

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 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] Described herein are agents, for example, IL-34 antisense oligonucleotides, that inhibit IL-34 gene expression. In one aspect, the disclosure provides an antisense oligonucleotide for inhibiting expression of IL-34, comprising a nucleotide sequence selected from the group consisting of: 5'-TCCATGACCCGGAAGCAGTT-3' (SEQ ID NO: 5), wherein at least one nucleoside is a chemically modified nucleoside and/or at least one linkage is a modified internucleoside linkage; and 5'-tgaCCXGGAAGCAgtt-3' (SEQ ID NO: 15), wherein a is LNA adenosine, t is LNA thymidine, g is LNA guanosine, and X is 5-methylcytidine, or a pharmaceutically acceptable salt thereof.

[0008a] In another aspect, the disclosure provides a pharmaceutical composition for inhibiting the expression of IL-34, comprising (a) an antisense oligonucleotide of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.

[0008b] In yet another aspect, the disclosure provides a use of an antisense oligonucleotide as described herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an inflammatory disease in a patient in need thereof. In some examples, the disclosure provides an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt

thereof, that includes the antisense oligonucleotide sequence of any of SEQ ID NOs:1-8 described herein. For example, an IL-34 antisense oligonucleotide of the disclosure can be an antisense oligonucleotide that includes the sequence: 5'-CTCACCAAGACCCACAG-3' (SEQ ID NO:1), wherein at least one nucleoside is a chemically modified nucleoside and/or at least one linkage is a modified internucleoside linkage; 5'-GGCTTTGGGCCGACCAGCT-3' (SEQ ID NO:2), wherein at least one nucleoside is a chemically modified nucleoside and/or at least one linkage is a modified internucleoside linkage; 5'-CTTTGGGCCGACCAGCTTC-3' (SEQ ID NO:3), wherein at least one nucleoside is a chemically modified nucleoside and/or at least one linkage is a modified internucleoside linkage; 5'-TGGGCCGACCAGCTTCAGG-3' (SEQ ID NO:4), wherein at least one nucleoside is a chemically modified nucleoside and/or at least one linkage is a modified internucleoside linkage; 5'-TCCATGACCCGGAAGCAGTT-3' (SEQ ID NO:5), wherein at least one nucleoside is a chemically modified nucleoside and/or at least one linkage is a modified internucleoside linkage; or 5'-TGTTTCATGTACTGAAG-3' (SEQ ID NO:6), wherein at least

one nucleoside is a chemically modified nucleoside and/or at least one linkage is a modified internucleoside linkage, or a pharmaceutically acceptable salt thereof. In some examples, the antisense oligonucleotide comprises the sequence of SEQ ID NO:3, wherein at least one nucleoside is a chemically modified nucleotide and/or at least one linkage is a modified internucleoside linkage. In some examples, the antisense oligonucleotide comprises the sequence of SEQ ID NO:3, wherein at least one cytidine is chemically modified. In some examples, the antisense oligonucleotide comprises the sequence of 5'-

CTTTGGGCXGCACCAGCTTC-3' (SEQ ID NO:7), wherein X is 5-methylcytidine. In some examples, the antisense oligonucleotide comprises the sequence of SEQ ID NO:5, wherein at least one cytidine is chemically modified; optionally, wherein the cytidine at position 10 of SEQ ID NO:5 is chemically modified and the nucleotide sequence is 5'-TCCATGACCXGGAAGCAGTT-3' (SEQ ID NO:8), and wherein X is 5-methylcytidine.

[0009] In some examples, an antisense oligonucleotide described herein can include ribonucleotides and/or deoxyribonucleotides. For example, in some examples described herein, an IL-34 antisense oligonucleotide, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-8, can include one or more ribonucleotides. In some examples described herein, an IL-34 antisense oligonucleotide, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-8, can include one or more deoxyribonucleotides. In some examples described herein, an IL-34 antisense oligonucleotide can include a mixture of ribonucleotides and deoxyribonucleotides.

[0010] In some examples described herein, an IL-34 antisense oligonucleotide can include one or more locked nucleic acid ("LNA") nucleotides. An IL-34 antisense oligonucleotide described herein, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-8, can include one or more LNA nucleotides, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 1-5, 5-10, 5-12, or more LNA nucleotides. In some examples, each of the nucleotides of an IL-34 antisense oligonucleotide described herein is an LNA nucleotide.

[0011] In particular examples, an IL-34 antisense oligonucleotide includes LNA nucleotides and the sequence of the IL-34 antisense oligonucleotide is selected from one of the following:

- 5'-cttTGGGCXGCACCAGCttc-3' (SEQ ID NO:9), wherein c is LNA cytidine, t is LNA thymidine, and X is 5-methylcytidine;

- 5'-ctttGGGCXGCACCAGcttc-3' (SEQ ID NO:10), wherein c is LNA cytidine, t is LNA thymidine, and X is 5-methylcytidine;
- 5'-cttTGGGCcgcCACCAGCttc-3' (SEQ ID NO:11), wherein c is LNA cytidine, t is LNA thymidine, and g is LNA guanosine;
- 5 • 5'-cttTGGGCcGCACCAGCttc-3' (SEQ ID NO:12), wherein c is LNA cytidine and t is LNA thymidine;
- 5'-ggcXGCACCAGCttc-3' (SEQ ID NO:13), wherein c is LNA cytidine, t is LNA thymidine, g is LNA guanosine, and X is 5-methylcytidine;
- 5'-cttTGGGCXGCACcag-3' (SEQ ID NO:14), wherein c is LNA cytidine, t is LNA thymidine, g is LNA guanosine, a is LNA adenosine, and X is 5-methylcytidine;
- 10 and
- 5'-tgaCCXGGAAGCAgtt-3' (SEQ ID NO:15), wherein a is LNA adenosine, t is LNA thymidine, g is LNA guanosine, and X is 5-methylcytidine,

or a pharmaceutically acceptable salt thereof.

