Discovery of a Small Molecule Wnt Pathway Inhibitor (SM04690) as a Potential Treatment for Degenerative Disc Disease

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Disclosures

• David Herman, Ph.D.
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  o Financial disclosure: Samumed, LLC; salary and equity
Disclaimer

• This presentation is not intended to provide a comprehensive overview of all studies using SM04690.

• SM04690 is an investigational compound currently in clinical trials; SM04690 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 SM04690 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.

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Degenerative disc disease (DDD)

- Intervertebral discs (IVDs) are composed of the nucleus pulposus (NP), a cellular, hydrated, proteoglycan core surrounded by fibrocartilage of the annulus fibrosus.

- Disc degeneration is an aberrant, cell-mediated response to progressive structural failure that may result in pain\(^1\).

- IVDs from patients with DDD have elevated β-catenin, indicating increased Wnt activity\(^2\) which contributes to DDD pathophysiology\(^3\).

Figure from McCann, MR & Séguin, CA. J Dev. Biol. 2016.
Mechanical stress and inflammation increase Wnt pathway activity in the disc\textsuperscript{1,2}

Wnt signaling triggers the degradation of intervertebral extracellular matrix through production of matrix degrading enzymes\textsuperscript{3}

Figure adaptations:
https://www.york.ac.uk/res/bonefromblood/background/osteogenesis.html
http://www.myspinedoc.com/conditions-diagnosis/conditions/degenerative-disc

Wnt Pathway and DDD

- Progenitor cells reside in the nucleus pulposus (NP) area of the disc and may be able to regenerate disc tissue\(^1\)\(^-\)\(^3\)
- In DDD, increased Wnt signaling suppresses progenitor cell proliferation, and induces senescence and apoptosis of NP cells \(^4\)\(^,\)\(^5\)
- Wnt signaling is involved in fibrosis of the annulus\(^6\)

**Hypothesis:** Inhibiting the Wnt Pathway regenerates disc tissue

https://www.york.ac.uk/res/bonefromblood/background/osteogenesis.html

Proposed therapy: SM04690

- SM04690 is a small molecule Wnt pathway inhibitor in development for the treatment of DDD and knee OA
- SM04690 demonstrated the following properties in preclinical studies:
  - Decreased inflammation
  - Inhibited fibrosis
  - Stimulated proliferation of NP cells and matrix production
  - Sustained IVD and minimal systemic exposure
  - Regenerated NP area in a DDD model
SM04690 demonstrated specific and potent inhibition of Wnt signaling

- Dose response of SM04690 treatment of SW480 cells transduced with TCF/LEF promoter-driven luciferase reporter (figure a)
- Expression of genes in the Wnt pathway in hMSCs following treatment with SM04690 or DMSO for 24hrs as measured by qRT-PCR (figure b)

TCF/LEF- Luciferase Reporter

Wnt Target Genes

EC$_{50}$ = 16nM

n=3, Mean ± SEM, * p<0.05, ***p<0.001 compared to vehicle
SM04690 decreased inflammatory cytokine secretion in PBMCs *in vitro*

- Several inflammatory cytokines in the disc are associated with the pathophysiology of DDD\(^1\)

**Cellular assays:**
- Peripheral blood mononuclear cells (PBMCs) stimulated with IgM and super antigen (sAg)
- SM04690 inhibited pro-inflammatory cytokine secretion compared to vehicle

\(n=3\) replicates, Mean ± SEM, \(*p<0.05, **p<0.01, ***p<0.001\) compared to vehicle

