CLAIMS

1. A polypeptide comprising at least two immunoglobulin antigen binding domains, which polypeptide is directed against or binds to chemokine receptor CXCR2 wherein said polypeptide includes a first antigen binding domain recognising a first epitope on CXCR2 and a second antigen binding domain recognising a second epitope on CXCR2.

2. The polypeptide of claim 1 wherein said first antigen binding domain is capable of binding to a linear peptide consisting of the sequence of amino acids set forth in SEQ ID No. 7 and said second antigen binding domain is either not capable of binding or binds with lower affinity to said linear peptide.

3. The polypeptide of claim 1 or claim 2 wherein said first antigen binding domain is comprised within a first immunoglobulin single variable domain and said second antigen binding domain is comprised within a second immunoglobulin single variable domain of an antibody.

4. The polypeptide of claim 3 wherein at least one of said first and second antigen binding domains is comprised within an antibody V_L domain or a fragment thereof.

5. The polypeptide of claim 3 wherein at least one of said first and second antigen binding domains is comprised within an antibody V_H domain or a fragment thereof.

6. The polypeptide of claim 4 or 5 wherein said first antigen binding domain is comprised in a V_L domain or a fragment thereof and said second antigen binding domain is comprised in a V_H domain or a fragment thereof.

7. The polypeptide of claim 4 or 5 wherein said first antigen binding domain is comprised in a V_H domain or fragment thereof and said second antibody binding domain is comprised in a V_L domain or a fragment thereof.

8. The polypeptide of any one of claims 3 to 7 wherein said first and second antigen binding domains are comprised within first and second domain antibodies (dAbs).

9. The polypeptide of claim 3 or claim 5 wherein at least one of said first and second antigen binding domains is comprised within a V_{HH} domain or fragment thereof from a single heavy chain of a heavy chain antibody obtainable from a Camelid or is a sequence-optimised, including humanised, variant thereof.

10. The polypeptide of claim 9 wherein each of said antigen binding domains is comprised within a V_{HH} domain or fragment thereof from a single heavy chain of a heavy chain antibody derived from a Camelid or is a sequence-optimised, including humanised, variant thereof.

11. The polypeptide of claim 9 or 10 wherein each V_{HH} sequence or fragment thereof includes one, two or three CDRs.

12. The polypeptide of any one of claims 9 to 11 wherein each V_{HH} sequence has the structure: FR-CDR-FR-CDR-FR-CDR-FR.

13. The polypeptide of any one of the preceding claims wherein said at least two antigen binding domains are joined by a linker.

14. The polypeptide of any one of claims 3 to 13 which has one of the following structures:

iv) FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4--LINKER--FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8
v) FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4--LINKER--FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8--LINKER--HLE
vi) FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4--LINKER--HLE--LINKER--FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8

wherein if FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 comprises the first antigen binding domain then FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8 comprises the second antigen domain and if FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 comprises the second antigen domain then FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8 comprises the first antigen binding domain and the HLE is a binding unit providing an increased in vivo half-life.

15. The polypeptide of claims 1 or 2 wherein each of said first and second antigen binding domains is comprised within a heavy chain antibody.

16. The polypeptide of claim 1 or 2 wherein said first antigen binding domain is comprised within a single chain of a first heavy chain antibody and said second antigen binding domain is comprised within a single chain of a second heavy chain antibody wherein said first and second heavy single chain antibodies are joined by a linker.

17. The polypeptide of claims 1 or 2 wherein each of said first and second antigen binding domains is comprised within an antibody consisting of two heavy chains and two light chains.

18. The polypeptide of claim 1 or 2 wherein said first and second antigen binding domains are comprised in first and second antibodies respectively each comprising two heavy and two light chains wherein said first and second antibodies are joined by a linker.

19. The polypeptide of claim 1 or 2 wherein said first and second antigen binding domains are comprised within first and second antibody Fab or F(ab)2 fragments respectively and wherein said first and second Fab or F(ab)2 fragments are joined by a linker.

20. The polypeptide of claim 19 wherein said first antigen binding domain is comprised within an antibody Fab fragment and said second antigen binding domain is comprised within a F(ab)2 fragment or visa versa.

