CLAIMS

1. An isolated antibody fragment, wherein the fragment is the knob domain of a bovine ultralong CDR-H3 or a portion thereof which binds to an antigen of interest, and which is 20 amino acids in length or more.

2. An isolated antibody fragment according to claim 1, which comprises at least two, or at least four, or at least six, or at least eight, or at least ten cysteine residues.

3. An isolated antibody fragment according to claim 1 or 2, which comprises at least one, or at least two, or at least three, or at least four, or at least five disulphide bonds.

4. An isolated antibody fragment according to any one of claims 1 to 3, which comprises a (Z_1) X_1 C X_2 motif at its N-terminal extremity, wherein:

   a. Z_1 is present or absent, and when Z_1 is present, Z_1 represents 1 amino acid or 2, 3, 4, or 5 independently selected amino acids; and,

   b. X_1 is any amino acid residue, preferably selected from the list consisting of Serine, Threonine, Asparagine, Alanine, Glycine, Proline, Histidine, Lysine, Valine, Arginine, Isoleucine, Leucine, Phenylalanine and Aspartic acid; and,

   c. C is cysteine; and,

   d. X_2 is an amino acid selected from the list consisting of Proline, Arginine, Histidine, Lysine, Glycine and Serine.

5. An isolated antibody fragment according to any one of claims 1 to 4, which comprises a (AB)n and/or (BA)n motif, wherein A is any amino acid residue, B is an aromatic amino acid selected from the group consisting of: tyrosine (Y), phenylalanine (F), tryptophan (W), and histidine (H), and wherein n is 1, 2, 3 or 4.

6. An isolated antibody fragment according to any one of the preceding claims, which is 25 amino acids in length or more, 30 amino acids in length or more, 35 amino acids in length or

more, 40 amino acids in length or more, 45 amino acids in length or more, and which is up to 55 amino acids in length.

7. An isolated antibody fragment according to any one of the preceding claims, which is between 20 and 45 or between 25 and 55 amino acids in length.

8. An isolated antibody fragment according to any one of the preceding claims, which further comprises a bridging moiety between two amino acids.

9. An isolated antibody fragment according to claim 8, wherein the bridging moiety comprises a feature selected from the group consisting of a disulphide bond, an amide bond (lactam), a thioether bond, an aromatic ring, an unsaturated aliphatic hydrocarbon chain, a saturated aliphatic hydrocarbon chain and a triazole ring.

10. An isolated antibody fragment according to any one of the preceding claims, which is fully bovine.

11. An isolated antibody fragment according to any one of claims 1 to 9, which is chimeric.

12. An isolated antibody fragment according to any one of claims 1 to 9, which is synthetic.

13. An isolated antibody fragment according to any one of the preceding claims, wherein the antigen of interest is the component C5 of the Complement, which has a sequence selected from the list consisting of SEQ ID NO: 157 to SEQ ID NO: 310, SEQ ID NO: 313, SEQ ID NO: 315, SEQ ID NO: 317, SEQ ID NO: 318, SEQ ID NO: 320, SEQ ID NO: 322, SEQ ID NO: 324, SEQ ID NO: 326 to SEQ ID NO: 331, SEQ ID NO: 334, SEQ ID NO: 336, SEQ ID NO: 339, SEQ ID NO: 341 to SEQ ID NO: 350, SEQ ID NO: 352, and SEQ ID NO: 572 to SEQ ID NO: 609 or any one of the same with at least 95%, 96%, 97%, 98% or 99% similarity or identity.

14. An isolated antibody fragment according to any one of claims 1 to 12, wherein the antigen of interest is human serum albumin, which has the sequence SEQ ID NO: 510.

15. A polypeptide comprising at least two isolated antibody fragments as defined in any one of claims 1 to 14, wherein the antibody fragments are linked together, optionally via a linker, for example a cleavable linker.

16. A polypeptide according to claim 15, wherein the at least two isolated antibody fragments bind to a same antigen.

17. A polypeptide according to claim 15, wherein the at least two isolated antibody fragments bind to different antigens.

18. A polypeptide according to any one of claims 15 to 17, wherein the polypeptide comprises at least one bridging moiety between two amino acids.

19. An isolated antibody fragment according to any one of claims 1 to 14, or a polypeptide according to any one of claims 15 to 18, wherein said fragment or polypeptide is fused to one or more effector molecules, optionally via a linker, for example a cleavable linker.

20. An isolated antibody fragment or a polypeptide according to claim 19, wherein the effector molecule is an antibody.

21. An isolated antibody fragment or a polypeptide according to claim 20, wherein the effector molecule is a full IgG.

22. An isolated antibody fragment or a polypeptide according to claim 20, wherein the effector molecule is selected from the list consisting of a Fab, a VHH, a VH, a VL, a scFv, and a dsscFv.

23. An isolated antibody fragment or a polypeptide according to any one of claims 20 to 22, wherein the effector molecule comprises an albumin binding domain.

24. An isolated antibody fragment or a polypeptide according to claim 19, wherein the effector molecule is albumin or a protein comprising an albumin binding domain.

