catastrophic; a major disability (including limb loss) and even death can result. Foot ulceration is the precursor to about 85% of lower extremity amputations in persons with diabetes (*see, e.g.*, Apelqvist, et al., What is the most effective way to reduce incidence of amputation in the diabetic foot? *Diabetes Metab Res. Rev.*, 16(1 Suppl.): S75-S83 (2000)). Thus, there is a need for accelerating or improving wound healing, including diabetic wound healing.

SUMMARY

Disclosed are IL-22 Fc fusion proteins, compositions comprising the same, and methods of using the same.

In one aspect, there is provided an interleukin (IL)-22 Fc fusion protein that binds to IL-22 receptor, said IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, wherein the IL-22 Fc fusion protein comprises an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8, and wherein the Fc region is not glycosylated. In certain embodiments, the disclosure provides an IL-22 Fc fusion protein that binds to IL-22 receptor, said IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, wherein the IL-22 Fc fusion protein comprises an amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, preferably at least 99% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12 and SEQ ID NO:14, and wherein the Fc region is not glycosylated. In certain embodiments, the N297 residue of the CH2 domain is changed to glycine or alanine. In certain other embodiments, the N297 residue is changed to Gly; while in other embodiments, the N297 residue is changed to Ala. In certain embodiments, the binding to IL-22 receptor triggers IL-22 receptor downstream signaling, including activating STAT3.

In certain embodiments, the IL-22 Fc fusion protein comprises an amino acid sequence having at least 98% sequence identity to the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12. In certain other embodiments, the IL-22 Fc fusion protein comprises an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12. In certain other embodiments, the IL-22 Fc fusion protein comprises an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8. In certain other embodiments, the IL-22 Fc fusion protein comprises an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO:12.

method comprising the step of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein. In certain embodiments, the method further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium. In certain embodiments, the host cell is a Chinese hamster ovary (CHO) cell; while in other embodiments, the host cell is an *E. coli* cell.

In another aspect, there is provided an IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an IgG4 Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG4 CH2 domain and an IgG4 CH3 domain, and wherein the Fc region is not glycosylated. In certain embodiments, the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31). In certain other embodiments, the N297 residue in the Fc region is changed and/or the T299 residue in the Fc region is changed. In certain embodiments, the N297 residue in the CH2 domain is changed, preferably to glycine or alanine. In certain particular embodiments, the N297 residue is changed to glycine. In certain other embodiments, the N297 residue is changed to alanine. In yet other embodiments, the T299 residue is changed to Ala, Gly or Val. In certain other embodiments, the linker is 8-20 amino acids long, 8-16 amino acids long, or 10-16 amino acids long.

In certain embodiments, the Fc region comprises the CH2 and CH3 domain of IgG1. In certain particular embodiments, the linker comprises the amino acid sequence DKTHT (SEQ ID NO:32). In certain embodiments, the linker comprises the amino acid sequence GGGDKTHT (SEQ ID NO:41). In certain embodiments, the linker is at least 11 amino acids long and comprises the amino acid sequence EPKSCDKTHT (SEQ ID NO:33). In certain other embodiments, the linker comprises the amino acid sequence VEPKSCDKTHT (SEQ ID NO:34), KVEPKSCDKTHT (SEQ ID NO:35), KKVEPKSCDKTHT (SEQ ID NO:36), DKKVEPKSCDKTHT (SEQ ID NO:37), VDKKVEPKSCDKTHT (SEQ ID NO:38), or KVDKKVEPKSCDKTHT (SEQ ID NO:39). In certain particular embodiments, the linker comprises the amino acid sequence EPKSSDKTHT (SEQ ID NO:40). In certain embodiments, the linker comprises the amino acid sequence VEPKSSDKTHT (SEQ ID NO:67), KVEPKSSDKTHT (SEQ ID NO:68), KKVEPKSSDKTHT (SEQ ID NO:66), DKKVEPKSSDKTHT (SEQ ID NO:64), VDKKVEPKSSDKTHT (SEQ ID NO:69), or KVDKKVEPKSSDKTHT (SEQ ID NO:65). In certain particular embodiments, the linker does not comprise the amino acid sequence of GGS (SEQ ID NO: 45), GGGS (SEQ ID NO:46) or GGGGS (SEQ ID NO:47). In separate embodiments, the IL-22 IgG1 Fc fusion protein comprises a linker sequence of GGGSTHT (SEQ ID NO:63). In other particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:12 or SEQ ID

NO:14. In certain other particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:12.

