

inflammatory bowel disease is not completely understood, although both environmental and genetic factors are believed to play a role in the disease. Environmental components may include alterations in flora of the gut which are affected by exposure to ingested foods and medications.

[0006] Inflammatory bowel disease is associated with abdominal pain, vomiting, diarrhea, rectal bleeding, severe cramps, muscle spasms, weight loss, malnutrition, fever, and anemia. Patients with inflammatory bowel disease may also suffer from skin lesions, joint pain, eye inflammation, and liver disorders, and children suffering from ulcerative colitis may suffer from growth defects. Although rarely fatal, these symptoms decrease quality of life for patients.

[0007] Thus, there is a pressing need to develop reliable methods of treating inflammatory disorders such as rheumatoid arthritis, osteoarthritis, or inflammatory bowel disease. There is a further need to identify methods of treatment that provide effective and permanent relief from symptoms across a broad spectrum of patients and which are not associated with negative side effects or cycles of inflammation and remission.

SUMMARY

[0008] The present application provides compositions of polynucleotides complementary to IL-34, or a portion thereof, and methods of using the compositions.

[0009] Disclosed herein, in certain aspects, are polynucleotides, comprising a nucleotide sequence according to: (a) 5'-CTTTGGGCCGACCAGCTTC-3' (SEQ ID NO: 3) or (b) 5'-TCCATGACCCGGAAGCAGTT-3' (SEQ ID NO: 5), wherein at least one cytidine of the nucleotide sequence is chemically modified, and at least one nucleoside is a 2'-O-(2-methoxyethyl) (2'-MOE) nucleoside; or a pharmaceutically acceptable salt thereof. In some embodiments, no more than 10 nucleosides of the polynucleotide are chemically modified. In some embodiments, the polynucleotide comprises six 2'-MOE nucleosides. In some embodiments, the polynucleotide comprises eight 2'-MOE nucleosides. In some embodiments, the polynucleotide comprises a nucleotide sequence is selected from the group consisting of: (a) 5'-CxTxTxTxGGGCXGCACCAGCxCxTxTx-3' (SEQ ID NO: 40), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, and X is 5-methylcytidine; (b) 5'-CxTxTxTGGGCXGCACCAGCTxCxTx-3' (SEQ ID NO: 41), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, and X is 5-methylcytidine; (c) 5'-TxCxCxAxTGACCXGGAAGCAxGxTxTx-3' (SEQ ID NO: 42), wherein Cx is 2'-O-(2-

methoxyethyl)cytidine, Ax is 2'-*O*-(2-methoxyethyl)adenosine, Tx is 2'-*O*-(2-methoxyethyl)thymidine, Gx is 2'-*O*-(2-methoxyethyl)guanosine, and X is 5-methylcytidine; and (d) 5'-TxCxCxATGACCXGGAAGCAGxTxTx-3' (SEQ ID NO: 43), wherein Cx is 2'-*O*-(2-methoxyethyl)cytidine, Tx is 2'-*O*-(2-methoxyethyl)thymidine, Gx is 2'-*O*-(2-methoxyethyl)guanosine, and X is 5-methylcytidine; or a pharmaceutically acceptable salt thereof. In some embodiments, the polynucleotide is complementary to IL-34. In some embodiments, the polynucleotide is an IL-34 antisense oligonucleotide. In some embodiments, the polynucleotide is an IL-34 siRNA. In some embodiments, at least one internucleoside linkage of the polynucleotide is selected from the group consisting of a phosphorothioate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, and an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage. In some embodiments, at least one internucleoside linkage of the polynucleotide is a phosphorothioate linkage. In some embodiments, all internucleoside linkages of the polynucleotide are phosphorothioate linkages. In some embodiments, the polynucleotide is 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the polynucleotide is 20 nucleotides in length or 20-25, 20-30, 20-35, 25-30, 25-35, or 30-35 nucleotides in length. In some embodiments, the polynucleotide is no more than 20, 25, or 30 nucleotides in length. In some embodiments, the polynucleotide is from 20 to 25 nucleotides in length. In some embodiments, the polynucleotide is 20 nucleotides in length.

[0010] Disclosed herein, in certain aspects, are pharmaceutical compositions, comprising (a) a polynucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is suitable for topical, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, or intraduodenal administration.

[0011] Disclosed herein, in certain embodiments, are methods of treating an inflammatory disease in a patient in need thereof, the method comprising administering to the patient in need thereof an effective amount of a polynucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein. In some embodiments,

Crohn's disease. In some embodiments, the inflammatory bowel disease is fibrostricturing Crohn's disease.

[0019] Disclosed herein, in certain embodiments, are polynucleotides disclosed herein, or a pharmaceutically-acceptable salt thereof, for use as a medicament.

[0020] Disclosed herein, in certain embodiments, are polynucleotides disclosed herein, or a pharmaceutically-acceptable salt thereof, for use in the treatment of an inflammatory disease. In some embodiments, the inflammatory disease is selected from the group consisting of an inflammatory bowel disease, rheumatoid arthritis, psoriasis, osteoarthritis, pouchitis, diabetes (type I and II), tissue or organ rejection, multiple sclerosis, periodontal inflammation, periodontitis, pigmented villonodular synovitis, hepatitis, sinusitis, colon cancer, colorectal cancer, colitis-associated colon cancer, sporadic colorectal cancer, coronary artery disease, or Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a CNS inflammatory disease, and an autoimmune disease. In some embodiments, the inflammatory disease is an inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is selected from the group consisting of Crohn's disease, inflammatory Crohn's disease, fibrostricturing Crohn's disease, gastroduodenal Crohn's disease, Crohn's (granulomatous) colitis, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behçet's disease, microscopic colitis, ulcerative proctitis, proctosigmoiditis, jejunoileitis, left-sided colitis, pancolitis, ileocolitis, ileitis, and indeterminate colitis. In some embodiments, the inflammatory bowel disease is inflammatory Crohn's disease. In some embodiments, the inflammatory bowel disease is fibrostricturing Crohn's disease.

[0021] Disclosed herein, in certain embodiments, are polynucleotides disclosed herein, or a pharmaceutically-acceptable salt thereof, for use in the treatment of fibrosis. In some embodiments, the fibrosis is intestinal fibrosis. In some embodiments, the fibrosis is pulmonary fibrosis. In some embodiments, the fibrosis is synovial fibrosis. In some embodiments, the fibrosis is selected from the group consisting of renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, and nephrogenic systemic fibrosis.

[0021a] Disclosed herein in certain aspects are uses of a polynucleotide, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein in the manufacture of a medicament for treating an inflammatory disease in a patient in need thereof.

[0021b] Disclosed herein in certain aspects are uses of a polynucleotide, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition in the manufacture of a medicament for the treatment of reducing or eliminating a fibrotic stricture in a patient suffering from an inflammatory disease.

[0021c] Disclosed herein in certain aspects are uses of a polynucleotide, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition in the manufacture of a medicament for preventing or treating fibrosis in a patient in need thereof.

[0021d] Disclosed herein in certain aspects is a polynucleotide, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] **FIG. 1** shows the results of the IL-34 ASOs on the modulation of IL-34 expression in cultured HT-29 cells. IL-34 RNA transcripts were evaluated by real-time PCR. Levels are