

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 embodiment examples, the ~~invention~~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 ~~invention~~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'-GGCTTTGGGCCGACCCAGCT-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'-CTTTGGGCCGACCCAGCTTC-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'-TGGGCCGACCCAGCTTCAGG-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

embodimentexamples, 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 embodimentexamples, the antisense oligonucleotide comprises the sequence of SEQ ID NO:3, wherein at least one cytidine is chemically modified.

In some embodimentexamples, the antisense oligonucleotide comprises the sequence of 5'-CTTTGGGCXGCACCAGCTTC-3' (SEQ ID NO:7), wherein X is 5-methylcytidine. In some

embodimentexamples, 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 embodimentexamples, an antisense oligonucleotide described herein can include ribonucleotides and/or deoxyribonucleotides. For example, in some embodimentexamples 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 embodimentexamples 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

embodimentexamples described herein, an IL-34 antisense oligonucleotide can include a mixture of ribonucleotides and deoxyribonucleotides.

**[0010]** In some embodimentexample 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 embodimentexamples, each of the nucleotides of an IL-34 antisense oligonucleotide described herein is an LNA nucleotide.

**[0011]** In particular embodimentexamples, 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 [embodiment 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 example, 5-  
 20 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'-MOE") nucleosides, 2'-deoxy-  
 25 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). [Embodiment 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 chemically-modified nucleosides. In  
 30 some [embodiment examples](#), at least one nucleoside of the IL-34 antisense oligonucleotide sequence is a chemically-modified nucleoside. For

example, in some [embodimentexamples](#), 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 [embodimentexamples](#), an IL-34 antisense oligonucleotide described herein includes 2'-MOE nucleosides. In some [embodimentexamples](#), the sequence of the IL-34 antisense oligonucleotide is selected from one of the following:

- 5'-CxTxTxTxGxGGCXGCACCAGxCxTxTxCx-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'-CxTxTxTxGxGxGCXGCACCAXGxCxTxTxCx-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'-CxTxTxTxGxGxGxCxXGxCxAXCxCxAXGxCxTxTxCx-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'-TxCxCxAxTxGxAXCxCxXGxGxAXAXGxCxAXGxTxTx-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 [embodimentexamples](#), an IL-34 antisense oligonucleotide described herein includes 2'-OMe nucleosides. In some [embodimentexamples](#), 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 [embodimentexamples](#), an IL-34 antisense oligonucleotide described herein includes one or more modified internucleoside linkages. For example, in some [embodimentexamples](#), 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 [embodimentexamples](#), at least one internucleoside linkage of the IL-34 antisense oligonucleotide sequence is a phosphorothioate linkage. For example, in some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), the antisense oligonucleotide is from 15-25 nucleotides in length. In particular [embodimentexamples](#), the antisense oligonucleotide is from 20-25 nucleotides in length. In some [embodimentexamples](#), 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 [embodimentexamples](#) an antisense oligonucleotide described herein includes a maximum number of nucleotides. In some [embodimentexamples](#), 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 [embodimentexample](#), 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 [embodimentexamples](#), the compound comprises an antisense oligonucleotide of SEQ ID NO:3, wherein at least one cytidine is chemically modified. In some [embodimentexamples](#), the compound comprises an antisense oligonucleotide of SEQ ID NO:7,  
10 wherein X is 5-methylcytidine.

**[0018]** In [embodimentexamples](#) 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 [embodimentexamples](#), one or more cytidines of an IL-34 antisense  
15 oligonucleotide are replaced with 5-methylcytidine. In some [embodimentexamples](#), an antisense oligonucleotide can include one or more modified nucleotides, for example, 5-methyl-2'-deoxycytidine. For example, in varying [embodimentexamples](#), 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 and 5-  
20 methyl-2'-deoxycytidine-5'-monophosphorothioate. For example, in [embodimentexamples](#) 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 [embodimentexamples](#), 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 method of  
30 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 embodiment examples, the fibrotic stricture is located in the intestine, for example, the large intestine or the small intestine. In particular embodiment examples, the fibrotic stricture is located in the large intestine. In some

embodimentexample, 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.

