

Claims

What is claimed is:

1. A compound comprising a first polypeptide and a second polypeptide, wherein:
 - 5 (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
 - 10 (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;
 - 15 (ii) a heavy chain variable domain of the first immunoglobulin (VH1) specific for said first target protein;
- wherein:
 - (i) said VL1 and VH1 associate to form a binding site that binds said first target protein;
 - 20 (ii) said VL2 and VH2 associate to form a binding site that binds said second target protein;
 - (iii) 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; and
 - 25 (iv) said first target protein is TNF-alpha and said second target protein is IL-23A or said first target protein is IL-23A and said second target protein is TNF-alpha,
- wherein:

- (i) said VL1 comprises SEQ ID NO:2, said VH1 comprises SEQ ID NO:1, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7; or
- (ii) said VL1 comprises SEQ ID NO:4 or 6, said VH1 comprises SEQ ID NO:3 or 5, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7; or
- (iii) said VL1 comprises SEQ ID NO:8, said VH1 comprises SEQ ID NO:7, said VL2 comprises SEQ ID NO:2 and said VH2 comprises SEQ ID NO:1; or
- (iv) said VL1 comprises SEQ ID NO:8, said VH1 comprises SEQ ID NO:7, said VL2 comprises SEQ ID NO:4 or 6 and said VH2 comprises SEQ ID NO:3 or 5.

2. The compound according to claim 1, wherein in (ii) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7.

3. The compound according to claim 1, wherein in (ii) said VL1 comprises SEQ ID NO:6, said VH1 comprises SEQ ID NO:5, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7.

4. The compound according to claim 1, wherein in (iv) said VL2 comprises SEQ ID NO:4, said VH2 comprises SEQ ID NO:3, said VL1 comprises SEQ ID NO:8 and said VH1 comprises SEQ ID NO:7.

5. The compound according to claim 1, wherein in (iv) said VL2 comprises SEQ ID NO:6, said VH2 comprises SEQ ID NO:5, said VL1 comprises SEQ ID NO:8 and said VH1 comprises SEQ ID NO:7.

6. 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.

5 7. The compound according to claim 6, wherein said first linker or said second linker comprises the amino acid sequence GGGSGGG (SEQ ID NO:9).

8. The compound according to claim 6, wherein said first linker and said second linker comprise the amino acid sequence GGGSGGG (SEQ ID NO:9).

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9. 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 C1 domain.

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10. The compound according to claim 9, 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.

20 11. The compound according to claim 10, wherein said third linker comprises the amino acid sequence FNRGES (SEQ ID NO:11).

12. The compound according to claim 10, wherein said fourth linker comprises the amino acid sequence VEPKSS (SEQ ID NO:12).

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13. The compound according to claim 10, wherein said third linker comprises the amino acid sequence FNRGES (SEQ ID NO:11) and said fourth linker comprises the amino acid sequence VEPKSS (SEQ ID NO:12).

14. The compound according to claim 10, wherein said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:10).

15. The compound according to claim 10, wherein said third linker and said fourth linker
5 comprise the amino acid sequence LGGGSG (SEQ ID NO:10).

16. The compound according to any one of the preceding claims, 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.

10 17. The compound according to any one of the preceding claims, 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.

15 18. The compound according to any one of the preceding claims, wherein said hinge region comprises the amino acid sequence EPKSCDKTHTCPPCP (SEQ ID NO:40).

19. The compound according to any one of the preceding claims, wherein said compound comprises two said first polypeptides and two said second polypeptides, wherein said two
20 first polypeptides are associated together via at least one disulfide bond.

20. The compound according to claim 1, wherein:

(i) 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;

25 (ii) 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;

(iii) 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;

(iv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:19 and
30 said second polypeptide comprises the amino acid sequence of SEQ ID NO:20;

- (v) said first polypeptide comprises the amino acid sequence of SEQ ID NO:21 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:22;
- (vi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:24;
- 5 (vii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:26;
- (viii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:28;
- (ix) said first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and
10 said second polypeptide comprises the amino acid sequence of SEQ ID NO:30;
- (x) said first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:32;
- (xi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:34; or
- 15 (xii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:35 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:36.

21. The compound according to claim 20, wherein said compound comprises two said
first polypeptides and two said second polypeptides, wherein said two first polypeptides are
20 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.

22. The compound according to claim 20 or 21, wherein said compound comprises two
said first polypeptides and two said second polypeptides, wherein each of said first
25 polypeptides comprises a CH1, a CH2 and a CH3 and each of said second polypeptides
comprises a CL and wherein the CH2 and CH3 of one of the first polypeptides associates
with the CH2 and CH3 of the other of the first polypeptides and the CH1 of each said first
polypeptides associates with the CL of one said second polypeptides to form a tetravalent
molecule.

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23. A first compound that competes with a second compound for binding to IL-23A and to TNF-alpha, wherein said first compound comprises a third polypeptide and fourth polypeptide, wherein:

(A) said third polypeptide comprises:

5 (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

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

(B) said fourth polypeptide comprises:

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

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

and wherein

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

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

(iii) said first target protein is TNF-alpha and said second target protein is IL-23A or said first target protein is IL-23A and said second target protein is TNF-alpha,

25 and wherein said second compound comprises a first polypeptide and a second polypeptide, wherein:

(i) 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;

(ii) 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;

- (iii) 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;
- (iv) 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;
- 5 (v) said first polypeptide comprises the amino acid sequence of SEQ ID NO:21 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:22;
- (vi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:24;
- (vii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and
10 said second polypeptide comprises the amino acid sequence of SEQ ID NO:26;
- (viii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:28;
- (ix) said first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:30;
- 15 (x) said first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:32;
- (xi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and
said second polypeptide comprises the amino acid sequence of SEQ ID NO:34; or
- (xii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:35 and
20 said second polypeptide comprises the amino acid sequence of SEQ ID NO:36.

24. A pharmaceutical composition comprising a compound according to any one of
claims 1 to 23.
- 25 25. A method of treating an autoimmune or an inflammatory disease comprising
administering a compound according to any one of claims 1 to 23 or a pharmaceutical
composition comprising said compound to a subject.
26. A compound according to any one of claims 1 to 23 for use in medicine.

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27. The compound according to claim 26, wherein said use is the treatment of an autoimmune or an inflammatory disease.
28. A pharmaceutical composition comprising a compound according to any one of
5 claims 1 to 23 for use in medicine.
29. The pharmaceutical composition according to claim 28, wherein said use is the treatment of an autoimmune or an inflammatory disease.
- 10 30. A nucleic acid comprising a nucleotide sequence encoding a polypeptide according to any one of claims 1 to 22.
31. A vector comprising a nucleic acid according to claim 30.
- 15 32. The vector according to claim 31, further comprising a promoter operably linked to said nucleic acid.
33. A cell comprising a nucleic acid according to claim 30 or a vector according to claim 31 or claim 32.
- 20 34. A method of producing a polypeptide according to any one of claims 1 to 20 comprising obtaining a cell according to claim 33 and expressing said nucleic acid in said cell.
- 25 35. The method according to claim 34, further comprising isolating and purifying said polypeptide.