COMPOUND TARGETING IL-23A AND B-CELL ACTIVATING FACTOR (BAFF) AND USES THEREOF

RELATED APPLICATION

This application claims the benefit of the filing date under 35 U.S.C. §119 of United States Provisional Applications Serial Number 62/196,170, filed July 23, 2015; Serial No. 62/201,067, filed August 4, 2015; and Serial No. 62/355, 302, filed June 27, 2016, all entitled COMPOUND TARGETING IL-23A AND B-CELL ACTIVATING FACTOR (BAFF) AND USES THEREOF, the entire contents of all of which are incorporated by reference herein.

BACKGROUND

Inflammation involves an innate and adaptive immune response that is required for fighting infection. However, when the inflammation becomes unchecked autoimmune or autoinflammatory diseases, neurodegenerative disease, and even cancer can develop. It is known that proinflammatory cytokines such as IL1, BAFF, TNF-alpha, IL6, IL12, IL17, IL18, and IL23 are involved in inflammation and specific pathways that activate immune cells. However, it is unclear whether or how the inhibition of one or more of these cytokines could result in treatment of autoimmune or autoinflammatory diseases.

Interleukin 23 (IL23) is a heterodimeric cytokine consisting of two subunits, p40 and p19. The p19 subunit is also referred to as IL-23A. While the p19 subunit is unique to IL23, the p40 subunit is shared with the cytokine IL12. IL23 is emerging as a key regulator of pathogenic Th17, γδ T and innate lymphoid cells (ILCs) driving the production of IL17, IL22 and other cytokines that lead to local tissue inflammation and damage. IL23 promotes upregulation of the matrix metalloprotease MMP9, increases angiogenesis, reduces CD8+ T cell infiltration, and has been implicated in the development of cancerous tumors. In addition, in conjunction with IL6 and TGFβ1, IL23 stimulates naive CD4+ T cells to differentiate into Th17 cells. In turn, the Th17 cells produce IL17, a proinflammatory cytokine that enhances T cell priming and stimulates the production of proinflammatory cytokines such as IL1, IL6, TNF-alpha, NOS-2, and also induces expression of chemokines resulting in inflammation and disease pathogenesis. IL23 exerts its effects via a cell surface receptor composed of the

IL12β1 subunit of IL12 receptor partnered with a unique IL23R subunit. Expression of the IL23R is restricted to specific populations of immune cells and is found primarily on subsets of T cells (αβ and γδ TCR+) and NK cells.

In mice, genetic ablation of the IL23p19 gene results in selective loss of IL23 function accompanied by severely compromised T-dependent immune responses, including reduced production of antigen-specific immunoglobulins and impaired delayed type hypersensitivity responses (Ghilardi N, et al. (2004) *J. Immunol.* 172(5): 2827-33). Knockout mice deficient in either IL23p40 or IL23p19, or in either subunit of the IL23 receptor (IL23R and IL12β1), develop less severe symptoms in animal models of multiple sclerosis, arthritis and inflammatory bowel disease. Similar results have been obtained using an antibody specific for IL23p19 in EAE and a T cell mediated colitis model further substantiates the role of IL23 in these disease settings (Chen Y. et al. (2006) *J. Clin. Invet.* 116(5):1317–26; Elson CO. Et al. (2007) *Gastroenterology* 132(7): 2359-70) .This highlights the importance of IL23 in chronic inflammation (Langowski et al. (2006) *Nature* 442 (7101): 461–5; Kikly K, et al. (2006) *Curr. Opin. Immunol.* 18 (6): 670–5). In addition, elevated IL23 production has been implicated as being a major factor in inflammatory arthritis and in inflammatory autoimmune diseases (Adamopoulos et al. (2011) *J. Immunol.* 187: 593-594; and Langris et al. (2005) *J. Exp. Med.* 201:233-240). A connection between IL23, its downstream cytokine IL22, and bone formation has been published in a mouse model system in which IL23 is overexpressed (Sherlock et al. (2012) Nat. Med. 18: 1069-76).

B-cell activating factor (BAFF) is a cytokine that belongs to the tumor necrosis factor (TNF) ligand superfamily and acts as a ligand for receptors BAFF-R (BR3), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) and BCMA (B-cell maturation antigen). The interaction between BAFF and its receptors triggers signals essential for the formation and maintenance of B cells, which in turn synthesizes immunoglobulins in response to invasion by a foreign substance. Appropriate levels of BAFF in a patient help maintain normal levels of immunity whereas inadequate levels can lead to immunodeficiency and excessive levels can result in abnormally high antibody production. When a patient exhibits autoimmunity, it produces antibodies against the tissues or organs of its own body. Autoimmune diseases, including lupus erythematosus and rheumatoid arthritis,

result from excessive levels of BAFF in the body. Thus it is important to modulate the production of BAFF in order to treat the patients having these diseases.

BAFF can exist in three forms: membrane bound (mbBAFF), soluble trimeric BAFF (sBAFF) and a multimeric form consisting of 60 BAFF monomers (BAFF 60mer). The relative importance of the various forms of BAFF in normal and disease physiology is not well understood. As noted, BAFF binds to three receptors, BAFFR (BR3), TACI and BCMA. A proliferation-inducing ligand (APRIL), a related member of the TNF receptor ligand family, has been shown to bind with high affinity to TACI and BCMA. In contrast to the high affinity APRIL:BCMA interaction, the BAFF:BCMA interaction is of low affinity (1-2 μM) and is not believed to be play an important role *in vivo* (Bossen and Schneider, 2006).

Soluble BAFF is expressed at high levels in individuals with systemic lupus erythematosus (SLE) and in inflamed target organs such as the kidney. Soluble BAFF serves as a critical factor for B cell homeostasis and survival (Kalled et al., 2005; Mackay et al., 2003; Smith and Cancro, 2003; Patke et al., 2004). Autoantibody formation by BAFF-dependent B cells results in glomerular IC deposits, initially at the glomerular basement membrane (GBM), mesangium and interstitial tissue within the proximal tubular epithelial cells (PTEC). These IC deposits lead to complement fixation and neutrophil activation resulting in local kidney damage. Inflammatory mediators (*e.g.* IL6, IL8, MCP-1) produced by the damaged kidney cells (MC, PTEC, renal fibroblasts, endothelial cells) fuel an inflammatory cycle by increasing immune cell infiltration (*e.g.* B cells, T cells, dendritic cells, neutrophils and macrophages).

Anti-BAFF monoclonal antibody belimumab (Benlysta®) has the demonstrated ability to decrease autoantibody formation and has provided significant benefit to patients with systemic lupus erythematosus (SLE). However, efficacy of belimumab in SLE patients is moderate at best, and there is substantial room for improvement (Furie et al., 2011). Therefore, there remains a need for new compositions with increased efficacy for treating and preventing autoimmune or inflammatory diseases. Furthermore, identification of more efficacious treatments should allow for administration of reduced dosages, as well as lower

costs associated with the treatment.

SUMMARY

Provided herein are compounds specific for BAFF and IL23A, compositions comprising such compounds, as well as methods of use and production thereof.

Aspects of the disclosure relate to 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:2, said VH1 comprises SEQ ID NO:1, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:3; or

(ii) 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

(iii) said VL1 comprises SEQ ID NO:85, said VH1 comprises SEQ ID NO:84, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:4; or

(iv) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:85 and said VH2 comprises SEQ ID NO:84; or

(v) said VL1 comprises SEQ ID NO:87, said VH1 comprises SEQ ID NO:86, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:3; or

(vi) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:87 and said VH2 comprises SEQ ID NO:86; or

(vii) 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

(viii) 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

(ix) 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; or

(x) 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.

In some embodiments, 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. In some embodiments, said first linker or said second linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first polypeptide further comprises a third linker between said VH2 or said VL1 and said hinge region, and said second polypeptide further comprises a fourth linker after said VH1 (at its C-terminal end) or said VL2 (at its C-terminal end). In some embodiments, said third linker of said first polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82), and said fourth linker of said second polypeptide comprises the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In other embodiments, said third linker of said first polypeptide comprises the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83), and said fourth linker of said second polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82). In some embodiments, said third linker of said first polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82) or the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In other embodiments, said forth linker of said second polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82) or the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In some embodiments, said third linker comprises the amino acid sequence VEPKSC (SEQ ID NO:72) or the amino acid sequence FNRGEC (SEQ ID NO:71). In some embodiments, said fourth linker comprises the amino acid sequence FNRGEC (SEQ ID NO:71) or the amino acid sequence VEPKSC (SEQ ID NO:72). In some embodiments, said

third linker comprises the amino acid sequence VEPKSC (SEQ ID NO:72) and said fourth linker comprises the amino acid sequence FNRGEC (SEQ ID NO:71).

In some embodiments, said first polypeptide further comprises a heavy chain constant region 1 domain (CH1) between said VH2 or said VL1 (depending on the configuration) and the hinge region and said second polypeptide further comprises a light chain constant region domain (CL) at the C-terminal end of said VH1 or VL2 (depending on the configuration), wherein said CL and said CH1 are associated together via a disulfide bond to form a C1 domain. In some embodiments, said first linker (between said VL1 and said VH2) or said second linker (between said VL2 and said VH1) comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first polypeptide further comprises a third linker between said VH2 or said VL1 (depending on the configuration) and said CH1, and said second polypeptide further comprises a fourth linker between said VH1 or said VL2 (depending on the configuration) and said CL. In some embodiments, said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:70). In some embodiments, said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:70). In some embodiments, said third linker and/or said fourth linker comprise an optional cysteine residue. In some embodiments, said third linker and/or said fourth linker comprise the amino acid sequence GGCGGG (SEQ ID NO:135) or LGGCGGGS (SEQ ID NO:136).

In some embodiments, 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 a conventional antibody.

In some embodiments, 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. In some embodiments, said hinge region comprises the amino acid sequence EPKSCDKTHTCPPCP (SEQ ID NO:76). The hinge region of SEQ ID NO:76 is present in, for example, SEQ ID NO:5 polypeptide. In other embodiments, the hinge region comprises the amino acid sequence LEPKSSDKTHTCPPCP (SEQ ID NO:130). The hinge region of SEQ ID NO:130 is present in, for example, SEQ ID NO:9 polypeptide. In still other embodiments, the hinge region comprises the amino acid sequence ESKYGPPCPPCP (SEQ

ID NO:134). The hinge region of SEQ ID NO:134 is present in, for example, SEQ ID NO:13 polypeptide.

In some embodiments, 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. In some embodiments, 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 and wherein each of said first polypeptide is associated to one said second polypeptide via at least one disulfide bond.

In some embodiments,

(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:21 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:22; or

(x) 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; or

(xi) 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; or

(xii) 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; or

(xiii) 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; or

(xiv) 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; or

(xv) 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

(xvi) 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; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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

(xxi) 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

(xxii) 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

(xxiii) 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

(xxiv) 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

(xxv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:53 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:54; or

(xxvi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:55 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:56; or

(xxvii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:57 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:58; or

(xxviii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:59 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:60; or

(xxix) 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

(xxx) 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

(xxxi) 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

(xxxii) 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.