5 **[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 embodimentexample, methods of the inventiondisclosure may be used to treat asthma, chronic obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis (IPF). In some embodimentexample, the inflammatory disease is an inflammatory bowel disease. In some embodimentexample, 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 embodimentexample, the inflammatory bowel disease is inflammatory Crohn's disease or fibrostricturing Crohn's disease.

20 **[0025]** In some embodimentexample, 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 embodimentexample, the IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, is administered orally.

**[0026]** In some embodimentexample, 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 embodimentexample, 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

5 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 [embodimentexamples](#), 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

10 idiopathic pulmonary fibrosis (IPF). In some [embodimentexamples](#), the inflammatory disease is an inflammatory bowel disease. In some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), the inflammatory disease is an inflammatory

25 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

30 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 [embodimentexamples](#), the inflammatory disease is an inflammatory bowel disease. In some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#) 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 [embodimentexamples](#), the cell forms part of an intestinal fibrostricture. In the aforementioned [embodimentexamples](#), 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 [embodimentexamples](#), 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 embodimentexamples 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 embodimentexamples, the collagen is COL1A1 (collagen 1A), COL3A1 (collagen 3A), or a mixture thereof. In certain embodimentexamples, the pharmaceutical preparation can be administered orally. In certain embodimentexamples, the subject is a human.

**[0032]** In various embodimentexamples, the inventiondisclosure 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 inventiondisclosure 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 embodimentexamples, the inventiondisclosure 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 embodimentexamples, the fibrosis is intestinal fibrosis. In some embodimentexamples, the fibrosis is pulmonary fibrosis. In other embodimentexamples, 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 embodimentexamples, the fibrosis is intestinal fibrosis. In some embodimentexamples, the fibrosis is pulmonary fibrosis. In other embodimentexamples, the fibrosis is renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, or nephrogenic systemic fibrosis.

[0035] In some embodimentexamples, 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 embodimentexamples, the inflammatory bowel disease is inflammatory Crohn's disease or fibrostricturing Crohn's disease.

[0036] In some embodimentexamples, 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 embodimentexamples, the colitis is acute colitis. In some embodimentexamples, the colitis is chronic colitis.

[0037] In some embodimentexamples of the inventiondisclosure 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 inventiondisclosure described herein, can be administered by various administration routes. In various embodimentexamples, 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 embodimentexample, the IL-34 antisense oligonucleotide can be administered orally to the patient having fibrosis, for example, intestinal fibrosis or pulmonary fibrosis.

[0039] The inventiondisclosure 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 inventiondisclosure 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 embodimentexamples of the inventiondisclosure, 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 inventiondisclosure can include modified nucleotides, for example, nucleotides containing modified bases, for example, 5-methyl-2'-deoxycytidine.

5 [0041] In some embodimentexamples of the inventiondisclosure, 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  
10 embodimentexamples, the pharmaceutical composition is administered parenterally. In some embodimentexamples, the pharmaceutical composition is administered orally. In some embodimentexamples, the pharmaceutical composition includes an enteric coating, for example, an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