15 **[0012]** Additionally, in examples described herein, IL-34 antisense oligonucleotides can include chemically modified nucleosides, for example, 2'-*O*-methyl ("2'-OMe") ribonucleosides, for example, 2'-*O*-methylcytidine, 2'-*O*-methylguanosine, 2'-*O*-methylthymidine, 2'-*O*-methyluridine, and/or 2'-*O*-methyladenosine. IL-34 antisense oligonucleotides described herein, can also include one or more chemically-modified bases, including a 5-methylpyrimidine, for
 20 example, 5-methylcytosine; and/or a 5-methylpurine, for example, 5-methylguanine. IL-34 antisense oligonucleotides described herein, can also include any of the following chemically-modified nucleosides: 5-methyl-2'-*O*-methylcytidine, 5-methyl-2'-*O*-methylthymidine, 5-methylcytidine, 5-methyluridine, and/or 5-methyl-2'-deoxycytidine. Additionally, IL-34 antisense oligonucleotides described herein can include one or more 2'-*O*-(2-methoxyethyl) ("2'-
 25 MOE") nucleosides, 2'-deoxy-2'-fluoro nucleosides, 2'-fluoro-β-D-arabinonucleosides, bridged nucleic acids, LNA nucleotides, constrained ethyl' (cET) nucleic acids, tricyclo-DNAs (tcDNA), 2'-*O*,4'-*C*-ethylene linked nucleic acids (ENA), and/or peptide nucleic acids (PNA). Examples described herein include IL-34 antisense oligonucleotides of any of SEQ ID NOs:1-15, or a pharmaceutically acceptable salt thereof, that include one or more of any of the aforementioned
 30 chemically-modified nucleosides. In some examples, at least one nucleoside of the IL-34 antisense oligonucleotide sequence is a chemically-modified nucleoside. For

example, in some examples, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 1-5, 1-10, 1-14, 1-15, 1-16, 1-19, 5-10, 5-14, 5-15, 5-19, 10-14, 10-15, or 10-19 nucleosides of the IL-34 antisense oligonucleotide sequence are nucleosides.

[0013] In particular examples, an IL-34 antisense oligonucleotide described herein includes 2'-MOE nucleosides. In some examples, the sequence of the IL-34 antisense oligonucleotide is selected from one of the following:

- 5'-CxTxTxTxGxGGCXGCACCAGxCxTxTxTx-3' (SEQ ID NO:16), 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;
- 5'-TxCxCxAxTxGACCXGGAAGCxAxGxTxTx-3' (SEQ ID NO:17), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, Gx is 2'-O-(2-methoxyethyl)guanosine, Ax is 2'-O-(2-methoxyethyl)adenosine, and X is 5-methylcytidine;
- 5'-CxTxTxTxGxGxGCXGCACCAXGxCxTxTxTx-3' (SEQ ID NO:18), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, Gx is 2'-O-(2-methoxyethyl)guanosine, Ax is 2'-O-(2-methoxyethyl)adenosine, and X is 5-methylcytidine;
- 5'-TxCxCxAxTxGxACCXGGAAGxCxAxGxTxTx-3' (SEQ ID NO:19), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, Gx is 2'-O-(2-methoxyethyl)guanosine, Ax is 2'-O-(2-methoxyethyl)adenosine, and X is 5-methylcytidine;
- 5'-CxTxTxTxGxGxGxCxXGxCxAXCxCxAXGxCxTxTxTx-3' (SEQ ID NO:20), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, Gx is 2'-O-(2-methoxyethyl)guanosine, Ax is 2'-O-(2-methoxyethyl)adenosine, and X is 5-methylcytidine; and
- 5'-TxCxCxAxTxGxAXCxCxXGxGxAXAXGxCxAXGxCxTxTx-3' (SEQ ID NO:21), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, Gx is 2'-O-(2-methoxyethyl)guanosine, Ax is 2'-O-(2-methoxyethyl)adenosine, and X is 5-methylcytidine,

or a pharmaceutically acceptable salt thereof.

[0014] Additionally, in some examples, an IL-34 antisense oligonucleotide described herein includes 2'-OMe nucleosides. In some examples, the sequence of the IL-34 antisense oligonucleotide is selected from one of the following:

- 5'-CyTyTyTyGyGGCXGCACCAGyCyTyTyCy-3' (SEQ ID NO:22), wherein Cy is 2'-*O*-methylcytidine, Ty is 2'-*O*-methylthymidine, Gy is 2'-*O*-methylguanosine, and X is 5-methylcytidine; and
- 5'-TyCyCyAyTyGACCXGGAAGCyAyGyTyTy-3' (SEQ ID NO:23), wherein Cy is 2'-*O*-methylcytidine, Ty 2'-*O*-methylthymidine, Gy is 2'-*O*-methylguanosine, Ay is 2'-*O*-methyladenosine, and X is 5-methylcytidine,

or a pharmaceutically acceptable salt thereof.

[0015] In some examples, an IL-34 antisense oligonucleotide described herein includes one or more modified internucleoside linkages. For example, in some examples, the IL-34 antisense oligonucleotide is an antisense oligonucleotide wherein at least one internucleoside linkage of the sequence is 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, or a boranophosphate linkage. In particular examples, at least one internucleoside linkage of the IL-34 antisense oligonucleotide sequence is a phosphorothioate linkage. For example, in some examples, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 1-5, 1-10, 1-14, 1-15, 1-16, 1-19, 5-10, 5-14, 5-15, 5-19, 10-14, 10-15, or 10-19 internucleoside linkages of the IL-34 antisense oligonucleotide sequence are phosphorothioate linkages. In some examples, all of the internucleoside linkages of the antisense oligonucleotide sequence are phosphorothioate linkages.

[0016] The number of nucleotides included in IL-34 antisense oligonucleotides described herein may vary. For example, in some examples, the antisense oligonucleotide is from 15-20, 15-25, 15-30, 15-35, 20-25, 20-30, 20-35, 25-30, 25-35, or 30-35 nucleotides in length. In particular examples, the antisense oligonucleotide is from 15-25 nucleotides in length. In particular examples, the antisense oligonucleotide is from 20-25 nucleotides in length. In some examples, the antisense oligonucleotide is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26,

27, 28, 29, 30, 31, 32, 33, 34, or 35 nucleotides in length. In some examples an antisense oligonucleotide described herein includes a maximum number of nucleotides. In some examples, an IL-34 antisense oligonucleotide is no more than 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, or 35 nucleotides in length.

5 **[0017]** In an example, provided herein is a compound comprising an antisense oligonucleotide of any one of SEQ ID NOs:1-23, or a pharmaceutically acceptable salt thereof. For example, in some examples, the compound comprises an antisense oligonucleotide of SEQ ID NO:3, wherein at least one cytidine is chemically modified. In some examples, the compound comprises an antisense oligonucleotide of SEQ ID NO:7, wherein X is 5-
10 methylcytidine.