21. The polypeptide of claim 1 or 2 wherein said first and second antigen binding domains are comprised within first and second antibody single chain Fv (scFvs) or fragments thereof respectively and wherein said first and second scFvs are joined by a linker.

22. The polypeptide of any one of claims 13, 14, 16, 18, 19, 20, or 21 wherein the linker joins the C-terminal of one immunoglobulin comprising an antigen binding domain to the N-terminal of a second immunoglobulin comprising an antigen binding domain.

23. The polypeptide of any one of claims 13, 14, 16, or 18 to 22 wherein the linker is a peptide comprising an amino acid sequence not of immunoglobulin origin.

24. The polypeptide of claim 23 wherein the peptide linker is between 3 and 50 amino acids long

25. The polypeptide of claim 24 wherein the number of amino acids in the linker is selected from 3 to 9, 10 to 15, 16 to 20, 21 to 25, 26 to 35, 36 to 40, 41 to 45 or 46 to 50.

26. The polypeptide of claim 24 wherein the linker is 35 amino acids long.

27. The polypeptide of claim 24 wherein the linker which is constituted solely from two different amino acids.

28. The polypeptide of claim 27 wherein the linker is constituted from amino acids glycine and serine.

29. The polypeptide of claim 27 wherein the linker is constituted from amino acids proline and serine and optionally alanine.

30. The polypeptide of any one of claims 23 to 26 wherein the linker is constituted solely of alanine.

31. The polypeptide of claim 26 wherein the peptide linker consists of the amino acid sequence set forth in SEQ ID No 220.

32. The polypeptide of any one of the preceding claims which includes CDR amino acid sequences derived from or characteristic of camelid single heavy chain antibodies.

33. The polypeptide of any one of claims 9 to 14 wherein the amino acid sequences of the framework regions are derived from or characteristic of camelid single heavy chain antibodies.

34. The polypeptide of any one of claims 9 to 14 wherein the amino acid sequences of the framework regions are sequence-optimised, including humanised, variants thereof.

35. The polypeptide of claims 1-34 comprising the structure of claim 14, wherein the first antigen binding domain is selected from SEQ ID No. 213, 214, 216 and 219 or a polypeptide having at least 80% identity to one of these , and the second antigen binding domain is selected from SEQ ID No. 215, 217 and 218, or a polypeptide having at least 80% identity to one of these.

36. The polypeptide of claims 1-34 comprising the structure as claimed in claim 14 wherein in said second immunoglobulin of a single variable domain CDR1 comprises an amino acid sequence as set forth in SEQ ID No 141, CDR2 comprises the amino acid sequence set forth in SEQ ID No 236 and CDR3 comprises the amino acid sequence set forth in SEQ ID No 181 and wherein in said first immunoglobulin of a single variable domain CDR4 comprises an amino acid sequence as set forth in SEQ ID No 146, CDR5 comprises the amino acid sequence set forth in SEQ ID No 237 and CDR6 comprises the amino acid sequence set forth in SEQ ID No 186.

37. The polypeptide of claim 36 in which the amino acid sequences of CDR1, CDR2, CDR3, CDR4, CDR5 or CDR6 have at least 80% amino acid identity with the any one of the amino acid sequences set forth in SEQ ID Nos 141, 236, 181, 146, 237 or 186.

38. The polypeptide of claim 36 wherein the amino acid sequences differ from those set forth in SEQ ID Nos 141, 236, 181, 146, 237 or 186 only in conservative amino acid changes.

39. The polypeptide of any one of claim 36 wherein the first antigen binding domain is selected from SEQ ID No. 216 or a polypeptide having at least 80% identity to SEQ ID No.216, and the second antigen binding domain is selected from SEQ ID No. 217 or a polypeptide having at least 80% identity to SEQ ID No.217.