15 [0042] In embodimentexamples of the inventiondisclosure, 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  
20 administering 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 embodimentexamples, methods of the inventiondisclosure include administering at least 1 µg, at least 5 µg, at least 10 µg, at  
25 least, 20 µg, at least, 30 µg, at 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 embodimentexamples, methods of the inventiondisclosure 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, from 60mg to 70mg, from 70mg to 80mg, from 80mg to 90mg, from 90mg to 100mg, from  
30 100mg to 150mg, 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 embodimentexamples, 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 embodimentexamples, an IL-34 inhibitor described herein can include the  
20 nucleotide sequence of any 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 embodimentexample 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 inventiondisclosure can be an siRNA that includes the  
30 sequence: 5'-CTCACCAAGACCCACAG-3' (SEQ ID NO:1); 5'-GGCTTTGGGCCGACACCAGCT-3' (SEQ ID NO:2); 5'-CTTTGGGCCGACACCAGCTTC-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 embodimentexamples, 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 embodimentexamples, 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 embodimentexamples, at least one internucleoside linkage of the IL-34 inhibitor sequence is a phosphorothioate linkage. For example, in some embodimentexamples, 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 embodimentexamples, 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 embodimentexamples, the IL-34 siRNA is from 20-25, 20-30, or 25-30 nucleotides in length. In some embodimentexamples, the IL-34 siRNA is 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodimentexamples an IL-34 siRNA described herein includes a maximum number of nucleotides. In some embodimentexamples, 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 embodimentexamples 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 [embodiment examples](#), one or more cytidines of an IL-34 siRNA are replaced with 5-methylcytidine. In some [embodiment examples](#), an IL-34 siRNA can include one or more modified nucleotides, for example, 5-methyl-2'-deoxycytidine. For example, in varying [embodiment 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 [embodiment 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 acceptable salt thereof, can each be substituted with 5-methylcytidine.

**[0050]** Additionally, in [embodiment 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 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. 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- $\beta$ -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). [Embodiment Examples](#) described herein include IL-34 inhibitors of any of SEQ ID NOs:1-23, or a pharmaceutically acceptable salt thereof, that include one or more of any of the aforementioned chemically modified nucleosides. In particular [embodiment 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.

**[0051]** In some [embodiment 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 embodiment 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 embodimentexamples 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 [embodimentexamples](#), the fibrotic stricture is located in the intestine, for example, the large intestine or the small intestine. In particular [embodimentexamples](#), the fibrotic stricture is located in the large intestine. In some [embodimentexamples](#), 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 [embodimentexamples](#), the IL-34 inhibitor, for example, the IL-34 siRNA is administered topically, parenterally, orally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. In a particular [embodimentexample](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 embodimentexamples, the inflammatory disease is an inflammatory bowel disease. In some embodimentexamples, 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 embodimentexamples, 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 embodimentexamples 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 embodimentexamples, the cell forms part of an intestinal fibrostricture. In the aforementioned embodimentexamples, 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 embodimentexamples, methods described herein can be used to inhibit expression of one or more collagens in a cell of a subject. In certain embodimentexamples, the pharmaceutical preparation can be administered orally. In certain embodimentexamples, the subject is a human.

**[0063]** In some embodimentexamples, the inventiondisclosure 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 [embodimentexamples](#), the fibrosis is intestinal fibrosis. In some [embodimentexamples](#), the fibrosis is pulmonary fibrosis. In other [embodimentexamples](#), 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 [embodimentexamples](#), the fibrosis is intestinal fibrosis. In some [embodimentexamples](#), the fibrosis is pulmonary fibrosis. In other [embodimentexamples](#), the fibrosis is renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, or nephrogenic systemic fibrosis.

[0066] In various [embodimentexamples](#), 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 [embodimentexample](#), the IL-34 inhibitor can be administered orally to the patient having fibrosis, for example, intestinal fibrosis or pulmonary fibrosis.

[0067] The [inventiondisclosure](#) 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 [inventiondisclosure](#), including IL-34 siRNAs of the [inventiondisclosure](#), can target various regions of mouse and/or human IL-34 mRNA for binding.

[0068] In some [embodimentexamples](#) of the [inventiondisclosure](#), 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 [embodimentexamples](#), the pharmaceutical composition is administered parenterally. In some [embodimentexamples](#), the pharmaceutical composition is administered orally. In some [embodimentexamples](#), the pharmaceutical composition includes an enteric coating, for example, an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

[0069] In [embodimentexamples](#) of the [inventiondisclosure](#), 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 embodiment examples, methods of the invention disclosure include administering at least 1 µg, at least 5 µg, at least 10 µg, at least, 20 µg, at least, 30 µg, at  
10 least, 40 µg, at least, 50 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 embodiment examples, methods of the invention 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  
15 mg, from 100 mg to 150 mg, from 150 mg to 200 mg, from 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 ~~IL-34~~ antisense oligonucleotide for inhibiting expression of IL-34, comprising a nucleotide sequence selected from the group consisting of:

5 ~~5'-CTCAGCAAGACCCACAG-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'-GGCTTTGGGCGGCACCAGCT-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;~~

10 ~~5'-CTTTGGGCGGCACCAGCTTC-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;~~

15 ~~5'-TGGGCGGCACCAGCTTCAGG-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; and~~

20 ~~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.~~

- 25 ~~2. The antisense oligonucleotide of claim 1, wherein the nucleotide sequence is SEQ ID NO:3, and wherein at least one cytidine is chemically modified.~~

3. ~~—The antisense oligonucleotide of claim 2, wherein the nucleotide sequence is 5'-CTTTGGGCXGCACCAGCTTC-3' (SEQ ID NO:7), and wherein X is 5-methylcytidine.~~

4. ~~—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.~~

5. ~~—The antisense oligonucleotide of any one of claims 1-4, wherein the antisense oligonucleotide comprises one or more locked nucleic acids (LNA).~~

6. ~~—The antisense oligonucleotide of any one of claims 1-5, wherein each of the nucleotides of the antisense oligonucleotide comprises a locked nucleic acid (LNA).~~

7. ~~—An IL-34 antisense oligonucleotide of comprising a nucleotide sequence selected from the group consisting of:~~

~~5'-cttTGGGCXGCACCAGCtte-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'-cttTGGGCcgCACCAGCtte-3' (SEQ ID NO:11), wherein c is LNA cytidine, t is LNA thymidine, and g is LNA guanosine;~~

~~5'-cttTGGGCGCACCAGCtte-3' (SEQ ID NO:12), wherein c is LNA cytidine and t is LNA thymidine;~~

~~5'-ggcXGCACCAGCtte-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; 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.

~~8.3. An IL-34~~ The antisense oligonucleotide of any one of claims 1 or 2, of comprising  
awherein the nucleotide sequence ~~selected from the group consisting of:~~ is

~~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;~~

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'-CxTxTxTxGxGxGxCxXGxCxAxCxCxAxGxCxTxTxCx-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 5'-TxCxCxAxTxGxAxCxCxXGxCxAxAxCxCxAxGxCxTxTx-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.

10 95. The antisense oligonucleotide of any one of claims 1-84, wherein the antisense  
oligonucleotide comprises ~~one or more~~ ribonucleotides,;

~~10. The antisense oligonucleotide of any one of claims 1-8, wherein the antisense  
oligonucleotide comprises one or more deoxyribonucleotides, or;~~

~~11. The antisense oligonucleotide of any one of claims 1-8, wherein the antisense  
oligonucleotide comprises a mixture of ribonucleotides and deoxyribonucleotides.~~

15 126. The antisense oligonucleotide of any one of claims 1-115, wherein the antisense  
oligonucleotide comprises at least one internucleoside linkage ~~of the sequence is~~ selected from  
the group consisting of a phosphorothioate linkage, a phosphorodithioate linkage, a  
phosphotriester linkage, an alkylphosphonate linkage, an aminoalkylphosphotriester linkage, an  
20 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.

25 137. The antisense oligonucleotide of ~~any one of claims 1-126~~, wherein the antisense  
oligonucleotide comprises at least one ~~internucleoside linkage of the sequence is a~~  
phosphorothioate linkage-; optionally

~~14.—The antisense oligonucleotide any one of claims 1-13, wherein all internucleoside linkages of the antisense oligonucleotide sequence are phosphorothioate linkages.~~

~~15.—The antisense oligonucleotide of any one of claims 1-14, wherein one or more cytidines are replaced with 5-methylcytidine.~~

5 ~~16.—The antisense oligonucleotide of any one of claims 1-15 wherein the antisense oligonucleotide is 20 nucleotides in length or 20-25, 20-30, 20-35, 25-30, 25-35, or 30-35 nucleotides in length.~~

~~17.—The antisense oligonucleotide of claim 16, wherein the antisense oligonucleotide is from 20-25 nucleotides in length.~~