25. An isolated antibody fragment or a polypeptide according to claim 23 or 24, wherein the albumin binding domain comprises SEQ ID NO: 435 for CDR-H1, SEQ ID NO: 436 for CDR-H2, SEQ ID NO: 437 for CDR-H3, SEQ ID NO: 430 for CDR-L1, SEQ ID NO: 431 for CDR-L2 and SEQ ID NO: 432 for CDR-L3; or a heavy chain variable domain selected from SEQ ID NO: 434 and SEQ ID NO: 444 and a light chain variable domain selected from SEQ ID NO: 429 and SEQ ID NO: 443.

26. A pharmaceutical composition comprising an isolated antibody fragment as defined in any one of claims 1 to 14 or any one of claims 19 to 35, or a polypeptide as defined in any one of claims 15 to 25, in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier.

27. An isolated antibody fragment as defined in any one of claims 1 to 14 or any one of claims 19 to 25, or a polypeptide as defined in any one of claims 15 to 25, for use in therapy.

28. A polynucleotide encoding an isolated antibody fragment as defined in any one of claims 1 to 14 or any one of claims 19 to 25, or a polypeptide as defined in any one of claims 15 to 25.

29. A vector comprising a polynucleotide according to claim 28.

30. A host cell comprising the polynucleotide or vector of claim 28 or 29 respectively.

31. A process for producing an isolated antibody fragment as defined in any one of claims 1 to 14 or any one of claims 19 to 25, or a polypeptide as defined in any one of claims 15 to 25, said process comprising expressing an isolated antibody fragment as defined in any one of claims 1 to 14 or any one of claims 19 to 25, or a polypeptide as defined in any one of claims 15 to 25, from a host cell defined in claim 30.

32. A method of producing an isolated antibody fragment as defined in any one of claims 1 to 14 or any one of claims 19 to 25, or a polypeptide as defined in any one of claims 15 to 25, said method comprising a step of chemical synthesis.

33. A method according to claim 32, wherein the chemical synthesis comprises a step of incorporating a coupling reagent with a radioisotope.

34. A method according to claim 33, wherein the radioisotope is an alpha emitting radioisotope, preferably Astatine 211.

35. A method of producing an isolated antibody fragment as defined in any one of claims 1 to 14 or any one of claims 19 to 25, or a polypeptide as defined in any one of claims 15 to 25, said method comprising:

a) immunising a bovine with an immunogenic composition, and;

b) isolating antigen-specific memory B-cells, and;

c) sequencing the cDNA of CDR-H3 or portions thereof, and;

d) expressing or synthesising the knob domain of the ultralong CDR-H3 or portion thereof,

e) wherein the immunogenic composition comprises an antigen of interest or immunogenic portion thereof, or DNA encoding the same.

36. A method according to claim 35, wherein said method further comprises a step of screening, for example for binding to said antigen of interest, and wherein, optionally, the screening step is preceded by a step of reformatting the ultralong CDR-H3 or the knob domain of the ultralong CDR-H3 or portion thereof into a screening format,

37. , wherein the step of reformatting the ultralong CDR-H3 or the knob domain of the ultralong CDR-H3 or portion thereof into a screening format comprises fusing the ultralong CDR-H3 or the knob domain of the ultralong CDR-H3 or portion thereof, to a carrier, optionally via a linker, for example a cleavable linker.

38. A method according to claim 36, wherein the carrier is an Fc polypeptide.

39. A method according to claim 38, wherein the Fc polypeptide is a scFc.

40. A library comprising at least one isolated antibody fragment as defined in any one of claims 1 to 14.

41. A library according to claim 40, which is a synthetic library.

42. A library according to claim 40, which is a phage library.

43. A library according to claim 42, which is a naive library.

44. A library according to claim 42, which is an immune library.

45. A library according to claim 43 or 44, wherein the library is prepared from cattle.

46. A phage display library, comprising a plurality of recombinant phages;
each of the plurality of recombinant phages comprising an M13-derived expression vector,

wherein the M13-derived expression vector comprises a polynucleotide sequence encoding an isolated antibody fragment as defined in any one of claims 1 to 14.

47. A method for producing an isolated antibody fragment which binds to an antigen of interest as defined in any one of claims 1 to 14, said method comprising:

a) generating a phage display library of ultralong CDR-H3 sequences; and,

b) enriching the phage display library against the antigen of interest to produce an enriched population of phage which bind the antigen of interest; and,

c) sequencing an ultralong CDR-H3 from the enriched population of phage obtained in step b); and,

d) expressing or synthesising an isolated antibody fragment derived from the ultralong CDR-H3 obtained in step c).

48. A method for producing an isolated antibody fragment which binds to an antigen of interest as defined in any one of claims 1 to 14, said method comprising:

a) generating a phage display library of isolated antibody fragments as defined in any one of claims 1 to 14; and,

b) enriching the phage display library against the antigen of interest to produce an enriched population of phage which bind the antigen of interest; and,

c) sequencing an isolated antibody fragment from the enriched population of phage obtained in step b); and,

d) expressing or synthesising an isolated antibody fragment obtained in step c).