In some embodiments, 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.

In some embodiments, said compound comprises two said first polypeptides and two said second polypeptides, and 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 to form a tetravalent molecule. In some embodiments, said compound comprises two said first polypeptides and two said second polypeptides, wherein each of said first polypeptides comprises a CH1, a hinge, a CH2 and a CH3 and each of said second polypeptides comprises a CL and 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 (e.g., a monomer, a monomeric antibody as described in the Examples section) (e.g., compounds E and V). In some embodiments, said compound comprises two said first polypeptides and two said second polypeptides, wherein each of said first polypeptides comprises a third linker, a hinge, a CH2 and a CH3, and each of said second polypeptides comprises a fourth linker and 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 third linker of each said first polypeptides associates with the fourth linker of one said second polypeptides to form a tetravalent molecule (e.g., a monomer, a monomeric antibody as described in the Examples section) (e.g., compounds U and T).

Other aspects of the disclosure relate to 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

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

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

(iii) 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:21 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:22; or

(x) 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; or

(xi) 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; or

(xii) 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; or

(xiii) 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; or

(xiv) 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; or

(xv) 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

(xvi) 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; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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

(xxi) 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

(xxii) 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

(xxiii) 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

(xxiv) 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

(xxv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:53 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:54; or

(xxvi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:55 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:56; or

(xxvii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:57 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:58; or

(xxviii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:59 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:60; or

(xxix) 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

(xxx) 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

(xxxi) 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

(xxxii) 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.

Other aspects of the disclosure relate to 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 polypeptides 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:2, said VH1 comprises SEQ ID NO:1, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:3; or

(ii) 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

(iii) said VL1 comprises SEQ ID NO:85, said VH1 comprises SEQ ID NO:84, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:4; or

(iv) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:85 and said VH2 comprises SEQ ID NO:84; or

(v) said VL1 comprises SEQ ID NO:87, said VH1 comprises SEQ ID NO:86, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:3; or

(vi) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:87 and said VH2 comprises SEQ ID NO:86; or

(vii) 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

(viii) 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

(ix) 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; or

(x) 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.

In some embodiments relating to the above aspect, 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. In some embodiments, said first linker or said second linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, each of said first polypeptides further comprises a third linker between said VH2 (or said VL1) and said CH1, and each of said second polypeptides further comprises a

fourth linker between said VH1 (or said VL2) and said CL. In some embodiments, said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:70). In some embodiments, said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:70). In some embodiments, said third linker and/or said fourth linker comprise an optional cysteine residue. In some embodiments, said third linker and/or said fourth linker comprise the amino acid sequence GGCGGG (SEQ ID NO:135) or LGGCGGGS (SEQ ID NO:136). In some embodiments, 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. In some embodiments, 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. In some embodiments, 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).

In some embodiments,

(i) 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

(ii) 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

(iii) 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

(iv) 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

(v) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:21 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:22; or

(vi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:25 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:26; or

(vii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:29 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:30; or

(viii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:33 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:34; or

(ix) 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

(x) 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

(xi) 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

(xii) 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

(xiii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:53 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:54; or

(xiv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:55 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:56; or

(xv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:57 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:58; or

(xvi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:59 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:60; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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.

Other aspects of the disclosure relate to 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; and wherein (i) 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
(ii) 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
(iii) 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
(iv) 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
(v) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:21 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:22; or
(vi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:25 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:26; or
(vii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:29 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:30; or
(viii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:33 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:34; or
(ix) 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
(x) 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
(xi) 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
(xii) 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

(xiii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:53 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:54; or

(xiv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:55 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:56; or

(xv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:57 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:58; or

(xvi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:59 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:60; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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.

Other aspects of the disclosure relate to 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:

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

(v) a heavy chain variable domain of a second immunoglobulin (VH2)

specific for a second target protein;

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

wherein each of said second polypeptides comprises:

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

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

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;

wherein

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

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

g) 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

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

(ii) 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

(iii) said VL1 comprises SEQ ID NO:85, said VH1 comprises SEQ ID NO:84, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:4; or

(iv) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:85 and said VH2 comprises SEQ ID NO:84; or

(v) said VL1 comprises SEQ ID NO:87, said VH1 comprises SEQ ID NO:86, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:3; or

(vi) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:87 and said VH2 comprises SEQ ID NO:86; or

(vii) 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

(viii) 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

(ix) 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; or

(x) 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.

In some embodiments relating to the above aspect, 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. In some embodiments, said first linker or said second linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, each of said first polypeptides further comprises a third linker between said VH2 or said VL1 and said hinge region, and each of said second polypeptides further

comprises a fourth linker at the C-terminal end of said VH1 or said VL2. In some embodiments, said third linker of said first polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82), and said fourth linker of said second polypeptide comprises the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In other embodiments, said third linker of said first polypeptide comprises the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83), and said fourth linker of said second polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82). In some embodiments, said third linker of said first polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82) or the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In other embodiments, said forth linker of said second polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82) or the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In some embodiments, said third linker comprises the amino acid sequence VEPKSC (SEQ ID NO:72) or the amino acid sequence FNRGEC (SEQ ID NO:71). In some embodiments, said fourth linker comprises the amino acid sequence FNRGEC (SEQ ID NO:71) or the amino acid sequence VEPKSC (SEQ ID NO:72). In some embodiments, said third linker comprises the amino acid sequence VEPKSC (SEQ ID NO:72) and said fourth linker comprises the amino acid sequence FNRGEC (SEQ ID NO:71). In some embodiments, 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. In some embodiments, 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. In some embodiments, 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). In some embodiments, (i) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:9 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:10; or

(ii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:11 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:12; or
(iii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:17 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:18; or
(iv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:19 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:20; or
(v) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:23 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:24; or
(vi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:27 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:28; or
(vii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:31 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:32; or
(viii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:35 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:36; or
(ix) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:39 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:40; or
(x) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:43 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:44; or
(xi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:47 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:48; or
(xii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:51 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:52.

Yet other aspects of the disclosure relate to a pharmaceutical composition comprising a compound described herein, such as a compound described above.

Other aspects of the disclosure relate to a method of treating an autoimmune or an inflammatory disease comprising administering a compound described herein, such as a compound described above, or a pharmaceutical composition comprising said compound to a subject.

Yet other aspects of the disclosure relate to a compound described herein, such as a compound described above, for use in medicine. In some embodiments, said use is the treatment of an autoimmune or an inflammatory disease.

Other aspects of the disclosure relate to a pharmaceutical composition comprising a compound described herein, such as a compound described above, for use in medicine. In some embodiments, said use is the treatment of an autoimmune or an inflammatory disease.

Yet other aspects of the disclosure relate to a nucleic acid comprising a nucleotide sequence encoding a polypeptide described herein, such as a polypeptide described above. Other aspects of the disclosure relate to a vector comprising said nucleic acid. In some embodiments, the vector comprises a promoter operably linked to said nucleic acid. Other aspects of the disclosure relate to a cell comprising said nucleic acid or said vector.

Other aspects of the disclosure relate to a method of producing a compound or polypeptide as described herein, such as a polypeptide described above, comprising obtaining a cell described herein, such a cell described above, and expressing a nucleic acid as described herein in said cell. In some embodiments, the method further comprises isolating and purifying said polypeptide or compound.

The details of one or more embodiments of the disclosure are set forth in the description below. Other features or advantages of the present disclosure will be apparent from the following drawings and detailed description of several embodiments, and also from the appending claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure, which can be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1A is a diagram of an exemplary compound specific for BAFF and IL23A. The first polypeptide chain contains CH3, CH2, VH_2 (VH_{II}) and VL_1 (VL_I) domains. The second

polypeptide chain contains VH_1 (VH_I) and VL_2 (VL_{II}) domains. VL_1 and VH_1 are specific for a first target protein (either BAFF or IL23A) and VL_2 and VH_2 are specific for a second target protein (either IL23A or BAFF). The upper panel shows each polypeptide chain separately. The lower panel shows a tetravalent compound (e.g., a monomer, a monomeric antibody as described in the Examples section) formed through association of the CH2 and CH3 domains of one first polypeptide with the CH2 and CH3 domains of another first polypeptide. The binding domains for the first and second target protein are formed through association of VH_1 and VL_1 and through association VH_2 and VL_2, respectively.

FIG. 1B is a diagram of another exemplary compound specific for BAFF and IL23A. The first polypeptide chain contains CH3, CH2, CH1, VH_2 (VH_{II}) and VL_1 (VL_I) domains. The second polypeptide chain contains CL, VH_1 (VH_I) and VL_2 (VL_{II}) domains. VL_1 and VH_1 are specific for a first target protein (either BAFF or IL23A) and VL_2 and VH_2 are specific for a second target protein (either IL23A or BAFF). The upper panel shows each polypeptide chain separately. The lower panel shows a tetravalent compound (e.g., a monomer, a monomeric antibody as described in the Examples section) formed through association of the CH2 and CH3 domains of one first polypeptide with the CH2 and CH3 domains of another first polypeptide. The binding domains for the first and second target protein are formed through association of VH_1 and VL_1 and through association VH_2 and VL_2, respectively. The compound is further associated through interactions between the CL and CH1 domains.

FIG. 2 is a graph showing the serum concentrations (mean ± SD) for Compound A (closed squares), Compound B (open squares), Compound C (closed triangles) and Compound D (open triangles) in male cynomolgus monkeys following a single 1 mg/kg intravenous dose, as described in Example 10.

FIG. 3. Shows the predicted human serum concentration-time profile of Compound B, following a 100 mg s.c. dose administered once every two-weeks, as described in Example 11. The dotted line represents the targeted C_{min} (30 nM).

FIG. 4 shows graphical summary of monomer percentage vs. concentration for Compound B, as described in Example 14.

FIG. 5 shows that Compound B maintains functional potency vs. anti-BAFF *in vivo*. Mice were dosed equimolar with either anti-BAFF or Compound B and challenged with human BAFF minicircle to induce B cell expansion. On day 14 spleens were collected and analyzed by flow cytometry for mouse B220+ B cells as a measure of functional blockade of BAFF.

FIG. 6 shows that Compound B maintains functional potency vs. Anti-IL23 in vivo. Evaluation of Compound B in the IL23 induced cytokine assay. Mice were dosed equimolar with either anti-IL23 or compound B and challenged with human IL23 twice to induce ear inflammation. Twenty four hours after the final injection, ears were collected and analyzed for mouse IL17A and mouse IL22 as a measure of functional blockade of IL23.