10 ~~18.—The antisense oligonucleotide of any one of claims 1-15, wherein the antisense oligonucleotide is no more than 20, 25, 30, or 35 nucleotides in length.~~

~~19.—A compound comprising an antisense oligonucleotide of any one of claims 1-18 or a pharmaceutically acceptable salt thereof.~~

15 ~~20.—A compound comprising an antisense oligonucleotide of any one of claims 1-3 and 5-18, wherein the antisense oligonucleotide comprises the nucleotide sequence of SEQ ID NO:3, and wherein at least one cytidine is chemically modified, or a pharmaceutically acceptable salt thereof.~~

20 ~~21.—The compound of claim 20, wherein the antisense oligonucleotide comprises the nucleotide sequence 5'-CTTTGGGCXGCACCAGCTTC-3' (SEQ ID NO:7), and wherein X is 5-methylcytidine.~~

~~22.—A method of treating an inflammatory disease, the method comprising administering to a patient in need thereof an effective amount of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

25 ~~23.—A method of inhibiting inflammatory cytokine production in cells of a patient suffering from an inflammatory disease, the method comprising administering an effective amount of an~~

~~IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

24. — ~~A method of reducing or inhibiting an IL-34 mediated inflammatory response in cells of a patient suffering from an inflammatory disease, the method comprising administering an effective amount of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

25. — ~~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, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

26. — ~~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, the method comprising administering an effective amount of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

27. — ~~A method of reducing or eliminating a fibrotic stricture in a patient suffering from an inflammatory disease, the method comprising administering an effective amount of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

28. — ~~The method of claim 27, wherein the fibrotic stricture is located in the intestine.~~

29. — ~~The method of any one of claims 22-28, wherein said 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.~~

30. — ~~The method of claim 29, wherein said inflammatory disease is an inflammatory bowel disease.~~

31. — ~~The method of claim 30, 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.~~

32. — ~~The method of claim 31, wherein said inflammatory bowel disease is inflammatory Crohn's disease.~~

33. — ~~The method of claim 31, wherein said inflammatory bowel disease is fibrostricturing Crohn's disease.~~

34. ~~The method of any one of claims 22-33, wherein the IL-34 antisense oligonucleotide is administered topically, parenterally, orally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally.~~

35. — ~~The method of claim 34, wherein the IL-34 antisense oligonucleotide is administered orally.~~

36. — ~~The method of any one of claims 22-35, wherein the patient is a human.~~

37. A pharmaceutically acceptable composition for inhibiting the expression of comprising an-IL-34, comprising (a) an antisense oligonucleotide of any one of claims 1-187, or a pharmaceutically acceptable salt thereof, and (b) or a compound of any one of claims 19-21, and a pharmaceutically acceptable excipient.

38. — ~~The pharmaceutical composition of claim 37, wherein the pharmaceutical composition is suitable for topical, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, or intraduodenal administration.~~

~~399.~~ Use of an ~~IL-34~~ antisense oligonucleotide of any one of claims 1-~~18~~, or a pharmaceutically acceptable salt thereof, ~~or a compound of any one of claims 19-21~~, in the manufacture of a medicament for ~~the treatment treating of~~ an inflammatory disease in a patient in need thereof.

5 ~~4010.~~ The use of claim ~~39~~, wherein ~~said 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, ~~or~~ 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.

15 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.

20 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.

25 15. The use of any one of claims 11-14, wherein the patient is a human.

~~41.—The use of claim 40, wherein said inflammatory disease is an inflammatory bowel disease.~~

~~42.—The use of claim 41, wherein 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.~~

5 ~~43.—The use of claim 42, wherein said inflammatory bowel disease is inflammatory Crohn's disease.~~

~~44.—The use of claim 42, wherein said inflammatory bowel disease is fibrostricturing Crohn's disease.~~

10 ~~45.—A method of inhibiting IL-34 expression in a cell of a subject, the method 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, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

15 ~~46.—A method of inhibiting expression of one or more collagens in a cell of a subject, the method 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, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