[0018] In examples described herein, a nucleoside of an IL-34 antisense oligonucleotide, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-15, or a pharmaceutically acceptable salt thereof, can be substituted with a chemically modified nucleoside. For example, in some examples, one or more cytidines of an IL-34 antisense
15 oligonucleotide are replaced with 5-methylcytidine. In some examples, an antisense oligonucleotide can include one or more modified nucleotides, for example, 5-methyl-2'-deoxycytidine. For example, in varying examples, an IL-34 antisense oligonucleotide of the present disclosure includes or can include nucleotides including deoxycytidine and/or 5-methyl-2'-deoxycytidine, including, but not limited to, 5-methyl-2'-deoxycytidine 5'-monophosphate
20 and 5-methyl-2'-deoxycytidine-5'-monophosphorothioate. For example, in examples described herein, one or more cytidine nucleosides of an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-15, or a pharmaceutically acceptable salt thereof, can each be substituted with 5-methylcytidine. In some particular examples, one cytidine nucleoside of an IL-34 antisense oligonucleotide described herein is substituted with 5-methylcytidine.

25 **[0019]** Also described herein are methods of treatment wherein an IL-34 antisense oligonucleotide is administered to a patient in need thereof. For example, described herein are methods of treating an inflammatory disease, comprising administering to a patient in need thereof an effective amount of an IL-34 antisense oligonucleotide described herein, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-23. Also described herein is a
30 method of inhibiting inflammatory cytokine production in cells of a patient suffering from an inflammatory disease, comprising administering an effective amount of an IL-34 antisense

oligonucleotide described herein, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-15.

[0020] Also described herein is a method of reducing or inhibiting an IL-34 mediated inflammatory response in a cell or cells of a patient suffering from an inflammatory disease, comprising administering an effective amount of an IL-34 antisense oligonucleotide, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-15. Also described herein, is a method of treating an inflammatory disease associated with altered IL-34 expression in a patient in need thereof, the method comprising administering an effective amount of an IL-34 antisense oligonucleotide. For example, described herein is a method of treating an inflammatory disease associated with increased IL-34 expression in a patient in need thereof, where the method includes administering an effective amount of an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-23, or a pharmaceutically acceptable salt thereof. Increased IL-34 expression may be relative to a control level of IL-34 expression, for example, a mean or median level of IL-34 measured in a healthy control patient or a cohort of healthy control patients, or a level of IL-34 measured in the patient prior to onset or detection of the disease associated with increased IL-34 expression.

[0021] Also described herein is a method of treating an inflammatory disease associated with altered IL-34 expression in a patient in need thereof, comprising administering an effective amount of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-23.

[0022] Also described herein is a method of inhibiting IL-34-mediated macrophage colony-stimulating factor receptor (M-CSFR-1) signaling in cells of a patient suffering from an inflammatory disease, comprising administering an effective amount of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-23.

[0023] Also described herein is a method of reducing or eliminating a fibrotic stricture in a patient suffering from an inflammatory disease, comprising administering an effective amount of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-23. In some examples, the fibrotic stricture is located in the intestine, for example, the large intestine or the small intestine. In particular examples, the fibrotic stricture is located in the large intestine. In some

examples, the fibrotic stricture is localized to one or more portions of the large and/or small intestine, for example, the cecum, the ileum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon, the rectum, the anus, the duodenum, and/or the jejunum.

[0024] Methods described herein may be used to treat one or more inflammatory diseases including, but not limited to, an inflammatory bowel disease, rheumatoid arthritis, psoriasis, osteoarthritis, 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, Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a CNS inflammatory disease, and an autoimmune disease. In some examples, methods of the disclosure may be used to treat asthma, chronic obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis (IPF). In some examples, the inflammatory disease is an inflammatory bowel disease. In some examples, the inflammatory bowel disease is Crohn's disease, gastroduodenal Crohn's disease, Crohn's (granulomatous) colitis, inflammatory Crohn's disease, fibrostricturing Crohn's disease, 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, or indeterminate colitis. In particular examples, the inflammatory bowel disease is inflammatory Crohn's disease or fibrostricturing Crohn's disease.

[0025] In some examples, the IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, is administered topically, parenterally, orally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. In a particular example, the IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, is administered orally.

[0026] In some examples, the patient in need of treatment is a human.

[0027] Also described herein is a pharmaceutically acceptable composition comprising an IL-34 antisense oligonucleotide described herein, for example, an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, of any one of SEQ ID NOs:1-23, and a pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is suitable for topical, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, or intraduodenal administration.

[0028] Also described herein is an IL-34 antisense oligonucleotide for use as a medicament. For example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-23 can be for use as a medicament.

[0029] Also described herein is use of an IL-34 antisense oligonucleotide, for example, an

IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-23, in the manufacture of a medicament for the treatment of an inflammatory disease. In some examples, the inflammatory disease is an inflammatory bowel disease, rheumatoid arthritis, psoriasis, osteoarthritis, 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, Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a CNS inflammatory disease, or an autoimmune disease. Also described herein is use of an IL-34 antisense oligonucleotide in the manufacture of a medicament for the treatment of asthma, chronic obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis (IPF). In some examples, the inflammatory disease is an inflammatory bowel disease. In some examples, the inflammatory bowel disease is 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, or indeterminate colitis. In some examples, the inflammatory bowel disease is inflammatory Crohn's disease or fibrostricturing Crohn's disease.

[0030] Also described herein is an IL-34 antisense oligonucleotide, for example, an IL-34 antisense oligonucleotide of any one of SEQ ID NOs:1-23, for use in the treatment of an inflammatory disease. In some examples, the inflammatory disease is an inflammatory bowel disease, rheumatoid arthritis, psoriasis, osteoarthritis, 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, Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a CNS inflammatory disease, or an autoimmune disease. Also described herein is an IL-34 antisense oligonucleotide for use in

the treatment of asthma, chronic obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis (IPF). In some examples, the inflammatory disease is an inflammatory bowel disease. In some examples, the inflammatory bowel disease is 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, or indeterminate colitis. In some examples, the inflammatory bowel disease is inflammatory Crohn's disease or fibrostricturing Crohn's disease.

