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"The Development of a Novel Gene Therapy, Flexion's FX201, for the Treatment of Osteoarthritis"

Background: Osteoarthritis is a complex multifactorial disorder that is the most frequent cause of pain, loss of function, and disability in adults[1]. Many modalities of treatment involve symptom alleviation but typically lead to joint replacement in end-stage disease. Consequently, there has been a shift towards the prevention of disease progression of early osteoarthritis. Due to advances in biochemical marker development, pro-inflammatory interleukins, specifically interleukin 1β (IL1β), has come into focus[2]. IL1β is implicated in many of the pathological advancement of osteoarthritis such as degradation of cartilage, bony malformation, and thickening of synovial tissue[3-5]. Previously, IL1 receptor antagonist (IL1ra) proved to be effective at preventing cartilage breakdown and osteoarthritis progression. This led to the development of a drug called Anakinra. Despite the promising results in reduced pain, due to its short half-life, Anakinra proved to be no more effective than a placebo for long term treatment [6-12]. To address this issue, Flexion Therapeutics developed FX201, a helper-dependent adenovirus (HDAd) vector to carry the coding sequence for IL1ra under the control of an inflammation-responsive promoter.

Aims: This project will determine the efficacy of Flexion's FX201, a gene therapy product for the delivery of human interleukin 1 receptor antagonist, to reduce inflammatory output of osteoarthritic synoviocytes. Additionally, this project will identify target patient populations for clinical trials with FX201. We hypothesize that FX201 will reduce inflammatory output to a greater extent in cells derived from patients with high circulating levels of IL1β, TNFα and IFNγ than in cells from patients with low circulating levels of these same inflammatory cytokines.

Methods: 12 patients were selected from Louisiana State University Health Sciences Center biorepository and subdivided into high/low pain scores based on knee injury and osteoarthritis outcome scores (KOOS) and pro-/anti-inflammatory profile based on circulating levels of IL1β, TNFα and IFNγ. Synoviocytes from previously frozen synovial tissue were extracted, plated in media, and incubated at 37^{o} C 5% CO_2. Synoviocytes were then treated with FX201 and measure cytokine release by cells before and after infection. A multiplex analysis containing 11 pro- and anti-inflammatory cytokines, and 6 proteins involved in cartilage turnover was used to measure secreted protein levels before and after FX201 treatment. Quantitative PCR was secondarily used to confirm decreases in cytokine production.

Expected Results: Patient's extracted synoviocytes will quantitatively show a reduction in pro-inflammatory cytokines and proteins involved in cartilage degradation when treated with FX201. Cells from patients with high levels of inflammation will show a greater effect than cells from patients with low levels of inflammation.

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