SM04690 exhibited broad anti-inflammatory properties

- *In vitro* anti-inflammatory activity of SM04690 was measured on the DiscoverX BioMAP® platform using an empirical scale (0-5), with 0=weak activity and 5=highly potent activity.
- SM04690 demonstrated comparable or better anti-inflammatory activity than two standard anti-inflammatory drugs across several assays.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Immunosuppression</th>
<th>Anti-Inflammatory</th>
<th>Th1/Th2/Th17 Inhibition</th>
<th>Cell Cytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T Cell</td>
<td>B cell</td>
<td>Th17</td>
<td>Th1</td>
</tr>
<tr>
<td>SM04690 (37 nM)</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>2</td>
<td>3</td>
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<tr>
<td>(120nM)</td>
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<td></td>
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<tr>
<td>Prednisolone</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>(120nM)</td>
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</tbody>
</table>

PBMC: peripheral blood mononuclear cells; HDF: human dermal fibroblasts; EC: endothelial cells; LPS: lipopolysaccharide
SM04690 inhibited fibrosis in human dermal fibroblasts *in vitro*

- Human dermal fibroblasts treated with TGFβ1 to induce fibrosis
- Treated with SM04690 for 48hrs
- SM04690 decreased TGFβ1-induced smooth muscle actin

EC$_{50}$ = 16.7 nM

**TGF-β1 Stimulated**

<table>
<thead>
<tr>
<th>Control</th>
<th>DMSO</th>
<th>SM04690 (30 nM)</th>
<th>SM04690 (10 nM)</th>
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</thead>
<tbody>
<tr>
<td><img src="image" alt="Control" /></td>
<td><img src="image" alt="DMSO" /></td>
<td><img src="image" alt="SM04690 (30 nM)" /></td>
<td><img src="image" alt="SM04690 (10 nM)" /></td>
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</table>

*αSMA / DAPI*
SM04690 induced proliferation and differentiation of primary NP-derived progenitor cells

- Primary NP-derived progenitor cells isolated from rat coccygeal discs were treated with SM04690 or DMSO control
- SM04690 significantly increased cell proliferation and differentiation into chondrocyte-like cells detected by Alcian Blue staining after 12 days compared to vehicle

Mean progenitor cell count at 5 days

Mean Alcian Blue absorbance at 12 days

n=3 ; *p<0.05; **p<0.01 compared with vehicle
SM04690 demonstrated sustained residence time in IVDs and minimal systemic exposure

- Rat IVD injection with 10 µL of SM04690 (0.033 µg, 0.33 µg, or 3.3 µg)
- Prolonged residence in the disc observed after a single SM04690 injection (0.33 µg or 3.3 µg) through 180 days
- 0.33 µg/disc SM04690, showed sustained release in the disc and rapid plasma clearance

**Disc Pharmacokinetics**

**Disc vs. Plasma Pk (0.33µg dose)**
**In vivo rat needle puncture model of DDD**

- Rat coccygeal intervertebral disc ‘needle puncture’
- Injected SM04690 or vehicle into each disc, 1 week after injury
- Radiographed pre-surgery, 1, 4 and 6 weeks after injury
- Calculated Disc Height Index (DHI)
- Blinded histological evaluation of the disc 8 weeks post-injury
SM04690 maintained disc height index after injury

Significantly higher DHI observed in the SM04690-treated group compared to vehicle, 5 weeks post-treatment

C8/9 and C9/10 discs
SM04690 regenerated NP and improved disc health 8 weeks after injury

All images 40x magnification

Significantly decreased histological score observed in the SM04690-treated group compared to vehicle, 8 weeks post-treatment

8 weeks post-injury: C8/9, C9/10 stained with Safranin O/Fast green (top) or Masson’s Trichrome (bottom). Histology scored on integrity of AF, AF and NP border and cellularity (right).

N=9, *p<0.05 compared to vehicle

SM04690 in DDD Summary

*In vitro*
- Inhibited inflammation and fibrosis
- Induced the proliferation and differentiation of NP-derived progenitor cells

*In vivo*
- Sustained disc and minimal systemic exposure
- In a rat model of DDD compared to vehicle
  - Regenerated NP and IVD structure
  - Maintained DHI and improved disc health

- SM04690 has potential as a treatment for DDD
- Phase 1 study projected Q2 2017
Thank you