

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

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Objectives:

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 ($EC_{50}=11\text{nM}$) inhibitor of Wnt signaling. *In vitro*, SM04690 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, resulting in increased ($p<0.05$) DHI, and decreased ($p<0.05$) histology scores as compared to 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.