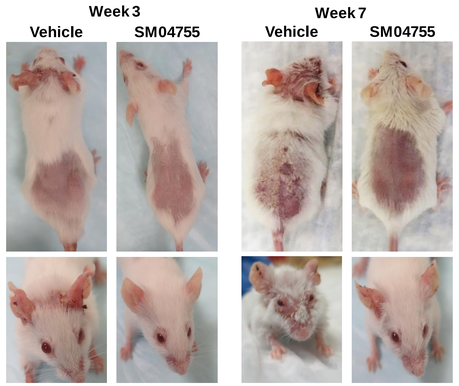

Figure 2. Vehicle- or SM04755-treated mice following 3 weeks and 7 weeks of daily topical treatment. Decreased skin lesions and improved skin health observed in SM04755 treated mice compared to vehicle. (n= 5/group)

SM04755 reduced epidermal thickness and inflammation in a mouse model of psoriasis

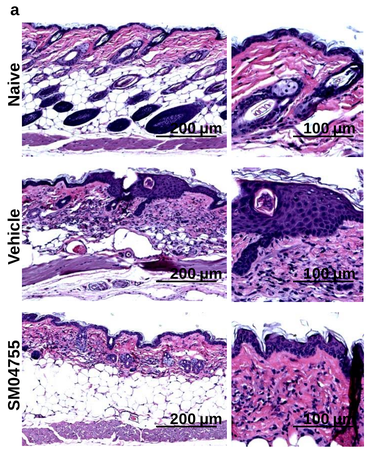

Figure 3. (a) H&E stained skin sections from naive or psoriatic mice treated with vehicle or SM04755 following 7 weeks of treatment. Decreased epidermal thickness, skin lesions and inflammatory cells, along with increased adipose layer in SM04755 treated mice compared to vehicle. **(b)** Epidermal thickness in lesional and non-lesional skin in **(a)** (n=5 sections/mouse, 5 mice/group, Mean ± SEM, ***p<0.001 vs vehicle).

SM04755 reduced ear thickness, spleen weight and improved overall health in a mouse model of psoriasis

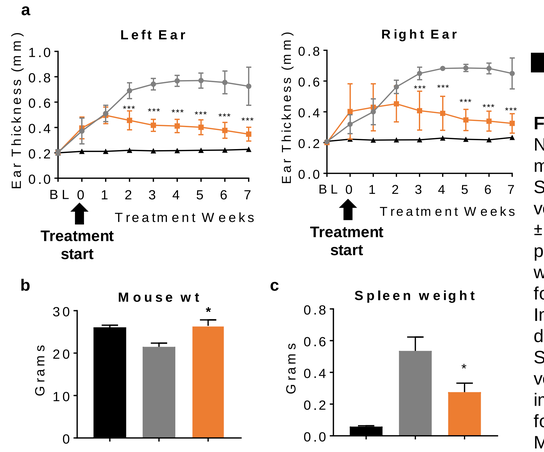

Figure 4. (a) Ear thickness from Naive, vehicle- or SM04755-treated mice. Decreased ear thickness with SM04755 treatment compared to vehicle at multiple timepoints. Mean ± SD, n= 5, ***p<0.001, BL- baseline prior to T cell injection. **(b)** Mouse weights and **(c)** spleen weights following 7 weeks of treatment. Improved mouse weight and decreased spleen weight with SM04755 treatment compared to vehicle, showing overall improvement in animal health. n=3 for naïve, n=5 for vehicle, SM04755, Mean ± SEM, *p<0.05 vs vehicle.