DETAILED DESCRIPTION OF THE INVENTION

Described herein compounds that bind to both BAFF and IL-23A (also referred to as IL23p19 or IL23A). To date, there have been no approved compounds that target both BAFF and IL23A. There are limited studies with simultaneous neutralization of two/more key inflammatory mediators using biotherapeutics approach and these studies failed to show improvement in clinical outcomes that were measured for rheumatoid arthritis (RA). In addition, such combinations may increase side effects, such as the risk of infection (see, e.g., Genovese, M.C., Cohen, S., Moreland, L., Lium, D., Robbins, S., et al. (2004). *Arth. Rheum. 50, 1412-9;* Genovese, M.C., Cohen, S., Moreland, L., Lium, D., Robbins, S., et al. *(2004). Arth. Rheum. 50, 1412-9; and* Weinblatt, M., Schiff, M., Goldman, A. Kremer, J., Luggen, M., et al. *(2007). Ann.Rheum.Dis.66, 228-34).* Further, such bi-specific compounds have been difficult to design, due to issues related to solubility (e.g., aggregation) and stability (e.g., poor pharmacokinetics).

Surprisingly, some of the compounds described herein that bind to BAFF and IL-23A have been found to have similar or improved properties compared to individual antibodies that target either IL-23A or BAFF. Some compounds were also found to have suitable pharmacokinetics and were soluble at suitable ranges for dosing purposes. Further, in some embodiments, there are advantages of single administration over multiple individual dose administration from the perspective of side effects of the individual therapies, and lower

dosage. In addition, in some embodiments, the CMC properties of the compounds showed that some compounds had high melting temperatures (Tm) and low aggregation. In one aspect, one exemplary compound showed particularly low aggregation at high concentrations. The compounds described herein are believed to have one or more advantageous properties, e.g., decreased side effects, increased ease and safety of administration, an increased half-life, increased binding affinity, or increased inhibitory activity, compared to standard antibody molecules, e.g., an IgG molecule or antigen-binding fragment (*e.g.*, Fab).

Accordingly, aspects of the disclosure relate to compounds specific for both BAFF and IL-23A, as well as methods of use and production of such compounds. In one aspect, the subject technology relates to compositions with increased efficacy for treating and preventing autoimmune or inflammatory diseases, such as systemic lupus erythematosus (SLE), systemic lupus erythematosus with kidney involvement/ Lupus Nephritis (LN), ANCA-associated vasculitis (AAV), primary Sjogren's syndrome (pSS), chronic graft versus host disease (cGVHD), systemic sclerosis (SSc), Rheumatoid Arthritis (RA), Psoriasis (Ps), Ankylosing Spondylitis (AS), and Psoriatic Arthritis (PA). A BAFF/IL23A dual antagonist will inhibit both autoantibody/immune complex and IL23 axis-mediated end organ damage, and may achieve superior induction and maintenance of clinical response than current Standard of Care for the treatment of SLE and LN. Compared to co-administration of a BAFF antibody and an IL-23 antibody to inhibit both pathways at the same time, a BAFF/IL23A dual antagonist is more convenient to patient that can lead to improved compliance and reduced pain. A BAFF/IL23A dual antagonist should allow for administration of reduced dosages, as well as lower costs associated with the treatment. In addition, a BAFF/IL23A antagonist may also be beneficial in the treatment of a cluster of diseases involving dysregulated B cells/autoantibody and IL23-mediated tissue damage including primary Sjogren's syndrome (pSS), chronic graft versus host disease (cGVHD), systemic sclerosis (SSc) and ANCA-associated vasculitis (AAV).

It is difficult to design a dual-targeting therapeutic molecule that brings two pharmacological entities together and maintains the functional potency of each component, while at the same time has biophysical properties suitable for large scale manufacture. Development of dual-targeting molecules has been hampered with many issues related to in

vitro and in vivo stability, such as poor expression, aggregation, limited shelf-life, poor serum stability and poor pharmacokinetic properties in vivo (Demarest SJ, Glaser SM. (2008). Curr Opin Drug Discov Devel. 11, 675–87).

Here we disclose a method to create dual-targeting molecules that inhibit both BAFF and IL23 function. The dual-targeting molecules of the subject technology have advantageous and surprising properties such as high melting temperatures (Tm), low aggregation at high concentrations, and predicted human PK properties that allows once every two weeks or less frequent s.c. administration.

Compounds

Aspects of the disclosure relate to a compound specific for both BAFF and IL23A. An exemplary protein sequence for BAFF and an exemplary protein sequence for IL23A are shown below.

>sp|Q9Y275|B-cell Activating Factor (BAFF) - TN13B_HUMAN Tumor necrosis factor ligand superfamily member 13B OS=Homo sapiens GN=TNFSF13B PE=1 SV=1
MDDSTEREQSRLTSCLKKREEMKLKECVSILPRKESPSVRSSKDGKLLAATLLLALLSCCLT
VVSFYQVAALQGDLASLRAELQGHHAEKLPAGAGAPKAGLEEAPAVTAGLKIFEPPAPGEGN
SSQNSRNKRAVQGPEETVTQDCLQLIADSETPTIQKGSYTFVPWLLSFKRGSALEEKENKIL
VKETGYFFIYGQVLYTDKTYAMGHLIQRKKVHVFGDELSLVTLFRCIQNMPETLPNNSCYSA
GIAKLEEGDELQLAIPRENAQISLDGDVTFFGALKLL(SEQ ID NO:80)

>NP_057668.1 - IL23A [Homo sapiens]
MLGSRAVMLLLLLPWTAQGRAVPGGSSPAWTQCQQLSQKLCTLAWSAHPLVGHMDLREEGDE
ETTNDVPHIQCGDGCDPQGLRDNSQFCLQRIHQGLIFYEKLLGSDIFTGEPSLLPDSPVGQL
HASLLGLSQLLQPEGHHWETQQIPSLSPSQPWQRLLLRFKILRSLQAFVAVAARVFAHGAAT
LSP (amino acids 1-19 are a predicted signal sequence)(SEQ ID NO:81)

In some embodiments, the compound comprises a first polypeptide and a second polypeptide. In some embodiments, the 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). In some embodiments, the first polypeptide further comprises a heavy chain

constant region 1 (CH1). In some embodiments, the second polypeptide comprises: (i) a light chain variable domain of the second immunoglobulin (VL2) specific for the second target protein; (ii) a heavy chain variable domain of the first immunoglobulin (VH1) specific for the first target protein. In some embodiments, the second polypeptide further comprises a light chain constant region (CL).

It is to be understood that the variable domains and constant domains/regions of the first polypeptide can be in any order and that the variable domains and constant domains/regions (if any) of the second polypeptide can be in any order. Multiple exemplary configurations for the domains/regions on the first and second polypeptide from N- terminus to C-terminus are shown below.

First polypeptide configuration 1: N-VL1-VH2-hinge-CH2-CH3-C

First polypeptide configuration 2: N-VH2-VL1-hinge-CH2-CH3-C

First polypeptide configuration 3: N-VL1-VH2-CH1-hinge-CH2-CH3-C

First polypeptide configuration 4: N-VH2-VL1-CH1-hinge-CH2-CH3-C

Second polypeptide configuration 1: N-VL2-VH1-C

Second polypeptide configuration 2: N-VH1-VL2-C

Second polypeptide configuration 3: N-VL2-VH1-CL-C

Second polypeptide configuration 4: N-VH1-VL2-CL-C

Exemplary configurations of the compound are shown in FIGs. 1A and 1B.

In some embodiments, the variable regions of the first polypeptide and the second polypeptide associate with one another to form a binding site for the first target protein and a binding site for the second target protein. In some embodiments, the VL1 of the first polypeptide and the VH1 of the second polypeptide associate to form a binding site that binds the first target protein and the VL2 of the second polypeptide and the VH2 of the first polypeptide associate to form a binding site that binds the second target protein. In some embodiments, the first target protein is BAFF and the second target protein is IL23A. In other embodiments, the first target protein is IL23A and the second target protein is BAFF. It

is to be understood that the terms "first" and "second" are not meant to imply a level of importance to either target protein.

Exemplary combinations of sequences for each of VL1, VH1, VL2, and VH2 are provided below in Table 1 and also in Table 2 in Example 1.

Table 1. Exemplary combinations of sequences for VL1, VH1, VL2, and VH2.

Combination Number	**VL1 sequence**	**VH1 sequence**	**VL2 sequence**	**VH2 sequence**
1	SEQ ID NO:2	SEQ ID NO:1	SEQ ID NO:4	SEQ ID NO:3
2	SEQ ID NO:4	SEQ ID NO:3	SEQ ID NO:2	SEQ ID NO:1
3	SEQ ID NO:85	SEQ ID NO:84	SEQ ID NO: 4	SEQ ID NO: 3
4	SEQ ID NO:4	SEQ ID NO:3	SEQ ID NO:85	SEQ ID NO:84
5	SEQ ID NO:87	SEQ ID NO:86	SEQ ID NO:4	SEQ ID NO:3
6	SEQ ID NO:4	SEQ ID NO:3	SEQ ID NO:87	SEQ ID NO:86
7	SEQ ID NO:89	SEQ ID NO:88	SEQ ID NO:4	SEQ ID NO:3
8	SEQ ID NO:4	SEQ ID NO:3	SEQ ID NO:89	SEQ ID NO:88
9	SEQ ID NO:91	SEQ ID NO:90	SEQ ID NO:4	SEQ ID NO:3
10	SEQ ID NO:4	SEQ ID NO:3	SEQ ID NO:91	SEQ ID NO:90

In some embodiments, the compound comprises a VL1 sequence comprising a first light chain CDR1, CDR2, and CDR3 and a VH1 sequence comprising a first heavy chain CDR1, CDR2, and CDR3, a VL2 sequence comprising a second light chain CDR1, CDR2 and CDR3, and a VH2 sequence comprising a second heavy chain CDR1, CDR2, and CDR3. In some embodiments, the CDRs are the CDRs of one or more VL1, VH1, VL2, and VH2 sequences provided in Table 1. Exemplary light chain and heavy chain CDR sequences for the VL1, VH1, VL2, and VH2 sequences provided in Table 1 are shown below:

SEQ ID NO: 1 CDRs: GGTFNNNAIN (SEQ ID NO:92) (CDR1), GIIPMFGTAKYSQNFQG (SEQ ID NO:93) (CDR2), SRDLLLFPHHALSP (SEQ ID NO:94) (CDR3)

SEQ ID NO: 2 CDRs: QGDSLRSYYAS (SEQ ID NO:95) (CDR1), GKNNRPS (SEQ ID NO:96) (CDR2), SSRDSSGNHWV (SEQ ID NO:97) (CDR3)

SEQ ID NO: 3 CDRs: GYTFTDQTIH (SEQ ID NO:98) (CDR1), YIYPRDDSPKYNENFKG (SEQ ID NO:99) (CDR2), PDRSGYAWFIY (SEQ ID NO:100) (CDR3)

SEQ ID NO: 4 CDRs: KASRDVAIAVA (SEQ ID NO:101) (CDR1), WASTRHT (SEQ ID NO:102) (CDR2), HQYSSYPFT (SEQ ID NO:103) (CDR3)

