GENE EDITING TO IMPROVE JOINT FUNCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation application of U.S. patent application Ser. No. 17/166,343, filed on Feb. 3, 2021, which is a continuation of U.S. patent application Ser. No. 16/916,014, filed on Jun. 29, 2020, which is a continuation application of International Application No. PCT/US2020/014139, filed on Jan. 17, 2020, which claims priority to Provisional Patent Application No. 62/794,340, filed on Jan. 18, 2019, U.S. Provisional Patent Application No. 62/894,184, filed on Aug. 30, 2019, and U.S. Provisional Patent Application No. 62/914,635, filed on Oct. 14, 2019, each of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] Compositions and Methods for treating synovial joint dysfunction are described herein. In addition, methods for gene-editing synovial cells and/or synoviocytes, chondrocytes, synovial macrophages, and synovial fibroblasts, and uses of gene-edited synovial cells and/or synoviocytes, chondrocytes, synovial macrophages, and synovial fibroblasts, in the treatment of diseases such as osteoarthritis are disclosed herein.

BACKGROUND OF THE INVENTION

[0003] Treatment of osteoarthritis, degenerative joint disease, and other joint dysfunction is complex and there are few long term options for either symptomatic relief or restoring joint function. Osteoarthritis (OA) is the leading cause of disability due to pain. Neogi, *Osteoarthritis Cartilage* 2013; 21:1145-53. All mammal species are affected: working animals, domestic pets, and their owners all suffer OA-related discomfort, pain, and disability, depending on the degree of disease progression.

[0004] OA is a complex disease characterized by a progressive course of disability. Systemic inflammation is associated with OA and with OA disease progression. Inflammation is driven by increased levels of pro-inflammatory cytokines. New methods and compositions to treat this disease are acutely needed. Disclosed herein are compositions and methods useful for treating OA as well as other inflammatory joint disorders.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0005] The sequence listing contained in the file named "Sequence Listing 123994-5001-US01.txt" and having a size of 17.1 kilobytes, has been submitted electronically herewith via EFS-Web, and the contents of the .txt file are hereby incorporated by reference in their entirety.

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention provides compositions and methods for treating joint disorders that are characterized by an inflammatory component. In some aspects, the compositions and methods are to prevent the progression of osteoarthritis and other arthritides and to treat osteoarthritis and other arthritides in a mammalian joint. According to exemplary embodiments, at least a portion of the joint synovial cells and/or synoviocytes, chondrocytes, synovial macrophages, or synovial fibroblasts are gene-edited to reduce the expression of inflammatory cytokines. In some aspects, at least a portion of the joint synovial cells and/or synoviocytes, chondrocytes, synovial macrophages, or synovial fibroblasts, are gene-edited to reduce the expression of IL-1α, IL-1β, or both IL-1α, IL-1β.

[0007] In some embodiments, the gene-editing causes expression of one or more cytokine and/or growth factor genes to be silenced or reduced in at least a portion of the cells comprising a mammalian joint. In some aspects, the cells are synovial cells. In some aspects, the cells are synovial fibroblasts. In some aspects, the cells are synoviocytes. In some aspects, the cells are chondrocytes. In some aspects, the cells are synovial macrophages.

[0008] In some embodiments, the one or more cytokine and/or growth factor genes is/are selected from the group comprising IL-1α, and IL-1β.

[0009] In some embodiments, the gene-editing comprises the use of a programmable nuclease that mediates the generation of a double-strand or single-strand break at said one or more cytokine and/or growth factor genes.

[0010] In some embodiments, the gene-editing comprises one or more methods selected from a CRISPR method, a TALE method, a zinc finger method, and a combination thereof.

[0011] In some embodiments, the gene-editing comprises a CRISPR method.

[0012] In some embodiments, the CRISPR method is a CRISPR-Cas9 method.

[0013] In some embodiments, the gene-editing comprises a TALE method.

[0014] In some embodiments, the gene-editing comprises a zinc finger method.

[0015] In some embodiments, the gene-editing causes expression of one or more cytokine and/or growth factor genes to be silenced or reduced in at least a portion of the cells comprising the joint. In some embodiments, the portion of cells edited are synoviocytes. In an aspect, the portion of cells edited are synovial fibroblasts. In some embodiments, the portion of cells edited are synoviocytes. In some embodiments, the portion of cells edited are chondrocytes. In some embodiments, the portion of cells edited are synovial macrophages.

[0016] In some embodiments, an adeno-associated virus (AAV) delivery system is used to deliver the gene-editing system. In some embodiments, the AAV delivery system is injected into a joint.

[0017] Some aspects of the present invention provide a pharmaceutical composition for the treatment or prevention