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

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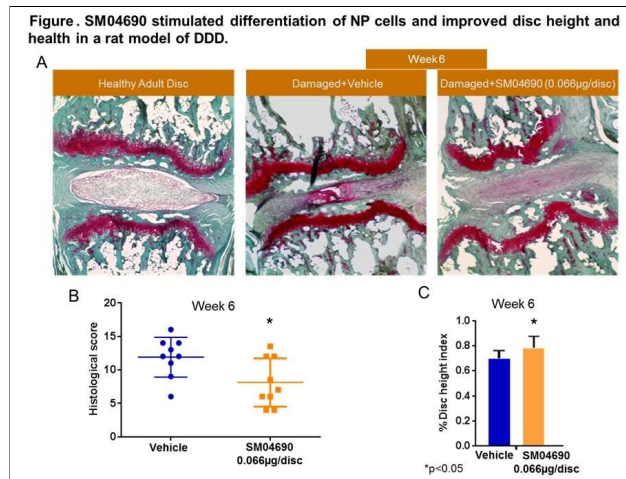
Abstract:

Purpose: Degenerative Disc Disease (DDD) is a major cause of low back pain. It is characterized by degenerative changes in the intervertebral disc, nucleus pulposus (NP), and cartilage matrix, resulting in decreased disc height and loss of shock absorption capability. Treatment of DDD is limited to pain management with analgesics, steroids or surgical procedures; no current therapy can reverse disc degeneration. Wnt signaling in disc progenitor cells potentially plays an important role in DDD by regulating degenerative changes and repair mechanisms, such as the proliferation and differentiation of resident NP cells. SM04690, a novel, small-molecule, Wnt pathway inhibitor was evaluated in a series of preclinical studies to determine its potential to induce proliferation and differentiation of primary NP cells, thereby promoting disc healing.

Methods: Wnt pathway inhibition was measured using a cell based luciferase reporter assay controlled by a Wnt-responsive promoter. *In vitro* proliferation of NP cells from rat coccygeal discs, treated with vehicle or SM04690 for 5 days, was measured by cell doubling index (CDI= cell number/initial cell number/days). Differentiation of NP cells into "chondrocyte-like" NP cells with vehicle or SM04690 treatment for 12 days was measured by Alcian blue staining and absorbance based quantification. Pharmacokinetics were evaluated by intradiscal (ID) injection in rats and rabbits, followed by analysis of compound concentrations in the disc and plasma. *In vivo* efficacy following a single ID injection of SM04690 was evaluated in a rat coccygeal intervertebral disc needle puncture model, using radiographic measurement of disk height (disc height index (DHI) = DH/vertebral height). Disc health was measured by histological scoring (total 4-16) of sections stained with Safranin O/Fast Green or Masson's Trichrome for integrity of annulus fibrosus (AF), border between AF and NP, cellularity, and matrix of NP.

Results: SM04690 demonstrated potent ($EC_{50} \sim 11nM$) and selective inhibition of Wnt signaling. SM04690 induced dose-dependent proliferation of NP cells *in vitro* with CDI ~ 2 fold higher in cells treated with SM04690 as compared to vehicle ($p < 0.05$). Cells treated with SM04690 also showed significantly increased Alcian blue absorbance ($p < 0.01$), indicating differentiation to chondrocyte-like cells and production of proteoglycan components of the extracellular matrix. Single ID injection of SM04690 resulted in disc concentrations $> EC_{50}$ for > 180 days, with minimal systemic exposure or toxicity, as measured by behavioral changes, animal health, and gross and microscopic morphology changes. In the *in vivo* rat DDD model, a single ID injection of SM04690 (0.066 μg /disc) increased Safranin O/Fast Green- and Masson's Trichrome- stained cartilage matrix (Figure A), and decreased histology scores ($p < 0.05$; Figure B), indicating reduced AF lamellar disorganization and fragmentation, larger NP area, increased number of NP cells and increased ECM vs. vehicle control. Radiographic measurement of disc height demonstrated significantly increased % DHI ($p < 0.05$; Figure C), in SM04690 treated rats compared to vehicle control, indicating an improvement in the disc health.

Conclusions: Wnt signaling plays a critical role in progression of DDD and NP cell differentiation and possibly disc regeneration. SM04690, a small molecule Wnt pathway inhibitor promoted proliferation and differentiation of NP cells *in vitro*. In a pre-clinical rodent model for DDD, SM04690 regenerated NP cells, cartilage matrix, improved disc height, health and shape compared to vehicle, with minimal exposure in plasma or systemic toxicity. These data suggested that SM04690 has potential as a disease modifying therapy for DDD.



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