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 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 ~~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 at amino acid residue N297. 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 at amino acid residue N297. 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 embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8 or SE ID NO:10. In particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8. 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 ~~aspect~~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

region of the IL-22 Fc fusion arm (the monomer IL-22 Fc fusion) comprises a hole and the Fc region of the Fc arm (the monomer Fc without linking to IL-22) comprises a knob. In certain other embodiments, the monomeric IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:61 and SEQ ID NO:62. In certain other embodiments, the Fc region of both arms further comprises an N297G mutation.

In one ~~aspect~~embodiment, there is provided a monomeric IL-22 Fc fusion protein comprising an IL-22 Fc fusion arm comprising the amino acid sequence of SEQ ID NO:61, and an Fc arm comprising the amino acid sequence of SEQ ID NO:62.

In a further ~~aspect~~embodiment, there is provided a method of making the monomeric IL-22 Fc fusion protein described herein, comprising the step of culturing one or more host cells comprising one or more nucleic acid molecules capable of expressing IL-22 Fc arm comprising the amino acid sequence of SEQ ID NO:61 and the Fc arm comprising the amino acid sequence of SEQ ID NO:62. In certain other embodiments, the method further comprises the step of obtaining the monomeric IL-22 Fc fusion protein from the cell culture or culture medium. In certain embodiments, the host cell is an E. coli cell. In certain embodiments, the disclosureprovides a composition or pharmaceutical composition comprising the monomeric IL-22 Fc fusion protein.

In yet another aspect, there is provided an isolated nucleic acid encoding the IL-22 Fc fusion protein described herein. In certain embodiments, the nucleic acid encodes the IL-22 Fc fusion protein comprising 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, preferably SEQ ID NO:8 or SEQ ID NO:12, more preferably SEQ ID NO:8. In certain other embodiments, the nucleic acid comprises the polynucleotide 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. In certain particular embodiments, the nucleic acid comprises the polynucleotide sequence of SEQ ID NO:7 or SEQ ID NO:11, preferably SEQ ID NO:7. In certain embodiments, the isolated nucleic acid comprises a polynucleotide sequence that is at least 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the polynucleotide 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. In certain embodiments, the isolated nucleic acid comprises a polynucleotide sequence that is at least 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the polynucleotide 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

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 an IL-22 polypeptide or an 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. In yet another aspect, there is provided use of a pharmaceutical composition comprising IL-22 Fc fusion proteins described herein ~~or the compositions described herein~~ in the manufacture of a medicament for treating IBD in a patient. 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 ~~invention~~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, epithelial cell proliferation, epithelial cell differentiation, epithelial cell migration or epithelial wound healing in the intestine, 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 ~~invention~~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 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, which condition includes a pathology of atherosclerotic plaque formation. In yet another aspect, there is provided use of a pharmaceutical composition comprising an IL-22 polypeptide or an IL-22 Fc fusion protein described herein~~, or a composition comprising 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. 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 yet another aspect, there is provided use of a pharmaceutical composition comprising an IL-22 Fc fusion protein described herein ~~or a composition comprises an IL-22 Fc fusion protein described herein~~ in the manufacture of a medicament for treating metabolic syndrome. 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 yet another aspect, there is provided use of a pharmaceutical composition comprising an IL-22 Fc fusion protein described herein ~~or a composition comprising an IL-22 Fc fusion protein described herein~~ in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both. 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 yet another aspect, there is provided use of a pharmaceutical composition comprising an IL-22 polypeptide, or an IL-22 Fc fusion protein described herein ~~or a composition described herein~~ in the manufacture of a medicament for accelerating or improving wound healing in a subject. 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 kidney injury or~~ acute pancreatitis in a subject in need thereof. In yet a further aspect, there is provided use of a pharmaceutical composition comprising IL-22 Fc fusion proteins described herein ~~or the compositions described herein~~ in the manufacture of a medicament for treating ~~acute kidney injury or~~ acute pancreatitis in a patient.

WHAT IS CLAIMED IS:

1. 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% sequence identity to the amino acid sequence of SEQ ID NO:8, and wherein the Fc region is not glycosylated at amino acid residue N297.

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 at amino acid residue N297.

