Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04690) as a Potential Disease Modifying Treatment for Knee Osteoarthritis

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DISCLOSURES

- Vishal Deshmukh, Ph.D.
  - Financial disclosure: Samumed, LLC; salary and equity
- Charlene Barroga, Ph.D.
  - Financial disclosure: Samumed, LLC; salary and equity
- Yong Hu, Ph.D.
  - Financial disclosure: Former employee of Samumed, LLC; equity
- John D. Hood, Ph.D.
  - Financial disclosure: Co-founder and former employee of Samumed, LLC
- Yusuf Yazici, M.D.
  - Financial disclosure: Samumed, LLC; salary and equity
Pathophysiology of Osteoarthritis

- Mechanical forces and inflammation result in degenerative tissue remodeling in OA.
- Induce cartilage catabolic enzymes - matrix metalloproteinases (MMPs), aggrecanases, etc.
- Cartilage loss and subchondral bone remodeling

**Figure adapted from Bush J & Beier F. Nature Med. 2013;19(6):667-9.**
The Wnt signaling pathway is involved in stem cell control and regeneration of tissues.

Increased Wnt signaling contributes to the pathophysiology of OA.

Wnt signaling is involved in increased bone formation and cartilage breakdown.

Progenitor cells reside in the synovium and subchondral bone.

**Hypothesis:** Inhibiting the Wnt Pathway protects and regenerates cartilage


Proposed Therapy: SM04690

• SM04690 is a small molecule Wnt inhibitor in development for the treatment of OA

• SM04690 demonstrated the following properties in pre-clinical studies:
  – Decreased inflammation
  – Decreased cartilage degradation
  – Regenerated cartilage
  – Sustained local exposure and no observable systemic toxicity
In vitro Efficacy- SM04690
Decreased inflammation: SM04690 suppressed inflammatory cytokines

- IL1β, TNFα and IL-6 are associated with the pathophysiology of OA\(^1\)

**Cellular assay:**
- Synovial fibroblasts stimulated with IL1β and THP-1 monocytes stimulated with LPS to induce cytokine production
- Then treated with SM04690
- Cytokine production quantified by ELISA
- Dose dependent inhibition of both TNFα and IL-6 production demonstrated in both cell types

Decreased cartilage degradation: SM04690 inhibited protease production

- In OA, cytokines induce cartilage catabolic enzymes
- Increased Wnt signaling increases protease expression
- Dose dependent inhibition of protease expression demonstrated

Cellular assay – human chondrocytes:

Induce proteases

TNFα + Oncostatin M

Treat

SM04690 or Control

Measure

qPCR: MMP 1, 3, & 13

**** p<0.001

* p<0.05

Decreased cartilage degradation: SM04690 inhibited GAG and Nitric Oxide release

- Glycosaminoglycan (GAG) are components of cartilage matrix
- Secreted/extracellular GAG = cartilage breakdown
- Inhibition of GAG and Nitric Oxide (NO) release demonstrated

**Cellular assay – human chondrocytes:**

<table>
<thead>
<tr>
<th>Induce catabolism</th>
<th>Treat</th>
<th>Measure</th>
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<tbody>
<tr>
<td>IL1β or TNFα + Oncostatin M</td>
<td>SM04690 or Control</td>
<td>Secreted GAG and NO</td>
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**SM04690 protected chondrocytes from catabolic breakdown**
Regenerated cartilage: SM04690 induced functional chondrogenesis

21 day cellular assay – hMSCs:
• Treated with SM04690 every 7 days
• Cells stained for biomarkers and gene expression measured by qPCR
• Increased sulfated glycosaminoglycans (sGAG) with SM04690 treatment
• Functional chondrocytes-cartilage matrix synthesis

Chondrogenic Genes

GAG

Osteogenic Genes

Fold Change Over DMSO

SOX9

Aggrecan

Col2A

TGFb1

TIMP1

DMSO

SM04690 (30nM)

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Fold Change Over DMSO

Col1A

Osteocalcin

ALPL

BMP4

DMSO

SM04690 (30nM)

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*p<0.05

**p<0.01

***p<0.001
In vivo Efficacy
SM04690 had sustained local exposure and no systemic toxicity

Rats (Sprague Dawley):
• Single intra-articular injection (0.3ug)
• Compound is retained in joint above the target concentration level (~30 nM) for >6 months
• Compound is undetectable in plasma at all time points

Intra-articular (IA) injection in Rats (Sprague Dawley) and Dogs (Beagle):
• Single or multiple (6 or 9 once-monthly) IA injections
• No systemic toxicity - body weight, target or non-target organ effects, ECG and clinical pathology at doses up to 400X the expected clinical dose
Decreased cartilage degradation: ACLT + pMMx model of OA

- Rat ACLT + pMMx model- anterior cruciate ligament transection (ACLT) combined with partial medial meniscectomy (pMMx)
- Inject SM04690 single dose, intra-articular after 1 week
- Rat knee analyzed 5 and 13 weeks post-surgery for OA cartilage pathology

- qPCR evaluation of protease enzymes in cartilage
- Decreased protease expression in cartilage with SM04690 treatment

SM04690 protected cartilage from catabolic breakdown
SM04690 regenerated cartilage: ACLT + pMMx model of OA

- qPCR evaluation of cartilage production markers
- Increased expression of cartilage markers with SM04690 treatment
- Increased sulfated glycosaminoglycans (sGAG) - cartilage matrix
- No change in Col10a (hypertrophic marker)

Week 5

SM04690 induced chondrocyte and cartilage matrix production
SM04690 regenerated cartilage: Improved OA biomarkers and OARSI scores

- Decreased serum COMP and increased serum PIIANP observed with SM04690 treatment
- Safranin O-stained sections from the rat knee scored (blinded) using OARSI system
- OARSI cartilage pathology score measures cartilage matrix loss, fissures and subchondral bone remodeling, based on stage and grade of cartilage damage

SM04690 improved joint health

*\(p<0.05\) \,**\(p<0.01\)

N=12 rats/group
SM04690 regenerated cartilage

- Safranin O-stained sections from the rat knee analyzed 13 weeks post-surgery for OA cartilage pathology
- Increased cartilage thickness and decreased fissures observed with a single intra-articular injection of SM04690

SM04690 increased cartilage thickness
Summary

• Wnt signaling is a critical pathway in osteoarthritis

• In preclinical models, SM04690:
  – Inhibited inflammatory cytokine and protease production
  – Induced chondrogenesis
  – Had sustained local availability and no systemic exposure
  – Had no observable systemic toxicity

• Phase 1 clinical data
  – Poster SAT0428, Saturday June 11th, 10:15-11:45
Thank you