SEQ ID NO: 84 CDRs: DHIFSIHWMQ (SEQ ID NO:104) (CDR1), EIFPGSGTTDYNEKFKG (SEQ ID NO:105) (CDR2), GAFDY (SEQ ID NO:106) (CDR3)

SEQ ID NO: 85 CDRs: RASQDIGNRLS (SEQ ID NO:107) (CDR1 ATSSLDS (SEQ ID NO:108) (CDR2), LQYASSPFT (SEQ ID NO:109) (CDR3)

SEQ ID NO: 86 CDRs: DHIFSIHWMQ (SEQ ID NO:110) (CDR1), EIFPGSGTTDYNEKFKG (SEQ ID NO:111) (CDR2), GAFDY (SEQ ID NO: 112) (CDR3)

SEQ ID NO: 87 CDRs: RASQDIGNRLN (SEQ ID NO:112) (CDR1 ATSSLDS (SEQ ID NO:113) (CDR2), LQYASSPFT (SEQ ID NO:114) (CDR3)

SEQ ID NO: 88 CDRs: GYSFSTFFIH (SEQ ID NO:115) (CDR1), RIDPNSGATKYNEKFES (SEQ ID NO:116) (CDR2), GEDLLIRTDALDY (SEQ ID NO:117) (CDR3)

SEQ ID NO: 89 CDRs: KASQNAGIDVA (SEQ ID NO:118) (CDR1), SKSNRYT (SEQ ID NO: 119) (CDR2), LQYRSYPRT (SEQ ID NO:120) (CDR3)

SEQ ID NO: 90 CDRs: GYSFSTFFIH (SEQ ID NO:121) (CDR1), GRIDPNSGATKYNEKFES (SEQ ID NO:122) (CDR2), GEDLLIRTDALDY (SEQ ID NO:123) (CDR3)

SEQ ID NO: 91 CDRs: KASQNAGIDVA (SEQ ID NO:124) (CDR1), SKSNRYT (SEQ ID NO:125) (CDR2), LQYRSYPRT (SEQ ID NO:126) (CDR3)

In some embodiments, the compound comprises a VH1, VL1, VH2, and/or VL2 that comprises a sequence that is at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, or 99%) identical (residue per residue for the entire length of the sequence) to a sequence described in Table 1. The "percent identity" of two amino acid sequences is determined using the algorithm of Karlin and Altschul Proc. Natl. Acad. Sci. USA 87:2264-68, 1990, modified as in Karlin and Altschul Proc. Natl. Acad. Sci. USA 90:5873-77, 1993. Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. J. Mol. Biol. 215:403-10, 1990. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to the protein molecules of interest. Where gaps exist between two sequences, Gapped BLAST can be utilized as described in Altschul et al., Nucleic Acids Res. 25(17):3389-3402, 1997. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

In some embodiments, the compound comprises a VH1, VL1, VH2, and/or VL2 that comprises a sequence comprising one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) mutations in a sequence described in Table 1. Such mutations can be conservative amino acid substitutions. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Conservative substitutions of amino acids include, for example, substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

The amino acid sequences of the hinge region, CH2 and CH3 of the compound (and optionally the CH1 and CL, if the compound contains such regions) may be derived from any appropriate source, e.g., a constant region of an antibody such as an IgG1, IgG2, IgG3, or IgG4. Antibody heavy and light chain constant regions amino acid sequences are well known in the art, e.g., those provided in the IMGT database (www.imgt.org) or at www.vbase2.org/vbstat.php., both of which are incorporated by reference herein.

Furthermore, in some expression systems the C-terminal lysine residue of the CH3 Domain may be post-translationally removed. Accordingly, the C-terminal lysine residue of the CH3 Domain is an optional amino acid residue. Specifically provided by the instant invention are molecules lacking the C-terminal lysine residue of the CH3 Domain. Also specifically encompassed by the instant invention are such constructs comprising the C-terminal lysine residue of the CH3 Domain. In some embodiments, the amino acid sequences of the CH2 and CH3 are derived from an IgG1 (e.g., SEQ ID NO:75) or an IgG4 (e.g., SEQ ID NO:73). In some embodiments, the CL comprises the amino acid sequence of a kappa CL or a lambda CL. In some embodiments, the hinge region comprises the amino acid sequence EPKSCDKTHTCPPCP (SEQ ID NO: 76). The hinge region of SEQ ID NO:76 is present in, for example, SEQ ID NO:5 polypeptide. In other embodiments, the hinge region comprises the amino acid sequence LEPKSSDKTHTCPPCP (SEQ ID NO:**130**). The hinge region of SEQ ID NO:130 is present in, for example, SEQ ID NO:9 polypeptide. The hinge region of SEQ ID NO:130 is also present at the beginning of the Fc domain of SEQ ID NO:129. In still other embodiments, the hinge region comprises the amino acid sequence ESKYGPPCPPCP (SEQ ID NO:**134**). The hinge region of SEQ ID NO:134 is present in, for example, SEQ ID NO:13 polypeptide. The hinge region of SEQ ID NO:134 is also present at the beginning of the Fc domain of SEQ ID NO:127.

In some embodiments, the CH2 and/or CH3 of the compound (and optionally the CH1 and CL, if the compound contains such regions) may comprise one or more amino acid substitutions that differ from a wild type CH2 or CH3, e.g., one or more amino acid substitutions in a wild type IgG1 CH2 or CH3 or one or more amino acid substitutions in a wild type IgG4 CH2 or CH3 (SEQ ID NO: 39 provides an exemplary wild-type IgG1). Such substitutions are known in the art (see, e.g., US7704497, US7083784, US6821505, US 8323962, US6737056, and US7416727).

In some embodiments, the CH2 comprises an amino acid substitution at 234, 235, 252, 254, and/or 256, numbered according to the EU index as in Kabat for a conventional antibody (Kabat et al. Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, 1991, which is incorporated by reference herein in its entirety). It is to be understood that all amino acid positions described herein refer to the numbering of

the EU index as in Kabat for a conventional antibody. In some embodiments, the CH2 comprises an amino acid substitution at position 252, 254, and/or 256. In some embodiments, the amino acid at position 252 is tyrosine, phenylalanine, serine, tryptophan, or threonine. In some embodiments, the amino acid at position 254 is threonine. In some embodiments, the amino acid at position 254 is serine, arginine, glutamine, glutamic acid, or aspartic acid. In some embodiments, the CH2 comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256 (referred to herein as a YTE mutant). In some embodiments, the CH2 comprises an amino acid substitution at position 234 and/or 235. In some embodiments, the CH2 comprises an alanine at position 234 and an alanine at position 235, also referred to herein as KO mutant. In some embodiments, the CH2 comprises a tyrosine at position 252, a threonine at position 254, a glutamic acid a position 256, an alanine at position 234 and an alanine at position 235, also referred to herein as KO-YTE mutant.

In some embodiments, one or more linkers may be used to connect domains/regions together on the first and/or second polypeptide. For example, the first polypeptide may comprise a linker between the VL1 and VH2. The first polypeptide further comprises a linker between the VL1 or VH2 (depending on the configuration as discussed above) and the hinge (e.g., -VL1-linker-hinge or -VH2-linker-hinge). If the first polypeptide comprises a CH1, *e.g.*, first polypeptide may comprise a linker between the VL1 or VH2 (depending on the configuration as discussed above) and the CH1 (e.g., -VL1-linker-CH1 or -VH2-linker-CH1). In another example, the second polypeptide may comprise a linker between the VL2 and VH1. The second polypeptide may further comprise a linker after the VL2 or VH1 (depending on the configuration discussed above, e.g., -VL2-linker or -VH1-linker) at the C-terminal end of the polypeptide chain. If the second polypeptide further comprises a CL, the second polypeptide may further comprise a linker between the VL2 or VH1 (depending on the configuration as discussed above) and the CL (as in, e.g., -VL2-linker-CL or -VH1-linker-CL). It is to be understood that any number of linkers may be used to connect any domain or region to any other another domain or region on the first polypeptide and/or that any number of linkers may be used to connect any domain or region to any other another domain or region on the second polypeptide.

Any suitable linker known in the art is contemplated for use herein. In some embodiments, the linker is a peptide linker. In some embodiments, the peptide linker comprises at least two amino acids, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids. In some embodiments, the peptide linker is no more than 50, 40, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 amino acids in length. In some embodiments, the peptide linker is between 2 and 50, 2 and 40, 2 and 30, 2 and 20, 2 and 10, 2 and 9, 2 and 8, 2 and 7, or 2 and 6 amino acids in length. In some embodiments, the peptide linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69), LGGGSG (SEQ ID NO:70), FNRGEC (SEQ ID NO:71), VEPKSC (SEQ ID NO:72), GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82), GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83) or a combination thereof. In some embodiments, the peptide linker may comprise multiple copies of a linker sequence, e.g., multiple copies of the sequence GGGSGGGG (SEQ ID NO:69), LGGGSG (SEQ ID NO:70), FNRGEC (SEQ ID NO:71), VEPKSC (SEQ ID NO:72), or a combination thereof.

In some embodiments, the first and second polypeptides have the following configurations:

First polypeptide configuration 1: N-VL1-VH2-hinge-CH2-CH3-C,

First polypeptide configuration 2: N-VH2-VL1-hinge-CH2-CH3-C,

Second polypeptide configuration 1: N-VL2-VH1-C,

Second polypeptide configuration 2: N-VH1-VL2-C,

wherein the first linker between VL1 and VH2 of the first polypeptide or the second linker between VL2 and VH1 of the second polypeptide comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, the first polypeptide further comprises a third linker between the VH2 or VL2 and said hinge region and the second polypeptide further comprises a fourth linker after said VH1 or VL2 (at its C-terminus). In some embodiments, said third linker of said first polypeptide comprises the amino acid sequence

GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82), and said fourth linker of said second polypeptide comprises the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In other embodiments, said third linker of said first polypeptide comprises the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83), and said fourth linker of said second polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82). In some embodiments, said third linker of said first polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82) or the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In other embodiments, said forth linker of said second polypeptide comprises the amino acid sequence GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK (SEQ ID NO:82) or the amino acid sequence GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE (SEQ ID NO:83). In some embodiments, said third linker comprises the amino acid sequence VEPKSC (SEQ ID NO:72) or the amino acid sequence FNRGEC (SEQ ID NO:71). In some embodiments, said fourth linker comprises the amino acid sequence FNRGEC (SEQ ID NO:71) or the amino acid sequence VEPKSC (SEQ ID NO:72). In some embodiments, said third linker comprises the amino acid sequence VEPKSC (SEQ ID NO:72) and said fourth linker comprises the amino acid sequence FNRGEC (SEQ ID NO:71). The amino acid sequence FNRGEC (SEQ ID NO:71) is the last six amino acid residues of the CL domain (SEQ ID NO:77) and the amino acid VEPKSC (SEQ ID NO: 72) includes the last amino acid of the CH1 and the first five amino acid residues of the hinge region of SEQ ID NO:76 (as in SEQ ID NO:5).