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 in the Fc region the N297 residue is changed and/or the T299 residue is changed;

wherein optionally the N297 residue is changed to Gly, Ala, Gln, Asp, or Glu;

wherein optionally the N297 residue is changed to Gly or Ala;

wherein optionally the N297 residue is changed to Gly;

wherein optionally the T299 residue is changed to Ala, Gly, or Val.

11. The IL-22 Fc fusion protein of any one of claims 1-10, 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. The IL-22 Fc fusion protein of any one of claims 1-13, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

15. The IL-22 Fc fusion protein of any one of claims 1-13, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:10.

16. The IL-22 Fc fusion protein of any one of claims 1-13, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:16.

17. The IL-22 Fc fusion protein of any one of claims 6-16, wherein the IL-22 Fc fusion protein is produced by a 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;

wherein optionally the method further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium;

wherein optionally the host cell is a CHO cell.

18. The IL-22 Fc fusion protein of any one of claims 1-17, wherein the IL-22 fusion protein is selected from the group consisting of (a) a dimeric IL-22 Fc fusion protein, and

(b) a monomeric IL-22 Fc fusion protein.

19. The IL-22 Fc fusion protein of any one of claims 1-18, wherein the IL-22 polypeptide comprises the amino acid sequence of SEQ ID NO:4.

20. An isolated nucleic acid encoding the IL-22 Fc fusion protein of any one of claims 1-19.

21. The isolated nucleic acid of claim 20, wherein the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

22. The isolated nucleic acid of claim 20, wherein the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:10.

23. The isolated nucleic acid of claim 20 or 21, comprising the polynucleotide sequence of SEQ ID NO:7.

24. The isolated nucleic acid of claim 20 or 22, comprising the polynucleotide sequence of SEQ ID NO:9.

25. A vector comprising the nucleic acid of any one of claims 20-24.

26. A host cell comprising the vector of claim 25.

27. The host cell of claim 26, 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.

28. A method of making an IL-22 Fc fusion protein comprising the step of culturing the host cell of claim 26 or 27 under conditions suitable for expression of the IL-22 Fc fusion protein.

29. The method of claim 28, 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.

30. The method of claim 28 or 29, wherein the host cell is selected from the group consisting of (a) an *E. coli* cell, and

(b) a CHO cell.

31. A pharmaceutical composition comprising a therapeutically effective amount of an IL-22 Fc fusion protein according to any one of claims 1-19 and at least one pharmaceutically acceptable carrier.

32. The pharmaceutical composition of claim 31, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

33. The pharmaceutical composition of claim 31, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:10.

34. The pharmaceutical composition of any one of claims 31-33, wherein the IL-22 Fc fusion protein is produced in a CHO cell.

35. The pharmaceutical composition of any one of claims 31-34, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:16.

36. The pharmaceutical composition of any one of claims 31-35, further comprising an additional therapeutic agent.

37. A pharmaceutical composition comprising an IL-22 polypeptide or an IL-22 Fc fusion protein of any one of claims 1-19 and at least one pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier is a gelling agent.

38. The pharmaceutical composition of claim 37, 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;

wherein optionally the gelling agent is hydroxypropyl methylcellulose.

39. The pharmaceutical composition of claim 37 or 38, wherein the pharmaceutical composition is for topical administration.

40. Use of the pharmaceutical composition of any one of claims 31-36 in the manufacture of a medicament for treating inflammatory bowel disease (IBD) in a subject in need thereof.

41. Use of a pharmaceutical composition comprising IL-22 Fc fusion proteins of any one of claims 1-19 in the manufacture of a medicament for treating IBD in a patient.

42. The use of claim 40 or 41, wherein the IBD is ulcerative colitis or Crohn's disease.

43. The use of any one of claims 40-42, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

44. The use of any one of claims 40-42, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:10.

45. The use of any one of claims 40-44, wherein the subject is to be co-administered with at least one additional therapeutic agent;

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

46. Use of the pharmaceutical composition of any one of claims 31-36 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, epithelial cell proliferation, epithelial cell differentiation, epithelial cell migration or epithelial wound healing in the intestine, of a subject in need thereof.

47. The use of claim 46, wherein the epithelial cell is intestinal epithelial cell.

48. The use of claim 46 or 47, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

49. The use of claim 42 or 43, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:10.

50. The use of any one of claims 46-49, wherein the subject is to be co-administered with at least one additional therapeutic agent;

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

51. Use of the pharmaceutical composition of any one of claims 31-36 in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof.