In certain embodiments, the IL-22 Fc fusion protein comprises the CH2 and CH3 domain of IgG4. In certain other embodiments, the linker comprises the amino acid sequence SKYGPP (SEQ ID NO:43). In certain particular embodiments, the linker comprises the amino acid sequence RVESKYGPP (SEQ ID NO:44). In certain embodiments, none of the linkers comprise the amino acid sequence GGS (SEQ ID NO:45), GGGS (SEQ ID NO:46) or GGGGS (SEQ ID NO:47). In other particular aspects, there is provided an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10. In particular aspects, there is provided an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8. In yet other particular aspects, there is provided an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO: 16. In another embodiment, the IL-22 Fc fusion protein is produced by the method comprising the step of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein. In certain embodiments, the IL-22 Fc fusion protein is produced by the method that further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium. In certain embodiments, the host cell is a Chinese hamster ovary (CHO) cell. In certain other embodiments, the host cell is an *E. coli* cell.

In yet another embodiment, there is provided a composition comprising an IL-22 Fc fusion protein, said IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, and wherein the composition has an afucosylation level in the CH2 domain of no more than 5%. In certain embodiments, the afucosylation level is no more than 2%, more preferably less than 1%. In certain embodiments, the afucosylation level is measured by mass spectrometry. In certain embodiments, the Fc region comprises the CH2 and CH3 domain of IgG4. In certain embodiments, the Fc region comprises a CH2 and CH3 domain of IgG1. In certain other embodiments, the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31). In certain embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26. In certain embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24. In certain embodiments, the composition is produced by the process comprising the steps of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein, and obtaining the IL-22 Fc fusion protein from the cell culture or culture medium, wherein the composition has an afucosylation level in the CH2 domain of the Fc region of no more than 5%. In certain embodiments, the afucosylation level is no more than 2%, more preferably less than 1%. In certain embodiments, the IL-22 Fc fusion protein is

sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13; SEQ ID NO:23 or SEQ ID NO:25, wherein the isolated nucleic acid is capable of encoding an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8, 10, 12, or 14. In another aspect, there is provided a vector comprising the nucleic acid described herein. In yet another aspect, there is provided a host cell comprising the vector described herein. In certain embodiments, the host cell is a prokaryotic cell or eukaryotic cell. In certain particular embodiments, the host cell is a prokaryotic cell, including without limitation, an *E. coli* cell. In certain other embodiments, the host cell is a eukaryotic cell, including without limitation, a CHO cell. In certain embodiments, the host cell comprises a vector comprising a nucleic acid encoding the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

In a further related aspect, there is provided a method of making an IL-22 Fc fusion protein comprising the step of culturing the host cell described herein under conditions suitable for expression of the IL-22 Fc fusion protein. In certain embodiments, the method further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium. The IL-22 Fc fusion protein can be obtained from the cell culture or culture medium by any methods of protein isolation or purification known in the art, including without limitation, collecting culture medium, freezing/thawing, centrifugation, cell lysis, homogenization, ammonium sulfate precipitation, HPLC, and affinity, gel filtration, and ion exchanger column chromatography. In certain embodiments, the method further comprises the step of removing afucosylated IL-22 Fc fusion protein. In certain other embodiments, the afucosylated IL-22 Fc fusion protein is removed by affinity column chromatography. In certain embodiments, the host cell is an *E. coli* cell. In other embodiments, the host cell is a CHO cell.

In yet another aspect, there is provided a pharmaceutical composition comprising the IL-22 Fc fusion protein described herein and at least one pharmaceutically acceptable carrier. In certain embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:24, or SEQ ID NO:26. In other embodiments, the Fc region of the IL-22 Fc fusion protein is not glycosylated. In certain embodiments, the Fc region of the IL-22 Fc fusion protein is not glycosylated while the IL-22 polypeptide is glycosylated. In certan such embodiments, the IL-22 Fc fusion protein is produced in CHO cells. In certain embodiments, the IL-22 Fc fusion protein does not induce antibody dependent cellular cytotoxicity. In yet other embodiments, the pharmaceutical composition further comprises dexamethasone or a TNF antagonist. In certain particular embodiments, the dexamethasone or a TNF antagonist is present at a suboptimal amount.

In certain other embodiments, the pharmaceutical composition comprising IL-22 Fc fusion proteins has an afucosylation level in the CH2 domain of no more than 5%, preferably no more than 2%, more preferably less than 1%. In certain particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26, preferably SEQ ID NO:24. In certain other embodiments, the IL-22 Fc fusion protein is produced in CHO cells. In certain particular embodiments, the subject is a human. In certain embodiments, the pharmaceutical composition is administered systematically or topically. In certain other embodiments, the pharmaceutical composition is administered intravenously, subcutaneously, intraperitoneally or topically.

