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

Vishal Deshmukh, Melinda Pedraza, Lisa Lamangan, and Yusuf Yazici
Samumed, LLC, San Diego, CA, USA

Poster #1097

Background

- Psoriasis (PSO) is an auto-immune disease, characterized by inflammation and fibrosis, producing patches of red, itchy, and scaly skin.[1]
- Wnt signaling plays an important role in the pathology of PSO by regulating inflammation, keratinocyte proliferation, and dermal fibrosis.[2,3]
- Treatment of mild to moderate PSO (<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-induced mouse PSO model.[4]

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

- Immune reconstitution model: (**Figure 1**): Peripheral blood mononuclear cells (PBMCs) were isolated from F2 (BALB/c x 129/SvJ) mice and analyzed by flow cytometry to identify H-2Dd 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).[5]
- 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 PBMCs stimulated with CD3/CD28 or Phorbol 12-myristate 13-acetate (PMA) and treated with SM04755 or vehicle, using an ELISA platform (Meso Scale Discovery).

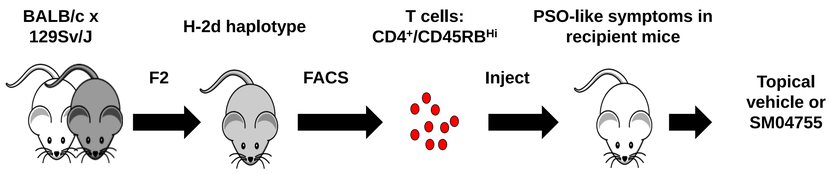

Figure 1. Schematic for reconstitution of ICR scid mice with MHA mismatched CD4+ T lymphocytes model of psoriasis.

Results

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

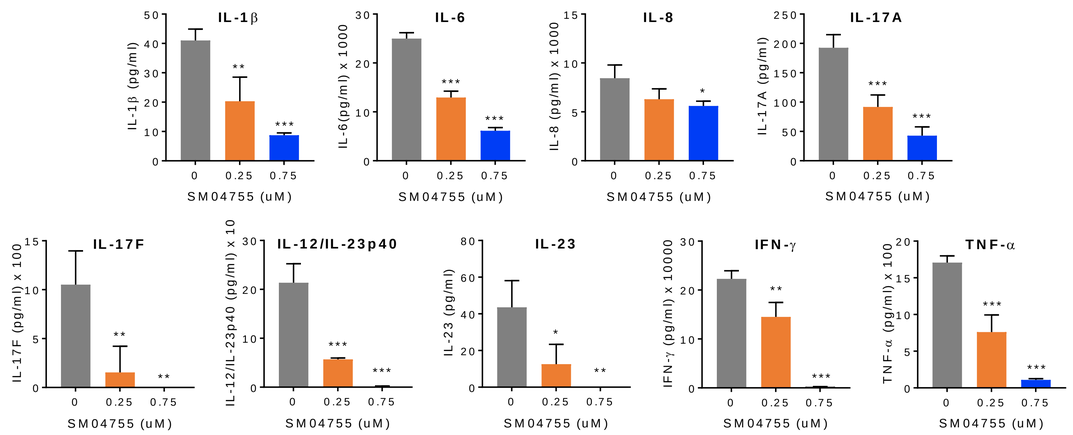

Figure 2. Dose-dependent inhibition of pro-inflammatory cytokine secretion by SM04755 in primary human PBMCs stimulated with CD3/CD28 demonstrated inhibition of T cell receptor dependent response (n=3, mean ± SD, *p<0.05, **p<0.01, ***p<0.001).