40. A polypeptide of any of claims 1-34, comprising SEQ ID No.221.

41. The polypeptide of claims 1-34 comprising the structure as claimed in claim 14 wherein in said second immunoglobulin of a single variable domain CDR1 comprises an amino acid sequence as set forth in SEQ ID No 141, CDR2 comprises the amino acid sequence set forth in SEQ ID No 236 and CDR3 comprises the amino acid sequence set forth in SEQ ID No 181 and wherein in said first immunoglobulin of a single variable domain CDR4 comprises an amino acid sequence as set forth in SEQ ID No 145, CDR5 comprises the amino acid sequence set forth in SEQ ID No 165 and CDR6 comprises the amino acid sequence set forth in SEQ ID No 185.

42. The polypeptide of claim 41 in which the amino acid sequences of CDR1, CDR2, CDR3, CDR4, CDR5 or CDR6 have at least 80% amino acid identity with the any one of the amino acid sequences set forth in SEQ ID Nos 141, 236, 181, 145, 165 or 185.

43. The polypeptide of claim 41 wherein the amino acid sequences differ from those set forth in SEQ ID Nos 141, 236, 181, 145, 165 or 185 only in conservative amino acid changes.

44. The polypeptide of any one of claims 41 to 43 wherein the first antigen binding domain is selected from SEQ ID No. 216 or a polypeptide having at least 80% identity to SEQ ID No.216, and the second antigen binding domain is selected from SEQ ID No. 218 or a polypeptide having at least 80% identity to SEQ ID No.218.

45. A polypeptide of any of claims 1-34, comprising SEQ ID No.222.

46. The polypeptide of claims 1-34 comprising the structure as claimed in claim 14 wherein in said second immunoglobulin of a single variable domain CDR1 comprises an amino acid sequence as set forth in SEQ ID No 141, CDR2 comprises the amino acid sequence set forth in SEQ ID No 236 and CDR3

comprises the amino acid sequence set forth in SEQ ID No 181 and wherein in said first immunoglobulin of a single variable domain CDR4 comprises an amino acid sequence as set forth in SEQ ID No 143, CDR5 comprises the amino acid sequence set forth in SEQ ID No 235 and CDR6 comprises the amino acid sequence set forth in SEQ ID No 183.

47. The polypeptide of claim 46 in which the amino acid sequences of CDR1, CDR2, CDR3, CDR4, CDR5 or CDR6 have at least 80% amino acid identity with the any one of the amino acid sequences set forth in SEQ ID Nos 141, 236, 181, 143, 235 or 183.

48. The polypeptide of claim 46 wherein the amino acid sequences differ from those set forth in SEQ ID Nos 141, 236, 181, 143, 235 or 183 only in conservative amino acid changes.

49. The polypeptide of any one of claims 46 to 48 wherein the first antigen binding domain is selected from SEQ ID No. 216 or a polypeptide having at least 80% identity to SEQ ID No.216, and the second antigen binding domain is selected from SEQ ID No. 215 or a polypeptide having at least 80% identity to SEQ ID No.215.

50. A polypeptide of any of claims 1-34, comprising SEQ ID No.216 and SEQ ID No.215, separated by a linker with the SEQ ID No. 220.

51. The polypeptide of claims 1-34 comprising the structure as claimed in claim 14 wherein in said second immunoglobulin of a single variable domain CDR1 comprises an amino acid sequence as set forth in SEQ ID No 151, CDR2 comprises the amino acid sequence set forth in SEQ ID No 171 and CDR3 comprises the amino acid sequence set forth in SEQ ID No 191 and wherein in said first immunoglobulin of a single variable domain CDR4 comprises an amino acid sequence as set forth in SEQ ID No 146, CDR5 comprises the amino acid sequence set forth in SEQ ID No 237 and CDR6 comprises the amino acid sequence set forth in SEQ ID No 186.

52. The polypeptide of claim 51 in which the amino acid sequences of CDR1, CDR2, CDR3, CDR4, CDR5 or CDR6 have at least 80% amino acid identity with the any one of the amino acid sequences set forth in SEQ ID Nos 151, 171, 191, 146, 237 or 186.

53. The polypeptide of claim 51 wherein the amino acid sequences differ from those set forth in SEQ ID Nos 151, 171, 191, 146, 237 or 186 only in conservative amino acid changes.