~~47.—The method of claim 45 or 46, wherein the cell is an intestinal cell.~~

~~48.—The method of claim 47, wherein the cell is an intestinal stromal cell.~~

~~49.—The method of claim 45 or 46, wherein the cell forms part of an intestinal fibrostricture.~~

20 ~~50.—The method of claim 45 or 46, wherein the subject is in need of treatment of a disease selected from inflammatory Crohn's disease or fibrostricturing Crohn's disease.~~

~~51.—The method of claim 46, wherein the one or more collagens is selected from the group consisting of collagen 1A, collagen 3A, and a mixture thereof.~~

25 ~~52.—The method of claim 45 or 46, wherein the pharmaceutical preparation is administered orally.~~

53. — ~~The method of claim 45 or 46, wherein the subject is a human.~~

54. — ~~A method for preventing or treating fibrosis, the method comprising administering to a patient in need thereof a therapeutically effective amount of an IL-34 antisense oligonucleotide, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, or a compound of any one of claims 19-21.~~

55. — ~~The method of claim 54, wherein the fibrosis is intestinal fibrosis.~~

56. — ~~The method of claim 54, wherein the fibrosis is pulmonary fibrosis.~~

57. — ~~The method of claim 54, wherein the fibrosis is selected from the group consisting of renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, and nephrogenic systemic fibrosis.~~

58. — ~~A method of preventing or treating intestinal fibrosis, the method comprising administering to a patient in need thereof, a pharmaceutically effective amount of a pharmaceutical preparation comprising an IL-34 antisense oligonucleotide of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, or a compound of any one of claims 19-21.~~

59. — ~~The method of claim 58, wherein the pharmaceutical preparation is administered orally.~~

60. — ~~The method of claim 58 or 59, wherein the patient is a human.~~

61. — ~~The method of any one of claims 58-60, wherein the patient is also suffering from Crohn's disease.~~

62. — ~~A method of preventing or treating pulmonary fibrosis, the method comprising administering to a patient in need thereof, a pharmaceutically effective amount of a pharmaceutical preparation comprising an IL-34 antisense oligonucleotide of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, or a compound of any one of claims 19-21.~~

63. — ~~The method of claim 62, wherein the pharmaceutical preparation is administered orally.~~

64. — ~~The method of claim 62 or 63, wherein the patient is human.~~

65. — ~~An IL-34 antisense oligonucleotide of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, or a compound of any one of claims 19-21 for use as a medicament.~~

66. — ~~An IL-34 antisense oligonucleotide of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, or a compound of any one of claims 19-21 for use in the treatment of an inflammatory disease.~~

67. — ~~The IL-34 antisense oligonucleotide for use as claimed in claim 66, wherein said 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, or Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a CNS inflammatory disease, or an autoimmune disease.~~

68. — ~~The IL-34 antisense oligonucleotide for use as claimed in claim 67, wherein said inflammatory disease is an inflammatory bowel disease.~~

69. — ~~The IL-34 antisense oligonucleotide for use as claimed in claim 68, wherein 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.~~

70. — ~~The IL-34 antisense oligonucleotide for use as claimed in claim 69, wherein the inflammatory bowel disease is inflammatory Crohn's disease.~~

71. — ~~The IL-34 antisense oligonucleotide for use as claimed in claim 69, wherein the inflammatory bowel disease is fibrostricturing Crohn's disease.~~

72. — ~~An IL-34 antisense oligonucleotide of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, for use in the treatment of fibrosis.~~

73. — ~~The IL-34 antisense oligonucleotide for use as claimed in claim 72, wherein the fibrosis is intestinal fibrosis.~~

5 74. — ~~The IL-34 antisense oligonucleotide for use as claimed in claim 72, wherein the fibrosis is pulmonary fibrosis.~~

75. — ~~The IL-34 antisense oligonucleotide for use as claimed in claim 72, wherein the fibrosis is selected from the group consisting of renal fibrosis, cardiac fibrosis, endomyocardial fibrosis, myelofibrosis, retroperitoneal fibrosis, and nephrogenic systemic fibrosis.~~