52. Use of a pharmaceutical composition comprising IL-22 Fc fusion proteins of any one of claims 1-19 in the manufacture of a medicament for treating acute pancreatitis in a patient.

53. The use of claim 51 or 52, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

54. The use of claim 51 or 52, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:10.

55. The use of any one of claims 51-54, wherein the subject is to be co-administered with at least one additional therapeutic agent;

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

56. Use of a pharmaceutical composition of any one of claims 31-39 in the manufacture of a medicament for accelerating or improving wound healing in a subject.

57. Use of a pharmaceutical composition comprising an IL-22 polypeptide, or an IL-22 Fc fusion protein of any one of claims 1-19 in the manufacture of a medicament for accelerating or improving wound healing in a subject.

58. The use of claim 56 or 57, wherein the wound is a chronic wound or an infected wound.

59. The use of any one of claims 56-58, wherein the subject is diabetic;

wherein optionally the diabetic subject has type II diabetes.

60. The use of any one of claims 56-59, wherein the wound is a diabetic foot ulcer.

61. The use of any one of claims 56-60, wherein the pharmaceutical composition is to be administered until there is complete wound closure.

62. The use of any one of claims 56-61, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

63. The use of any one of claims 56-61, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:10.

64. The use of any one of claims 56-63, wherein the subject is to be co-administered with 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.

65. Use of a pharmaceutical composition of any one of claims 31-36 in the manufacture of a medicament for preventing or treating a cardiovascular condition, which condition includes a pathology of atherosclerotic plaque formation.

66. Use of a pharmaceutical composition comprising an IL-22 polypeptide or an IL-22 Fc fusion protein of any one of claims 1-19 in the manufacture of a medicament for preventing or treating a cardiovascular condition, which condition includes a pathology of atherosclerotic plaque formation.

67. The use of claim 65 or 66, 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.

68. The use of claim 65 or 66, 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.

69. The use of any one of claims 65-68, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

70. The use of any one of claims 65-68, wherein the IL-22 Fc protein comprises the amino acid sequence of SEQ ID NO:10.

71. The use of any one of claims 65-70, wherein the subject is to be co-administered with at least one additional therapeutic agent.

72. The use of claim 65 or 66, wherein the subject has been identified to be at risk to develop a cardiovascular condition.

73. The use of any one of claims 65-72, wherein the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.

74. Use of a pharmaceutical composition of any one of claims 31-36 in the manufacture of a medicament for treating metabolic syndrome.

75. Use of a pharmaceutical composition comprising an IL-22 Fc fusion protein of any one of claims 1-19 in the manufacture of a medicament for treating metabolic syndrome.

76. The use of claim 74 or 75, 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.

77. The use of any one of claims 74-76, wherein the subject is in need of a change in HDL/LDL lipid profile.
78. The use of any one of claims 74-77, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.
79. The use of any one of claims 74-77, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:10.
80. The use of any one of claims 74-79, wherein the subject is to be co-administered with at least one additional therapeutic agent;
    wherein optionally the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.
81. Use of a pharmaceutical composition of any one of claims 31-36 in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both.
82. Use of a pharmaceutical composition comprising an IL-22 Fc fusion protein of any one of claims 1-19 in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both.
83. The use of claim 81 or 82, wherein the subject is in need of a change in HDL/LDL lipid profile.
84. The use of any one of claims 80-83, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.
85. The use of any one of claims 80-83, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:10.
86. The use of any one of claims 80-85, wherein the subject is to be co-administered with 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.
87. The use of any one of claims 40-86, wherein the subject is a human.

WHAT IS CLAIMED IS:

1. 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% 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.

2. The IL-22 Fc fusion protein of claim 1, wherein the amino acid sequence has at least 96%, at least 97%, at least 98%, or 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;

   wherein optionally the amino acid sequence has 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;

   wherein optionally the amino acid sequence has at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12;

   wherein optionally the amino acid sequence has at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8, or

   the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12;

   wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

3. The IL-22 Fc fusion protein of claim 1 or 2, wherein the IL-22 Fc fusion protein is produced by the process 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;

   wherein optionally the process further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium;

wherein optionally the host cell is a CHO cell.

4. An IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an IgG 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 Fc region is not glycosylated.

