Claims

1. A compound comprising a first polypeptide and a second polypeptide, wherein:

(A) said first polypeptide comprises:

(i) a light chain variable domain of a first immunoglobulin (VL1) specific for a first target protein;

(ii) a heavy chain variable domain of a second immunoglobulin (VH2) specific for a second target protein; and

(iii) a hinge region, a heavy chain constant region 2 (CH2) and a heavy chain constant region 3 (CH3); and

(B) said second polypeptide comprises:

(i) a light chain variable domain of the second immunoglobulin (VL2) specific for said second target protein;

(ii) a heavy chain variable domain of the first immunoglobulin (VH1) specific for said first target protein;

wherein:

a) said VL1 and VH1 associate to form a binding site that binds said first target protein;

b) said VL2 and VH2 associate to form a binding site that binds said second target protein;

c) said heavy chain constant region 2 (CH2) comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256, numbered according to the EU index as in Kabat for the CH2 of a conventional antibody; and

d) said first target protein is B-cell activating factor (“BAFF”) and said second target protein is Interleukin-23A (“IL-23A”)

or said first target protein is IL-23A and said second target protein is BAFF,

and wherein:

(i) said VL1 comprises the amino acid sequence of SEQ ID NO:2, said VH1 comprises the amino acid sequence of SEQ IDNO:1, said VL2 comprises the amino acid sequence of SEQ ID NO:4 and said VH2 comprises the amino acid sequence of SEQ ID NO:3; or

(ii) said VL1 comprises the amino acid sequence of SEQ ID NO:4, said VH1 comprises the amino acid sequence of SEQ ID NO:3, said VL2 comprises the amino acid sequence of SEQ ID NO:2 and said VH2 comprises the amino sequence of SEQ ID NO:1; or

(iii) said VL1 comprises the amino acid sequence of SEQ ID NO:89, said VH1 comprises the amino acid sequence of SEQ ID NO:88, said VL2 comprises the amino acid sequence of SEQ ID NO:4 and said VH2 comprises the amino acid sequence of SEQ ID NO:3; or

(iv) said VL1 comprises the amino acid sequence of SEQ ID NO:4, said VH1 comprises the amino acid sequence of SEQ ID NO:3, said VL2 comprises the amino acid sequence SEQ ID NO:89 and said VH2 comprises the amino acid sequence of SEQ ID NO:88; or

(v) said VL1 comprises the amino acid sequence of SEQ ID NO:91, said VH1 comprises the amino acid sequence of SEQ ID

NO:90, said VL2 comprises the amino acid sequence of SEQ ID NO:4 and said VH2 comprises the amino acid sequence of SEQ ID NO:3; or

(vi) said VL1 comprises the amino acid sequence of SEQ ID NO:4, said VH1 comprises the amino acid sequence of SEQ ID NO:3, said VL2 comprises the amino acid sequence of SEQ ID NO:91 and said VH2 comprises the amino acid sequence of SEQ ID NO:90.

2. The compound according to claim 1, wherein said first polypeptide further comprises a first linker between said VL1 and said VH2 and said second polypeptide further comprises a second linker between said VL2 and said VH1.

3. The compound according to claim 2, wherein said first linker or said second linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69).

4. The compound according to claim 2, wherein said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69).

5. The compound according to claim 1, wherein said first polypeptide further comprises a heavy chain constant region 1 domain (CH1) and said second polypeptide further comprises a light chain constant region domain (CL), wherein said CL and said CH1 are associated together via a disulfide bond to form a Cl domain.

6. The compound according to claim 5, wherein said first polypeptide further comprises a third linker between said VH2 and said CH1 and said second polypeptide further comprises a fourth linker between said VH1 and said CL.

7. The compound according to claim 6, wherein said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:70).

8. The compound according to claim 6, wherein said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:70).

9. The compound according to claim 1, wherein said heavy chain constant region 2 (CH2) comprises an alanine at positions 234 and an alanine at position 235, numbered according to the EU index as in Kabat for the CH2 of a conventional antibody.

10. The compound according to claim 1, wherein the amino acid sequence of said hinge region, said heavy chain constant region 2 (CH2) or said heavy chain constant region 3 (CH3) is derived from a IgG1 or from a IgG4.

11. The compound according to claim 1, wherein said hinge region comprises the amino acid sequence EPKSCDKTHTCPPCP (SEQ ID NO:76), the amino acid sequence LEPKSSDKTHTCPPCP (SEQ ID NO:130) or the amino acid sequence ESKYGPPCPPCP (SEQ ID NO:134).

