

CLAIMS

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

(A) said first polypeptide comprises in the direction from the N-terminus to the C-terminus:

- (i) a light chain variable domain of a first immunoglobulin (VL1) specific for interleukin 23 p19 subunit ("IL-23A");
- (ii) a first linker;
- (iii) a heavy chain variable domain of a second immunoglobulin (VH2) specific for B-cell activating factor ("BAFF");
- (iv) a third linker;
- (v) a human IgG heavy chain constant region 1 (CH1);
- (vi) a human IgG hinge region;
- (vii) a human IgG heavy chain constant region 2 (CH2) comprising a tyrosine at position 252, a threonine at position 254 and a glutamic acid at position 256, numbered according to the EU index as in Kabat; and
- (viii) a human IgG heavy chain constant region 3 (CH3); and

(B) said second polypeptide comprises in the direction from the N-terminus to the C-terminus:

- (i) a light chain variable domain of the second immunoglobulin (VL2) specific for BAFF;
- (ii) a second linker;
- (iii) a heavy chain variable domain of the first immunoglobulin (VH1) specific for IL-23A;
- (iv) a fourth linker; and
- (v) a light chain constant region (CL),

wherein:

- a) said VL1 and VH1 associate to form a binding site that binds IL-23;
- b) said VL2 and VH2 associate to form a binding site that binds BAFF;
- c) said CL and said CH1 form a C1 domain; and
- d) said CH1, said hinge region, said CH2, and said CH3 form a constant region derived from a human IgG1 or from a human IgG4,

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:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:89 and said VH2 comprises SEQ ID NO:88,

further wherein:

- (1) said first linker comprises the amino acid sequence of SEQ ID NO: 69;
- (2) said second linker comprises the amino acid sequence of SEQ ID NO: 69;
- (3) said third linker comprises the amino acid sequence of SEQ ID NO: 70; and
- (4) said fourth linker comprises the amino acid sequence of SEQ ID NO: 70.

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

- (A) said first polypeptide comprises in the direction from the N-terminus to the C-terminus:
 - (i) a VL1 specific for IL-23A;
 - (ii) a first linker;
 - (iii) a VH2 specific for B-cell activating factor BAFF;

- (iv) a third linker;
- (v) a human IgG CH1;
- (vi) a human IgG hinge region;
- (vii) a human IgG CH2 comprising a tyrosine at position 252, a threonine at position 254 and a glutamic acid at position 256, numbered according to the EU index as in Kabat; and
- (viii) a human IgG CH3; and

(B) said second polypeptide comprises in the direction from the N-terminus to the C-terminus:

- (i) a VL2 specific for BAFF;
- (ii) a second linker;
- (iii) a VH1 specific for IL-23A;
- (iv) a fourth linker; and
- (v) a CL,

wherein:

- a) said VL1 and VH1 associate to form a binding site that binds IL-23;
- b) said VL2 and VH2 associate to form a binding site that binds BAFF;
- c) said CL and said CH1 form a C1 domain; and
- d) said CH1, said hinge region, said CH2, and said CH3 form a constant region derived from a human IgG1 or from a human IgG4,

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:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:89 and said VH2 comprises SEQ ID NO:88,

further wherein the compound comprises at least one feature selected from features (1)-(6) and at least one feature selected from features (7)-(9),

wherein said features (1)-(6) are:

(1) to bind human BAFF with a dissociation constant (KD) of 10^{-10} M or lower;

(2) to inhibit human BAFF trimer-induced NFkB activation in cells *in vitro* comparably to or more potently than (i) an anti-BAFF antibody comprising a VH comprising the amino acid sequence of SEQ ID NO: 1 and a VL comprising the amino acid sequence of SEQ ID NO: 2, (ii) a BAFF antagonist protein comprising the amino acid sequence of SEQ ID NO: 131, and (iii) an anti-BAFF antibody comprising a VH comprising the amino acid sequence of SEQ ID NO: 132 and a VL comprising the amino acid sequence of SEQ ID NO: 133;

(3) to inhibit human BAFF 60mer-induced NFkB activation in cells *in vitro* more potently than (i) an anti-BAFF antibody comprising a VH comprising the amino acid sequence of SEQ ID NO: 1 and a VL comprising the amino acid sequence of SEQ ID NO: 2, (ii) a BAFF antagonist protein comprising the amino acid sequence of SEQ ID NO: 131, and (iii) an anti-BAFF antibody comprising a VH comprising the amino acid sequence of SEQ ID NO: 132 and a VL comprising the amino acid sequence of SEQ ID NO: 133;

(4) to inhibit membrane-bound human BAFF-induced NFkB activation in cells *in vitro* more potently than (i) an anti-BAFF antibody comprising a VH comprising the amino acid sequence of SEQ ID NO: 1 and a VL comprising the amino acid sequence of SEQ ID NO: 2, (ii) a BAFF antagonist protein comprising the amino acid sequence of SEQ ID NO: 131, and (iii) an anti-BAFF antibody comprising a VH comprising the amino acid sequence of SEQ ID NO: 132 and a VL comprising the amino acid sequence of SEQ ID NO: 133,

