Dual-Axis Gene Therapy With the Use of Stem Cells Overexpressing Transforming Growth Factor-β3 in Combination With Interleukin-1β and Tumor Necrosis Factor-α RNA Silencing for Osteoarthritis Control in a Large-Animal Osteochondral Chip Fracture Model

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Intra-articular injection of mesenchymal stem cells co-expressing a growth factor and cytokine-suppressing genes was effective in reducing progression of osteoarthritis in this osteoarthritis model. This beneficial effect may occur by modulation of synovial fluid constituents, inflammation, cytokine profile, or direct cartilage repair. Authors’ addresses: Texas A&M University, 4475 TAMU, College Station, TX 77843 (Watts); Cornell University, Department of Clinical Sciences, College of Veterinary Medicine, Ithaca, NY 14853 (Nixon); e-mail: awatts@cvm.tamu.edu. *Corresponding and presenting author. © 2013 AAEP.

1. Introduction
Dual-axis gene therapy with anti-cytokine and anabolic growth factors may provide synergistic effects not apparent in single-target manipulation. The purpose of this study was to investigate the potential of intra-articular injection of mesenchymal stem cells (MSCs) overexpressing the anabolic transforming growth factor-β3 gene, concurrent with an RNA interference motif to suppress the catabolic interleukin (IL)-1β and tumor necrosis factor (TNF)-α cytokines, in an equine model for treatment of osteoarthritis (OA).

2. Materials and Methods
Early OA was induced in one middle carpal joint by osteochondral fragmentation in 13 skeletally mature Thoroughbreds. The contralateral joint was sham-operated. Second-passage autologous bone marrow–derived MSCs (10e6) were transfected with long hairpin silencing construct against IL-1β and tumor necrosis factor-α and transduced with Ad-transforming growth factor-β3. Treatments with either MSCs (n = 6) or placebo (n = 7) were injected into OA joints 14 days after OA induction. Sham joints were injected with placebo. Observations were a mix of blinded and nonblinded.
3. Results

No adverse treatment effects were observed. When comparing MSC versus placebo-injected OA joints, there were significant improvements in range of motion and effusion in the week after injection, higher glycosaminoglycan (GAG) content of opposing third-carpal bone cartilage, significantly improved gene expression of cartilage matrix metalloproteinase-13 and synovial membrane IL-1β, and reduced synovial fibrosis.