Disclosed is a pharmaceutical composition comprising an IL-22 polypeptide or IL-22 Fc fusion protein described herein and at least one pharmaceutically acceptable carrier. In one aspect, there is provided a pharmaceutical composition comprising the IL-22 Fc fusion protein as described herein and at least one pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier is a gelling agent. In certain embodiments, the gelling agent is a polysaccharide. In some embodiments, the gelling agent is, without limitation, methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, POE-POP block polymers, alginate, hyaluronic acid, polyacrylic acid, hydroxyethyl methylcellulose or hydroxypropyl methylcellulose. In some embodiments, the polysaccharide is a cellulosic agent such as, without limitation, hydroxyethyl methylcellulose or hydroxypropyl methylcellulose. In certain embodiments, the gelling agent is hydroxypropyl methylcellulose. In some embodiments, the pharmaceutical composition is for topical administration. In certain embodiments, the pharmaceutical composition for topical administration comprises an IL-22 polypeptide. In some embodiments, the pharmaceutical composition for topical administration comprises an IL-22 Fc fusion protein. In certain embodiments, the pharmaceutical composition for topical administration comprises an IL-22 polypeptide without an Fc fusion.

In another aspect, there is provided use of the pharmaceutical composition described herein in the manufacture of a medicament for treating inflammatory bowel disease (IBD) in a subject in need thereof. Disclosed is use of a pharmaceutical composition comprising IL-22 Fc fusion proteins described herein in the manufacture of a medicament for treating IBD in a patient. In one aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for treating IBD in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8. In another aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for treating IBD in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10. Also disclosed are methods of treating IBD in a subject in need thereof comprising administering to the subject the pharmaceutical composition comprising an IL-22 Fc fusion protein of the disclosure. In certain embodiments, the IBD is ulcerative colitis. In

SEQ ID NO:14, preferably SEQ ID NO:8. In certain embodiments, the IL-22 Fc fusion protein is produced in E. coli or a CHO cell. In certain embodiments, the subject is a human. In certain other embodiments, the pharmaceutical composition is administered intravenously, subcutaneously, intraperitoneally or topically.

In certain embodiments, the disclosure provides methods of treating any one or combination of the following diseases using an IL-22 polypeptide or an IL-22 Fc fusion protein of this disclosure: Type II diabetes, Type II diabetes with morbid obesity, wounds (including diabetic wounds and diabetic ulcers), burns, ulcers (including pressure ulcer and venous ulcer), graft versus host disease (GVHD), atherosclerosis, cardiovascular disease, metabolic syndrome, endotoxemia (acute and mild), sepsis, acute coronary heart disease, hypertension, dyslipemia, obesity, hyperglycemia, lipid metabolism disorders, hepatitis, acute hepatitis, renal failure, acute renal failure, acute kidney injury, renal draft failure, post cadaveric renal transplant delayed graft function, contrast induced nephropathy, pancreatitis, acute pancreatitis, liver fibrosis and lung fibrosis. In certain embodiments, acute pancreatitis can be mild to moderate to severe disease. In certain embodiments, acute pancreatitis includes disease post ERCP (endoscopic retrograde cholangiopancreatography). In some further embodiments, the patient to be treated for the above disease is in need of a change in his HDL/LDL lipid profile, which IL-22 polypeptide or IL-22 Fc fusion proteins can alter in the patient to increase HDL and decrease LDL. In certain other embodiments, the disclosure provides uses of an IL-22 polypeptide or an IL-22 Fc fusion protein in the preparation of a medicament for the treatment of any one or combinations of the above diseases.

In a further aspect, there is provided use of the pharmaceutical composition described herein in the manufacture of a medicament for inhibiting microbial infection in the intestine, preserving goblet cells in the intestine during a microbial infection, enhancing epithelial cell integrity during a microbial infection, enhancing epithelial cell proliferation during a microbial infection, enhancing epithelial cell differentiation during a microbial infection, enhancing epithelial cell migration during a microbial infection, or enhancing epithelial wound healing in the intestine during a microbial infection, of a subject in need thereof. Also disclosed are methods of inhibiting microbial infection in the intestine, or preserving goblet cells in the intestine during a microbial infection, of a subject in need thereof comprising the step of administering to the subject the pharmaceutical composition comprising the IL-22 Fc fusion protein of the disclosure. In certain embodiments, the disclosure provides methods of enhancing epithelial cell integrity, mucosal healing, epithelial cell proliferation, epithelial cell differentiation, epithelial cell migration or epithelial wound healing in the intestine in a subject in need thereof comprising administering to the subject the

pharmaceutical composition comprising the IL-22 Fc fusion protein of the disclosure. In certain embodiments, the epithelial cell is intestinal epithelial cell.

