

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; and

d) said first target protein is BAFF and said second target protein is IL-23A or said first target protein is IL-23A and said second target protein is BAFF;

and wherein:

(i) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:91 and said VH2 comprises SEQ ID NO:90; or

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

(iii) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:2 and said VH2 comprises SEQ ID NO: 1; or

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

(v) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:89 and said VH2 comprises SEQ ID NO:88; or

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

2. A compound **according to claim 1** selected from the following:

(i) one **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;

(ii) one **according to claim 1 or 2(i)** wherein said first linker or said second linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69);

(iii) one **according to claim 1 or 2(i)** wherein said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69);

(iv) one **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;

(v) one **according to claim 1 or 2(iv)** 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;

(vi) one **according to claim 2(v)**, wherein said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:70);

(vii) one **according to claim 2(v)**, wherein said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:70);

(viii) one **according to claim 1 or claim 2(i) to (vii)**, 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;

(ix) one **according to claim 1 or claim 2(i) to (viii)**, 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;

(x) one **according to claim 1 or claim 2(i) to (ix)**, 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);

(xi) one **according to claim 1 or claim 2(i) to (x)**, wherein said compound comprises two said first polypeptides and two said second polypeptides, wherein said two first polypeptides are associated together via at least one disulfide bond;

(xii) one **according to claim 1**, wherein:

(a) 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

(b) 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

(c) 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

(d) 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

(e) 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

(f) 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

- (g) 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
- (h) 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
- (i) said first polypeptide comprises the amino acid sequence of SEQ ID NO:37 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:38; or
- (j) said first polypeptide comprises the amino acid sequence of SEQ ID NO:39 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:40; or
- (k) said first polypeptide comprises the amino acid sequence of SEQ ID NO:41 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:42; or
- (l) said first polypeptide comprises the amino acid sequence of SEQ ID NO:43 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:44; or
- (m) said first polypeptide comprises the amino acid sequence of SEQ ID NO:45 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:46; or
- (n) said first polypeptide comprises the amino acid sequence of SEQ ID NO:47 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:48; or
- (o) 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; or
- (p) said first polypeptide comprises the amino acid sequence of SEQ ID NO:51 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:52; or
- (q) 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; or
- (r) said first polypeptide comprises the amino acid sequence of SEQ ID NO:63 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:64; or
- (s) said first polypeptide comprises the amino acid sequence of SEQ ID NO:65 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:66; or

(t) said first polypeptide comprises the amino acid sequence of SEQ ID NO:67 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:68;

(xiii) one **according to claim 2(xii)(a) through (t)** wherein said compound comprises two of said first polypeptides and two of said 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;

(xiv) one **according to claim 2 (xii)(a) through (t) or claim 2 (xiii)** wherein said compound comprises two of said first polypeptides and two of said second polypeptides, wherein each of said first polypeptides comprises a CH1, hinge, a CH2 and a CH3 and each of said second polypeptides comprises a CL and further 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 one said second polypeptides to form a tetravalent molecule.

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

(A) said third 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 fourth 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;

and 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;
- and
- c) said first target protein is BAFF and said second target protein is IL-23A or said first target protein is IL-23A and said second target protein is BAFF, 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: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
 - (ix) said first polypeptide comprises the amino acid sequence of SEQ ID NO:37 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:38; or
 - (x) said first polypeptide comprises the amino acid sequence of SEQ ID NO:39 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:40; or

(xi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:41 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:42; or

(xii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:43 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:44; or

(xiii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:45 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:46; or

(xiv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:47 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:48; or

(xv) 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; or

(xvi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:51 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:52; or

(xvii) 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; or

(xviii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:63 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:64; or

(xix) said first polypeptide comprises the amino acid sequence of SEQ ID NO:65 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:66; or

(xx) said first polypeptide comprises the amino acid sequence of SEQ ID NO:67 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:68.

4. 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; and

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

and wherein:

(i) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:91 and said VH2 comprises SEQ ID NO:90; or

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

(iii) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:2 and said VH2 comprises SEQ ID NO: 1; or

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

(v) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:89 and said VH2 comprises SEQ ID NO:88; or

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

5. A compound **according to claim 4** selected from the following:

(i) one **according to claim 4** wherein each of said first polypeptides further comprises a first linker between said VL1 and said VH2, and each of said second polypeptides further comprises a second linker between said VL2 and said VH1;

(ii) one **according to claim 5(i)** wherein said first linker or said second linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69);

(iii) one **according to claim 5(i)** wherein said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69);

(iv) one **according to claim 5(i)** wherein each of said first polypeptides further comprises a third linker between said VH2 and said CHI, and each of said second polypeptides further comprises a fourth linker between said VH1 and said CL;

(v) one **according to claim 5(iv)** wherein said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:70);

(vi) one **according to claim 5(iv)** wherein said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:70);

(vii) one **according to claim 4**, 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;

(viii) one **according to claim 4**, 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;

(ix) one **according to claim 4**, 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);

(x) one **according to claim 4**, wherein:

(a) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:5 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:6; or

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

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

(d) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO: 15 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO: 16; or

(e) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:37 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:38; or

(f) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:41 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:42; or

(g) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:45 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:46; or

(h) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:49 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:50; or

(i) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:61 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:62; or

(j) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:63 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:64; or

(k) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:65 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:66; or

(l) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:67 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:68.

6. A pharmaceutical composition comprising a compound **according to any one of claims 1 to 5**.

7. Use of a compound according to **any one of claims 1 to 5** or a pharmaceutical composition comprising said compound for the treatment of an autoimmune or an inflammatory disease in a subject in need thereof.

8. Use of a compound according to **any one of claims 1 to 5** in the preparation of a medicament for use in human therapy.

9. The use of **claim 8**, wherein said medicament is for use in the treatment of an autoimmune or an inflammatory disease.

10. A nucleic acid selected from the following:

(i) one comprising a nucleotide sequence encoding a polypeptide **according to any one of claims 1 to 5**;

(ii) a vector comprising a nucleic acid **according to (i)**; or

(iii) a vector comprising a nucleic acid **according to (i)** further comprising a promoter operably linked to said nucleic acid.

11. A cell comprising a nucleic acid or a vector **according to claim 10(i) to (iii)**.

12. A method of producing a polypeptide according to **any one of claims 1 to 5** comprising obtaining a cell **according to claim 11** and expressing said nucleic acid in said cell.

13. The method **according to claim 12**, further comprising isolating and purifying said polypeptide.

14. The use **according to claim 7 or 9** wherein the autoimmune or an inflammatory disease comprises systemic lupus erythematosus (SLE), systemic lupus erythematosus with kidney involvement, Lupus Nephritis (LN), ANCA-associated vasculitis (AAV), primary Sjögren's syndrome (pSS), chronic graft versus host disease (cGVHD), systemic sclerosis (SSc), Rheumatoid Arthritis (RA), Psoriasis (Ps), Ankylosing Spondylitis (AS) or Psoriatic Arthritis (PA).