5. The IL-22 Fc fusion protein of claim 4, wherein the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31).

6. The IL-22 Fc fusion protein of claim 4 or 5, wherein in the Fc region the N297 residue is changed and/or the T299 residue is changed;

   wherein optionally the N297 residue is changed to Gly or Ala;

   wherein optionally the N297 residue is changed to Gly;

   wherein optionally the T299 residue is changed to Ala, Gly or Val.

7. The IL-22 Fc fusion protein of any one of claims 4-6, wherein the linker is 8-20 amino acids long;

   wherein optionally the linker is 8-16 amino acids long, or

   10-16 amino acids long.

8. The IL-22 Fc fusion protein of any one of claims 4-7, wherein the Fc region comprises the CH2 and CH3 domain of IgG1.

9. The IL-22 Fc fusion protein of claim 8, wherein the linker comprises the amino acid sequence DKTHT (SEQ ID NO:32);

   wherein optionally the linker is at least 11 amino acids long and comprises the amino acid sequence EPKSCDKTHT (SEQ ID NO:33);

   wherein optionally 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).

10. The IL-22 Fc fusion protein of any one of claims 4-9, wherein the linker comprises the amino acid sequence EPKSSDKTHT (SEQ ID NO:40);

wherein optionally 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).

11. The IL-22 Fc fusion protein of claim 4 or 9, wherein the linker does not comprise the amino acid sequence GGS (SEQ ID NO:45).

12. The IL-22 Fc fusion protein of any one of claims 4- 11 comprising the amino acid sequence of SEQ ID NO:12 or SEQ ID NO:14;

wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:12.

13. The IL-22 Fc fusion protein of any one of claims 4-7, wherein the Fc region comprises the CH2 and CH3 domain of IgG4;

wherein optionally the linker comprises the amino acid sequence SKYGPP (SEQ ID NO:43);

wherein optionally the linker comprises the amino acid sequence RVESKYGPP (SEQ ID NO:44).

14. The IL-22 Fc fusion protein of any one of claims 4-7 and 13 comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:10;

wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

15. The IL-22 Fc fusion protein of any one of claims 4-14 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;

wherein optionally the method further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium;

wherein optionally the host cell is a CHO cell.

16. The IL-22 Fc fusion protein of any one of claims 1-15, wherein the IL-22 fusion protein is selected from the group consisting of (a) a dimeric IL-22 Fc fusion protein, and

(b) a monomeric IL-22 Fc fusion protein.

17. The IL-22 Fc fusion protein of any one of claims 1-16, wherein the IL-22 polypeptide comprises the amino acid sequence of SEQ ID NO:4.

18. A monomeric IL-22 Fc fusion protein comprising an IL-22 Fc fusion arm comprising the amino acid sequence of SEQ ID NO:61, and an Fc arm comprising the amino acid sequence of SEQ ID NO:62.

19. The monomeric IL-22 Fc fusion protein of claim 18 produced by the process comprising the step of culturing one or more host cells comprising one or more nucleic acid molecules capable of expressing the IL-22 Fc fusion arm comprising the amino acid sequence of SEQ ID NO:61 and the Fc arm comprising the amino acid sequence of SEQ ID NO:62;

wherein optionally the method further comprises the step of obtaining the monomeric IL-22 Fc fusion protein from the cell culture or culture medium;

wherein optionally the one or more host cells are E. coli cells or CHO cells.

20. A method of making the monomeric IL-22 Fc fusion protein of any one of claims 18-19, comprising the step of culturing one or more host cells comprising one or more nucleic acid molecules capable of expressing the IL-22 Fc arm comprising the amino acid sequence of SEQ ID NO:61 and the Fc arm comprising the amino acid sequence of SEQ ID NO:62.

21. The method of claim 20 further comprising the step of obtaining the monomeric IL-22 Fc fusion protein from the cell culture or culture medium;

wherein optionally the one or more host cells are E. coli cells.

22. 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%.

23. The composition of claim 22 wherein the afucosylation level is no more than 2%;

wherein optionally the afucosylation level is less than 1%;

wherein optionally the afucosylation level is measured by mass spectrometry.

24. The composition of any one of claims 22-23, wherein the Fc region comprises the CH2 and CH3 domain of IgG1 or IgG4;

wherein optionally the Fc region is selected from the group consisting of (a) a Fc region comprising the CH2 and CH3 domain of IgG1, and

(b) a Fc region comprising the CH2 and CH3 domain of IgG4.