[0031] Also described herein is a method of inhibiting IL-34 expression in a cell of a subject, comprising administering to the subject a pharmaceutically effective amount of a pharmaceutical preparation that includes an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, for example, an antisense oligonucleotide of any one of SEQ ID NOs:1-23. Also described herein is a method of inhibiting expression of one or more collagens in a cell of a subject, comprising administering to the subject a pharmaceutically effective amount of a pharmaceutical preparation comprising an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, for example, an antisense oligonucleotide of any one of SEQ ID NOs:1-23. In some examples of the aforementioned methods, the cell is an intestinal cell, for example, an intestinal stromal cell, an intestinal epithelial cell, an intestinal stem cell, a secretory cell, an enterocyte, a Goblet cell, an enteroendocrine cell, a Paneth cell, a transit amplifying cell, a microfold cell, a cup cell, or a tuft cell. In some examples, the cell forms part of an intestinal fibrostricture. In the aforementioned examples, subject can be a subject in need of treatment of an inflammatory disease or fibrosis, for example, inflammatory Crohn's disease or fibrostricturing Crohn's disease. In some examples, methods described herein can be used to inhibit expression of one or more collagens in a cell of a subject, for example, a type I collagen, a type II collagen, a type III collagen, a type IV collagen, a type V collagen, a type VI collagen, a type VII collagen, a type VIII collagen, a type IX collagen, a type X collagen, a type XI collagen, a type XII collagen, a type XIII collagen, a type XIV collagen, a type XV collagen, a type XVI collagen, a type XVII collagen, a type XVIII collagen, a type XIX collagen, a type XX collagen, a type XXI collagen, a type XXII collagen, a type XXIII collagen, a type XXIV collagen, a type XXV collagen, a type XXVI collagen, a type XXVII collagen, a type XXVIII

collagen, or a type XXIX collagen. For example, in examples described herein, the collagen is COL1A1, COL1A2II, COL2A1, COL3A1, COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6, COL5A1, COL5A2, COL5A3, COL6A1, COL6A2, COL6A3, COL6A5, COL7A1, COL8A1, COL8A2, COL9A1, COL9A2, COL9A3, COL10A1, COL11A1, COL11A2, COL12A1, COL13A1, COL14A1, COL15A1, COL16A1, COL17A1, COL18A1, COL19A1, COL20A1, COL21A1, COL22A1, COL23A1, COL24A1, COL25A1, EMID2, COL27A1, COL28A1, or COL29A1. In particular examples, the collagen is COL1A1 (collagen 1A), COL3A1 (collagen 3A), or a mixture thereof. In certain examples, the pharmaceutical preparation can be administered orally. In certain examples, the subject is a human.

[0032] In various examples, the disclosure is a method of treating or preventing fibrosis, for example, intestinal fibrosis, pulmonary fibrosis, or liver fibrosis, or preventing collagen deposition, comprising inhibiting IL-34 in a patient suffering from fibrosis. The disclosure also can be a method of treating or preventing fibrosis or preventing collagen deposition, where the method comprises inhibiting IL-34 in a cell, for example, an intestinal cell. In some examples, the disclosure can be a method of treating or preventing fibrosis or preventing collagen deposition in a patient, where the method comprises administering to the patient an effective amount of a specific inhibitor of IL-34, for example, an IL-34 antisense oligonucleotide, for example, an IL-34 antisense oligonucleotide that includes the nucleotide sequence of any one of SEQ ID NOs:1-23, or a pharmaceutically acceptable salt thereof.

[0033] Also described herein is use of an IL-34 antisense oligonucleotide in the manufacture of a medicament for the treatment of fibrosis. In some examples, the fibrosis is intestinal fibrosis. In some examples, the fibrosis is pulmonary fibrosis. In other examples, the fibrosis is renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, or nephrogenic systemic fibrosis.

[0034] Also described herein is an IL-34 antisense oligonucleotide for use in the treatment of fibrosis. In some examples, the fibrosis is intestinal fibrosis. In some examples, the fibrosis is pulmonary fibrosis. In other examples, the fibrosis is renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, or nephrogenic systemic fibrosis.

[0035] In some examples, the patient suffering from fibrosis, for example, intestinal fibrosis, has previously suffered from an inflammatory bowel disease or is suffering from an inflammatory bowel disease, or an inflammatory bowel disease preceded intestinal fibrosis in the patient. In some examples, the inflammatory bowel disease is inflammatory Crohn's disease or fibrostricturing Crohn's disease.

[0036] In some examples, the patient suffering from intestinal fibrosis previously suffered from colitis or is suffering from colitis, or colitis preceded intestinal fibrosis in the patient. In some examples, the colitis is acute colitis. In some examples, the colitis is chronic colitis.

[0037] In some examples of the disclosure the patient is a mammal, for example, a primate, for example, a human.

[0038] It will be appreciated that the IL-34 antisense oligonucleotide administered to the patient having fibrosis in methods of the disclosure described herein, can be administered by various administration routes. In various examples, the IL-34 antisense oligonucleotide can be administered by one or several routes, including orally, topically, parenterally, *e.g.*, by subcutaneous injection, by inhalation spray, or rectally. The term parenteral as used herein includes subcutaneous injections, intrapancreatic administration, and intravenous, intramuscular, intraperitoneal, and intrasternal injection or infusion techniques. In a preferred example, the IL-34 antisense oligonucleotide can be administered orally to the patient having fibrosis, for example, intestinal fibrosis or pulmonary fibrosis.

[0039] The disclosure can provide methods that include administration of a IL-34 antisense oligonucleotide capable of targeting IL-34 RNA for degradation, interfering with RNA splicing, or preventing IL-34 gene expression or protein translation. The IL-34 antisense oligonucleotides of the disclosure can target various regions of mouse and/or human IL-34 mRNA for binding.

The human IL-34 mRNA sequence is the sequence of NCBI Reference Sequence:

NM_001172771.1 (SEQ ID NO:24), NM_001172772.1 (SEQ ID NO:25), or NM_152456.2 (SEQ ID NO:26). The mouse IL-34 mRNA sequence is the sequence of NCBI Reference Sequence: NM_001135100.2 (SEQ ID NO:27) or NM_029646.3 (SEQ ID NO:28).

[0040] The sequence of the IL-34 antisense oligonucleotide may be selected from multiple sequences capable of targeting IL-34 RNA. In some examples of the disclosure, the antisense oligonucleotide is an antisense oligonucleotide phosphorothioate, *i.e.*, an oligonucleotide where

at least some of the internucleotide linkages are phosphorothioate linkages suitable for delivery to cells of a patient. Additionally, antisense oligonucleotides of the disclosure can include modified nucleotides, for example, nucleotides containing modified bases, for example, 5-methyl-2'-deoxycytidine.