10 76. — ~~An IL-34 inhibitor comprising a nucleotide sequence selected from the group consisting of:~~

~~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;~~

15 ~~5'-GGCTTTGGGCCCGCACCAGCT-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;~~

20 ~~5'-CTTTGGGCCCGCACCAGCTTC-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'-TGGGCCCGCACCAGCTTCAGG-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;~~

25 ~~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'-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.~~

5     ~~77. The IL-34 inhibitor of claim 76, wherein the nucleotide sequence is SEQ ID NO:3, and wherein at least one cytidine is a chemically modified.~~

~~78. The IL-34 inhibitor of claim 77, wherein the nucleotide sequence is 5'-CTTTGGGCXGCACCAGCTTC-3' (SEQ ID NO:7), and wherein X is 5-methylcytidine.~~

10     ~~79. The IL-34 inhibitor of claim 76, 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.~~

~~80. The IL-34 inhibitor of any one of claims 76-79, wherein the antisense oligonucleotide comprises one or more locked nucleic acids (LNA).~~

15     ~~81. The IL-34 inhibitor of claim 76-80, wherein each of the nucleotides of the antisense oligonucleotide comprises a locked nucleic acid (LNA).~~

~~82. The IL-34 inhibitor of any one of claims 76-81, wherein the IL-34 inhibitor is an IL-34 siRNA, or a pharmaceutically acceptable salt thereof.~~

20     ~~83. The IL-34 inhibitor of claim 82, wherein at least one internucleoside linkage of the sequence 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.~~

25

84. — ~~The IL-34 inhibitor of claim 82 or 83, wherein at least one internucleoside linkage of the sequence is a phosphorothioate linkage.~~

85. — ~~The IL-34 inhibitor any one of claims 82-84, wherein all internucleoside linkages of the sequence are phosphorothioate linkages.~~

5 86. — ~~The IL-34 inhibitor of any one of claims 82-85, wherein one or more cytidines are replaced with 5-methylcytidine.~~

87. — ~~The IL-34 inhibitor of any one of claims 82-86 wherein the IL-34 siRNA is 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 20-25, 20-30, or 25-30 nucleotides in length.~~

10 88. — ~~The IL-34 inhibitor of claim 87, wherein the IL-34 siRNA is from 20-25 nucleotides in length.~~

89. — ~~The IL-34 inhibitor of any one of claims 82-86, wherein the IL-34 siRNA is no more than 20, 25, or 30 nucleotides in length.~~

15 90. — ~~A method of treating an inflammatory disease, the method comprising administering to a patient in need thereof an effective amount of an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.~~

91. — ~~A method of inhibiting inflammatory cytokine production in cells of a patient suffering from an inflammatory disease, the method comprising administering an effective amount of an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.~~

20 92. — ~~A method of reducing or inhibiting an IL-34 mediated inflammatory response in cells of a patient suffering from an inflammatory disease, the method comprising administering an effective amount of an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.~~

25 93. — ~~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 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.~~

94.—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, the method comprising administering an effective amount of an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.

5 95.—A method of reducing or eliminating a fibrotic stricture in a patient suffering from an inflammatory disease, the method comprising administering an effective amount of an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.

96.—The method of claim 95, wherein the fibrotic stricture is located in the intestine.

10 97.—The method of any one of claims 90-96, wherein said 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  
15 lesions, a CNS inflammatory disease, or an autoimmune disease.

98.—The method of claim 97, wherein said inflammatory disease is an inflammatory bowel disease.

20 99.—The method of claim 98, 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.

25 100.—The method of claim 99, wherein said inflammatory bowel disease is inflammatory Crohn's disease.

101.—The method of claim 99, wherein said inflammatory bowel disease is fibrostricturing Crohn's disease.

