Accepted as poster #THU0046 at Annual European Congress of Rheumatology (EULAR) 2018, Amsterdam, Netherlands, June 13-16, 2018

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

Vishal Deshmukh, Melinda Pedraza, Lisa Tran, and Yusuf Yazici

Samumed, LLC, San Diego, CA

Background: Psoriasis (PSO) is an autoimmune disease, causing patches of thick, inflamed, scaly skin due to excessive proliferation of skin cells[1]. Wnt signaling plays an important role in PSO, regulating inflammation and keratinocyte proliferation. SM04755, a novel, topical small-molecule Wnt pathway inhibitor was previously shown to inhibit inflammation and keratinocyte proliferation *in vitro* and in an IMQ-induced mouse PSO model[2].

Objective: In this study, the effects of SM04755 on inflammation and skin health were evaluated in two models that closely resemble human PSO pathophysiology: reconstitution of ICR *scid* mice with minor histocompatibility mismatched naïve $CD4^+$ T lymphocytes[3] and an IL-23 intra-dermal injection model[4].

Methods: For (A) immune reconstitution model, peripheral blood mononuclear cells were isolated from F_2 (BALB/c x 129/SvJ) mice and analyzed by flow cytometry to identify $H\text{-}2D^d$ 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 visible PSO-like signs, mice were randomized and treated with SM04755 (400 $\mu g/cm^2$) or vehicle. After 14 weeks, 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 skin immune cell infiltration were histologically evaluated. For (B) the IL-23 model, rIL-23 was injected intra-dermally into mouse ears, every other day for 35 days. Mice were randomized on Day 16 and treated with SM04755 (400 $\mu g/cm^2$) or vehicle or Clobetasol daily for 20 days. Ear thickness was measured every 3 days. Skin immune cell infiltration was histologically evaluated.

Results: (A) Immune reconstitution of ICR *scid* mice resulted in PSO-like signs, with skin lesions and increased thickness of the skin and ears. Treatment with topical SM04755 (400 $\mu g/cm^2$) significantly ($p<0.01$) decreased skin and ear thicknesses and improved skin appearance compared to vehicle. Body weights were significantly ($p<0.05$) higher in treated compared to vehicle mice. SM04755 significantly reduced histologically measured epidermal thickness ($p<0.05$) and immune cell infiltration in the skin compared to vehicle. Further, inflammatory cytokine levels in the skin, ears, spleen and plasma and spleen weight were significantly ($p<0.05$) reduced in SM04755 treated animals compared with vehicle. (B) Intradermal IL-23 injection into mouse ears resulted in inflammation and ear thickening by day 16 compared to sham. Treatment with topical SM04755 (400 $\mu g/cm^2$) significantly ($p<0.05$) decreased ear thickness, immune cell infiltration, and improved appearance compared to vehicle.

Conclusion: In two mouse models of (A) minor histocompatibility mismatched T lymphocyte reconstitution-induced PSO and (B) IL-23 injection-induced PSO, topically applied SM04755 inhibited key pathophysiological features of PSO at macro- and microscopic levels, compared to vehicle. SM04755 has potential as a topical therapy for PSO. Clinical trials are ongoing.

Reference: [1]National PSO Foundation. [2]Deshmukh et al., *Arthritis Rheumatol* 2016;68(suppl 10). [3]Schon et al., *Nature Medicine* 1997;3:183-8. [4]Mabuchi et al., *J Immunol* 2011;187:5026-31.