Introduction: Degenerative Disc Disease (DDD) involves degeneration of intervertebral disc (IVD) structure, namely the nucleus pulposus (NP), annulus fibrosus (AF), and cartilage matrix. In DDD, Wnt signaling regulates proliferation and differentiation of resident NP cells. SM04690, a small-molecule, Wnt pathway inhibitor, was evaluated in preclinical studies to determine its potential as a DDD treatment by its effects on NP cells. Methods: In vitro proliferation of rat NP cells were measured by cell doubling index (CDI = cell number/initial cell number/days). Differentiation of NP cells into chondrocyte-like cells were measured by Alcian blue staining and absorbance based quantification. SM04690 pharmacokinetics were evaluated by its intradiscal injection in rats, then analysis of drug concentrations over time in disc and plasma. In vivo efficacy was evaluated in a rat coccygeal IVD needle puncture model. Radiographic measurement of disc height index (DHI), and histological scoring of Safranin O-stained sections for AF integrity, AF/NP border and NP matrix cellularity was performed. Results: In vitro, SM4690 increased NP CDI ~2-fold vs. vehicle (p<0.05) and increased Alcian blue absorbance (p<0.01). Intradiscal injection of SM04690 resulted in disc concentrations >EC₅₀ for >180 days, with minimal systemic exposure or toxicity. In vivo, SM04690 increased Safranin O-stained cartilage matrix (figure 1A), resulting in increased DHI (p<0.05) (figure 1C), and improved histology scores (p<0.05) vs. vehicle (figure 1B). Conclusions: 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.
SM04690 stimulated differentiation of NP cells and improved disc height and health in a rat DDD model (A) Representative images from IVDs treated with vehicle or SM04690 6 weeks post-treatment and stained with Safranin O/Fast green show less fragmented AF, larger NP and extracellular matrix area, and more NP cells compared to vehicle. (B) Week 6 histology scoring for vehicle and SM04690-treated discs (C) Week 6 DHI showing significantly higher %DHI with SM04690 treatment as compared to vehicle. (n=9, Mean ± SD, *p<0.05).