54. The polypeptide of claims 51-53 wherein the first antigen binding domain is selected from SEQ ID No. 219 or a polypeptide having at least 80% identity to SEQ ID No.219, and the second antigen binding domain is selected from SEQ ID No. 217 or a polypeptide having at least 80% identity to SEQ ID No.217.

55. A polypeptide of any of claims 1-34, comprising SEQ ID No.223.

56. The polypeptide of claims 1-34 comprising the structure as claimed in claim 14 wherein in said second immunoglobulin of a single variable domain CDR1 comprises an amino acid sequence as set forth in SEQ ID No 151, CDR2 comprises the amino acid sequence set forth in SEQ ID No 171 and CDR3 comprises the amino acid sequence set forth in SEQ ID No 191 and wherein in said first immunoglobulin of a single variable domain CDR4 comprises an amino acid sequence as set forth in SEQ ID No 145, CDR5 comprises the amino acid sequence set forth in SEQ ID No 165 and CDR6 comprises the amino acid sequence set forth in SEQ ID No 185.

57. The polypeptide of claim 56 in which the amino acid sequences of CDR1, CDR2, CDR3, CDR4, CDR5 or CDR6 have at least 80% amino acid identity with the any one of the amino acid sequences set forth in SEQ ID Nos 151, 171, 191, 145,165 or 185.

58. The polypeptide of claim 56 wherein the amino acid sequences differ from those set forth in SEQ ID Nos 151, 171, 191, 145,165 or 185 only in conservative amino acid changes.

59. The polypeptide of any one of claims 56 to 58 wherein the first antigen binding domain is selected from SEQ ID No. 219 or a polypeptide having at least 80% identity to SEQ ID No.219, and the second antigen binding domain is selected from SEQ ID No. 218 or a polypeptide having at least 80% identity to SEQ ID No.218.

60. A polypeptide of any of claims 1-34, comprising SEQ ID No.224.

61. The polypeptide of claims 1-34 comprising the structure as claimed in claim 14 wherein in said second immunoglobulin of a single variable domain CDR1 comprises an amino acid sequence as set forth in SEQ ID No 151, CDR2 comprises the amino acid sequence set forth in SEQ ID No 171 and CDR3 comprises the amino acid sequence set forth in SEQ ID No 191 and wherein in said first immunoglobulin of a single variable domain CDR4 comprises an amino acid sequence as set forth in SEQ ID No 143, CDR5 comprises the amino acid sequence set forth in SEQ ID No 235 and CDR6 comprises the amino acid sequence set forth in SEQ ID No 183.

62. The polypeptide of claim 61 in which the amino acid sequences of CDR1, CDR2, CDR3, CDR4, CDR5 or CDR6 have at least 80% amino acid identity with the any one of the amino acid sequences set forth in SEQ ID Nos 151, 171, 191, 143, 235 or 183.

63. The polypeptide of claim 61 wherein the amino acid sequences differ from those set forth in SEQ ID Nos 151, 171, 191, 143, 235 or 183 only in conservative amino acid changes.

64. The polypeptide of any one of claims 61-63 wherein the first antigen binding domain is selected from SEQ ID No. 219 or a polypeptide having at least 80% identity to SEQ ID No.219, and the second antigen binding domain is selected from SEQ ID No. 215 or a polypeptide having at least 80% identity to SEQ ID No.215.

65. A polypeptide of any of claims 1-34, comprising SEQ ID No.219 and SEQ ID No.215, separated by a linker with the SEQ ID No. 220.

66. The polypeptide of any one of claims 1 to 65 comprising sequence-optimised framework regions, including partially or fully humanised framework regions.

67. The polypeptide of any one of claim 1 to 66 which cross-reacts with non-human primate CXCR2.

68. The polypeptide of claim 67 wherein the primate is Cynomolgus monkey

69. The polypeptide of any one of claims 1 to 68 which does not cross-react with CXCR2 from non-primate species.

70.The polypeptide of any one of claims 1 to 69 which does not cross-react with other receptors of the CXC chemokine family.