5 **[0041]** In some examples of the disclosure, a method of treating fibrosis, for example, intestinal fibrosis, preventing intestinal fibrosis or pulmonary fibrosis, or preventing collagen deposition in a patient includes administering a pharmaceutical composition, for example, a pharmaceutical composition comprising a specific inhibitor of IL-34, for example, an IL-34 antisense oligonucleotide, and a pharmaceutically acceptable excipient. In some examples, the
10 pharmaceutical composition is administered parenterally. In some examples, the pharmaceutical composition is administered orally. In some examples, the pharmaceutical composition includes an enteric coating, for example, an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

[0042] In examples of the disclosure, methods of treating and/or preventing an inflammatory
15 disease (for example, inflammatory Crohn's disease or fibrostricturing Crohn's disease), treating, reducing, and/or eliminating fibrotic strictures in a patient (for example, in a patient suffering from fibrostricturing Crohn's disease), treating fibrosis (for example, intestinal fibrosis or pulmonary fibrosis), preventing fibrosis (for example, intestinal fibrosis or pulmonary fibrosis), or treating, ameliorating, or preventing collagen deposition in a patient include administering
20 varying amounts of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising an IL-34 antisense oligonucleotide, for example, an IL-34 antisense oligonucleotide that includes a sequence of one of SEQ ID NOs:1-23, or a pharmaceutically acceptable salt thereof. In some examples, methods of the disclosure include administering at least 1 µg, at least 5 µg, at least 10 µg, at least, 20 µg, at least, 30 µg, at
25 least, 40 µg, at least, 50 µg, at least, 60 µg, at least, 70 µg, at least, 80 µg, at least, 90 or at least 100µg of the antisense oligonucleotide. In some examples, methods of the disclosure include administering from 35mg to 500mg, from 1 mg to 10mg, from 10 mg to 20 mg, from 20mg to 30mg, from 30mg to 40mg, from 40mg to 50 mg, from 50mg to 60mg, form 60mg to 70mg, from 70mg to 80mg, from 80mg to 90mg, from 90mg to 100mg, from 100mg to 150mg,
30 from 150mg to 200mg, from 200mg to 250mg, from 250mg to 300mg, from 300mg to 350mg, from 350mg to 400mg, from 400mg to 450mg, from 450mg to 500mg,

from 500mg to 600mg, from 600mg to 700mg, from 700mg to 800mg, from 800mg to 900mg, from 900mg to 1g, from 1mg to 50mg, from 20mg to 40mg, or from 1mg to 500mg of the IL-34 antisense oligonucleotide or a pharmaceutical composition comprising the IL-34 antisense oligonucleotide.

5 **[0043]** Also provided herein is a method of preventing or treating hepatic fibrosis, pulmonary fibrosis, or intestinal fibrosis, where the method comprises administering to a patient in need thereof a pharmaceutical preparation comprising an IL-34 inhibitor, for example, an IL-34 antisense oligonucleotide such as an IL-34 antisense oligonucleotide disclosed herein. Also provided are methods of preventing or treating renal fibrosis, cardiac fibrosis, endomyocardial
10 fibrosis, idiopathic pulmonary fibrosis, myelofibrosis, retroperitoneal fibrosis, and/or nephrogenic systemic fibrosis, where the method comprises administering to a patient in need thereof a pharmaceutical preparation comprising an IL-34 antisense oligonucleotide such as an IL-34 antisense oligonucleotide disclosed herein.

[0044] Also described herein are nucleotide-based IL-34 inhibitors that include, but are not
15 limited to, IL-34 small hairpin RNAs (shRNAs), IL-34 small interfering RNAs (siRNAs), and IL-34 morpholino oligomers, IL-34 microRNAs (miRNAs), and compositions that include such compounds. In some examples, an IL-34 inhibitor described herein can include the nucleotide sequence of any one of SEQ ID NOs:1-23, or a pharmaceutically acceptable salt thereof. In some examples, an IL-34 inhibitor described herein can include the nucleotide sequence of any
20 one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof. For example, IL-34 inhibitors include IL-34 small hairpin RNAs, IL-34 small interfering RNAs, IL-34 microRNAs, and IL-34 morpholino oligomers that include the nucleotide sequence of any one of SEQ ID NOs:1-23, for example, the nucleotide sequence of any one of SEQ ID NOs:1-8, and compositions that include such compounds, for example, compositions that include a
25 pharmaceutically acceptable excipient.

[0045] In particular examples described herein, an IL-34 inhibitor is an IL-34 siRNA that includes the nucleotide sequence of any one of SEQ ID NOs:1-23, for example, the nucleotide sequence of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof. For example, an IL-34 siRNA of the disclosure can be an siRNA that includes the sequence: 5'-
30 CTCACCAAGACCCACAG-3' (SEQ ID NO:1); 5'-GGCTTTGGGCCGCACCAGCT-3' (SEQ ID NO:2); 5'-CTTTGGGCCGCACCAGCTTC-3' (SEQ ID NO:3); 5'-

TGGGCCGCACCAGCTTCAGG-3' (SEQ ID NO:4); 5'-TCCATGACCCGGAAGCAGTT-3' (SEQ ID NO:5); 5'-TGTTTCATGTACTGAAG-3' (SEQ ID NO:6); 5'-CTTTGGGCXGCACCAGCTTC-3' (SEQ ID NO:7), wherein X is 5-methylcytidine; or 5'-TCCATGACCXGGAAGCAGTT-3' (SEQ ID NO:8), wherein X is 5-methylcytidine, or a pharmaceutically acceptable salt of an IL-34 siRNA of one of SEQ ID NOs:1-8.

[0046] Also described herein are pharmaceutically acceptable compositions that include an IL-34 siRNA of any one of SEQ ID NOs:1-23, for example, an siRNA of the nucleotide sequence of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0047] In some examples, an IL-34 inhibitor described herein, for example, an IL-34 siRNA described herein, includes one or more modified internucleoside linkages. For example, in some examples, the IL-34 inhibitor is an IL-34 siRNA wherein at least one internucleoside linkage of the sequence is 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, or a boranophosphate linkage. In particular examples, at least one internucleoside linkage of the IL-34 inhibitor sequence is a phosphorothioate linkage. For example, in some examples, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 1-5, 1-10, 1-14, 1-15, 1-16, 1-19, 5-10, 5-14, 5-15, 5-19, 10-14, 10-15, or 10-19 internucleoside linkages of the IL-34 inhibitor sequence are phosphorothioate linkages. In some examples, all of the internucleoside linkages of the IL-34 inhibitor sequence are phosphorothioate linkages.