25. The composition of any one of claims 22-24, wherein the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31).

26. The composition of claim 24, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26;

wherein optionally the IL-22 Fc fusion protein comprises an amino acid sequence selected from the group consisting of (a) the amino acid sequence of SEQ ID NO:24, and

(b) the amino acid sequence of SEQ ID NO:26.

27. The composition of any one of claims 22-26, wherein 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%.

28. The composition of claim 27 wherein the afucosylation level is no more than 2%;

wherein optionally the afucosylation level is less than 1%.

29. The composition of any one of claims 27-28 wherein the IL-22 Fc fusion protein is obtained by purification;

wherein optionally the IL-22 Fc fusion protein is purified by affinity chromatography.

30. The composition of any one of claims 27-29 wherein the host cell is a CHO cell.

31. The composition of any one of claims 22-30 wherein the IL-22 polypeptide comprises the amino acid sequence of SEQ ID NO:4.

32. An isolated nucleic acid encoding the IL-22 Fc fusion protein of any one of claims 1-19 and 22-31.

33. The isolated nucleic acid of claim 32, wherein the nucleic acid encodes the IL-22 Fc fusion protein comprising 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;

wherein optionally the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12;

wherein optionally the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

34. The isolated nucleic acid of any one of claims 32-33 comprising the polynucleotide 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 optionally the isolated nucleic acid comprises the polynucleotide sequence of SEQ ID NO:7 or SEQ ID NO:11;

wherein optionally the isolated nucleic acid comprises the polynucleotide sequence of SEQ ID NO:7.

35. A vector comprising the nucleic acid of any one of claims 32-34.

36. A host cell comprising the vector of claim 35.

37. The host cell of claim 36, 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.

38. A method of making an IL-22 Fc fusion protein comprising the step of culturing the host cell of any one of claims 36-37 under conditions suitable for expression of the IL-22 Fc fusion protein.

39. The method of claim 38, 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.

40. The method of claim 38 or 39, wherein the host cell is selected from the group consisting of (a) an *E. coli* cell, and

(b) a CHO cell.

41. A pharmaceutical composition comprising a therapeutically effective amount of an IL-22 Fc fusion protein according to any one of claims 1-19 and 22-31 and at least one pharmaceutically acceptable carrier.

42. The pharmaceutical composition of claim 41, wherein 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;

wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12.

wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

43. The pharmaceutical composition of any one of claims 41-42, wherein the IL-22 Fc fusion protein is produced in a CHO cell.

44. The pharmaceutical composition of any one of claims 41-43, wherein the Fc region of the IL-22 Fc fusion protein is not glycosylated.

45. The pharmaceutical composition of any one of claims 41-44, further comprising an additional therapeutic agent.

46. A pharmaceutical composition comprising an IL-22 polypeptide or an IL-22 Fc fusion protein of any one of claims 1-19 and 22-31 and at least one pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier is a gelling agent.

47. The pharmaceutical composition of claim 46, 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;

wherein optionally the gelling agent is hydroxypropyl methylcellulose.

48. The pharmaceutical composition of any one of claims 46-47, wherein the *pharmaceutical composition is for topical administration.*

49. Use of the pharmaceutical composition of any one of claims 41-45 in the manufacture of a medicament for treating inflammatory bowel disease (IBD) in a subject in need thereof.

50. Use of a pharmaceutical composition comprising IL-22 Fc fusion proteins of any one of claims 1-19 or the compositions of any one of claims 22-31 in the manufacture of a medicament for treating IBD in a patient.

51. The use of claim 49 or 50, wherein the IBD is ulcerative colitis or Crohn's disease.

52. The use of any one of claims 49-51, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14;

wherein optionally the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12;

wherein optionally the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

53. The use of any one of claims 49-52, wherein the subject is to be co-administered with at least one additional therapeutic agent;

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

54. Use of the pharmaceutical composition of any one of claims 41-45 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, epithelial

cell proliferation, epithelial cell differentiation, epithelial cell migration or epithelial wound healing in the intestine, of a subject in need thereof.

