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 examples, the method further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium. In certain examples, the host cell is a Chinese hamster ovary (CHO) cell; while in other examples, the host cell is an *E. coli* cell.

In another example, the present disclosure refers to an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:12.

In yet another example, the present disclosure refers to an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:14.

In another example, the present disclosure refers to an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:20.

In another example, the present disclosure refers to an IL-22 Fc fusion protein consisting of the amino acid sequence of SEQ ID NO:12.

In yet another example, the present disclosure refers to an IL-22 Fc fusion protein consisting of the amino acid sequence of SEQ ID NO:14.

In another example, the present disclosure refers to an IL-22 Fc fusion protein consisting of the amino acid sequence of SEQ ID NO:20.

In another example, the disclosure provides 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. In certain examples, the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31). In certain other examples, the N297 residue in the Fc region is changed and/or the T299 residue in the Fc region is changed. In certain examples, the N297 residue in the CH2 domain is changed, preferably to glycine or alanine. In certain particular examples, the N297 residue is changed to glycine. In certain other examples, the N297 residue is changed to alanine. In yet other examples, the T299 residue is changed to Ala, Gly or Val. In certain other examples, the linker is 8-20 amino acids long, 8-16 amino acids long, or 10-16 amino acids long.

In certain examples, the Fc region comprises the CH2 and CH3 domain of IgG1. In certain particular examples, the linker comprises the amino acid sequence DKTHT (SEQ ID NO:32). In certain examples, the linker comprises the amino acid sequence GGGDKTHT (SEQ ID NO:41). In certain examples, the linker is at least 11 amino acids long and comprises the amino acid sequence EPKSCDKTHT (SEQ ID NO:33). In certain other examples, 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 examples, the linker comprises the amino acid sequence EPKSSDKTHT (SEQ ID NO:40). In certain examples, 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 examples, 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 examples, the IL-22 IgG1 Fc fusion protein comprises a linker sequence of GGGSTHT (SEQ ID NO:63). In other particular examples, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:12 or SEQ ID

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

In another example, 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 examples, acute pancreatitis can be mild to moderate to severe disease. In certain examples, acute pancreatitis includes disease post ERCP (endoscopic retrograde cholangiopancreatography). In some further examples, 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 a related example, 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 example, the disclosure provides 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 other related examples, 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 examples, the epithelial cell is intestinal epithelial cell.

In one aspect, the present disclosure refers to the use of the IL-22 Fc fusion protein disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting microbial infection in the intestine of a subject in need thereof.

In one aspect, the present disclosure refers to the use of the IL-22 Fc fusion protein disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof.

In one aspect, the present disclosure refers to the use of the IL-22 Fc fusion protein disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for accelerating or improving wound healing in a subject in need thereof.

In another example, 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 one aspect, the present disclosure refers to the use of the IL-22 Fc fusion protein disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing or treating a cardiovascular condition in a subject in need thereof, 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.

In another example, 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 one aspect, the present disclosure refers to the use of the IL-22 Fc fusion protein disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating metabolic syndrome in a subject in need thereof.

In another example, 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 another example, 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 examples, the subject has been identified to be at risk to develop a cardiovascular condition. In certain examples, the subject is genetically at risk of developing a cardiovascular condition. In one or more examples, the indicia of atherosclerosis include plaque accumulation. In some examples, 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 yet another example, 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.

WHAT IS CLAIMED IS:

1. 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 an IgG1 Fc region or an IgG4 Fc region, and wherein the Fc region is not glycosylated.

2. The IL-22 Fc fusion protein of claim 1, wherein the Fc region comprises a hinge region comprising the amino acid sequence of CPPCP (SEQ ID NO:31).

3. The IL-22 Fc fusion protein of claim 1 or 2, wherein the Fc region comprises an altered glycosylation consensus site.

4. The IL-22 Fc fusion protein of claim 3, wherein the Fc region comprises an insertion, a deletion, or a substitution mutation that results in an aglycosylated Fc region.

5. The IL-22 Fc fusion protein of any one of claims 1-4, wherein in the Fc region the amino acid residue at position 297 (numbering according to the EU index) of the Fc region is changed and/or the amino acid residue at position 299 (numbering according to the EU index) of the Fc region is changed.

6. The IL-22 Fc fusion protein of claim 5, wherein the amino acid residue at position 297 (numbering according to the EU index) of the Fc region is Gly, Ala, Gln, Asp, or Glu.

7. The IL-22 Fc fusion protein of claim 6, wherein the amino acid residue at position 297 (numbering according to the EU index) of the Fc region is Gly or Ala.