71. The polypeptide of claims 1-70 wherein said first antigen binding domain binds to an epitope comprising amino acids F11, F14 and W15 of SEQ ID No. 1

72. The polypeptide of claims 1-71 wherein said epitope is linear.

73. The polypeptide of claims 1-72 wherein said second antigen binding domain binds to an epitope within the external loops of human CXCR2 (amino acid residues 106-120, 184-208 and 274-294 of SEQ ID No. 1)

74. The polypeptide of claims 1-73 wherein said epitope is within amino acid residues 106-120 and of SEQ ID No. 1)

75. The polypeptide of claims 1-74 wherein said epitope is confomational.

76. The polypeptide of claims 1-75 wherein said second antigen binding domain binds to an epitope of CXCR2, comprising amino acid residues W112, G115, I282 and T285 of SEQ ID No. 1.

77. The polypeptide of any one of claims 1 to 76 which can specifically bind to human CXCR2 with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/litre or less, and preferably 10^{-7} to 10^{-12} moles/litre or less and more preferably 10^{-8} to 10^{-12} moles/litre.

78. The polypeptide of any one of claims 1 to 77 which can specifically bind to human CXCR2 with a rate of association (k_{on}-rate) of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$.

79. The polypeptide of any one of claims 1 to 78 which can specifically bind to human CXCR2 with a rate of dissociation (k_{off} rate) between 1 s^{-1} and 10^{-6} s^{-1}, preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.

80. The polypeptide of any one of claims 1 to 79 which can specifically bind to human CXCR2 with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.

81.The polypeptide of any one of claims 1 to 80 capable of inhibiting binding of Gro-α to human CXCR2 with an IC50 of less than 20nM.

82.The polypeptide of any one of claims 1 to 81 capable of inhibiting Gro-α-induced calcium release from RBL cells expressing human CXCR2 with an IC50 of less than 100nM.

83. The polypeptide of any one of claims 1 to 82 capable of inhibiting Gro-α-induced accumulation of [^{35}S]GTPγS in human CHO-CXCR2 membranes with an IC50 of less than 50nM.

84.The polypeptide of any one of claims 1 to 83 wherein said polypeptide is in substantially isolated form.

85. The polypeptide of any one claims 1 to 84 which is a multiparatopic construct.

86. The polypeptide according to any one of claims 1 to 85 which is modified to have an increased in vivo half-life, compared to the corresponding unmodified amino acid sequence.

87. The polypeptide according to claim 86 wherein said increased half-life is provided by one or more binding units chosen from the group consisting of serum proteins or fragments thereof, binding units that can bind to serum proteins, an Fc portion, and small proteins or peptides that can bind to serum proteins.

88. The polypeptide according to claim 86 wherein said one or more other binding units that provide the polypeptide with increased half-life is chosen from the group consisting of human serum albumin or fragments thereof.

89. The polypeptide according to 86, wherein said one or more other binding units that provide the polypeptide with increased half-life are chosen from the group consisting of binding units that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).

90. The polypeptide according to claim 86 wherein said increased half-life is provided by one or more other binding units chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, "dAb"'s , amino acid sequences that are suitable for use as a dAb, or Nanobodies that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).

91. The polypeptide according to claim 88 which is an immunoglobulin single variable domain that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).

92. The polypeptide according to claim 88 wherein the serum protein is human serum albumin.

93. The polypeptide of claim 92 wherein the further antigen binding domain comprises SEQ ID No.228 (Alb8).

94. The polypeptide according to any of claims 86 to 93 that has a serum half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding unmodified polypeptide.

95. A polypeptide according to any of claims 86 to 94 that has a serum half-life that is increased by more than 1 hour, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding unmodified polypeptide.

96. A polypeptide according to any of claims 86 to 95 that has a serum half-life in human of at least about 12 hours, preferably at least 24 hours, more preferably at least 48 hours, even more preferably at least 72 hours or more; for example, of at least 5 days (such as about 5 to 10 days), preferably at least 9 days (such as about 9 to 14 days), more preferably at least about 10 days (such as about 10 to 15 days), or at least about 11 days (such as about 11 to 16 days), more preferably at least about 12 days (such as about 12 to 18 days or more), or more than 14 days (such as about 14 to 19 days).