SM04755 dose-dependently inhibited inflammatory cytokine secretion in primary human PBMCs stimulated with PMA

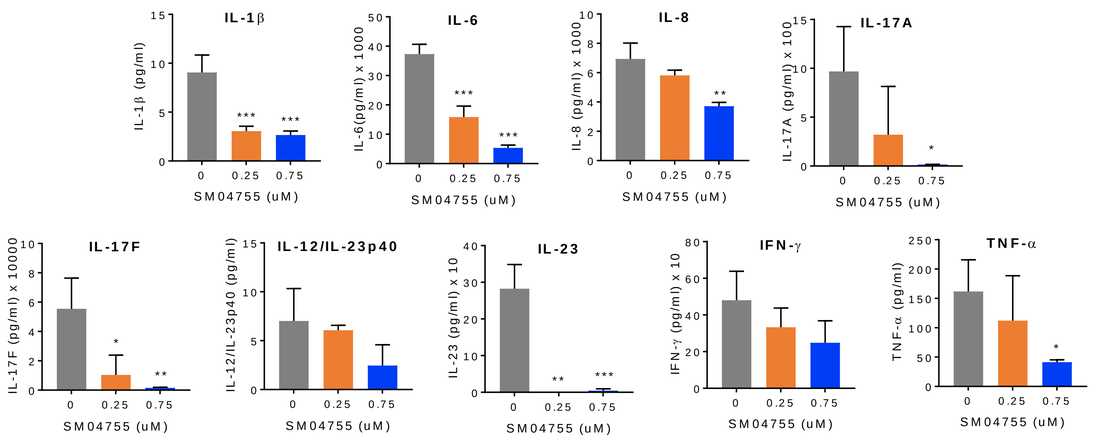

Figure 3. Dose-dependent inhibition of pro-inflammatory cytokine secretion by SM04755 in primary human PBMCs stimulated with PMA demonstrated inhibition of T cell signaling response (n=3, mean ± SD, *p<0.05, **p<0.01, ***p<0.001).

Results

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

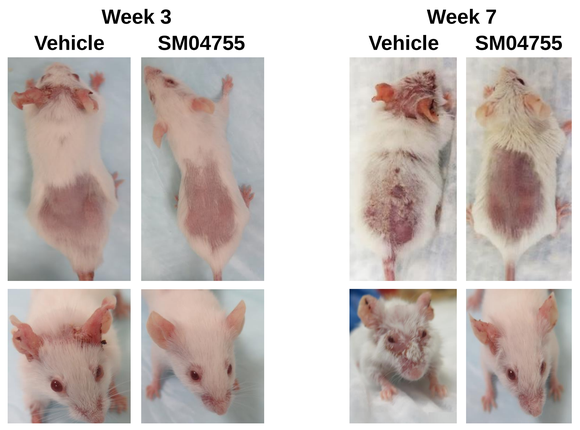

Figure 4. Vehicle- or SM04755-treated mice following 3 weeks and 7 weeks of daily topical treatment. Decreased skin lesions and improved skin health were observed in SM04755-treated mice compared with vehicle-treated mice (n=5 mice/group).

SM04755 reduced epidermal thickness and inflammation in a mouse psoriasis model

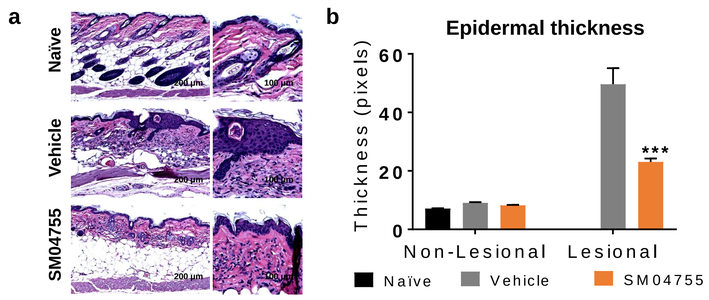

Figure 5. (a) H&E-stained skin sections from naïve or psoriatic mice treated with vehicle or SM04755 following 7 weeks of treatment. Decreased epidermal thickness, skin lesions and inflammatory cells, along with increased adipose layer, were observed in SM04755-treated mice compared with vehicle-treated mice. **(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 and spleen weight and improved overall health in a mouse psoriasis model