8. The IL-22 Fc fusion protein of claim 6 or 7, wherein the amino acid residue at position 297 (numbering according to the EU index) of the Fc region is Gly.

9. The IL-22 Fc fusion protein of any one of claims 5-8, wherein the amino acid residue at position 299 (numbering according to the EU index) is Ala, Gly or Val.

10. The IL-22 Fc fusion protein of any one of claims 1-9, wherein the linker is 8-20 amino acids long.

11. The IL-22 Fc fusion protein of claim 10, wherein the linker is 8-16 amino acids long.

12. The IL-22 Fc fusion protein of claim 10, wherein the linker is 10-16 amino acids long.

13. The IL-22 Fc fusion protein of any one of claims 1-12, wherein the Fc region is an IgG1 Fc region.

14. The IL-22 Fc fusion protein of claim 13, wherein the linker comprises the amino acid sequence DKTHT (SEQ ID NO:32).

15. The IL-22 Fc fusion protein of claim 14, wherein the linker is at least 11 amino acids long and comprises the amino acid sequence EPKSCDKTHT (SEQ ID NO:33).

16. The IL-22 Fc fusion protein of claim 15, wherein 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).

17. The IL-22 Fc fusion protein of any one of claims 1-14, wherein the linker comprises the amino acid sequence EPKSSDKTHT (SEQ ID NO:40).

18. The IL-22 Fc fusion protein of claim 17, wherein 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).

19. The IL-22 Fc fusion protein of claim 1 or 14, wherein the linker does not comprise the amino acid sequence GGS (SEQ ID NO:45).

20. The IL-22 Fc fusion protein of any one of claims 1-14, 17, and 19, comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:12.

21. The IL-22 Fc fusion protein of claim 20, comprising an amino acid sequence having at least 96% sequence identity to the amino acid sequence of SEQ ID NO:12.

22. The IL-22 Fc fusion protein of claim 21, comprising an amino acid sequence having at least 97% sequence identity to the amino acid sequence of SEQ ID NO:12.

23. The IL-22 Fc fusion protein of claim 22, comprising an amino acid sequence having at least 98% sequence identity to the amino acid sequence of SEQ ID NO:12.

24. The IL-22 Fc fusion protein of claim 23, comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO:12.

25. The IL-22 Fc fusion protein of claim 1 comprising the amino acid sequence of SEQ ID NO:12.

26. The IL-22 Fc fusion protein of claim 1 comprising the amino acid sequence of SEQ ID NO:14.

27. The IL-22 Fc fusion protein of claim 1 comprising the amino acid sequence of SEQ ID NO:20.

28. The IL-22 Fc fusion protein of claim 1 consisting of the amino acid sequence of SEQ ID NO:12.

29. The IL-22 Fc fusion protein of claim 1 consisting of the amino acid sequence of SEQ ID NO:14.

30. The IL-22 Fc fusion protein of claim 1 consisting of the amino acid sequence of SEQ ID NO:20.

31. The IL-22 Fc fusion protein of any one of claims 1-12, wherein the Fc region comprises an IgG4 Fc region.

32. The IL-22 Fc fusion protein of claim 31, wherein the linker comprises the amino acid sequence SKYGPP (SEQ ID NO:43).

33. The IL-22 Fc fusion protein of claim 32, wherein the linker comprises the amino acid sequence RVESKYGPP (SEQ ID NO:44).

34. The IL-22 Fc fusion protein of any one of claims 1-33, wherein the IL-22 fusion protein is a dimeric IL-22 Fc fusion protein.

35. The IL-22 Fc fusion protein of any one of claims 1-33, wherein the IL-22 fusion protein is a monomeric IL-22 Fc fusion protein.

36. The IL-22 Fc fusion protein of any one of claims 1-35, wherein the IL-22 polypeptide comprises the amino acid sequence of SEQ ID NO:4.

37. The IL-22 Fc fusion protein of any one of claims 1-36, wherein the IL-22 polypeptide is a human IL-22 polypeptide.

38. The IL-22 Fc fusion protein of any one of claims 1-37, wherein the IL-22 Fc fusion protein binds to IL-22 receptor.

39. The IL-22 Fc fusion protein of claim 38, wherein the IL-22 receptor is a human IL-22 receptor.

40. An isolated nucleic acid encoding the IL-22 Fc fusion protein of any one of claims 1-39.

41. The isolated nucleic acid of claim 40, comprising the polynucleotide sequence of SEQ ID NO:11.

42. The isolated nucleic acid of claim 40, comprising the polynucleotide sequence of SEQ ID NO:13.

43. The isolated nucleic acid of claim 40, comprising the polynucleotide sequence of SEQ ID NO:19.

44. A vector comprising the nucleic acid of any one of claims 40-43.

45. A host cell comprising the vector of claim 44.

46. The host cell of claim 45, wherein the host cell is a prokaryotic cell or eukaryotic cell.

47. The host cell of claim 46, wherein the host cell is an *E. coli* cell or a CHO cell.

48. The host cell of claim 47, wherein the host cell is a CHO cell.

49. A method of making an IL-22 Fc fusion protein comprising the step of culturing the host cell of any one of claims 45-48 under conditions suitable for expression of the IL-22 Fc fusion protein.