[0048] The number of nucleotides included in IL-34 inhibitors described herein may vary. For example, in some examples, the IL-34 siRNA is from 20-25, 20-30, or 25-30 nucleotides in length. In some examples, the IL-34 siRNA is 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some examples an IL-34 siRNA described herein includes a maximum number of nucleotides. In some examples, an IL-34 siRNA is no more than 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

[0049] In examples described herein, a nucleoside of an IL-34 inhibitor, for example, an IL-34 siRNA of any one of SEQ ID NOs:1-23, for example, an IL-34 siRNA of the nucleotide

sequence of any one of SEQ ID NOs:1-8, can be substituted with a chemically modified nucleoside. For example, in some examples, one or more cytidines of an IL-34 siRNA are replaced with 5-methylcytidine. In some examples, an IL-34 siRNA can include one or more modified nucleotides, for example, 5-methyl-2'-deoxycytidine. For example, in varying
5 examples, an IL-34 siRNA of the present disclosure includes or can include nucleotides including deoxycytidine and/or 5-methyl-2'-deoxycytidine, including, but not limited to, 5-methyl-2'-deoxycytidine 5'-monophosphate and 5-methyl-2'-deoxycytidine-5'-monophosphorothioate. For example, in examples described herein, one or more cytidine nucleosides of an IL-34 siRNA of any one of SEQ ID NOs:1-23, or a pharmaceutically
10 acceptable salt thereof, can each be substituted with 5-methylcytidine.

[0050] Additionally, in examples described herein, IL-34 inhibitors, for example, IL-34 siRNAs described herein, can include chemically modified nucleosides, for example, 2'-*O*-methyl ("2'-OMe") ribonucleosides, for example, 2'-*O*-methylcytidine, 2'-*O*-methylguanosine, 2'-*O*-methylthymidine, 2'-*O*-methyluridine, and/or 2'-*O*-methyladenosine. IL-34 inhibitors
15 described herein, can also include one or more chemically modified bases, including a 5-methylpyrimidine, for example, 5-methylcytosine, and/or a 5-methylpurine, for example, 5-methylguanine. IL-34 inhibitors described herein, can also include any of the following chemically modified nucleosides: 5-methyl-2'-*O*-methylcytidine, 5-methyl-2'-*O*-methylthymidine, 5-methylcytidine, 5-methyluridine, and/or 5-methyl-2'-deoxycytidine.

20 Additionally, IL-34 inhibitors described herein can include one or more 2'-*O*-(2-methoxyethyl) ("2'-MOE") nucleosides, 2'-deoxy-2'-fluoro nucleosides, 2'-fluoro- β -D-arabinonucleosides, bridged nucleic acids, LNA nucleotides, constrained ethyl' (cET) nucleic acids, tricyclo-DNAs (tcDNA), 2'-*O*,4'-*C*-ethylene linked nucleic acids (ENA), and/or peptide nucleic acids (PNA). Examples described herein include IL-34 inhibitors of any of SEQ ID NOs:1-23, or a
25 pharmaceutically acceptable salt thereof, that include one or more of any of the aforementioned chemically modified nucleosides. In particular examples, an IL-34 siRNA, or a pharmaceutically acceptable salt thereof, includes the sequence of any of SEQ ID NOs:1-23, that is modified to include one or more of any of the aforementioned chemically modified nucleosides.

30 **[0051]** In some examples, the disclosure provides a method of treating an inflammatory disease, a method of inhibiting inflammatory cytokine production in cells of a patient suffering

from an inflammatory disease, a method of reducing or inhibiting an IL-34 mediated inflammatory response in one or more cells of a patient suffering from an inflammatory disease, a method of treating an inflammatory disease associated with altered IL-34 expression in a patient in need thereof, a method of inhibiting IL-34-mediated M-CSFR-1 signaling in one or more cells of a patient suffering from an inflammatory disease, a method for preventing or treating fibrosis, a method of preventing or treating intestinal fibrosis, and/or a method of reducing or eliminating a fibrotic stricture in a patient suffering from an inflammatory disease, where the method includes administering an IL-34 inhibitor described herein, for example, an IL-34 siRNA. The aforementioned methods can include a step of administering to a patient in need thereof an effective amount of an IL-34 inhibitor (for example, an IL-34 small hairpin RNA, an IL-34 small interfering RNA, an IL-34 microRNA, or an IL-34 morpholino oligomer of SEQ ID NOs:1-23, for example, any one of SEQ ID NOs:1-8, or a composition that includes such an IL-34 inhibitor), or a pharmaceutically acceptable salt thereof. For example, the aforementioned methods can include a step of administering to a patient in need thereof an effective amount of an IL-34 siRNA of any of SEQ ID NOs:1-23, for example, any of SEQ ID NOs:1-8, or a composition that includes such an IL-34 siRNA, or a pharmaceutically acceptable salt thereof. In some examples, the inflammatory disease is an inflammatory bowel disease, for example, inflammatory Crohn's disease or fibrostricturing Crohn's disease.

[0052] Also disclosed herein is a method of inhibiting IL-34 expression in a cell of a subject or inhibiting expression of one or more collagens in a cell of a subject, where the method includes administering an IL-34 inhibitor, for example, an IL-34 siRNA described herein. For example, the aforementioned methods can include a step of administering to the subject a pharmaceutically effective amount of a pharmaceutical preparation that includes an IL-34 inhibitor (for example, an IL-34 small hairpin RNA, an IL-34 small interfering RNA, an IL-34 microRNA, or an IL-34 morpholino oligomer of SEQ ID NOs:1-23, for example, any one of SEQ ID NOs:1-8, or a composition that includes such an IL-34 inhibitor), or a pharmaceutically acceptable salt thereof. For example, the aforementioned methods can include a step of administering to the subject a pharmaceutically effective amount of a pharmaceutical preparation that includes an IL-34 siRNA of any of SEQ ID NOs:1-23, for example, any one of SEQ ID NOs:1-8, or a composition that includes such an IL-34 siRNA, or a pharmaceutically acceptable

salt thereof. In some examples of the aforementioned methods, the subject is in need of treatment of inflammatory Crohn's disease or fibrostricturing Crohn's disease.

[0053] Also described herein are methods of treatment wherein an IL-34 siRNA is administered to a patient in need thereof. For example, described herein are methods of treating an inflammatory disease, comprising administering to a patient in need thereof an effective amount of an IL-34 siRNA of any one of SEQ ID NOs:1-8. Also described herein is a method of inhibiting inflammatory cytokine production in cells of a patient suffering from an inflammatory disease, comprising administering an effective amount of an IL-34 siRNA of any one of SEQ ID NOs:1-8.