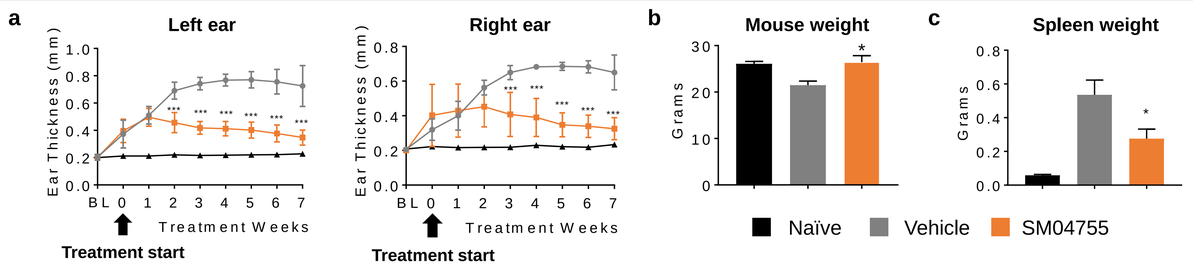

Figure 6. (a) Ear thickness from naïve, vehicle-, or SM04755-treated mice. SM04755 treatment decreased ear thickness compared with vehicle at multiple timepoints (mean ± SD, n=5, ***p<0.001). **(b)** Mouse weights and **(c)** spleen weights following 7 weeks of treatment. SM04755 treatment improved mouse weight and decreased spleen weight compared with vehicle, showing overall improvement in animal health (n=3 for naïve, n=5 for vehicle and SM04755, mean ± SEM, *p<0.05 vs vehicle).

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

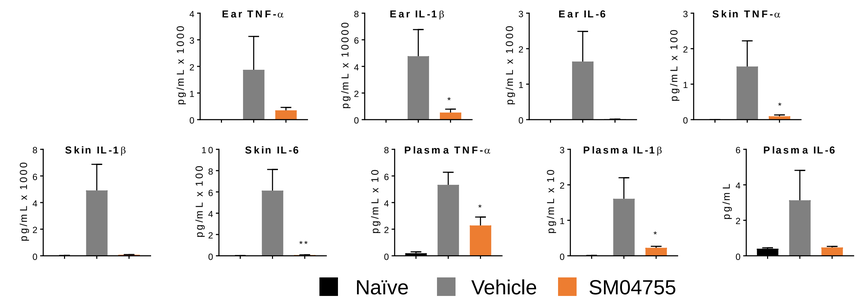

Figure 7. Measurement of pro-inflammatory cytokines (TNF-α, IL1-β, IL-6) in mouse ears, skin and plasma, following 7 weeks of treatment with either vehicle or SM04755 (n=3 for naïve, n=5 for vehicle and SM04755, mean ± SEM, *p<0.05 vs vehicle). There were reduced levels of inflammatory cytokines in the ears, skin, and plasma of SM04755-treated mice compared with vehicle.

Conclusions

- Previous studies have shown that SM04755 inhibited inflammation, epidermal thickening, and fibrosis in the imiquimod-induced psoriasis model in mice.[4]
- 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.
- 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, and improved skin appearance and mouse weight compared with vehicle.
- Topically applied SM04755 also inhibited the production of proinflammatory cytokines compared with vehicle.
- SM04755, a small molecule inhibitor of Wnt signaling, showed potential as a topical therapy for psoriasis.
- A phase 1 trial in psoriasis patients is ongoing in Australia (ACTRN12617001178336).

References

1. National PSO Foundation
2. Gudjonsson JE, et al. *JID.* 2010;130:1849-59.
3. Akhmetshina A, et al. *Nat Comm.* 2012;3:735.
4. Deshmukh V, et al. *Arthritis Rheumatol.* 2016;68 (suppl 10).
5. Schon MP, et.al. *Nat Med.* 1997;3:183-8.

9381 Judicial Drive ● San Diego, CA 92121 ● Email: info@samumed.com