In some embodiments, the first and second polypeptides have the following configurations:

First polypeptide configuration 3: N-VL1-VH2-CH1-hinge-CH2-CH3-C,

First polypeptide configuration 4: N-VH2-VL1-CH1-hinge-CH2-CH3-C,

Second polypeptide configuration 3: N-VL2-VH1-CL-C,

Second polypeptide configuration 4: N-VH1-VL2-CL-C,

wherein the first linker between said VL1 and said VH2 of the first polypeptide or said second linker between said VL2 and said VH1 of the second polypeptide comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first polypeptide further comprises a third linker between said VH2 or VL1 and said CH1 and said second polypeptide further comprises a fourth linker between said VH1 or said VL2 and said CL. In some embodiments, said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:70). In some embodiments, said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:70). In some embodiments, said third linker and/or said fourth linker comprise an optional cysteine residue. In some embodiments, said third linker and/or said fourth linker comprise the amino acid sequence GGCGGG (SEQ ID NO:135) or LGGCGGGS (SEQ ID NO:136).

In some embodiments, 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 a conventional antibody.

In some embodiments, the compound comprises two first polypeptides and two second polypeptides. In some embodiments, 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 to form a tetravalent molecule (e.g., the two first polypeptides dimerize through associations between their respective hinge CH2 and CH3 domains to form a tetravalent molecule comprising two binding sites specific for the first target protein and two binding sites specific for the second target protein), a monomer or a monomeric antibody as described in the Examples section. If the first polypeptide further comprises a CH1 domain, and the second polypeptide further comprises a CL domain, the CH1 and CL domains may also participate in formation of a tetravalent molecule (e.g., the two first polypeptides dimerize through associations between their respective hinge, CH2 and CH3 domains and the CH1 of each said first polypeptides associates with the CL of one said second polypeptides to form a tetravalent molecule comprising two binding sites for the first target protein and two binding sites for the second target protein) a monomer, a monomeric antibody as described in the

Examples section. In some embodiments, the two first polypeptides are associated together via at least one disulfide bond. In some embodiments, said compound comprises two said first polypeptides and two said second polypeptides, wherein each of said first polypeptides comprises a third linker, a hinge, a CH2 and a CH3, and each of said second polypeptides comprises a fourth linker and 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 third linker of each said first polypeptides associates with the fourth linker of one said second polypeptides to form a tetravalent molecule (e.g., a monomer, a monomeric antibody as described in the Examples section) (e.g., compounds U and T).

In some embodiments, the disclosure relates to 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 polypeptides 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:2, said VH1 comprises SEQ ID NO:1, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:3; or

(ii) 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

(iii) said VL1 comprises SEQ ID NO:85, said VH1 comprises SEQ ID NO:84, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:4; or

(iv) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:85 and said VH2 comprises SEQ ID NO:84; or

(v) said VL1 comprises SEQ ID NO:87, said VH1 comprises SEQ ID NO:86, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:3; or

(vi) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:87 and said VH2 comprises SEQ ID NO:86; or

(vii) 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

(viii) 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

(ix) 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; or

(x) 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.

In some embodiments relating to the above aspect, 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. In some embodiments, said first linker or said second linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69). In some embodiments, each of said first polypeptides further comprises a third linker between said VH2 or said VL1 and said CH1, and each of said second polypeptides further comprises a fourth linker between said VH1 or said VL2 and said CL. In some embodiments, said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:70). In some embodiments, said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:70). In some embodiments, said third linker and/or said fourth linker comprise an optional cysteine residue. In some embodiments, said third linker and/or said fourth linker comprise the amino acid sequence GGCGGG (SEQ ID NO:135) or LGGCGGGS (SEQ ID NO:136). In some embodiments, 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. In some embodiments, 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. In some embodiments, 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). In some embodiments, (i) 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

(ii) 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

(iii) 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

(iv) 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

(v) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:21 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:22; or

(vi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:25 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:26; or

(vii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:29 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:30; or

(viii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:33 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:34; or

(ix) 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

(x) 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

(xi) 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

(xii) 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

(xiii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:53 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:54; or

(xiv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:55 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:56; or

(xv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:57 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:58; or

(xvi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:59 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:60; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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.

Other aspects of the disclosure relate to 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; and wherein (i) 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

(ii) 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

(iii) 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

(iv) 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

(v) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:21 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:22; or

(vi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:25 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:26; or

(vii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:29 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:30; or

(viii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:33 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:34; or

(ix) 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

(x) 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

(xi) 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

(xii) 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

(xiii) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:53 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:54; or

(xiv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:55 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:56; or

(xv) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:57 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:58; or

(xvi) each of said first polypeptides comprises the amino acid sequence of SEQ ID NO:59 and each of said second polypeptides comprises the amino acid sequence of SEQ ID NO:60; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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.

Also contemplated herein are other compounds that compete for binding with a compound as described herein, e.g., a test compound that competes with a compound as described herein for binding to BAFF and IL23A. In some embodiments, the test compound may have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity (amino acid per amino acid over the entire length of the sequence) with a compound as described herein. Competitive binding may be determined using any assay known in the art, e.g., equilibrium binding, ELISA, surface plasmon resonance, or spectroscopy.

In some embodiments, the compound described herein specifically binds to both BAFF and IL23A. A compound that "specifically binds" to an antigen or an epitope is a term well understood in the art, and methods to determine such specific binding are also well known in the art. A molecule is said to exhibit "specific binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular target antigen than it does with alternative targets. A compound "specifically binds" to a target antigen or epitope if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, a compound that specifically (or preferentially) binds to an antigen (e.g., BAFF or IL23A) or an antigenic

epitope therein is a compound that binds this target antigen with greater affinity, avidity, more readily, and/or with greater duration than it binds to other antigens or other epitopes in the same antigen. It is also understood by reading this definition that, for example, a compound that specifically binds to a first target antigen may or may not specifically or preferentially bind to a second target antigen. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding. In some examples, a compound that "specifically binds" to a target antigen or an epitope thereof may not bind to other antigens or other epitopes in the same antigen.

In some embodiments, a compound as described herein has a suitable binding affinity for BAFF and IL23 or antigenic epitopes thereof. As used herein, "binding affinity" refers to the apparent association constant or K_A. The K_A is the reciprocal of the dissociation constant (K_D). The compound described herein may have a binding affinity (K_D) of at least 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12} M or lower for one or both of the target antigens or antigenic epitopes. An increased binding affinity corresponds to a decreased K_D. In some embodiments, the compound described herein has a binding affinity (K_D) of at least 10^{-11}M or lower for one or both of the target antigens or antigenic epitopes. Higher affinity binding of a compound for a first antigen and a second antigen relative to a third antigen can be indicated by a higher K_A (or a smaller numerical value K_D) for binding the first antigen and second antigen than the K_A (or numerical value K_D) for binding the third antigen. In such cases, the compound has specificity for the first antigen and second antigen (e.g., a first protein in a first conformation or mimic thereof and a second protein in a first conformation or mimic thereof) relative to the third antigen (e.g., the same first or second protein in a second conformation or mimic thereof; or a third protein). Differences in binding affinity (e.g., for specificity or other comparisons) can be at least 1.5, 2, 3, 4, 5, 10, 15, 20, 37.5, 50, 70, 80, 91, 100, 500, 1000, 10,000 or 10^5 fold.

Binding affinity (or binding specificity) can be determined by a variety of methods including, equilibrium binding, ELISA, surface plasmon resonance, or spectroscopy (e.g., using a fluorescence assay). Exemplary conditions for evaluating binding affinity are in HBS-P buffer (10 mM HEPES pH 7.4, 150 mM NaCl, 0.005% (v/v) Surfactant P20). These

techniques can be used to measure the concentration of bound binding protein as a function of target protein concentration. The concentration of bound binding protein ([Bound]) is related to the concentration of free target protein ([Free]) and the concentration of binding sites for the binding protein on the target where (N) is the number of binding sites per target molecule by the following equation:

[Bound] = [N][Free]/(Kd+[Free])

It is not always necessary to make an exact determination of K_A, though, since sometimes it is sufficient to obtain a quantitative measurement of affinity, e.g., determined using a method such as ELISA or FACS analysis, is proportional to K_A, and thus can be used for comparisons, such as determining whether a higher affinity is, *e.g.*, 2-fold higher, to obtain a qualitative measurement of affinity, or to obtain an inference of affinity, e.g., by activity in a functional assay, *e.g.*, an in vitro or in vivo assay.

In some embodiments, the compound comprises a first polypeptide and a second polypeptide as defined in Table 2A. In some embodiments, the compound comprises:

(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:21 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:22; or

(x) 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; or

(xi) 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; or

(xii) 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; or

(xiii) 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; or

(xiv) 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; or

(xv) 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

(xvi) 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; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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

(xxi) 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

(xxii) 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

(xxiii) 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

(xxiv) 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

(xxv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:53 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:54; or

(xxvi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:55 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:56; or

(xxvii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:57 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:58; or

(xxviii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:59 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:60; or

(xxix) 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

(xxx) 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

(xxxi) 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

(xxxii) 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.

Methods of producing compounds, nucleic acids, vectors, and cells

Aspects of the disclosure also include nucleic acids that encode compounds described

herein or polypeptides described herein (e.g., first or second polypeptides described herein), which may be encoded together or separately. The polynucleotides encoding the compounds described herein or polypeptides described herein may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art.

In some embodiments, the nucleic acid is comprised within a vector, such as an expression vector. In some embodiments, the vector comprises a promoter operably linked to the nucleic acid.

A variety of promoters can be used for expression of the compounds described herein or polypeptides described herein, including, but not limited to, cytomegalovirus (CMV) intermediate early promoter, a viral LTR such as the Rous sarcoma virus LTR, HIV-LTR, HTLV-1 LTR, the simian virus 40 (SV40) early promoter, *E. coli* lac UV5 promoter, and the herpes simplex tk virus promoter.

Regulatable promoters can also be used. Such regulatable promoters include those using the lac repressor from *E. coli* as a transcription modulator to regulate transcription from lac operator-bearing mammalian cell promoters [Brown, M. et al., Cell, 49:603-612 (1987)], those using the tetracycline repressor (tetR) [Gossen, M., and Bujard, H., Proc. Natl. Acad. Sci. USA 89:5547-5551 (1992); Yao, F. et al., Human Gene Therapy, 9:1939-1950 (1998); Shockelt, P., et al., Proc. Natl. Acad. Sci. USA, 92:6522-6526 (1995)]. Other systems include FK506 dimer, VP16 or p65 using astradiol, RU486, diphenol murislerone, or rapamycin. Inducible systems are available from Invitrogen, Clontech and Ariad.

