Preclinical Evidence for SM04690, a Small Molecule Wnt Pathway Inhibitor, as a Potential Treatment for Degenerative Disc Disease

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Objective: To evaluate the potential of SM04690, a novel, small-molecule, Wnt pathway inhibitor, to promote disc healing in a rodent model of degenerative disc disease (DDD).

Design: 1. In vitro: Wnt pathway inhibition was measured using a cell-based reporter assay, proliferation of rat NP cells by cell doubling index (CDI = cell number/initial cell number/days), and differentiation of NP cells into ‘chondrocyte-like’ cells by Alcian blue absorbance based quantification. Myofibroblast differentiation was assessed in TGF-β1 stimulated human dermal fibroblasts by measuring smooth muscle actin (αSMA) using immunocytochemistry. 2. In vivo: Histological and anatomical effects of intervertebral disc (IVD) injection of SM04690 in a rat coccygeal needle puncture model of DDD was evaluated.

Setting: In vitro and in vivo experiments.

Interventions: Single, intradiscal injection of SM04690 (0.33 µg/disc).

Main Outcome Measures: 1. In vitro: CDI and Alcian blue absorbance. 2. In vivo: Disc height index (DHI = disc height/vertebral height) and histological scoring of Safranin O-stained sections for annulus fibrosis (AF) integrity, AF and NP border, cellularity, and NP matrix.

Results: 1. In vitro: SM04690 induced dose-dependent proliferation of NP cells with CDI ~2-fold greater than vehicle (p<0.05). SM04690-treated cells showed increased Alcian blue absorbance vs. vehicle (P<0.01), indicating differentiation to “chondrocyte-like” cells and production of proteoglycan components of extracellular matrix (ECM). SM04690 inhibited TGF-β1-induced expression of α-SMA (EC50=16.7 nM). 2. In vivo: In the rat model, SM04690 increased Safranin O/Fast Green stained cartilage matrix (Figure A) vs. vehicle. SM04690 decreased histology scores at 8 weeks (P<0.05; Figure B), indicating reduced AF lamellar disorganization and fragmentation, larger NP area, increased cellularity of NP and increased ECM vs. vehicle. Radiographic measurement of disc height demonstrated increased DHI at 6 weeks (P<0.05; Figure C) in SM04690-treated rats vs. vehicle.

Conclusions: Findings support SM04690 as a potential DDD treatment. Further clinical trials are needed to advance understanding of the SM04690 molecule.
Figure: SM04690 stimulated differentiation of NP cells and improved disc height and health in a rat model of DDD.