55. The use of claim 54, wherein the epithelial cell is intestinal epithelial cell.

56. The use of any one of claims 54-55, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14;

wherein optionally the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12;

wherein optionally the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

57. The use of any one of claims 54-56, wherein the subject is to be co-administered with at least one additional therapeutic agent;

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

58. Use of the pharmaceutical composition of any one of claims 41-45 in the manufacture of a medicament for treating acute kidney injury or acute pancreatitis in a subject in need thereof.

59. Use of a pharmaceutical composition comprising IL-22 Fc fusion proteins of any one of claims 1-19 or the compositions of any one of claims 22-31 in the manufacture of a medicament for treating acute kidney injury or acute pancreatitis in a patient.

60. The use of claim 58 or 59, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14;

wherein optionally the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12;

wherein optionally the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

61. The use of any one of claims 58-60, wherein the subject is to be co-administered with at least one additional therapeutic agent;

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

62. Use of a pharmaceutical composition of any one of claims 41-48 in the manufacture of a medicament for accelerating or improving wound healing in a subject.

63. Use of a pharmaceutical composition comprising an IL-22 polypeptide, or an IL-22 Fc fusion protein of any one of claims 1-19 or a composition of any one of claims 22-31 in the manufacture of a medicament for accelerating or improving wound healing in a subject.

64. The use of claim 62-63, wherein the wound is a chronic wound or an infected wound.

65. The use of any one of claims 62-64, wherein the subject is diabetic;

wherein optionally the diabetic subject has type II diabetes.

66. The use of any one of claims 62-65, wherein the wound is a diabetic foot ulcer.

67. The use of any one of claims 62-66, wherein the pharmaceutical composition is to be administered until there is complete wound closure.

68. The use of any one of claims 62-67, wherein the IL-22 Fc fusion protein comprises 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;

wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

69. The use of any one of claims 62-68, wherein the subject is to be co-administered with 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.

70. Use of a pharmaceutical composition of any one of claims 41-45 in the manufacture of a medicament for preventing or treating a cardiovascular condition, which condition includes a pathology of atherosclerotic plaque formation.

71. Use of a pharmaceutical composition comprising an IL-22 polypeptide or an IL-22 Fc fusion protein of any one of claims 1-19, or a composition comprising an IL-22 Fc

fusion protein of any one of claims 22-31 in the manufacture of a medicament for preventing or treating a cardiovascular condition, which condition includes a pathology of atherosclerotic plaque formation.

72. The use of claim 70 or 71, 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.
73. The use of claim 70 or 71, 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.
74. The use of any one of claims 70-73, wherein the IL-22 Fc fusion protein comprises 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;

wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.
75. The use of any one of claims 70-74, wherein the subject is to be co-administered with at least one additional therapeutic agent.
76. The use of claim 70-71, wherein the subject has been identified to be at risk to develop a cardiovascular condition.
77. The use of any one of claims 70-76, wherein the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.
78. Use of a pharmaceutical composition of any one of claims 41-45 in the manufacture of a medicament for for treating metabolic syndrome.
79. Use of a pharmaceutical composition comprising an IL-22 Fc fusion protein of any one of claims 1-19 or a composition comprises an IL-22 Fc fusion protein of any one of claims 22-31 in the manufacture of a medicament for treating metabolic syndrome.
80. The use of claim 78-79, 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.
81. The use of any one of claims 78-80, wherein the subject is in need of a change in HDL/LDL lipid profile.

82. The use of any one of claims 78-81, wherein the IL-22 Fc fusion protein comprises 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;

wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

83. The use of any one of claims 78-82, wherein the subject is to be co-administered with at least one additional therapeutic agent;
wherein optionally the pharmaceutical composition is to be administered intravenously, subcutaneously or intraperitoneally.

84. Use of a pharmaceutical composition of any one of claims 41-45 in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both.

85. Use of a pharmaceutical composition comprising an IL-22 Fc fusion protein of any one of claims 1-19 or a composition comprising an IL-22 Fc fusion protein of any one of claims 22-31 in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both.

86. The use of claim 84 or 85, wherein the subject is in need of a change in HDL/LDL lipid profile.

87. The use of any one of claims 84-86, wherein the IL-22 Fc fusion protein comprises 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;

wherein optionally the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

88. The use of any one of claims 84-87, wherein the subject is to be co-administered with 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.

89. The use of any one of claims 49-88, wherein the subject is a human.