In one aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for inhibiting microbial infection in the intestine, preserving goblet cells in the intestine during a microbial infection, enhancing epithelial cell integrity during a microbial infection, enhancing epithelial cell proliferation during a microbial infection, enhancing epithelial cell differentiation during a microbial infection, enhancing epithelial cell migration during a microbial infection, or enhancing epithelial wound healing in the intestine during a microbial infection, of a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.

In one aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for inhibiting microbial infection in the intestine, preserving goblet cells in the intestine during a microbial infection, enhancing epithelial cell integrity during a microbial infection, enhancing epithelial cell proliferation during a microbial infection, enhancing epithelial cell differentiation during a microbial infection, enhancing epithelial cell migration during a microbial infection, or enhancing epithelial wound healing in the intestine during a microbial infection, of a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.

In another aspect, there is provided use of a pharmaceutical composition described herein in the manufacture of a medicament for preventing or treating a cardiovascular condition in a subject in need thereof, which condition includes a pathology of atherosclerotic plaque formation. Disclosed is use of a pharmaceutical composition comprising an IL-22 polypeptide or an IL-22 Fc fusion protein described herein in the manufacture of a medicament for preventing or treating a cardiovascular condition, which condition includes a pathology of atherosclerotic plaque formation. In one aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating a cardiovascular condition in a subject in need thereof, which condition includes a pathology of atherosclerotic plaque formation, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8. In another aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating a cardiovascular condition in a subject in need thereof, which condition includes a pathology of atherosclerotic plaque formation, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc protein that comprises the amino acid sequence of SEQ ID NO:10. Also disclosed is a method for preventing or treating a cardiovascular condition, which condition includes a pathology of atherosclerotic plaque formation, is provided. The method includes administering to a subject in need thereof a therapeutically effective amount of an IL-22 polypeptide or an IL-22 Fc fusion protein. The cardiovascular condition includes, for

example, coronary artery disease, coronary microvascular disease, stroke, carotid artery disease, peripheral arterial disease, and chronic kidney disease. The method can include further slowing down the progression of atherosclerotic plaque formation. The method can further include administering one or more additional therapeutic agent to the subject for the prevention or treatment of the cardiovascular condition.

In another aspect, there is provided use of a pharmaceutical composition described herein in the manufacture of a medicament for treating metabolic syndrome in a subject in need thereof. Disclosed is use of a pharmaceutical composition comprising an IL-22 Fc fusion protein described herein in the manufacture of a medicament for treating metabolic syndrome. In one aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for treating metabolic syndrome in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8. In another aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for treating metabolic syndrome in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10. Also disclosed is a method for treating metabolic syndrome is provided. The method includes administering to a subject in need thereof a therapeutically effective amount of an IL-22 polypeptide or an IL-22 Fc fusion protein. The method can further include reducing one or more risk factors associated with metabolic syndrome, including one or more of abdominal obesity, hyperglycemia, dyslipidemia, and hypertension. The method can further include reducing the level of bacterial lipopolysaccharide (LPS) in the subject. The method can further include administering one or more additional agent to the subject for the prevention or treatment of metabolic syndrome.

In certain embodiments, a method for delaying or slowing down the progression of atherosclerosis is provided. The method includes administering to a subject in need thereof a therapeutically effective amount of an IL-22 polypeptide or an IL-22 Fc fusion protein. The method can further include administering one or more additional agent to the subject for delaying or slowing down the progression of atherosclerosis.

In certain embodiments, a method of preventing indicia of atherosclerosis is provided. The method includes administering a therapeutically effective amount of an IL-22 polypeptide or an IL-22 Fc fusion protein to a subject at risk of atherosclerosis, wherein the IL-22 polypeptide of IL-22 Fc fusion protein is effective against the development of indicia of atherosclerosis. In certain embodiments, the subject has been identified to be at risk to develop a cardiovascular condition. In certain embodiments, the subject is genetically at risk of developing a cardiovascular condition. In one or more embodiments, the indicia of atherosclerosis include plaque accumulation. In some embodiments, the indicia of atherosclerosis include vascular inflammation. The method can further include administering one or more additional agent to the subject for preventing indicia of atherosclerosis.

In another aspect, there is provided use of a pharmaceutical composition described herein in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both, in a subject in need thereof. Disclosed is use of a pharmaceutical composition comprising an IL-22 Fc fusion protein described herein in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both. In one aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both, in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8. In another aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both, in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10. Also disclosed is a method of treating one or more of acute endotoxemia and sepsis is provided. The method includes administering to a subject in need thereof a therapeutically effective amount of an IL-22 polypeptide or an IL-22 Fc fusion protein. The method can further include administering one or more additional agent to the subject for treating one or more of acute endotoxemia and sepsis.