[0054] Also described herein is a method of reducing or inhibiting an IL-34 mediated inflammatory response in a cell or cells of a patient suffering from an inflammatory disease, comprising administering an effective amount of an IL-34 siRNA of any one of SEQ ID NOs:1-8. Also described herein, is a method of treating an inflammatory disease associated with altered IL-34 expression in a patient in need thereof, the method comprising administering an effective amount of an IL-34 siRNA. For example, described herein is a method of treating an inflammatory disease associated with increased IL-34 expression in a patient in need thereof, where the method includes administering an effective amount of an IL-34 siRNA of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof. Increased IL-34 expression may be relative to a control level of IL-34 expression, for example, a mean or median level of IL-34 measured in a healthy control patient or a cohort of healthy control patients, or a level of IL-34 measured in the patient prior to onset or detection of the disease associated with increased IL-34 expression.

[0055] Also described herein is a method of treating an inflammatory disease associated with altered IL-34 expression in a patient in need thereof, comprising administering an effective amount of an IL-34 siRNA of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof.

[0056] Also described herein is a method of inhibiting IL-34-mediated M-CSFR-1 signaling in cells of a patient suffering from an inflammatory disease, comprising administering an effective amount of an IL-34 siRNA of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof.

[0057] Also described herein is a method of reducing or eliminating a fibrotic stricture in a patient suffering from an inflammatory disease, comprising administering an effective amount of an IL-34 siRNA of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof. In some examples, the fibrotic stricture is located in the intestine, for example, the large intestine or the small intestine. In particular examples, the fibrotic stricture is located in the large intestine. In some examples, the fibrotic stricture is localized to one or more portions of the large and/or small intestine, for example, the cecum, the ileum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon, the rectum, the anus, the duodenum, and/or the jejunum.

[0058] In some examples, the IL-34 inhibitor, for example, the IL-34 siRNA is administered topically, parenterally, orally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. In a particular example, the IL-siRNA, or a pharmaceutically acceptable salt thereof, is administered orally.

[0059] Also described herein is a pharmaceutically acceptable composition comprising an IL-34 inhibitor described herein, for example, an IL-34 siRNA of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is suitable for topical, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, or intraduodenal administration.

[0060] Also described herein is an IL-34 inhibitor, for example, an IL-34 siRNA, for use as a medicament. For example, an IL-34 siRNA of any one of SEQ ID NOs:1-8 can be for use as a medicament.

[0061] Also described herein is use of an IL-34 inhibitor, for example, an IL-34 siRNA of any one of SEQ ID NOs:1-8, in the manufacture of a medicament for the treatment of an inflammatory disease. Also described herein is an IL-34 inhibitor, for example, an IL-34 siRNA of any one of SEQ ID NOs:1-8, for use in the treatment of an inflammatory disease. In some examples, the inflammatory disease is an inflammatory bowel disease, rheumatoid arthritis, psoriasis, osteoarthritis, 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, Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a CNS inflammatory disease, or an autoimmune disease. Also

described herein is use of an IL-34 antisense oligonucleotide in the manufacture of a medicament for the treatment of asthma, chronic obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis (IPF). In some examples, the inflammatory disease is an inflammatory bowel disease. In some examples, the inflammatory bowel disease is 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, or indeterminate colitis. In some examples, the inflammatory bowel disease is inflammatory Crohn's disease or fibrostricturing Crohn's disease.

[0062] Also described herein is a method of inhibiting IL-34 expression in a cell of a subject, comprising administering to the subject a pharmaceutically effective amount of a pharmaceutical preparation that includes an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, for example, an IL-34 siRNA of any one of SEQ ID NOs:1-8. Also described herein is a method of inhibiting expression of one or more collagens in a cell of a subject, comprising administering to the subject a pharmaceutically effective amount of a pharmaceutical preparation comprising an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, for example, an IL-34 siRNA of any one of SEQ ID NOs:1-8. In some examples of the aforementioned methods, the cell is an intestinal cell, for example, an intestinal stromal cell, an intestinal epithelial cell, an intestinal stem cell, a secretory cell, an enterocyte, a Goblet cell, an enteroendocrine cell, a Paneth cell, a transit amplifying cell, a microfold cell, a cup cell, or a tuft cell. In some examples, the cell forms part of an intestinal fibrostricture. In the aforementioned examples, subject can be a subject in need of treatment of an inflammatory disease or fibrosis, for example, inflammatory Crohn's disease or fibrostricturing Crohn's disease. In some examples, methods described herein can be used to inhibit expression of one or more collagens in a cell of a subject. In certain examples, the pharmaceutical preparation can be administered orally. In certain examples, the subject is a human.

[0063] In some examples, the disclosure can be a method of treating or preventing fibrosis or preventing collagen deposition in a patient, where the method comprises administering to the patient an effective amount of a specific inhibitor of IL-34, for example, an IL-34 siRNA of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof.

[0064] Also described herein is use of an IL-34 inhibitor, for example, an IL-34 siRNA, in the manufacture of a medicament for the treatment of fibrosis. In some examples, the fibrosis is intestinal fibrosis. In some examples, the fibrosis is pulmonary fibrosis. In other examples, the fibrosis is renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, or nephrogenic systemic fibrosis.

[0065] Also described herein is an IL-34 inhibitor, for example, an IL-34 siRNA, for use in the treatment of fibrosis. In some examples, the fibrosis is intestinal fibrosis. In some examples, the fibrosis is pulmonary fibrosis. In other examples, the fibrosis is renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, or nephrogenic systemic fibrosis.

[0066] In various examples, an IL-34 inhibitor, for example, an IL-34 siRNA, can be administered by one or several routes, including orally, topically, parenterally, *e.g.*, by subcutaneous injection, by inhalation spray, or rectally. In a preferred example, the IL-34 inhibitor can be administered orally to the patient having fibrosis, for example, intestinal fibrosis or pulmonary fibrosis.

[0067] The disclosure can provide methods that include administration of a IL-34 inhibitor capable of targeting IL-34 RNA for degradation, interfering with RNA splicing, or preventing IL-34 gene expression or protein translation. IL-34 inhibitors of the disclosure, including IL-34 siRNAs of the disclosure, can target various regions of mouse and/or human IL-34 mRNA for binding.