Regulatable promoters that include a repressor with the operon can be used. In one embodiment, the lac repressor from *Escherichia coli* can function as a transcriptional modulator to regulate transcription from lac operator-bearing mammalian cell promoters [M. Brown et al., Cell, 49:603-612 (1987)]; Gossen and Bujard (1992); [M. Gossen et al., Natl. Acad. Sci. USA, 89:5547-5551 (1992)] combined the tetracycline repressor (tetR) with the transcription activator (VP 16) to create a tetR-mammalian cell transcription activator fusion protein, tTa (tetR-VP 16), with the tetO-bearing minimal promoter derived from the human cytomegalovirus (hCMV) major immediate-early promoter to create a tetR-tet operator system to control gene expression in mammalian cells. In one embodiment, a tetracycline

inducible switch is used (Yao et al., Human Gene Therapy; Gossen et al., Natl. Acad. Sci. USA, 89:5547-5551 (1992); Shockett et al., Proc. Natl. Acad. Sci. USA, 92:6522-6526 (1995)).

Additionally, the vector can contain, for example, some or all of the following: a selectable marker gene, such as the neomycin gene for selection of stable or transient transfectants in mammalian cells; enhancer/promoter sequences from the immediate early gene of human CMV for high levels of transcription; transcription termination and RNA processing signals from SV40 for mRNA stability; SV40 polyoma origins of replication and ColE1 for proper episomal replication; internal ribosome binding sites (IRESes), versatile multiple cloning sites; and T7 and SP6 RNA promoters for in vitro transcription of sense and antisense RNA. Suitable vectors and methods for producing vectors containing transgenes are well known and available in the art.

An expression vector comprising the nucleic acid can be transferred to a host cell by conventional techniques (e.g., electroporation, liposomal transfection, and calcium phosphate precipitation) and the transfected cells are then cultured by conventional techniques to produce the compounds described herein. In some embodiments, the expression of the compounds described herein is regulated by a constitutive, an inducible or a tissue-specific promoter.

The host cells used to express the compounds described herein or polypeptides described herein may be either bacterial cells such as *Escherichia coli*, or, preferably, eukaryotic cells. In particular, mammalian cells, such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for immunoglobulins (Foecking et al. (1986) "Powerful And Versatile Enhancer-Promoter Unit For Mammalian Expression Vectors," Gene 45:101-106; Cockett et al. (1990) "High Level Expression Of Tissue Inhibitor Of Metalloproteinases In Chinese Hamster Ovary Cells Using Glutamine Synthetase Gene Amplification," Biotechnology 8:662-667).

A variety of host-expression vector systems may be utilized to express the compounds described herein or polypeptides described herein. Such host-expression systems represent

vehicles by which the coding sequences of the compounds described herein or polypeptides described herein may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express the compounds described herein in situ. These include, but are not limited to, microorganisms such as bacteria (e.g., *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing coding sequences for the compounds described herein; yeast (e.g., *Saccharomyces pichia*) transformed with recombinant yeast expression vectors containing sequences encoding the compounds described herein; insect cell systems infected with recombinant virus expression vectors (e.g., baclovirus) containing the sequences encoding the compounds described herein; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus (CaMV) and tobacco mosaic virus (TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing sequences encoding the molecules compounds described herein; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 293T, 3T3 cells, lymphotic cells (see U.S. Pat. No. 5,807,715), Per C.6 cells (human retinal cells developed by Crucell) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the compound being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of compounds described herein, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Rüther et al. (1983) "Easy Identification Of cDNA Clones," EMBO J. 2:1791-1794), in which the coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye et al. (1985) "Up-Promoter Mutations In The lpp Gene Of Escherichia Coli," Nucleic Acids Res. 13:3101-3110; Van Heeke et al. (1989) "Expression Of Human Asparagine Synthetase In Escherichia Coli," J. Biol. Chem. 24:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are

soluble and can easily be purified from lysed cells by adsorption and binding to a matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in Spodoptera frugiperda cells. The coding sequence may be cloned individually into non-essential regions (e.g., the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (e.g., the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the immunoglobulin molecule in infected hosts (e.g., see Logan et al. (1984) "Adenovirus Tripartite Leader Sequence Enhances Translation Of mRNAs Late After Infection," Proc. Natl. Acad. Sci. USA 81:3655-3659). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bitter et al. (1987) "Expression And Secretion Vectors For Yeast," Methods in Enzymol. 153:516-544).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein

products may be important for the function of the protein. For example, in certain embodiments, the compounds described herein may be expressed as a single gene product (e.g., as a single polypeptide chain, i.e., as a polyprotein precursor), requiring proteolytic cleavage by native or recombinant cellular mechanisms to form separate polypeptides of the compounds described herein. The disclosure thus encompasses engineering a nucleic acid sequence to encode a polyprotein precursor molecule comprising the polypeptides of the compounds described herein, which includes coding sequences capable of directing post translational cleavage of said polyprotein precursor. Post-translational cleavage of the polyprotein precursor results in the polypeptides of the compounds described herein. The post translational cleavage of the precursor molecule comprising the polypeptides of the compounds described herein may occur *in vivo* (i.e., within the host cell by native or recombinant cell systems/mechanisms, e.g. furin cleavage at an appropriate site) or may occur *in vitro* (e.g. incubation of said polypeptide chain in a composition comprising proteases or peptidases of known activity and/or in a composition comprising conditions or reagents known to foster the desired proteolytic action). Purification and modification of recombinant proteins is well known in the art such that the design of the polyprotein precursor could include a number of embodiments readily appreciated by a skilled worker. Any known proteases or peptidases known in the art can be used for the described modification of the precursor molecule, e.g., thrombin or factor Xa (Nagai et al. (1985) "Oxygen Binding Properties Of Human Mutant Hemoglobins Synthesized In Escherichia Coli," Proc. Nat. Acad. Sci. USA 82:7252-7255, and reviewed in Jenny et al. (2003) "A Critical Review Of The Methods For Cleavage Of Fusion Proteins With Thrombin And Factor Xa," Protein Expr. Purif. 31:1-11, each of which is incorporated by reference herein in its entirety)), enterokinase (Collins-Racie et al. (1995) "Production Of Recombinant Bovine Enterokinase Catalytic Subunit In Escherichia Coli Using The Novel Secretory Fusion Partner DsbA," Biotechnology 13:982-987 hereby incorporated by reference herein in its entirety)), furin, and AcTEV (Parks et al. (1994) "Release Of Proteins And Peptides From Fusion Proteins Using A Recombinant Plant Virus Proteinase," Anal. Biochem. 216:413-417 hereby incorporated by reference herein in its entirety)) and the Foot and Mouth Disease Virus Protease C3.

Different host cells have characteristic and specific mechanisms for the post-

translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, HeLa, COS, MDCK, 293, 293T, 3T3, WI38, BT483, Hs578T, HTB2, BT20 and T47D, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express compounds described herein may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the compounds described herein. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the compounds described herein.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al. (1977) "Transfer Of Purified Herpes Virus Thymidine Kinase Gene To Cultured Mouse Cells," Cell 11: 223-232), hypoxanthine-guanine phosphoribosyltransferase (Szybalska et al. (1992) "Use Of The HPRT Gene And The HAT Selection Technique In DNA-Mediated Transformation Of Mammalian Cells First Steps Toward Developing Hybridoma Techniques And Gene Therapy," Bioessays 14: 495-500), and adenine phosphoribosyltransferase (Lowy et al. (1980) "Isolation Of Transforming DNA: Cloning The Hamster aprt Gene," Cell 22: 817-823) genes can be employed in tk–, hgprt– or aprt– cells, respectively. Also, antimetabolite resistance can be used as the basis of

selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al. (1980) "Transformation Of Mammalian Cells With An Amplifiable Dominant-Acting Gene," Proc. Natl. Acad. Sci. USA 77:3567-3570; O'Hare et al. (1981) "Transformation Of Mouse Fibroblasts To Methotrexate Resistance By A Recombinant Plasmid Expressing A Prokaryotic Dihydrofolate Reductase," Proc. Natl. Acad. Sci. USA 78: 1527-1531); gpt, which confers resistance to mycophenolic acid (Mulligan et al. (1981) "Selection For Animal Cells That Express The Escherichia coli Gene Coding For Xanthine-Guanine Phosphoribosyltransferase," Proc. Natl. Acad. Sci. USA 78: 2072-2076); neo, which confers resistance to the aminoglycoside G-418 (Tolstoshev (1993) "Gene Therapy, Concepts, Current Trials And Future Directions," Ann. Rev. Pharmacol. Toxicol. 32:573-596; Mulligan (1993) "The Basic Science Of Gene Therapy," Science 260:926-932; and Morgan et al. (1993) "Human Gene Therapy," Ann. Rev. Biochem. 62:191-217) and hygro, which confers resistance to hygromycin (Santerre et al. (1984) "Expression Of Prokaryotic Genes For Hygromycin B And G418 Resistance As Dominant-Selection Markers In Mouse L Cells," Gene 30:147-156). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), 1993, Current Protocols in Molecular Biology, John Wiley & Sons, NY; Kriegler, 1990, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY; and in Chapters 12 and 13, Dracopoli et al. (eds), 1994, Current Protocols in Human Genetics, John Wiley & Sons, NY.; Colberre-Garapin et al. (1981) "A New Dominant Hybrid Selective Marker For Higher Eukaryotic Cells," J. Mol. Biol. 150:1-14.

The expression levels of compounds described herein or polypeptides described herein can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol. 3 (Academic Press, New York, 1987). When a marker in the vector system expressing a compound described herein is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the nucleotide sequence of a compound described herein or a polypeptide described herein, production of the polypeptide will also increase (Crouse et al. (1983) "Expression And Amplification Of Engineered Mouse Dihydrofolate Reductase Minigenes," Mol. Cell. Biol. 3:257-266).

The host cell may be co-transfected with two expression vectors, the first vector encoding the first polypeptide of a compound described herein and the second vector encoding the second polypeptide of a compound described herein. The two vectors may contain identical selectable markers which enable equal expression of both polypeptides. Alternatively, a single vector may be used which encodes both polypeptides. The coding sequences for the polypeptides of compounds described herein may comprise cDNA or genomic DNA.

Once a compound described herein or polypeptide described herein has been recombinantly expressed, it may be purified by any method known in the art for purification of polypeptides, polyproteins or antibodies (e.g., analogous to antibody purification schemes based on antigen selectivity) for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen (optionally after Protein A selection where the compound comprises an Fc domain (or portion thereof)), and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of polypeptides or antibodies.

Other aspects of the disclosure relate to a cell comprising a nucleic acid described herein or a vector described herein. The cell may be a prokaryotic or eukaryotic cell. In some embodiments, the cell in a mammalian cell. Exemplary cell types are described herein.

Yet other aspects of the disclosure relate to a method of producing a compound described herein or a polypeptide described herein (e.g., a first polypeptide or a second polypeptide), the method comprising obtaining a cell described herein and expressing nucleic acid described herein in said cell. In some embodiments, the method further comprises isolating and purifying a compound described herein or a polypeptide described herein.