In one other aspect, there is provided use of a pharmaceutical composition described herein in the manufacture of a medicament for accelerating or improving wound healing in a subject in need thereof. Disclosed is use of a pharmaceutical composition comprising an IL-22 polypeptide, or an IL-22 Fc fusion protein described herein in the manufacture of a medicament for accelerating or improving wound healing in a subject. In one aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for accelerating or improving wound healing in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8. In another aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for accelerating or improving wound healing in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10. Also disclosed is a method for accelerating or improving wound healing, or both, in a subject. The method includes administering to a subject in need thereof a therapeutically effective amount of an IL-22 polypeptide, an IL-22 Fc fusion protein or an IL-22 agonist. In certain embodiments, the wound is a chronic wound. In certain other embodiments, the wound is an infected wound. In certain embodiments, the subject is diabetic, including a subject with type II diabetes. In one or more embodiments, the wound is a diabetic foot ulcer. In certain embodiments, the therapeutically effective amount of an IL-22 polypeptide, IL-22 Fc fusion protein or IL-22 agonist is administered until there is complete wound closure. In some embodiments, the administration is systemic; and in other embodiments, the administration is topical. In certain embodiments, the IL-22 polypeptide, IL-22 Fc fusion protein or IL-22 agonist is in a formulation for topical administration. In certain embodiments, the topical formulation comprises an IL-22 polypeptide without an Fc fusion. In certain embodiments, the IL22 agonist is selected from the group consisting of an IL-22 polypeptide, an IL-22 Fc fusion protein, an IL-22 agonist, an IL-19 polypeptide, an IL-19 Fc fusion protein, an IL-19 agonist, an IL-20 polypeptide, an IL-20 Fc fusion protein, an IL-20 agonist, an IL-24 polypeptide, an IL-24 Fc fusion protein, an IL-24 agonist, an IL-26 polypeptide, an IL-26 Fc fusion protein, an IL-26 agonist, and an IL-22R1 agonist. In certain other embodiments, the IL-22 agonist is selected from the group consisting of an IL-22 polypeptide, an IL-22 Fc fusion protein, an IL-22 agonist, an IL-20 polypeptide, an IL-20 Fc fusion protein, an IL-20 agonist, an IL-24 polypeptide, an IL-24 Fc fusion protein, an IL-24 agonist and an IL-22R1 agonist. In certain embodiments, the IL-22R1 agonist is an anti-IL22R1 agonistic antibody.

In a certain embodiments, the disclosure provides methods of treating a metabolic syndrome comprising the step of administering to a subject in need thereof a therapeutically effective amount of one or more IL-22 agonists. In certain embodiments, the IL22 agonist is selected from the group consisting of an IL-22 polypeptide, an IL-22 Fc fusion protein, an IL-22 agonist, an IL-19 polypeptide, an IL-19 Fc fusion protein, an IL-19 agonist, an IL-20 polypeptide, an IL-20 Fc fusion protein, an IL-20 agonist, an IL-24 polypeptide, an IL-24 Fc fusion protein, an IL-24 agonist, an IL-26 polypeptide, an IL-26 Fc fusion protein, an IL-26

According to another embodiment, the subject is administered an IL-22 Fc fusion protein of the disclosure. In certain embodiments, the subject is a human. In certain embodiments, the IL-22 polypeptide or IL22 Fc fusion protein is administered intravenously, subcutaneously, intraperitoneally, systemically or topically.

In certain embodiments of these aspects, the Fc region of the IL-22 Fc fusion protein is not glycosylated. In certain embodiments, the N297 residue and/or the T299 residue of the Fc region is changed. In certain embodiments, the N297 residue of the Fc region is changed. In certain other embodiments, the N297 residue is changed to Gly or Ala, preferably Gly. In certain other embodiments, the T299 residue is changed, preferably to Val, Gly or Ala. In certain particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12 or EQ ID NO:14, preferably SEQ ID NO:8. In certain embodiments, the IL-22 Fc fusion protein is produced in E. coli. In certain embodiments, the subject is a human. In certain other embodiments, the pharmaceutical composition is administered intravenously, subcutaneously or topically.

In certain other embodiments, the pharmaceutical composition comprising IL-22 Fc fusion proteins has an afucosylation level in the CH2 domain of no more than 5%, preferably no more than 2%, more preferably less than 1%. In certain particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26, preferably SEQ ID NO:24. In certain other embodiments, the IL-22 Fc fusion protein is produced in CHO cells. In certain particular embodiments, the subject is a human. In certain other embodiments, the pharmaceutical composition is administered intravenously, subcutaneously or topically.

