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

Vishal Deshmukh, PhD, Allison Hood, Yusuf Yazici, MD
Disclosures

- Vishal Deshmukh, Ph.D.
  - Financial disclosure: Samumed, LLC; salary and equity
- Allison Hood
  - Financial disclosure: Former employee of Samumed, LLC
- Yusuf Yazici, M.D.
  - Financial disclosure: Samumed, LLC; salary and equity
Disclaimer

• This presentation is not intended to provide a comprehensive overview of all studies using SM04755.

• SM04755 is an investigational compound currently in clinical trials; SM04755 has not been approved by the US Food and Drug Administration (FDA) or any other pharmaceutical regulatory authority, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidate.

• While the complete mechanism of action (MOA) for SM04755 is unknown, further investigation is being conducted. All of the MOA information is based on non-clinical data and the relationship to clinical benefit is unknown.

• This presentation is intended as a scientific exchange of medical information, is provided for educational purposes only, and is not intended for any promotional purpose or to offer medical advice; the information contained in this presentation is confidential and proprietary and is not available for further distribution in any form whatsoever.
Scleroderma/Systemic Sclerosis – need for therapies

- Heterogeneous disease characterized by fibroblast dysfunction (fibrosis), small vessel vasculopathy and production of autoantibodies\(^1\)
- Can be classified based on degree of skin involvement
  - ‘Limited cutaneous’, ‘diffuse cutaneous’ and ‘without skin involvement’
- No FDA approved therapies exist
  - Treatment recommendations focused on immunosuppression and symptom management\(^2,3\)
- Majority of patients experience skin sclerosis\(^1,2\)

\(^1\) Van Den Hoogen, F., et al. (2013) Arth. & Rheum;
Sk

Skin pathobiology of Scleroderma

Clinical Pathology:\(^1\)

- Dermal thickening, hardening of the skin, vascular changes
  - Progression may lead to painful ulcerations and reactive hyperkeratosis

Histopathology:\(^2\)

- Early - endothelial cell apoptosis, perivascular inflammation
- Late - excess extra-cellular matrix (ECM) deposition and vasculopathy
  - Fibroblasts produce smooth muscle actin and release collagen, fibronectin and glycosaminoglycans
  - Fibroblast activity becomes independent; mediated by TGFβ, PDGF, IL4, IL13 and MCP-1 and other pathways (Notch, Hedgehog and Wnt)

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The Wnt/β-Catenin pathway

- Wnt signaling is present in many cells, particularly in high turn-over tissues
- Wnt signaling is often implicated in development, tissue repair and regeneration
- Normal Wnt signaling is crucial for organ development and tissue homeostasis including skin
- Various human diseases are associated with abnormal Wnt signaling including SCL

Image from Lim, et al. (2013) *Science.*

Wnt in Scleroderma

- Increased Wnt signaling leads to nuclear β-catenin in scleroderma fibroblasts
- TGFβ cross-talk with Wnt signaling promotes transdifferentiation of fibroblasts into myofibroblasts, increased collagen accumulation and dermal thickening
- Wnt activation drives upregulation of VEGF leading to angiogenesis

Samumed has identified a candidate molecule from preclinical studies - SM04755

- Topical small molecule
- Potent inhibitor of Wnt pathway
- Sustained local and minimal systemic exposure
- Anti-fibrotic
- Potentially inhibits angiogenesis
SM04755 is a potent inhibitor of Wnt activity

- *In vitro* screening in a luciferase based Wnt reporter assay
- Wnt pathway inhibition confirmed by qPCR for Wnt target genes.

**Relative Wnt inhibition**

![Graph showing relative Wnt inhibition](image)

EC50 = 156.8 nM

**Wnt Target Genes**

![Bar chart showing relative expression of Wnt target genes](image)

- Axin 2
- TCF4
- LEF1
- TCF7

DMSO, SM04755 (300 nM)

* *** **
SM04755 inhibited fibrotic gene expression in dermal fibroblasts in vitro

- Human dermal fibroblasts treated with TGFβ1 to induce fibrosis.
- SM04755 significantly inhibited TGFβ1-induced Col2A1, ACTA2, PAI-1 and CTGF gene expression compared to vehicle.

Mean ± SEM, ** p<0.01, *** p<0.001, ANOVA
SM04755 reversed fibrosis in human dermal fibroblasts *in vitro*

- Human dermal fibroblasts treated with TGFb1 to induce fibrosis
- Treated with SM04755 after 48hrs
- SM04755 decreased TGFb1-induced smooth muscle actin

![Graph showing the effect of SM04755 on TGF-β1-induced smooth muscle actin](image)

EC$_{50}$ = 125nM

**TGF-β1 Stimulated**

<table>
<thead>
<tr>
<th>Control</th>
<th>DMSO</th>
<th>SM04755 (0.03 µM)</th>
<th>SM04755 (0.1 µM)</th>
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αSMA / DAPI
SM04755 sustained local & minimal systemic exposure

*In vivo* PK following QD x 7 day topical dosing (100mg/ml) of SM04755 in healthy rat skin

- Minimal plasma concentrations with rapid clearance
  - $C_{\text{max}} < 20 \text{ng/ml}$ in plasma
- Sustained local exposure and penetration into healthy skin
  - Up to 40µM concentration in deeper layers (>80x expected Tx dose)
  - High levels of compound retained in the skin beyond 42 days
- No systemic toxicity observed
Bleomycin model for Scleroderma

- Bleomycin (50µg) injected sub-cutaneous, every other day for 30 days induced scleroderma like symptoms in mice
  - Thickening of the dermis, hardening of the skin and vascular changes in ~ 2 weeks

SM04755 (q.d., topical 0.25mg/ml & 0.5mg/ml)
- Topical treatment (40µl/cm²) started day 14
- Skin sections stained with H&E/MT and thickness of each layer measured at 4 areas/section, and >20 sections/mouse
SM04755 attenuated fibrosis in a mouse model of Scleroderma

- SM04755 (0.25mg/ml and 0.5mg/ml) topical treatment (40µl/cm²), started day 14
- Significantly reduced dermal and deep fascia thickness and increased adipose thickness on day 30 compared to vehicle treatment (**p<0.01)

N = 7 mice/group for treatment, 6 mice/group for vehicle and 3 mice/group for naïve, Mean ± SEM, ** p<0.01, ANOVA
SM04755 inhibited Wnt signaling and attenuated fibrosis in a mouse model of Scleroderma

- SM04755 inhibited expression of fibrotic genes and a Wnt signaling pathway gene (Axin2) in bleomycin mice, compared to vehicle
SM04755 may decrease angiogenesis

- Representative sections stained for CD31 on day 30
  - CD31 - endothelial cell marker (also found in macrophages and platelets)
- SM04755 treatment decreased CD31 staining
Preclinical data suggest that SM04755 may ameliorate fibrosis

- Wnt signaling is a pivotal pathway in fibrosis
- Inhibiting the Wnt pathway disrupts the fibrotic process
- SM04755 was a potent inhibitor of Wnt/β-catenin activity
- SM04755 reduced fibrosis and may reduce angiogenesis in an in vivo bleomycin model of SCL
Current status

- Phase 1, single blind, topical study in healthy subjects for SM04755 program
  - Primary objectives: safety and tolerability, dose ranging
  - Secondary objective: plasma pharmacokinetics
Thank you  

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