12. The compound according to claim 1, wherein:

(i) said first polypeptide comprises the amino acid sequence of SEQ ID NO:5 and

said second polypeptide comprises the amino acid sequence of SEQ ID NO:6; or

(ii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:7 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:8; or

(iii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:9 and

said second polypeptide comprises the amino acid sequence of SEQ ID NO:10; or

(iv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:11 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:12; or

(v) said first polypeptide comprises the amino acid sequence of SEQ ID NO:13 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:14; or

(vi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:15 and said second polypeptide comprises the amino acid sequence of SEQ ID

NO:16; or

(vii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:17 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:18; or

(viii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:19

and said second polypeptide comprises the amino acid sequence of SEQ ID NO:20; or

13. A pharmaceutical composition comprising a compound according to claim 1.

14. A compound comprising two first polypeptides and two second polypeptides;

wherein said two first polypeptides are associated together via at least one disulfide bond and wherein each of said first polypeptide is associated to one said second polypeptide via at least one disulfide bond;

wherein each of said first polypeptides comprises:

(i) a light chain variable domain of a first immunoglobulin (VL1) specific for a first target protein;

(ii) a heavy chain variable domain of a second immunoglobulin (VH2) specific for a second target protein;

(iii) a heavy chain constant region 1 (CH1), a hinge region, a heavy chain

constant region 2 (CH2) and a heavy chain constant region 3 (CH3);

and

wherein each of said second polypeptide comprises:

(i) a light chain variable domain of the second immunoglobulin (VL2) specific for said second target protein;

(ii) a heavy chain variable domain of the first immunoglobulin (VH1)
specific for said first target protein;

(iii) a light chain constant region domain (CL);

wherein the hinge, CH2 and CH3 of one of the first polypeptides associates with the hinge, CH2 and CH3 of the other of the first polypeptides and the CH1 of each said first polypeptides associates with the CL of said each second polypeptides to form a tetravalent molecule;

wherein

a) said VL1 and VH1 associate to form a binding site that binds said first target protein;

b) said VL2 and VH2 associate to form a binding site that binds said second target protein;

c) said heavy chain constant region 2 (CH2) comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256, numbered according to the EU index as in Kabat for the CH2 of a conventional antibody; and

d) said first target protein is B-cell activating factor ("BAFF") and said second target protein is Interleukin-23A ("IL-23A") or said first target protein is IL-23A and said second target protein is BAFF,

and wherein:

(i) said VL1 comprises the amino acid sequence of SEQ ID NO:2, said VH1 comprises the amino acid sequence of SEQ ID NO:1, said VL2 comprises the amino acid sequence of SEQ ID NO:4 and said VH2 comprises the amino acid sequence of SEQ ID NO:3; or

(ii) said VL1 comprises the amino acid sequence of SEQ ID NO:4, said VH1 comprises the amino acid sequence of SEQ ID NO:3, said VL2 comprises the amino acid sequence of SEQ ID NO:2 and said VH2 comprises the amino acid sequence of SEQ ID NO:1; or

(iii) said VL1 comprises the amino acid sequence of SEQ ID NO:89, said VH1 comprises the amino acid sequence of SEQ ID NO:88, said VL2 comprises the amino acid sequence of SEQ ID NO:4 and said VH2 comprises the amino acid sequence of SEQ ID NO:3; or

(iv) said VL1 comprises the amino acid sequence of SEQ ID NO:4, said VH1 comprises the amino acid sequence of SEQ ID NO:3, said VL2 comprises the amino acid sequence of SEQ ID NO:89 and said VH2 comprises the amino acid sequence of SEQ ID NO:88; or

(v) said VL1 comprises the amino acid sequence of SEQ ID NO:91, said VH1 comprises the amino acid sequence of SEQ ID NO:90, said VL2

comprises the amino acid sequence of SEQ ID NO:4 and said VH2 comprises the amino acid sequence of SEQ ID NO:3; or

(vi) said VL1 comprises the amino acid sequence of SEQ ID NO:4, said VH1 comprises the amino acid sequence of SEQ ID NO:3, said VL2 comprises the amino acid sequence of SEQ ID NO:91 and said VH2 comprises the amino acid sequence of SEQ ID NO:90.