In yet other embodiments, the N-glycan attached to the Fc region of the IL-22 Fc fusion protein is enzymatically removed by a glycolytic enzyme. In certain embodiments, the glycolytic enzyme is peptide-N-glycosidase (PNGase). In certain particular embodiments, the subject is a human.

In a further aspect, there is provided use of the pharmaceutical composition described herein in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof. Disclosed is use of a pharmaceutical composition comprising IL-22 Fc fusion proteins described herein in the manufacture of a medicament for treating acute pancreatitis in a patient. In one aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8. In another aspect, there is provided use of a pharmaceutical composition in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.

WHAT IS CLAIMED IS:

1. An interleukin (IL)-22 Fc fusion protein that binds to IL-22 receptor, said IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, wherein the IL-22 Fc fusion protein comprises an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8, and wherein the Fc region is not glycosylated.

2. The IL-22 Fc fusion protein of claim 1, wherein the amino acid sequence has at least 96% sequence identity to the amino acid sequence of SEQ ID NO:8.

3. The IL-22 Fc fusion protein of claim 1 or 2, wherein the amino acid sequence has at least 97% sequence identity to the amino acid sequence of SEQ ID NO:8.

4. The IL-22 Fc fusion protein of any one of claims 1-3, wherein the amino acid sequence has at least 98% sequence identity to the amino acid sequence of SEQ ID NO:8.

5. The IL-22 Fc fusion protein of any one of claims 1-4, wherein the amino acid sequence has at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8.

6. An IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an IgG4 Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG4 CH2 domain and an IgG4 CH3 domain, and wherein the Fc region is not glycosylated.

7. The IL-22 Fc fusion protein of any one of claims 1-6, wherein the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31).

8. The IL-22 Fc fusion protein of any one of claims 1-7, wherein the Fc region comprises an altered glycosylation consensus site.

9. The IL-22 Fc fusion protein of any one of claims 1-8, wherein the Fc region comprises an insertion, a deletion, or a substitution mutation that results in an aglycosylated Fc region.

10. The IL-22 Fc fusion protein of any one of claims 1-9, wherein the amino acid residue at position 297 as in the EU index of the Fc region is changed and/or the amino acid residue at position 299 as in the EU index of the Fc region is changed;

wherein optionally the amino acid residue at position 297 as in the EU index of the Fc region is Gly, Ala, Gln, Asp, or Glu;

wherein optionally the amino acid residue at position 297 as in the EU index of the Fc region is Gly or Ala;

wherein optionally the amino acid residue at position 297 as in the EU index of the Fc region is Gly; or

wherein optionally the amino acid residue at position 299 as in the EU index of the Fc region is Ala, Gly, or Val.

11. The IL-22 Fc fusion protein of any one of claims 1-5, wherein the Fc region comprises the CH2 and CH3 domain of IgG4.

12. The IL-22 Fc fusion protein of any one of claims 1-11, wherein the linker comprises the amino acid sequence SKYGPP (SEQ ID NO:43).

13. The IL-22 Fc fusion protein of any one of claims 1-11, wherein the linker comprises the amino acid sequence RVESKYGPP (SEQ ID NO:44).

14. An IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.

15. An IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.

16. An IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:16.

17. The IL-22 Fc fusion protein of any one of claims 1-16, wherein the Fc region is not N-glycosylated.

18. The IL-22 Fc fusion protein of any one of claims 1-17, wherein the IL-22 Fc fusion protein is a dimeric IL-22 Fc fusion protein.

19. The IL-22 Fc fusion protein of any one of claims 1-17, wherein the IL-22 Fc fusion protein is a monomeric IL-22 Fc fusion protein.

20. The IL-22 Fc fusion protein of any one of claims 1-13, wherein the IL-22 polypeptide comprises the amino acid sequence of SEQ ID NO:4.

21. The IL-22 Fc fusion protein of any one of claims 1-20, wherein the IL-22 polypeptide is a human IL-22 polypeptide.

22. The IL-22 Fc fusion protein of any one of claims 1-21, wherein the IL-22 receptor is a human IL-22 receptor.

23. An isolated nucleic acid encoding the IL-22 Fc fusion protein of any one of claims 1-22.

24. The isolated nucleic acid of claim 23, wherein the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

25. The isolated nucleic acid of claim 23, wherein the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:10.

26. The isolated nucleic acid of claim 23 or 24, comprising the polynucleotide sequence of SEQ ID NO:7.

27. The isolated nucleic acid of claim 23 or 25, comprising the polynucleotide sequence of SEQ ID NO:9.

28. A vector comprising the nucleic acid of any one of claims 23-27.

29. A host cell comprising the vector of claim 28.

30. The host cell of claim 29, wherein the host cell is a prokaryotic cell or eukaryotic cell;

wherein optionally the host cell is an *E. coli* cell or a CHO cell.