97. A polypeptide according to any of claims 1 to 96 which is pegylated.

98. A polypeptide according to any one of claims 1 to 96 which is pasylated

99. A polypeptide according to any one of claims 1 to 96 which is hesylated.

100. The polypeptide of claims 87-96 wherein said further antigen binding domain binds a serum protein with an affinity of less than 500nM, preferably less than 200 nM, more preferably less than 10nM, such as less than 500 pM.

101. A polypeptide according to any one of claims 1 to 100 which is capable of cross-blocking binding to CXCR2 with a polypeptide of any one of claims 40, 45, 50, 55, 60 or 65.

102. A polypeptide according to claim 101 comprising at least one immunoglobulin single variable domain which is directed against or binds to CXCR2.

103. A polypeptide according to claims 1-50 or 66-102 selected consisting of a sequence selected from SEQ ID No. 225, 226 or 227.

104. A nucleic acid molecule which encodes a polypeptide according to any one of claims 1 to 103.

105. A nucleic acid molecule encoding an immunoglobulin single variable domain comprising an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID Nos 25 to 43, 90, 213 to 219 and 221 to 245.

106. The nucleic acid molecule of claim 105 comprising a nucleotide sequence selected from the group consisting of the nucleic acid sequences set forth in SEQ ID Nos 192 to 211.

107. A nucleic acid molecule encoding a polypeptide comprising an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID Nos 44 to 69.

108. An expression vector comprising a nucleic acid molecule as claimed in any one of claims 104 to 107.

109. A host cell capable of expressing a polypeptide according to any one of claims 1 to 100 from a nucleic acid sequence according to any one of claims 104 to 107.

110. A monovalent, bivalent, multivalent, biparatopic or multiparatopic Nanobody obtainable by culturing the host cell of claim 109.

111. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 103 and a pharmaceutically acceptable carrier or diluent.

112. The polypeptide of any one of claims 1 to 103 for use as a medicament.

113. The polypeptide of any one of claims 1 to 103 for use in the treatment of chronic obstructive pulmonary disease (COPD) and exacerbations of COPD.

114. The polypeptide of any one of claims 1 to 103 for use in the treatment of Cystic Fibrosis, Asthma, severe Asthma, exacerbations of Asthma, allergic Asthma, Acute lung injury, Acute respiratory distress syndrome, Idiopathic pulmonary fibrosis, Airway remodeling, Bronchiolitis obliterans syndrome or Bronchopulmonary dysplasis.

115. The polypeptide of any one of claims 1 to 103 for use in the treatment of Atherosclerosis, Glomerulonephritis, Inflammatory Bowl Disease (Crohn's), Angiogenesis and diseases characterised by new blood vessel development including Macular degeneration, Diabetic retinopathy and Diabetic neuropathy, Multiple sclerosis, Psoriasis, Age-related Macula degenerative disease, Ocular Behcet Disease, Uveitis, Pulmonary Arterial Hypertension (PAH) including idiopathic PAH, familial PAH and associated PAH, Chronic inflammatory diseases, Rheumatoid arthritis, Osteoarthritis, non-small cell carcinoma, Colon cancer, Pancreatic cancer, Esophageal cancer, Ovarian cancer, Breast cancer, Solid tumors and Metasases, Melanoma, Hepatocellular carcinoma, Ischaemia reperfusion injury, Hemolytic transfusion induced-vaso-occlusion crisis in Sickle cell disease,

Ischemia/reperfusion injury, Acute stroke/myocardial infarct, Closed head injury, Posttraumatic inflammation or Insulin resistant diabetes.

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116. A method of treating chronic obstructive pulmonary disease (COPD) or exacerbations of (COPD) comprising administering to a subject an effective amount of a polypeptide according to any one of claims 1 to 103.

117. A method of treating a condition selected from the group consisting of Cystic Fibrosis, Asthma, severe Asthma, exacerbations of Asthma, allergic Asthma, Acute lung injury, Acute respiratory distress syndrome, Idiopathic pulmonary fibrosis, Airway remodeling, Bronchiolitis obliterans syndrome or Bronchopulmonary dysplasis comprising administering to a subject an effective amount of a polypeptide according to any one of claims 1 to 103.