15. A compound comprising a first polypeptide and a second polypeptide, wherein:

(A) said first polypeptide comprises:

(i) a light chain variable domain of a first immunoglobulin (VL1) specific for a first target protein;

(ii) a heavy chain variable domain of a second immunoglobulin (VH2) specific for a second target protein; and

(iii) a hinge region, a heavy chain constant region 2 (CH2) and a heavy chain constant region 3 (CH3); and

(B) said second polypeptide comprises:

(i) a light chain variable domain of the second immunoglobulin (VL2) specific for said second target protein;

(ii) a heavy chain variable domain of the first immunoglobulin (VH1) specific for said first target protein;

wherein:

a) said VL1 and VH1 associate to form a binding site that binds said first target protein;

b) said VL2 and VH2 associate to form a binding site that binds said second target protein;

c) said heavy chain constant region 2 (CH2) comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256, numbered according to the EU index as in Kabat for the CH2 of a conventional antibody; and

d) said first target protein is B-cell activating factor (“BAFF”) and said second target protein is Interleukin-23A (“IL-23A”) or said first target protein is IL-23A and said second target protein is BAFF,

and wherein:

(i) said first polypeptide comprises the amino acid sequence of SEQ ID NO:61 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:62.

16. A compound comprising a first polypeptide and a second polypeptide, wherein:

(A) said first polypeptide comprises:

(i) a light chain variable domain of a first immunoglobulin (VL1) specific for a first target protein;

(ii) a heavy chain variable domain of a second immunoglobulin (VH2) specific for a second target protein; and

(iii) a hinge region, a heavy chain constant region 2 (CH2) and a heavy chain constant region 3 (CH3); and

(B) said second polypeptide comprises:

(iii) a light chain variable domain of the second immunoglobulin (VL2) specific for said second target protein;

(iv) a heavy chain variable domain of the first immunoglobulin (VH1) specific for said first target protein;

wherein:

a) said VL1 and VH1 associate to form a binding site that binds said first target protein;

b) said VL2 and VH2 associate to form a binding site that binds said second target protein;

c) said heavy chain constant region 2 (CH2) comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256, numbered according to the EU index as in Kabat for the CH2 of a conventional antibody; and

d) said first target protein is B-cell activating factor (“BAFF”) and said second target protein is Interleukin-23A (“IL-23A”) or said first target protein is IL-23A and said second target protein is BAFF,

and wherein:

(i) said first polypeptide comprises the amino acid sequence of SEQ ID NO:49 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:50.

17. A compound comprising a first polypeptide and a second polypeptide, wherein:

(A) said first polypeptide comprises:

(i) a light chain variable domain of a first immunoglobulin (VL1) specific for a first target protein;

(ii) a heavy chain variable domain of a second immunoglobulin (VH2) specific for a second target protein; and

(iii) a hinge region, a heavy chain constant region 2 (CH2) and a heavy chain constant region 3 (CH3); and

(B) said second polypeptide comprises:

(i) a light chain variable domain of the second immunoglobulin (VL2) specific for said second target protein;

(ii) a heavy chain variable domain of the first immunoglobulin (VH1) specific for said first target protein;

wherein:

a) said VL1 and VH1 associate to form a binding site that binds said first target protein;

b) said VL2 and VH2 associate to form a binding site that binds said second target protein;

c) said heavy chain constant region 2 (CH2) comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256, numbered according to the EU index as in Kabat for the CH2 of a conventional antibody; and

d) said first target protein is B-cell activating factor (“BAFF”) and said second target protein is Interleukin-23A (“IL-23A”) or said first target protein is IL-23A and said second target protein is BAFF,

and wherein:

(e) said VL1 comprises the amino acid sequence of SEQ ID NO:4, said VH1 comprises the amino acid sequence of SEQ ID NO:3, said VL2 comprises the amino

acid sequence of SEQ ID NO:91 and said VH2 comprises the amino acid sequence of SEQ ID NO:90.

18. A compound comprising a first polypeptide and a second polypeptide, wherein:

(A) said first polypeptide comprises:

(i) a light chain variable domain of a first immunoglobulin (VL1) specific for a first target protein;

(ii) a heavy chain variable domain of a second immunoglobulin (VH2) specific for a second target protein; and

(iii) a hinge region, a heavy chain constant region 2 (CH2) and a heavy chain constant region 3 (CH3); and

(B) said second polypeptide comprises:

(i) a light chain variable domain of the second immunoglobulin (VL2) specific for said second target protein;

(ii) a heavy chain variable domain of the first immunoglobulin (VH1) specific for said first target protein;

wherein:

a) said VL1 and VH1 associate to form a binding site that binds said first target protein;

b) said VL2 and VH2 associate to form a binding site that binds said second target protein;

c) said heavy chain constant region 2 (CH2) comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256, numbered according to the EU index as in Kabat for the CH2 of a conventional antibody; and

d) said first target protein is B-cell activating factor (“BAFF”) and said second target protein is Interleukin-23A (“IL-23A”) or said first target protein is IL-23A and said second target protein is BAFF,

and wherein:

(i) said first polypeptide comprises the amino acid sequence of SEQ ID NO:11 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:12.