[0068] In some examples of the disclosure, a method of treating fibrosis, for example, intestinal fibrosis, preventing intestinal fibrosis or pulmonary fibrosis, or preventing collagen deposition in a patient includes administering a pharmaceutical composition, for example, a pharmaceutical composition comprising a specific inhibitor of IL-34, for example, an IL-34 siRNA, and a pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is administered parenterally. In some examples, the pharmaceutical composition is administered orally. In some examples, the pharmaceutical composition includes an enteric coating, for example, an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

[0069] In examples of the disclosure, methods of treating and/or preventing an inflammatory disease (for example, inflammatory Crohn's disease or fibrostricturing Crohn's

disease), treating, reducing, and/or eliminating fibrotic strictures in a patient (for example, in a patient suffering from fibrostricturing Crohn's disease), treating fibrosis (for example, intestinal fibrosis or pulmonary fibrosis), preventing fibrosis (for example, intestinal fibrosis or pulmonary fibrosis), or treating, ameliorating, or preventing collagen deposition in a patient include

5 administering varying amounts of an IL-34 inhibitor, for example an IL-34 siRNA, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising an IL-34 inhibitor, for example, an IL-34 siRNA of any one of SEQ ID NOs:1-8, or a pharmaceutically acceptable salt thereof. In some examples, methods of the disclosure include administering at least 1 µg, at least 5 µg, at least 10 µg, at least, 20 µg, at least, 30 µg, at least, 40 µg, at least, 50
10 µg, at least, 60 µg, at least, 70 µg, at least, 80 µg, at least, 90 µg or at least 100 µg of the IL-34 inhibitor. In some examples, methods of the disclosure include administering from 35 mg to 500 mg, from 1 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 150 mg, from 150 mg to 200 mg, from
15 200 mg to 250 mg, from 250 mg to 300 mg, from 300 mg to 350 mg, from 350 mg to 400 mg, from 400 mg to 450 mg, from 450 mg to 500 mg, from 500 mg to 600 mg, from 600 mg to 700 mg, from 700 mg to 800 mg, from 800 mg to 900 mg, from 900 mg to 1 g, from 1 mg to 50 mg, from 20 mg to 40 mg, or from 1 mg to 500 mg of the IL-34 inhibitor or a pharmaceutical composition comprising the IL-34 inhibitor.

20 **[0070]** Also provided herein is a method of preventing or treating hepatic fibrosis, pulmonary fibrosis, or intestinal fibrosis, where the method comprises administering to a patient in need thereof a pharmaceutical preparation comprising an IL-34 inhibitor, for example, an IL-34 siRNA disclosed herein. Also provided are methods of preventing or treating renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, idiopathic pulmonary fibrosis, myelofibrosis,
25 retroperitoneal fibrosis, and/or nephrogenic systemic fibrosis, where the method comprises administering to a patient in need thereof a pharmaceutical preparation comprising an IL-34 inhibitor such as an IL-34 siRNA disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

30 **[0071]** FIG. 1 is a graph showing normalized IL-34 mRNA expression levels in DLD-1, HT-29, HCT-116, and NCM-460 cells.

WHAT IS CLAIMED IS:

1. An antisense oligonucleotide for inhibiting expression of IL-34, comprising a nucleotide sequence selected from the group consisting of:
5'-TCCATGACCCGGAAGCAGTT-3' (SEQ ID NO: 5), wherein at least one nucleoside is a chemically modified nucleoside and/or at least one linkage is a modified internucleoside linkage; and
5'-tgaCCXGGAAGCagtt-3' (SEQ ID NO: 15), wherein a is LNA adenosine, t is LNA thymidine, g is LNA guanosine, and X is 5-methylcytidine, or a pharmaceutically acceptable salt thereof.
2. The antisense oligonucleotide of claim 1, wherein the nucleotide sequence is SEQ ID NO:5, and wherein at least one cytidine is chemically modified; optionally wherein the cytidine at position 10 of SEQ ID NO: 5 is chemically modified and the nucleotide sequence is 5'-TCCATGACCXGGAAGCAGTT-3' (SEQ ID NO: 8), and wherein X is 5-methylcytidine.
3. The antisense oligonucleotide of any one of claims 1 or 2, wherein the nucleotide sequence is 5'-TxCxCxAxTxGACCXGGAAGCxAxGxTxTx-3' (SEQ ID NO: 17), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, Gx is 2'-O-(2-methoxyethyl)guanosine, Ax is 2'-O-(2-methoxyethyl)adenosine, and X is 5-methylcytidine.
4. The antisense oligonucleotide of any one of claims 1 to 2, wherein the nucleotide sequence is 5'-TxCxCxAxTxGxACCXGGAAGxCxAxGxTxTx-3' (SEQ ID NO: 19), wherein Cx is 2'-O-(2-methoxyethyl)cytidine, Tx is 2'-O-(2-methoxyethyl)thymidine, Gx is 2'-O-(2-methoxyethyl)guanosine, Ax is 2'-O-(2-methoxyethyl)adenosine, and X is 5-methylcytidine.
5. The antisense oligonucleotide of any one of claims 1-4, wherein the antisense oligonucleotide comprises ribonucleotides, deoxyribonucleotides, or a mixture of ribonucleotides and deoxyribonucleotides.
6. The antisense oligonucleotide of any one of claim 1-5, wherein the antisense oligonucleotide comprises at least one internucleoside linkage 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.
7. The antisense oligonucleotide of claim 6, wherein the antisense oligonucleotide comprises at least one phosphorothioate linkage; optionally wherein all internucleoside linkages of the antisense oligonucleotide are phosphorothioate linkages.

8. A pharmaceutical composition for inhibiting the expression of IL-34, comprising (a) an antisense oligonucleotide of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.
9. Use of an antisense oligonucleotide of any one of claims 1-8, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an inflammatory disease in a patient in need thereof.
10. The use of claim 9, wherein the inflammatory disease is selected from the group consisting of an inflammatory bowel disease, rheumatoid arthritis, psoriasis, osteoarthritis, 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, Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a CNS inflammatory disease, or an autoimmune disease.
11. The use of claim 10, wherein the use prevents or treats fibrosis, or reduces or eliminates a fibrotic stricture in a patient suffering from an inflammatory disease.
12. The use of any one of claims 10 or 11, wherein the inflammatory disease is an inflammatory bowel disease.
13. The use of claim 12, wherein said inflammatory bowel disease is selected from the group consisting of Crohn's disease, gastroduodenal Crohn's disease, Crohn's (granulomatous) colitis, inflammatory Crohn's disease, fibrostricturing Crohn's disease, 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.
14. The use of any one of claims 11-13, wherein the medicament is to be administered topically, parenterally, orally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally.
15. The use of any one of claims 11-14, wherein the patient is a human.