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

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**Introduction**

- Psoriasis (PSO) is an autoimmune disease characterized by inflammation and fibrosis, producing patches of red, itchy, scaly skin.
- Wnt signaling plays an important role in the pathology of psoriasis, by regulating inflammation, keratinocyte proliferation, and dermal fibrosis.1
- Treatment of mild to moderate psoriasis (<10% BSA) with safety 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 (MD)-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 (Figure 1): PBMCs were isolated from F2 (BALB/c x 129/Sv) mice and analyzed by flow cytometry to identify H-2d haplotype donor mice. CD4+CD45RB+ cells from donor mice splenocytes were purified and injected intravenously into C17/1ICR Tac Prkdc.scid (ICR scid) mice (5x10^6 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/cm²) 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 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-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 immunnoassay platform (Meso Scale Discovery).

**Results**

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

**Figure 3.** (a) HA/4 stained skin sections from naïve or psoriatic mice treated with vehicle or SM04755 following 7 weeks of treatment. Decreased epidermal thickness, skin thickness 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 naïve or vehicle treated mice. (n=5 sections/mouse, 5 mice/group, Mean ± SEM, *p<0.001 vs vehicle).

**Discussion**

- Previous studies have shown that SM04755 inhibited inflammation and epidermal thickening in the IMG induced mouse psoriasis model.
- A mouse model of minor histocompatibility mismatched T lymphocyte reconstitution-induced PsO, 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.

**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=5 for naive, n=5 for vehicle, SM04755, Mean ± SEM, *p<0.05 vs vehicle.

**Figure 5.** Measurement of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in mouse ears, skin, and plasma following 7 weeks of treatment with vehicle or SM04755, (n=5 naive, n=5 vehicle, SM04755, Mean ± SEM, *p<0.05, **p<0.01 vs vehicle).

**Figure 6.** Dose-dependent inhibition of pro-inflammatory cytokine secretion 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=5, Mean ± SD, *p<0.05, **p<0.01, ***p<0.001).

**References**

1. Schon et al., Nature Medicine, Feb 1997
2. Deshmukh et al., Autoimmune Rheumatol, 2016; 68 (suppl 10)
3. Schon et al., Nature Medicine, Feb 1997

**Disclosures and Acknowledgements**

**Funding**

- National Psoriasis Foundation
- Deshmukh et al., Autoimmune Rheumatol, 2016; 68 (suppl 10)
- Schon et al., Nature Medicine, Feb 1997

**Authors’ Disclosures**

- Ownership: Brian Holmberg BS, Gary Mandel KD, PhD, Pharmacologists; Josh Greenhorn, BS, Pharmacology development; Luis Delbarrio, BS, Animal model development; Barry Kowalsky, PhD, Pharmacologists; Chryssoula Swaegers, PhD, Preclinical Models; David Heiman, PhD, Jayrn Tamblyn, MBChB

- Employment: Chryssoula Swaegers, PhD, Preclinical Models; David Heiman, PhD, Jayrn Tamblyn, MBChB

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