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

Background

- Degenerative Disc Disease (DDD), one of the main causes of low back pain, is characterized by degeneration of intervertebral discs (IVDs), which are composed of central nucleus pulposus (NP) surrounded by collagenous annulus fibrosis (AF) and cartilaginous endplates. IVDs are essential for load-bearing, mobility, flexibility, anchoring, and shock absorption of the vertebra.2,3
- The NP is comprised of progenitor cells that can differentiate into chondrocyte-like cells to form a proteoglycan and collagen-rich extracellular matrix (ECM), responsible for hydration and IVD function.1,2
- Wnt signaling plays a key role in IVD development and maturation. Excessive Wnt signaling results in inhibition of NP cell proliferation, upregulation of ECM degrading enzymes, and apoptosis of NP cells, leading to IVD degeneration and DDD.1,2
- Treatment of DDD is limited to analgesics or surgery aimed at relieving symptoms. No current therapy can reverse disc degeneration.2,3

Methods

- To identify Wnt signaling inhibitors, a small molecule chemical library was screened in a cultured Wnt pathway-based β-catenin/Lef-Lux reporter assay in SW480 colon cancer cells.
- In vitro proliferation of NP cells isolated from rat coccygeal discs, treated with vehicle or SM04690 for 5 days, was measured by cell doubling index (CDI=cell number/initial cell number)/day.
- Differentiation of NP progenitor cells into chondrocyte-like NP cells with 12 days of vehicle or SM04690 treatment was assessed by Alcian blue staining and absorbance based quantification.
- Pharmacokinetics were assessed by intradiscal injection of rats and rabbits, followed by analysis of compound concentrations in the disc and plasma by LC-MS.
- Rat coccygeal IVD needle puncture was used as a DDD model.
- Injured discs were analyzed 1 week and 6 weeks post-surgery.
- Safety: Dose/Green or Markon's Trichrome stained discs were histologically evaluated by blinded observers using a disc scoring system15 based on grading of the integrity of AF, border between AF and NP, and calcification of NP. Disc height index (DHI) was calculated by averaging the anterior, middle, and posterior portions of the disc height and dividing by the average height of the adjacent vertebral body.

Results

- SM04690 stimulated NP-derived progenitor cell proliferation
- CDI for primary NP-derived progenitor cells was ≥2-fold higher in cells treated with SM04690 compared to DMSO.3
- Increased Alcian blue staining indicated the presence of chondrocyte-like cells after 12 days of treatment with SM04690.

- SM04690 demonstrated sustained residence time in IVDs and minimal systemic exposure
- Residence time of >60 days observed after a single intradiscal injection of SM04690 at various doses. (30 nM, 100 nM, 300 nM, 1000 nM) was measured by Alcian blue staining and absorbance based quantification.
- Alcian blue staining and absorbance based quantification were used to assess the presence and quantity of chondrocyte-like cells after treatment with SM04690.
- Quantification of Alcian blue staining for the cells in the disc and plasma by LC-MS.

Discussion

- SM04690 demonstrated significant in vitro and in vivo efficacy in models of degenerative disc disease.
- The results indicate that SM04690 has potential as a therapeutic for the treatment of DDD.
- Further studies are needed to evaluate the long-term safety and efficacy of SM04690 in clinical trials.

References

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