31. A method of making an IL-22 Fc fusion protein comprising the step of culturing the host cell of claim 29 or 30 under conditions suitable for expression of the IL-22 Fc fusion protein.

32. The method of claim 31, further comprising the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium;

wherein optionally the method further comprises the step of removing afucosylated IL-22 Fc fusion protein;

wherein optionally the afucosylated IL-22 Fc fusion protein is removed by affinity column chromatography.

33. The method of claim 31 or 32, wherein the host cell is selected from the group consisting of (a) an *E. coli* cell, and

(b) a CHO cell.

34. A pharmaceutical composition comprising the IL-22 Fc fusion protein according to any one of claims 1-22 and at least one pharmaceutically acceptable carrier.

35. The pharmaceutical composition of claim 34, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

36. The pharmaceutical composition of claim 34, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:10.

37. The pharmaceutical composition of claim 34, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:16.

38. The pharmaceutical composition of claim 34, wherein the pharmaceutical composition comprises a therapeutically effective amount of the IL-22 Fc fusion protein.

39. The pharmaceutical composition of any one of claims 34-38, further comprising an additional therapeutic agent.

40. A pharmaceutical composition comprising the IL-22 Fc fusion protein of any one of claims 1-22 and at least one pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier is a gelling agent.

41. The pharmaceutical composition of claim 40, wherein the gelling agent is a polysaccharide;

wherein optionally the gelling agent is a cellulosic agent;

wherein optionally the gelling agent is methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, POE-POP block polymers, alginate, hyaluronic acid, polyacrylic acid, hydroxyethyl methylcellulose or hydroxypropyl methylcellulose; or

wherein optionally the gelling agent is hydroxypropyl methylcellulose.

42. The pharmaceutical composition of claim 40 or 41, wherein the pharmaceutical composition is for topical administration.

43. Use of the pharmaceutical composition of any one of claims 34-39 in the manufacture of a medicament for treating inflammatory bowel disease (IBD) in a subject in need thereof.

44. Use of a pharmaceutical composition in the manufacture of a medicament for treating IBD in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.
45. Use of a pharmaceutical composition in the manufacture of a medicament for treating IBD in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.
46. The use of any one of claims 43-45, wherein the subject is a patient.
47. The use of any one of claims 43-46, wherein the IBD is ulcerative colitis.
48. The use of any one of claims 43-46, wherein the IBD is Crohn's disease.
49. The use of any one of claims 43-48, wherein the subject is to be administered at least one additional therapeutic agent;
wherein optionally the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.
50. Use of the pharmaceutical composition of any one of claims 34-39 in the manufacture of a medicament for inhibiting microbial infection in the intestine, preserving goblet cells in the intestine during a microbial infection, enhancing epithelial cell integrity during a microbial infection, enhancing epithelial cell proliferation during a microbial infection, enhancing epithelial cell differentiation during a microbial infection, enhancing epithelial cell migration during a microbial infection, or enhancing epithelial wound healing in the intestine during a microbial infection, of a subject in need thereof.
51. Use of a pharmaceutical composition in the manufacture of a medicament for inhibiting microbial infection in the intestine, preserving goblet cells in the intestine during a microbial infection, enhancing epithelial cell integrity during a microbial infection, enhancing epithelial cell proliferation during a microbial infection, enhancing epithelial cell differentiation during a microbial infection, enhancing epithelial cell migration during a microbial infection, or enhancing epithelial wound healing in the intestine during a microbial infection, of a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.
52. Use of a pharmaceutical composition in the manufacture of a medicament for inhibiting microbial infection in the intestine, preserving goblet cells in the intestine during a microbial infection, enhancing epithelial cell integrity during a microbial infection, enhancing epithelial cell proliferation during a microbial infection, enhancing epithelial cell differentiation during a microbial infection, enhancing epithelial cell migration during a microbial infection, or enhancing epithelial wound healing in the intestine during a microbial infection, of a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.
53. The use of any one of claims 50-52, wherein the epithelial cell is intestinal epithelial cell.
54. The use of any one of claims 50-53, wherein the subject is to be administered at least one additional therapeutic agent;
wherein optionally the pharmaceutical composition is to be administered intravenously, intraperitoneally or subcutaneously.
55. Use of the pharmaceutical composition of any one of claims 34-39 in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof.