Results

SM04755 reduced inflammatory cytokines in the ears, skin, and plasma of mice in a psoriasis model

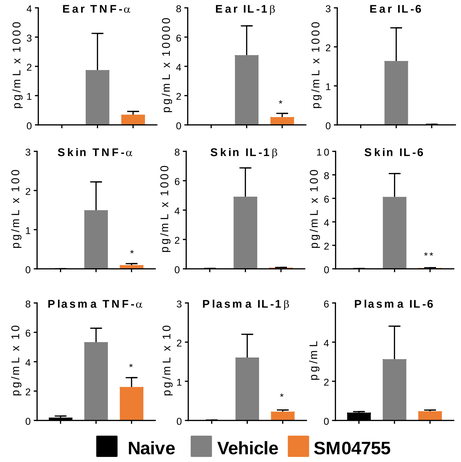

Figure 5. Measurement of pro-inflammatory cytokines (TNF-α, IL1-β, IL-6) in mouse ears, skin and plasma, following 7 weeks of treatment with vehicle or SM04755. (n=3 for naïve, n=5 for vehicle, SM04755, Mean ± SEM, *p<0.05, **p<0.01 vs vehicle)

SM04755 dose-dependently inhibited inflammatory cytokine secretion in primary human PBMCs stimulated with CD3/CD28 or PMA *in vitro*

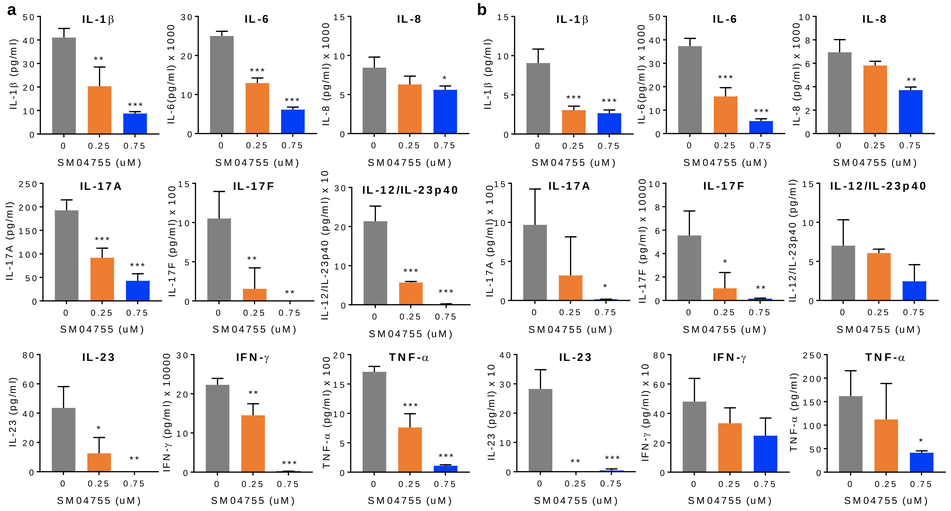

Figure 6. Dose-dependent inhibition of pro-inflammatory cytokine secretion by SM04755 in primary human PBMCs stimulated with **(a)** CD3/CD28 or **(b)** PMA demonstrated inhibition of T cell receptor and T cell signaling dependent responses. (n=3, Mean ± SD, *p<0.05, **p<0.01, ***p<0.001)

Discussion

- Previous studies have shown that SM04755 inhibited inflammation and epidermal thickening in the IMQ-induced mouse psoriasis model.
- A mouse model of minor histocompatibility mismatched T lymphocyte reconstitution-induced psoriasis, which closely mimics human disease was successfully developed and implemented.
- In the mouse model of psoriasis, topically applied SM04755 inhibited inflammation and decreased skin and ear thicknesses, improved skin appearance and mouse weight compared to vehicle.
- Topically applied SM04755 also inhibited the production of proinflammatory cytokines as compared to vehicle.
- SM04755 demonstrated a broad, dose-dependent inhibition of inflammatory cytokine production in PBMCs induced by inflammatory stimuli, CD3/CD28, and PMA, *in vitro*, further demonstrating the anti-inflammatory effects of this compound in primary T cells.
- SM04755, a small molecule inhibitor of Wnt signaling, showed potential as a topical therapy for psoriasis.
- A Phase 1 trial in psoriasis patients is on-going in Australia (ACTRN12617001178336).

References

1. *National PSO Foundation*
2. *Deshmukh et.al., Arthritis Rheumatol. 2016; 68 (suppl 10)*
3. *Schon et.al., Nature Medicine, Feb 1997*

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Disclosures:

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