DISCOVERY OF A SMALL MOLECULE WNT PATHWAY INHIBITOR (SM04690) AS A POTENTIAL TREATMENT FOR DEGENERATIVE DISC DISEASE

Vishal Deshmukh, Charlene Barroga, Haide Hu, Sunil KC and Yusuf Yazici
Samumed, LLC, San Diego, CA, USA

Corresponding Author- Yusuf Yazici,
Samumed, LLC, San Diego, CA, USA
yusuf@samumed.com

Aim:

Degenerative Disc Disease (DDD), involves degeneration of intervertebral disc structure, including the nucleus pulposus (NP), annulus fibrosus (AF), and cartilage matrix. Wnt signaling plays an important role in DDD, regulating the proliferation and differentiation of resident NP cells. SM04690, a novel, small-molecule, Wnt pathway inhibitor was evaluated in preclinical studies to determine its potential to induce proliferation and differentiation of NP cells, thereby promoting disc healing.

Methods:

Wnt pathway inhibition was measured using a cell-based reporter assay. *In vitro* proliferation of rat NP cells was measured by cell doubling index (CDI= cell number/initial cell number/days). Differentiation of NP cells into chondrocyte-like NP cells was measured by Alcian blue staining and absorbance based quantification. Pharmacokinetics were evaluated by intradiscal injection in rats, followed by analysis of compound concentrations in the disc and plasma. *In vivo* efficacy was evaluated in a rat coccygeal intervertebral disc needle puncture model using radiographic measurement of disc height index (DHI = disc height/vertebral height), and histological scoring of Safranin O- stained sections for AF integrity, AF and NP border, cellularity, and NP matrix.

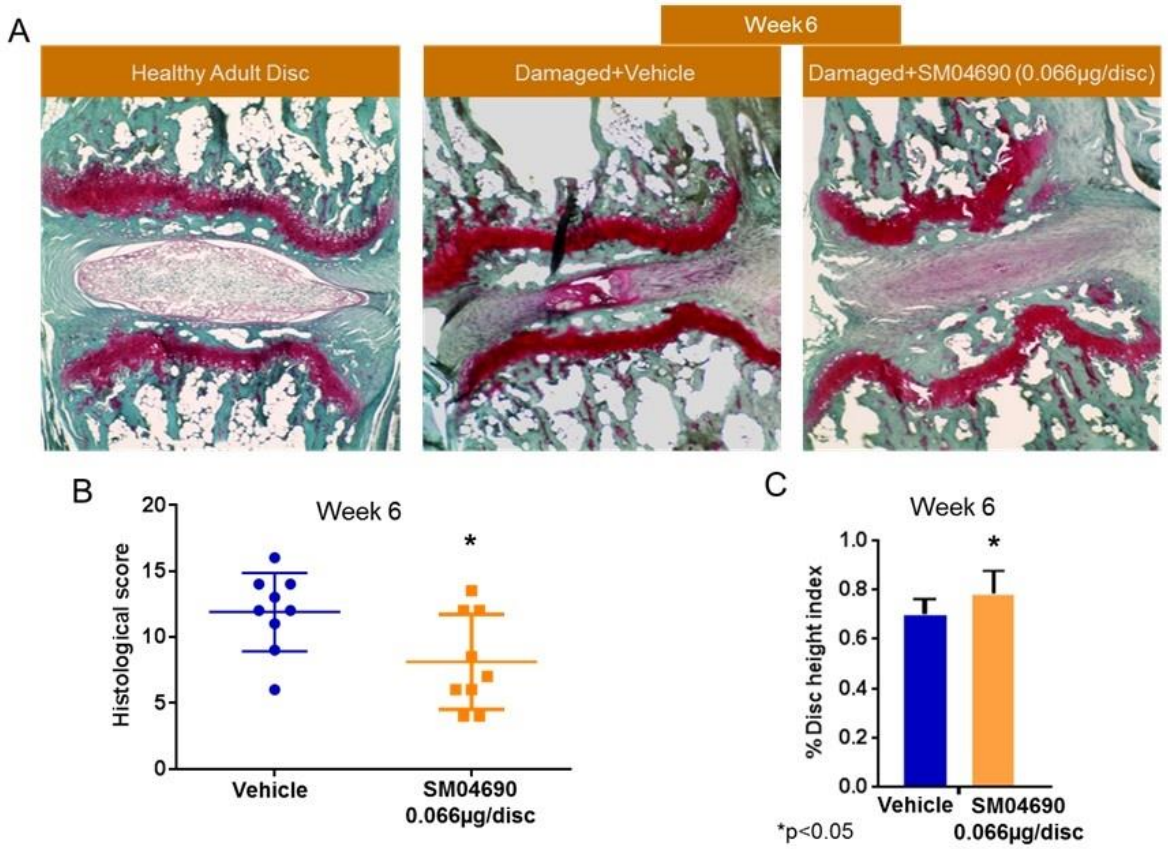
Results:

SM04690 was a potent (EC_{50}=11nM) inhibitor of Wnt signaling. *In vitro*, SM4690 increased (p<0.05) NP cell proliferation (CDI) ~2-fold vs. vehicle and increased Alcian blue absorbance, indicating differentiation to chondrocyte-like cells (p<0.01). Single intradiscal injection of SM04690 resulted in disc concentrations >EC_{50} for >180 days, with minimal systemic exposure or toxicity, measured as behavioral health, morphology and microscopic changes. In a rat DDD model, SM04690 treatment increased Safranin O-stained cartilage matrix (figure 1A), resulting in increased (p<0.05) DHI (figure 1C), and decreased (p<0.05) histology scores (figure 1B) vs. vehicle control.

Conclusion:

In a rat DDD model, SM04690 regenerated NP cells, and cartilage matrix. It also improved disc height, health, and shape compared to vehicle. SM04690 has potential as a treatment for DDD.

Figure. SM04690 stimulated differentiation of NP cells and improved disc height and health in a rat model of DDD.



*SM04690 stimulated differentiation of NP cells and improved disc height and health in a rat DDD model (A) Representative images from intravertebral discs treated with vehicle or SM04690 8 weeks post-injury and stained with Safranin O/Fast green show less interrupted and fragmented AF, larger NP and extracellular matrix area, and more NP cells compared with vehicle treatment. (B) Histology scores at week 6 for the vehicle and SM04690-treated discs as determined by the published histological evaluation scale (C) DHI based on radiographic images at week 6 showing significantly higher %DHI with SM04690 treatment as compared to the vehicle treatment. (n=9, Mean ± SD, *p<0.05).*