118. A method of treating a condition selected from the group consisting of Atherosclerosis, Glomerulonephritis, Inflammatory Bowl Disease (Crohn's), Angiogenesis and diseases characterised by new blood vessel development including Macular degeneration, Diabetic retinopathy and Diabetic neuropathy, Multiple sclerosis, Psoriasis, Age-related Macula degenerative disease, Ocular Behcet Disease, Uveitis, Pulmonary Arterial Hypertension (PAH) including idiopathic PAH, familial PAH and associated PAH, Chronic inflammatory diseases, Rhenumatoid arthritis, Osteoarthritis, non-small cell carcinoma, Colon cancer, Pancreatic cancer, Esophageal cancer, Ovarian cancer, Breast cancer, Solid tumors and Metasases, Melanoma, Hepatocellular carcinoma, Ischaemia perfusion injury Hemolytic transfusion induced vaso-occlusion crisis in Sickle cell disease, Ischemia/reperfusion injury, Acute stroke/myocardial infarct, Closed head injury, Posttraumatic inflammation and Insulin resistant diabetes.
by administering to a subject an effective amount of a polypeptide according to any one of claims 1 to 103.

119. Use of the polypeptide of any one of claims 1 to 103 in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease (COPD) or exacerbations of COPD.

120. Use of the polypeptide of any one of claims 1 to 103 in the manufacture of a medicament for the treatment of Asthma, severe Asthma, exacerbations of Asthma, allergic Asthma, Acute lung injury, Acute respiratory distress syndrome, Idiopathic pulmonary fibrosis, Airway remodeling, Bronchiolitis obliterans syndrome or Bronchopulmonary dysplasis.

121. Use of the polypeptide of any one of claims 1 to 103 in the manufacture of a medicament for the treatment of Atherosclerosis, Glomerulonephritis, Inflammatory

Bowl Disease (Crohn's), Angiogenesis and diseases characterised by new blood vessel development including Macular degeneration, Diabetic retinopathy and Diabetic neuropathy, Multiple sclerosis, Psoriasis, Age-related Macula degenerative disease, Ocular Behcet Disease, Uveitis, Pulmonary Arterial Hypertension (PAH) including idiopathic PAH, familial PAH and associated PAH, Chronic inflammatory diseases, Rhenumatoid arthritis, Osteoarthritis, non-small cell carcinoma, Colon cancer, Pancreatic cancer, Esophageal cancer, Ovarian cancer, Breast cancer, Solid tumors and Metasases, Melanoma, Hepatocellular carcinoma, Ischaemia reperfusion injury, Hemolytic transfusion induced-vaso-occlusion crisis in Sickle cell disease, Ischemia/reperfusion injury, Acute stroke/myocardial infarct, Closed head injury, Posttraumatic inflammation or insulin resistant diabetes.

The invention claimed is:

1. An isolated polypeptide comprising a first immunoglobulin single variable domain and a second immunoglobulin single variable domain, wherein each domain binds to the chemokine receptor CXCR2, and wherein the first immunoglobulin single variable domain binds a linear peptide consisting of the sequence of amino acids set forth in SEQ ID NO: 7 and the second immunoglobulin single variable domain does not bind to said linear peptide.

2. The isolated polypeptide of claim **1** wherein at least one of said first or second immunoglobulin single variable domains is a V_{HH} domain or fragment thereof.

3. The isolated polypeptide of claim **2** wherein said V_{HH} domain or fragment thereof is sequence-optimised.

4. The isolated polypeptide of claim **1** which has one of the following structures:

a) FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4—LINKER—FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8;

b) FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4—LINKER—FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8—LINKER—HLE; or

c) FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4—LINKER—HLE—LINKER—FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8

wherein if the first immunoglobulin single variable domain comprises FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 then the second immunoglobulin single variable domain comprises FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8 and if the second immunoglobulin single variable domain comprises FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 then the first immunoglobulin single variable domain comprises FR5-CDR4-FR6-CDR5-FR7-CDR6-FR8 and the HLE is a binding unit providing an increased in vivo half-life.