102.—~~The method of any one of claims 90-101, wherein the IL-34 inhibitor is administered topically, parenterally, orally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally.~~

103.—~~The method of claim 102, wherein the IL-34 inhibitor is administered orally.~~

5 104.—~~The method of any one of claims 90-103, wherein the patient is a human.~~

105.—~~A pharmaceutically acceptable composition comprising an IL-34 inhibitor of any one of claims 76-89, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.~~

10 106.—~~The method of claim 105, wherein the pharmaceutical composition is suitable for topical, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, or intraduodenal administration.~~

107.—~~Use of an IL-34 inhibitor of any one of claims 76-89, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an inflammatory disease.~~

15 108.—~~The use of claim 107, wherein said 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, or Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a~~  
20 ~~CNS inflammatory disease, or an autoimmune disease.~~

109.—~~The use of claim 108, wherein said inflammatory disease is an inflammatory bowel disease.~~

25 110.—~~The use of claim 109, wherein 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.

111.—The use of claim 110, wherein said inflammatory bowel disease is inflammatory Crohn's disease.

5 112.—The use of claim 110, wherein said inflammatory bowel disease is fibrostricturing Crohn's disease.

10 113.—A method of inhibiting IL-34 expression in a cell of a subject, the method comprising administering to the subject a pharmaceutically effective amount of a pharmaceutical preparation comprising an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.

114.—A method of inhibiting expression of one or more collagens in a cell of a subject, the method comprising administering to the subject a pharmaceutically effective amount of a pharmaceutical preparation comprising an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.

15 115.—The method of claim 113 or 114, wherein the cell is an intestinal cell.

116.—The method of claim 115, wherein the cell is an intestinal stromal cell.

117.—The method of claim 113 or 114, wherein the cell forms part of an intestinal fibrostricture.

20 118.—The method of claim 113 or 114, wherein the subject is in need of treatment of a disease selected from inflammatory Crohn's disease or fibrostricturing Crohn's disease.

119.—The method of claim 114, wherein the one or more collagens is selected from the group consisting of collagen 1A, collagen 3A, and a mixture thereof.

120.—The method of claim 113 or 114, wherein the pharmaceutical preparation is administered orally.

25 121.—The method of claim 113 or 114, wherein the subject is a human.

122.—A method for preventing or treating fibrosis, the method comprising administering to a patient in need thereof a therapeutically effective amount of an IL-34 inhibitor, or a pharmaceutically acceptable salt thereof, of any one of claims 76-89.

123.—The method of claim 122, wherein the fibrosis is intestinal fibrosis.

5 124.—A method of preventing or treating intestinal fibrosis, the method comprising administering to a patient in need thereof, a pharmaceutically effective amount of a pharmaceutical preparation comprising an IL-34 inhibitor of any one of claims 76-89, or a pharmaceutically acceptable salt thereof.

125.—The method of claim 124, wherein the pharmaceutical preparation is administered orally.

10 126.—The method of claim 124 or 125, wherein the patient is a human.

127.—The method of any one of claims 124-126, wherein the patient is also suffering from Crohn's disease.

128.—An IL-34 inhibitor of any one of claims 76-89, or a pharmaceutically acceptable salt thereof, for use as a medicament.

15 129.—An IL-34 inhibitor of any one of claims 76-89, or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory disease.

20 130.—The IL-34 inhibitor for use as claimed in claim 129, wherein said 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, or Sjogren's syndrome (SS), obesity, chronic inflammation, pulmonary sarcoidosis, skin lesions, a CNS inflammatory disease, or an autoimmune disease.

25 131.—The IL-34 inhibitor for use as claimed in claim 130, wherein said inflammatory disease is an inflammatory bowel disease.

132.—The IL-34 inhibitor for use as claimed in claim 131, wherein 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.

133.—The IL-34 inhibitor for use as claimed in claim 132, wherein the inflammatory bowel disease is inflammatory Crohn's disease.

134.—The IL-34 inhibitor for use as claimed in claim 132, wherein the inflammatory bowel disease is fibrostricturing Crohn's disease.

135.—An IL-34 inhibitor of any one of claims 76-89, or a pharmaceutically acceptable salt thereof, for use in the treatment of fibrosis.

136.—The IL-34 inhibitor for use as claimed in claim 135, wherein the fibrosis is intestinal fibrosis.