### Background

- Psoriasis (PSO) is an auto-immune disease, characterized by inflammation and fibrosis, producing patches of red, itchy, and scaly skin.  
- Wnt signaling plays an important role in the pathology of PSO by regulating inflammation, keratinocyte proliferation, and dermal fibrosis.  
- 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.  

**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+B+ cells from donor mice spleens were purified and injected intravenously into CB17/ICR-Tac Prkdcscid (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 weight and spleen weights were measured, and inflammation was evaluated by measuring cytokines (IL-1β, TNF-α, IL-6, IL-8, IL-17A, IL-17F, IL-23, IFN-γ, TNF-α, IL-4) 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).

### Results

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

- **SM04755 reduced epidermal thickness and inflammation in a mouse psoriasis model**

- **SM04755 reduced ear thickness and spleen weight and improved overall health in a mouse psoriasis model**

### Conclusions

- Previous studies have shown that SM04755 inhibited inflammation, epidermal thickening, and fibrosis in the imiquimod-induced psoriasis model in mice.  
- 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, topical 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 Psoriasis Foundation  