Methods of treatment and compositions for use in medicine

Other aspects of the disclosure relate to methods of treatment and compositions for use in medicine. Non-limiting examples of compounds for use in such methods and composition are those that comprise:

(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:21 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:22; or

(x) 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; or

(xi) 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; or

(xii) 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; or

(xiii) 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; or

(xiv) 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; or

(xv) 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

(xvi) 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; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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

(xxi) 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

(xxii) 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

(xxiii) 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

(xxiv) 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

(xxv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:53 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:54; or

(xxvi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:55 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:56; or

(xxvii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:57 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:58; or

(xxviii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:59 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:60; or

(xxix) 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

(xxx) 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

(xxxi) 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

(xxxii) 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.

In some embodiments, the method of treatment or the use is a method of treating an autoimmune or an inflammatory disease or use in such a method. In some embodiments, the method comprises administering a compound described herein or a pharmaceutical composition comprising said compound to a subject, e.g., a subject having or at risk for having an autoimmune or an inflammatory disease.

The subject to be treated by the methods described herein can be a mammal, more preferably a human. Mammals include, but are not limited to, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats. A human subject who needs the treatment may be a human subject having, at risk for, or suspected of having a disease. A subject having a disease can be identified by routine medical examination, e.g., a physical examination, a laboratory test, an organ functional test, a CT scan, or an ultrasound. A subject suspected of having any of such a disease might show one or more symptoms of the disease. Signs and symptoms for diseases, e.g., autoimmune and inflammatory diseases, are well known to those of ordinary skill in the art. A subject at risk for the disease can be a subject having one or more of the risk factors for that disease.

Non-limiting examples of autoimmune diseases include lupus nephritis (LN) (systemic lupus erythematosus (SLE) with kidney involvement), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), Sjogren's disease, graft versus host disease (GVHD) (e.g., chronic graft versus host disease (cGVHD)) , systemic sclerosis (SSc), Anti-Neutrophil Cytoplasmic Autoantibody (ANCA)-associated vasculitis (AAV), rheumatoid arthritis, psoriasis, type 1 diabetes, systemic lupus erythematosus, transplant rejection, autoimmune thyroid disease (Hashimoto's disease), sarcoidosis, scleroderma, granulomatous vasculitis, Crohn's disease, ulcerative colitis, Sjogren's disease, ankylosing spondylitis, psoriatic arthritis, polymyositis dermatomyositis, polyarteritis nodosa, immunologically mediated blistering skin diseases, Behcet's syndrome, multiple sclerosis, Goodpasture's disease or immune mediated glomerulonephritis.

Non-limiting examples of inflammatory diseases include including rheumatoid arthritis, systemic lupus erythematosus, alopecia areata, anklosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lymphoproliferative syndrome (ALPS), autoimmune thrombocytopenic purpura (ATP), Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue syndrome immune deficiency syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, cicatricial pemphigoid, cold agglutinin disease, Crest syndrome, Crohn's disease, Dego's disease, dermatomyasitis, dermatomyositis - juvenile, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia - fibromyositis, grave's disease, guillain-barre, hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP), Iga nephropathy, insulin dependent diabetes (Type I), juvenile arthritis, Meniere's disease, mixed connective tissue disease, multiple sclerosis, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychondritis, polyglancular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, sarcoidosis, scleroderma, Sjogren's syndrome, stiff-man syndrome, Takayasu arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, uveitis, vasculitis, vitiligo, and Wegener's granulomatosis. In some embodiments, the autoimmune or inflammatory disease is Crohn's disease, ankylosing spondylitis, or psoriatic arthritis.

To practice a method disclosed herein, an effective amount of a compound or pharmaceutical composition described herein can be administered to a subject (e.g., a human) in need of the treatment. Various delivery systems are known and can be used to administer the compounds of the subject technology. Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds of the subject technology can be administered, for example by infusion, bolus or injection, and can be administered together with other biologically active agents such as anti-inflammatory agents. Administration can be systemic or local. In preferred embodiments, the administration is by subcutaneous injection. Formulations for such injections may be prepared in, for example, prefilled syringes that may be administered once every other week.

"An effective amount" as used herein refers to the amount of each compound required to confer therapeutic effect on the subject, either alone or in combination with one or more other compounds. Effective amounts vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, the individual subject parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment. It will be understood by those of ordinary skill in the art, however, that a subject may insist upon a lower dose or tolerable dose for medical reasons, psychological reasons or for virtually any other reasons.

Empirical considerations, such as the half-life, generally will contribute to the determination of the dosage. For example, compounds that are compatible with the human immune system, such as compounds comprising regions from humanized antibodies or fully human antibodies, may be used to prolong half-life of the compound and to prevent the compound being attacked by the host's immune system. Frequency of administration may be determined and adjusted over the course of therapy, and is generally, but not necessarily,

based on treatment and/or suppression and/or amelioration and/or delay of a disease. Alternatively, sustained continuous release formulations of a compound may be appropriate. Various formulations and devices for achieving sustained release are known in the art.

In some embodiments, dosage is daily, every other day, every three days, every four days, every five days, or every six days. In some embodiments, dosing frequency is once every week, every 2 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, every 8 weeks, every 9 weeks, or every 10 weeks; or once every month, every 2 months, or every 3 months, or longer. The progress of this therapy is easily monitored by conventional techniques and assays. The dosing regimen (including the compound used) can vary over time.

In some embodiments, for an adult subject of normal weight, doses ranging from about 0.01 to 1000 mg/kg may be administered. In some embodiments, the dose is between 1 to 200 mg. The particular dosage regimen, i.e., dose, timing and repetition, will depend on the particular subject and that subject's medical history, as well as the properties of the compound (such as the half-life of the compound, and other considerations well known in the art).

For the purpose of the present disclosure, the appropriate dosage of a compound as described herein will depend on the specific compound (or compositions thereof) employed, the formulation and route of administration, the type and severity of the disease, whether the compound is administered for preventive or therapeutic purposes, previous therapy, the subject's clinical history and response to the antagonist, and the discretion of the attending physician. Typically the clinician will administer a compound until a dosage is reached that achieves the desired result. Administration of one or more compounds can be continuous or intermittent, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of a compound may be essentially continuous over a preselected period of time or may be in a series of spaced dose, e.g., either before, during, or after developing a disease.

As used herein, the term “treating” refers to the application or administration of a

compound or composition including the compound to a subject, who has a disease, a symptom of the disease, or a predisposition toward the disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease, the symptom of the disease, or the predisposition toward the disease.

Alleviating a disease includes delaying the development or progression of the disease, or reducing disease severity. Alleviating the disease does not necessarily require curative results. As used therein, "delaying" the development of a disease means to defer, hinder, slow, retard, stabilize, and/or postpone progression of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individuals being treated. A method that "delays" or alleviates the development of a disease, or delays the onset of the disease, is a method that reduces probability of developing one or more symptoms of the disease in a given time frame and/or reduces extent of the symptoms in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a number of subjects sufficient to give a statistically significant result.

"Development" or "progression" of a disease means initial manifestations and/or ensuing progression of the disease. Development of the disease can be detectable and assessed using standard clinical techniques as well known in the art. However, development also refers to progression that may be undetectable. For purpose of this disclosure, development or progression refers to the biological course of the symptoms. "Development" includes occurrence, recurrence, and onset. As used herein "onset" or "occurrence" of a disease includes initial onset and/or recurrence.

In some embodiments, the compound described herein is administered to a subject in need of the treatment at an amount sufficient to inhibit the activity of one or both of BAFF or IL23A by at least 20% (e.g., 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) *in vivo* or *in vitro*. Methods for determining the inhibitory capability of a compound are known in the art. Exemplary BAFF and IL23A inhibition assays are provided in the Examples.

Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the compound or pharmaceutical composition to the subject, depending

upon the type of disease to be treated or the site of the disease. This composition can also be administered via other conventional routes, e.g., administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques. In addition, it can be administered to the subject via injectable depot routes of administration such as using 1-, 3-, or 6-month depot injectable or biodegradable materials and methods.

Pharmaceutical compositions

Yet other aspects of the disclosure relate to pharmaceutical compositions comprising a compound described herein. A composition comprising a compound of the subject technology (e.g., compounds specific for both BAFF and IL23A) can be administered to a subject having or at risk of having an autoimmune or an inflammatory disease. The subject technology further provides for the use of a compound of the subject technology in the manufacture of a medicament for treatment of an autoimmune or an inflammatory disease. The compounds can be administered either alone or in combination with other compositions in the prevention or treatment of an autoimmune or an inflammatory disease. Non-limiting examples of compounds of the subject technology for use in such pharmaceutical compositions are those that comprise:

(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:21 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:22; or

(x) 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; or

(xi) 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; or

(xii) 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; or

(xiii) 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; or

(xiv) 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; or

(xv) 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

(xvi) 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; or

(xvii) 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

(xviii) 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

(xix) 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

(xx) 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

(xxi) 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

(xxii) 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

(xxiii) 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

(xxiv) 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

(xxv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:53 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:54; or

(xxvi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:55 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:56; or

(xxvii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:57 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:58; or

(xxviii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:59 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:60; or

(xxix) 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

(xxx) 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

(xxxi) 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

(xxxii) 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.

As used herein, the term "pharmaceutical composition" refers to the formulation of a compound described herein in combination with a pharmaceutically acceptable carrier. The pharmaceutical composition can further comprise additional agents (e.g. for specific delivery, increasing half-life, or other therapeutic compounds).

As used here, the term "pharmaceutically-acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the compound from one site (e.g., the delivery site) of the body, to another site (e.g., organ, tissue or portion of the body). A pharmaceutically acceptable carrier is "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the tissue of the subject (e.g., physiologically compatible, sterile, physiologic pH, etc.). Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, methylcellulose, ethyl cellulose, microcrystalline cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol (PEG); (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; (22) C2-C12 alcohols, such as ethanol; and (23) other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, coloring agents, release agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservative and antioxidants can also be present in the formulation. The terms such as "excipient", "carrier", "pharmaceutically acceptable carrier" or the like are used interchangeably herein.

In some embodiments, a compound of the subject technology in a composition is administered by injection, by means of a catheter, by means of a suppository, or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including a membrane, such as a sialastic membrane, or a fiber. Typically, when administering the composition, materials to which the compound of the subject technology does not absorb are used.

In other embodiments, the compounds of the subject technology are delivered in a controlled release system. In one embodiment, a pump may be used (see, e.g., Langer, 1990, Science 249:1527-1533; Sefton, 1989, CRC Crit. Ref. Biomed. Eng. 14:201; Buchwald et al., 1980, Surgery 88:507; Saudek et al., 1989, N. Engl. J. Med. 321:574). In another embodiment, polymeric materials can be used. (See, e.g., Medical Applications of Controlled Release (Langer and Wise eds., CRC Press, Boca Raton, Fla., 1974); Controlled Drug Bioavailability, Drug Product Design and Performance (Smolen and Ball eds., Wiley, New York, 1984); Ranger and Peppas, 1983, Macromol. Sci. Rev. Macromol. Chem. 23:61. See also Levy et al., 1985, Science 228:190; During et al., 1989, Ann. Neurol. 25:351; Howard et al., 1989, J. Neurosurg. 71:105.) Other controlled release systems are discussed, for example, in Langer, supra.