5. The isolated polypeptide of claim **4**, wherein the first immunoglobulin single variable domain has an amino acid sequence with at least 90% identity to the amino acid sequence of SEQ ID NO: 216 and the second immunoglobulin single variable domain has an amino acid sequence with at least 90% identity to the amino acid sequence of SEQ ID NO:217.

6. The isolated polypeptide of claim **5**, wherein the CDR amino acid sequences are selected from SEQ ID NOs: 141, 236, 181, 146, 237, or 186.

7. The isolated polypeptide of claim **4**, comprising the amino acid sequence as set forth in SEQ ID NO: 221.

8. The isolated polypeptide of claim **1** further comprising an HLE binding unit having the amino acid sequence of SEQ ID NO: 228.

9. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 225.

10. The isolated polypeptide of claim **4**, wherein the first immunoglobulin single variable domain comprises the amino acid sequence set forth in SEQ ID NO: 216 and the second immunoglobulin single variable domain comprises the amino acid sequence set forth in SEQ ID NO: 217.

11. The isolated polypeptide of claim **1** wherein in said second immunoglobulin single variable domain comprises 3 CDRs having the amino acid sequences set forth in SEQ ID NO: 141, 236 and 181 and wherein in said first immunoglobulin single variable domain comprises 3 CDRs having the amino acid sequence set forth in SEQ ID NO: 146, 237 and 186.

12. The isolated polypeptide of claim **1** wherein said first immunoglobulin single variable domain binds to an epitope comprising amino acids F11, F14 and W15 of SEQ ID NO: 1.

13. The isolated polypeptide of claim **12** wherein said epitope is linear.

14. The isolated polypeptide of claim **1** wherein said second immunoglobulin single variable antigen-binding domain binds to an epitope within the external loops of human CXCR2 (amino acid residues 106-120, 184-208 and 274-294 of SEQ ID NO: 1).

15. The isolated polypeptide of claim **14** wherein said epitope is within amino acid residues 106-120 and 274-294 of SEQ ID NO: 1.

16. The isolated polypeptide of claim **15** wherein said epitope is conformational.

17. The isolated polypeptide of claim **16** wherein said second immunoglobulin single variable domain binds to an epitope of CXCR2, comprising amino acid residues W112, G115, 1282 and T285 of SEQ ID NO: 1.

18. The isolated polypeptide of claim **1** which specifically binds to human CXCR2 with a dissociation constant (K_D) of 10^{-8} to 10^{-12} moles/liter or less.

19. The isolated polypeptide of claim **1** which specifically binds to human CXCR2 with a rate of association (k_{on}-rate) of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$.

20. The isolated polypeptide of claim **1** which specifically binds to human CXCR2 with a rate of dissociation (k_{off} rate) between 1 s^{-1} and 10^{-6} s^{-1}.

21. The isolated polypeptide of claim **1** which specifically binds to human CXCR2 with an affinity less than 500 pM.

22. The isolated polypeptide according to claim **1** which is modified to have an increased in vivo half-life, compared to the corresponding unmodified amino acid sequence.

23. The isolated polypeptide according to claim **22** wherein said increased half-life is provided by one or more binding units chosen from the group consisting of serum proteins or fragments thereof, binding units that bind to serum proteins, an Fc portion, and small proteins or peptides that bind to serum proteins.

24. The isolated polypeptide according to claim **23** wherein said binding unit is an immunoglobulin single variable domain that binds to serum albumin or a serum immunoglobulin.

25. The isolated polypeptide according to claim **23** wherein the serum protein is human serum albumin.

26. The isolated polypeptide according to claim **22** that has a serum half-life that is at least 5 times greater than the half-life of the corresponding unmodified polypeptide.

27. The isolated polypeptide according to claim **1** which is capable of cross-blocking the binding of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 221 to CXCR2.

28. A pharmaceutical composition comprising the isolated polypeptide of claim **1** and a pharmaceutically acceptable carrier or diluent.

29. The isolated polypeptide of claim **1** that binds the same epitopes as a polypeptide having the amino acid sequence of SEQ ID NO: 221.