(5) to inhibit human BAFF-induced proliferation of B cells *in vitro* more potently than an anti-BAFF antibody comprising a VH comprising the amino acid sequence of SEQ ID NO: 132 and a VL comprising the amino acid sequence of SEQ ID NO: 133, and

(6) to provide statistically significant inhibition of human BAFF-induced proliferation of B cells in mice intraperitoneally administered with said compound,

and wherein said features (7)-(9) are:

(7) to bind human interleukin 23 (IL-23) with a KD of 10^{-10} M or lower;

(8) to provide statistically significant inhibition of human IL-23-induced release of IL-17 in mice intraperitoneally administered with said compound; and

(9) to provide statistically significant inhibition of human IL-23-induced release of interleukin 22 (IL-22) in the skin in mice intraperitoneally administered with said compound.

3. The compound **according to claim 2**, wherein:

(1) said first linker comprises the amino acid sequence of SEQ ID NO: 69;

(2) said second linker comprises the amino acid sequence of SEQ ID NO: 69;

(3) said third linker comprises the amino acid sequence of SEQ ID NO: 70; and

(4) said fourth linker comprises the amino acid sequence of SEQ ID NO: 70.

4. The compound **according to any one of claims 1-3**, wherein:

(i) the amino acid sequence of said CH1, said hinge region, said CH2, and said CH3 are derived from an IgG1, wherein said hinge region comprises the amino acid sequence of SEQ ID NO: 76 and said CH2 comprises an alanine at positions 234 and an alanine at position 235, numbered according to the EU index as in Kabat for a conventional antibody; or

(ii) the amino acid sequence of said CH1, said hinge region, said CH2 and said CH3 are derived from a human IgG4 and said hinge region comprises the amino acid sequence of SEQ ID NO: 134.

5. The compound **according to claim 4**, wherein said CH1, said hinge region, said CH2, and said CH3 form a constant region comprising an amino acid sequence with at least 96% identity to (i) SEQ ID NO: 128 or (ii) SEQ ID NO: 74.

6. The compound **according to claim 4**, wherein said CH1, said hinge region, said CH2, and said CH3 form a constant region comprising an amino acid sequence of SEQ ID NO: 128 or SEQ ID NO: 74.

7. The compound **according to any one of claims 1-6**, wherein:
- (i) said first polypeptide comprises an amino acid sequence with at least 98% identity to SEQ ID NO:37 and said second polypeptide comprises an amino acid sequence with at least 98% identity to SEQ ID NO:38;
 - (ii) said first polypeptide comprises an amino acid sequence with at least 98% identity to SEQ ID NO:41 and said second polypeptide comprises an amino acid sequence with at least 98% identity to SEQ ID NO:42;
 - (iii) said first polypeptide comprises an amino acid sequence with at least 98% identity to SEQ ID NO:45 and said second polypeptide comprises an amino acid sequence with at least 98% identity to SEQ ID NO:46; or
 - (iv) said first polypeptide comprises an amino acid sequence with at least 98% identity to SEQ ID NO:49 and said second polypeptide comprises an amino acid sequence with at least 98% identity to SEQ ID NO:50.
8. The compound **according to claim 1**, wherein:
- (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;
 - (ii) 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;
 - (iii) 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
 - (iv) 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.
9. The compound **according to claim 1**, wherein 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-

- 10.** The compound **according to any one of claims 1-9**, 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 to form a tetravalent molecule.
- 11.** A pharmaceutical composition comprising a compound **according to any one of claims 1 to 10**.
- 12.** The compound according to **any one of claims 1 to 10** or the pharmaceutical composition comprising said compound for use as a medicament.
- 13.** The compound according to **any one of claims 1 to 10** or a pharmaceutical composition comprising said compound for use in human therapy.
- 14.** The compound **according to any one of claims 1 to 10** or a pharmaceutical composition comprising said compound for use in the treatment of an autoimmune or an inflammatory disease.
- 15.** Use of a compound **according to any one of claims 1 to 10** in the manufacture of a medicament for the treatment of an autoimmune or an inflammatory disease.
- 16.** A nucleic acid selected from the following:
- (i) one comprising a nucleotide sequence encoding a polypeptide **according to any one of claims 1 to 10**;
 - (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.
- 17.** A cell comprising a nucleic acid or a vector **according to claim 10(i) to (iii)**.
- 18.** A method of producing a polypeptide according to **any one of claims 1 to 10** comprising obtaining a cell **according to claim 17** and expressing said nucleic acid in said cell.
- 19.** The method **according to claim 18**, further comprising isolating and purifying said polypeptide.

20. The use **according to claim 15** 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).