50. The method of claim 49, further comprising the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium.

51. A pharmaceutical composition comprising the IL-22 Fc fusion protein according to any one of claims 1-39 and at least one pharmaceutically acceptable carrier.

52. The pharmaceutical composition of claim 51, further comprising an additional therapeutic agent.

53. A pharmaceutical composition comprising an IL-22 polypeptide or an IL-22 Fc fusion protein of any one of claims 1-39 and at least one pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier is a gelling agent.

54. The pharmaceutical composition of claim 53, wherein the gelling agent is a polysaccharide.

55. The pharmaceutical composition of claim 53 or 54, wherein the gelling agent is a cellulosic agent.

56. The pharmaceutical composition of claim 54, wherein 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.

57. The pharmaceutical composition of claim 56, wherein the gelling agent is hydroxypropyl methylcellulose.

58. Use of the IL-22 Fc fusion protein of any one of claims 1-39 or the pharmaceutical composition of claim 51 or 52 in the manufacture of a medicament for treating inflammatory bowel disease (IBD) in a subject in need thereof.

59. The use of claim 58, wherein the IBD is ulcerative colitis.

60. The use of claim 58, wherein the IBD is Crohn's disease.

61. Use of the IL-22 Fc fusion protein of any one of claims 1-39 or the pharmaceutical composition of claim 51 or 52 in the manufacture of a medicament for inhibiting microbial infection in the intestine of a subject in need thereof.

62. Use of the IL-22 Fc fusion protein of any one of claims 1-39 or the pharmaceutical composition of claim 51 or 52 in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof.

63. Use of the IL-22 Fc fusion protein of any one of claims 1-39 or the pharmaceutical composition of any one of claims 51-57 in the manufacture of a medicament for accelerating or improving wound healing in a subject in need thereof.

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

65. The use of claim 63 or 64, wherein the subject is diabetic.

66. The use of claim 65, wherein the diabetic subject has type II diabetes.

67. The use of any one of claims 63-66, wherein the wound is a diabetic foot ulcer.

68. The use of any one of claims 63-67, wherein the pharmaceutical composition is to be administered until there is complete wound closure.

69. Use of the IL-22 Fc fusion protein of any one of claims 1-39 or the pharmaceutical composition of claim 51 or 52 in the manufacture of a medicament for preventing or treating a cardiovascular condition in a subject in need thereof, 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.

70. The use of claim 69, wherein the subject has been identified to be at risk to develop a cardiovascular condition.

71. Use of the IL-22 Fc fusion protein of any one of claims 1-39 or the pharmaceutical

composition of claim 51 or 52 in the manufacture of a medicament for treating metabolic syndrome in a subject in need thereof.

72. The use of claim 71, further comprising reducing the level of bacterial lipopolysaccharide (LPS) in the subject.

73. The use of claim 71 or 72, wherein the subject is in need of a change in HDL/LDL lipid profile.

74. Use of the IL-22 Fc fusion protein of any one of claims 1-39 or the pharmaceutical composition of claim 51 or 52 in the manufacture of a medicament for treating acute endotoxemia, sepsis, or both, in a subject in need thereof.

75. The use of claim 74, wherein the subject is in need of a change in HDL/LDL lipid profile.

76. The use of any one of claims 58-75, wherein the subject is to be administered at least one additional therapeutic agent.

77. The use of any one of claims 58-76, wherein the IL-22 Fc fusion protein or the pharmaceutical composition is to be administered intravenously, subcutaneously, or intraperitoneally.

78. The use of any one of claims 58-77, wherein the IL-22 Fc fusion protein or the pharmaceutical composition is to be administered intravenously.

79. The use of any one of claims 58-77, wherein the IL-22 Fc fusion protein or the pharmaceutical composition is to be administered subcutaneously.

80. The use of any one of claims 58-79, wherein the subject is a patient.

81. The use of any one of claims 58-80, wherein the subject is a human.