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

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

Samumed, LLC, San Diego, CA

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 psoriasis (PSO) model. Further inflammation and skin effects were evaluated in an ICR *scid* mouse reconstitution model with minor histocompatibility mismatched naïve $CD4^+$ T lymphocytes, more closely resembling human PSO pathophysiology.

H-$2D^d$ haplotype donor mice were identified from F_2 (BALB/c x 129/SvJ) by flow cytometry. $CD4^+$/$CD45RB^{Hi}$ 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 for PSO-like signs (lesions, increased thickness). PSO mice were randomized and treated with SM04755 (400 $\mu g/cm^2$) or vehicle. After 14 weeks, body and spleen weights were measured, and inflammatory cytokines evaluated (IL-1β, TNF-α, IL-6) in tissues from skin, ears, spleen and plasma using ELISA. Epidermal thickness and infiltrating cells in skin were histologically evaluated.

Immune reconstitution of ICR *scid* mice resulted in PSO-like signs, with lesions and increased thickness of the skin and ears. Compared to vehicle, topical SM04755 (400 $\mu g/cm^2$) significantly ($p<0.01$) decreased skin and ear thicknesses and improved skin appearance. Body weights were also significantly ($p<0.05$) higher in treated mice. SM04755 significantly reduced microscopic epidermal thickness ($p<0.05$) and immune infiltration in the skin compared to vehicle. Inflammatory cytokine levels in the skin, ears, spleen and plasma, as well as spleen weight, were significantly ($p<0.05$) reduced in SM04755-treated animals compared with vehicle.

In a mouse model of minor histocompatibility mismatched T lymphocyte reconstitution-induced PSO, topical SM04755 inhibited inflammation and decreased skin and ear thicknesses compared to vehicle. SM04755 has potential as a topical therapy for PSO. Clinical trials are ongoing.