56. Use of a pharmaceutical composition in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.
57. Use of a pharmaceutical composition in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.
58. The use of any one of claims 55-57, wherein the subject is a patient.
59. The use of any one of claims 55-58, wherein the subject is to be administered at least one additional therapeutic agent;
wherein optionally the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.
60. Use of a pharmaceutical composition of any one of claims 34-42 in the manufacture of a medicament for accelerating or improving wound healing in a subject in need thereof.
61. Use of a pharmaceutical composition in the manufacture of a medicament for accelerating or improving wound healing in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.
62. Use of a pharmaceutical composition in the manufacture of a medicament for accelerating or improving wound healing in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.
63. The use of any one of claims 60-62, wherein the subject is a patient.
64. The use of any one of claims 60-63, wherein the wound is a chronic wound or an infected wound.
65. The use of any one of claims 60-64, wherein the subject is diabetic;
wherein optionally the diabetic subject has type II diabetes.
66. The use of any one of claims 60-65, wherein the wound is a diabetic foot ulcer.
67. The use of any one of claims 60-66, wherein the pharmaceutical composition is to be administered until there is complete wound closure.
68. The use of any one of claims 60-67, wherein the subject is to be administered at least one additional therapeutic agent for accelerating or improving wound healing;

wherein optionally the pharmaceutical composition is to be administered intravenously, subcutaneously, intraperitoneally or topically.

69. Use of a pharmaceutical composition of any one of claims 34-39 in the manufacture of a medicament for preventing or treating a cardiovascular condition in a subject in need thereof, which condition includes a pathology of atherosclerotic plaque formation.
70. Use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating a cardiovascular condition in a subject in need thereof, which condition includes a pathology of atherosclerotic plaque formation, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.
71. Use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating a cardiovascular condition in a subject in need thereof, which condition includes a pathology of atherosclerotic plaque formation, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc protein that comprises the amino acid sequence of SEQ ID NO:10.
72. The use of any one of claims 69-71, wherein the subject is a patient.
73. The use of any one of claims 69-72, wherein the cardiovascular condition is selected from the group consisting of coronary artery disease, coronary microvascular disease, stroke, carotid artery disease, peripheral arterial disease, and chronic kidney disease.
74. The use of any one of claims 69-73, further comprising slowing down the progression of atherosclerotic plaque formation or preventing indicia of atherosclerosis;
wherein optionally the indicia of atherosclerosis includes plaque accumulation or vascular inflammation.
75. The use of any one of claims 69-74, wherein the subject is to be administered at least one additional therapeutic agent.
76. The use of any one of claims 69-75, wherein the subject has been identified to be at risk to develop a cardiovascular condition.
77. The use of any one of claims 69-76, wherein the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.
78. Use of a pharmaceutical composition of any one of claims 34-39 in the manufacture of a medicament for treating metabolic syndrome in a subject in need thereof.
79. Use of a pharmaceutical composition in the manufacture of a medicament for treating metabolic syndrome in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.
80. Use of a pharmaceutical composition in the manufacture of a medicament for treating metabolic syndrome in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.
81. The use of any one of claims 78-80, wherein the subject is a patient.
82. The use of any one of claims 78-81, further comprising reducing one or more risk factors associated with metabolic syndrome, including one or more of abdominal obesity, hyperglycemia, dyslipidemia, and hypertension;

wherein optionally the use further comprises reducing the level of bacterial lipopolysaccharide (LPS) in the subject.

83. The use of any one of claims 78-82, wherein the subject is in need of a change in HDL/LDL lipid profile.
84. The use of any one of claims 78-83, wherein the subject is to be administered at least one additional therapeutic agent;
wherein optionally the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.
85. Use of a pharmaceutical composition of any one of claims 34-39 in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both, in a subject in need thereof.
86. Use of a pharmaceutical composition in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both, in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:8.
87. Use of a pharmaceutical composition in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both, in a subject in need thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of an IL-22 Fc fusion protein that comprises the amino acid sequence of SEQ ID NO:10.
88. The use of any one of claims 85-87, wherein the subject is a patient.
89. The use of any one of claims 85-88, wherein the subject is in need of a change in HDL/LDL lipid profile.
90. The use of any one of claims 85-89, wherein the subject is to be administered at least one additional therapeutic agent for treating acute endotoxemia, sepsis, or both;
wherein optionally the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.
91. The use of any one of claims 43-90, wherein the pharmaceutical composition is to be administered intravenously.
92. The use of any one of claims 43-90, wherein the pharmaceutical composition is to be administered subcutaneously.
93. The use of any one of claims 43-92, wherein the subject is a human.