Compounds of the subject technology can be administered as pharmaceutical compositions comprising a therapeutically effective amount of a binding agent and one or more pharmaceutically compatible ingredients.

In typical embodiments, the pharmaceutical composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous or subcutaneous administration to a subject, e.g., a human being. Typically, compositions for administration by injection are solutions in sterile isotonic aqueous buffer. Where necessary, the pharmaceutical can also include a solubilizing agent and a local anesthetic such as

lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the pharmaceutical is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the pharmaceutical is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

A pharmaceutical composition for systemic administration may be a liquid, e.g., sterile saline, lactated Ringer's or Hank's solution. In addition, the pharmaceutical composition can be in solid forms and re-dissolved or suspended immediately prior to use. Lyophilized forms are also contemplated.

The pharmaceutical composition can be contained within a lipid particle or vesicle, such as a liposome or microcrystal, which is also suitable for parenteral administration. The particles can be of any suitable structure, such as unilamellar or plurilamellar, so long as compositions are contained therein. Compounds can be entrapped in 'stabilized plasmid-lipid particles' (SPLP) containing the fusogenic lipid dioleoylphosphatidylethanolamine (DOPE), low levels (5-10 mol%) of cationic lipid, and stabilized by a polyethyleneglycol (PEG) coating (Zhang Y. P. et al., Gene Ther. 1999, 6:1438-47). Positively charged lipids such as N-[1-(2,3-dioleoyloxi)propyl]-N,N,N-trimethyl-amoniummethylsulfate, or "DOTAP," are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known. See, e.g., U.S. Patent Nos. 4,880,635; 4,906,477; 4,911,928; 4,917,951; 4,920,016; and 4,921,757.

The pharmaceutical compositions of this disclosure may be administered or packaged as a unit dose, for example. The term "unit dose" when used in reference to a pharmaceutical composition of the present disclosure refers to physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluent; i.e., carrier, or vehicle.

In some embodiments, a compound described herein may be conjugated to a therapeutic moiety, e.g., an anti-inflammatory agent. Techniques for conjugating such therapeutic moieties to polypeptides, including e.g., Fc domains, are well known; see, e.g., Amon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), 1985, pp. 243-56, Alan R. Liss, Inc.); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), 1987, pp. 623-53, Marcel Dekker, Inc.); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), 1985, pp. 475-506); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), 1985, pp. 303-16, Academic Press; and Thorpe et al. (1982) "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates," Immunol. Rev., 62:119-158.

Further, the pharmaceutical composition can be provided as a pharmaceutical kit comprising (a) a container containing a compound of the subject technology in lyophilized form and (b) a second container containing a pharmaceutically acceptable diluent (e.g., sterile water) for injection. The pharmaceutically acceptable diluent can be used for reconstitution or dilution of the lyophilized compound of the subject technology. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

In another aspect, an article of manufacture containing materials useful for the treatment of the diseases described above is included. In some embodiments, the article of manufacture comprises a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. In some embodiments, the container holds a composition that is effective for treating a disease described herein and may have a sterile access port. For example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle. The active agent in the composition is a compound of the subject technology. In some embodiments, the label on or associated with

the container indicates that the composition is used for treating the disease of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution, or dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present disclosure to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications cited herein are incorporated by reference for the purposes or subject matter referenced herein.

EXAMPLES

Example 1. Construction of exemplary compounds targeting IL23A and BAFF

The compounds of the subject technology were produced by recombinant methods known in the art (see, e.g., PCT Publications WO 2006/113665, WO 2008/157379, and WO 2010/080538, the contents of all of which are incorporated herein by reference). Table 2A provides exemplary compounds that bind to both IL23A and BAFF utilized in the Examples below. Briefly, plasmids encoding the first and second polypeptide for each compound were transfected together into CHO-S cells using FreeStyle MAX Reagent (CHO). The cells were cultured for 13-14 days and the compounds produced by the cells were purified using Protein-A chromatography. The compounds were further purified using a size exclusion chromatography.

Table 2A. Exemplary IL23A and BAFF binding compounds

Compound ID	**Large Chain vL**	**Large Chain vH**	**Small Chain vL**	**Small Chain vH**	**3rd and/or 4th Linker types**	**Constant Domain Isotype**	**SEQ ID NO: (1st/2nd polypeptides)**

Compound E	BAFF(1) VL (SEQ ID NO:2)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF(1) VH (SEQ ID NO:1)	LGGGSG (SEQ ID NO:70)	IgG1KO-YTE (SEQ ID NO:128)	5/6
Compound V	IL23A(1) VL (SEQ ID NO:4)	BAFF(1) VH (SEQ ID NO:1)	BAFF(1) VL (SEQ ID NO:2)	IL23A(1) VH (SEQ ID NO:3)	LGGGSG (SEQ ID NO:70)	IgG1KO-YTE (SEQ ID NO:128)	7/8
Compound U	BAFF(1) VL (SEQ ID NO:2)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF(1) VH (SEQ ID NO:1)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG1KO-YTE (SEQ ID NO:129)	9/10
Compound T	IL23A(1) VL (SEQ ID NO:4)	BAFF(1) VH (SEQ ID NO:1)	BAFF(1) VL (SEQ ID NO:2)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG1KO-YTE (SEQ ID NO:129)	11/12
Compound X	BAFF(1) VL (SEQ ID NO:2)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF(1) VH (SEQ ID NO:1)	LGGGSG (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO: 74)	13/14
Compound F	IL23A(1) VL (SEQ ID NO:4)	BAFF(1) VH (SEQ ID NO:1)	BAFF(1) VL (SEQ ID NO:2)	IL23A(1) VH (SEQ ID NO:3)	LGGGSG (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO: 74)	15/16
Compound W	BAFF(1) VL (SEQ ID NO:2)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF(1) VH (SEQ ID NO:1)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG4-Pro-YTE (SEQ ID NO:127)	17/18
Compound S	IL23A(1) VL (SEQ ID NO:4)	BAFF(1) VH (SEQ ID NO:1)	BAFF(1) VL (SEQ ID NO:2)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG4-Pro-YTE (SEQ ID NO:127)	19/20

Compound G	IL23A(1) VL (SEQ ID NO:4)	BAFF (4) VH (SEQ ID NO:84)	BAFF (4) VL (SEQ ID NO: 85)	IL23A(1) VH (SEQ ID NO:3)	LGGGS G (SEQ ID NO: 70)	IgG1KO-YTE (SEQ ID NO:128)	21/22
Compound AA	IL23A(1) VL (SEQ ID NO:4)	BAFF (4) VH (SEQ ID NO:84)	BAFF (4) VL (SEQ ID NO: 85)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG1KO-YTE (SEQ ID NO:129)	23/24
Compound I	IL23A(1) VL (SEQ ID NO:4)	BAFF (4) VH (SEQ ID NO:84)	BAFF (4) VL (SEQ ID NO: 85)	IL23A(1) VH (SEQ ID NO:3)	LGGGS G (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO: 74)	25/26
Compound AB	IL23A(1) VL (SEQ ID NO:4)	BAFF (4) VH (SEQ ID NO:84)	BAFF (4) VL (SEQ ID NO: 85)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG1KO-YTE (SEQ ID NO:129)	27/28
Compound K	IL23A(1) VL (SEQ ID NO:4)	BAFF (5) VH (SEQ ID NO:86)	BAFF (5) VL (SEQ ID NO:87)	IL23A(1) VH (SEQ ID NO:3)	LGGGS G (SEQ ID NO: 70)	IgG1KO-YTE (SEQ ID NO:128)	29/30
Compound AC	IL23A(1) VL (SEQ ID NO:4)	BAFF (5) VH (SEQ ID NO:86)	BAFF (5) VL (SEQ ID NO:87)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG1KO-YTE (SEQ ID NO:129)	31/32
Compound M	IL23A(1) VL (SEQ ID NO:4)	BAFF (5) VH (SEQ ID NO:86)	BAFF (5) VL (SEQ ID NO:87)	IL23A(1) VH (SEQ ID NO:3)	LGGGS G (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO: 74)	33/34
Compound AD	IL23A(1) VL (SEQ ID NO:4)	BAFF (5) VH (SEQ ID NO:86)	BAFF (5) VL (SEQ ID NO:87)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG4-Pro-YTE (SEQ ID NO:127)	35/36

Compound C	IL23A(1) VL (SEQ ID NO:4)	BAFF (6) VH (SEQ ID NO:88)	BAFF (6) VL (SEQ ID NO:89)	IL23A(1) VH (SEQ ID NO:3)	LGGGS G (SEQ ID NO: 70)	IgG1KO-YTE (SEQ ID NO:128)	37/38
Compound AE	IL23A(1) VL (SEQ ID NO:4)	BAFF (6) VH (SEQ ID NO:88)	BAFF (6) VL (SEQ ID NO:89)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG1KO-YTE (SEQ ID NO:129)	39/40
Compound D	IL23A(1) VL (SEQ ID NO:4)	BAFF (6) VH (SEQ ID NO:88)	BAFF (6) VL (SEQ ID NO:89)	IL23A(1) VH (SEQ ID NO:3)	LGGGS G (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO: 74)	41/42
Compound AF	IL23A(1) VL (SEQ ID NO:4)	BAFF (6) VH (SEQ ID NO:88)	BAFF (6) VL (SEQ ID NO:89)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG4-Pro-YTE (SEQ ID NO:127)	43/44
Compound A	IL23A(1) VL (SEQ ID NO:4)	BAFF (7) VH (SEQ ID NO:90)	BAFF (7) VL (SEQ ID NO:91)	IL23A(1) VH (SEQ ID NO:3)	LGGGS G (SEQ ID NO: 70)	IgG1KO-YTE (SEQ ID NO:128)	45/46
Compound AG	IL23A(1) VL (SEQ ID NO:4)	BAFF (7) VH (SEQ ID NO:90)	BAFF (7) VL (SEQ ID NO:91)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG1KO-YTE (SEQ ID NO:129)	47/48
Compound B	IL23A(1) VL (SEQ ID NO:4)	BAFF (7) VH (SEQ ID NO:90)	BAFF (7) VL (SEQ ID NO:91)	IL23A(1) VH (SEQ ID NO:3)	LGGGS G (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO:74)	49/50
Compound AH	IL23A(1) VL (SEQ ID NO:4)	BAFF (7) VH (SEQ ID NO:90)	BAFF (7) VL (SEQ ID NO:91)	IL23A(1) VH (SEQ ID NO:3)	E(C-1) (SEQ ID NO:82), K-coil(C-1) (SEQ ID NO:83)	Fc-IgG4-Pro-YTE (SEQ ID NO:127)	51/52

Compound H	BAFF (4) VL (SEQ ID NO:85	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF (4) VH (SEQ ID NO:84)	LGGGS G (SEQ ID NO: 70)	IgG1KO-YTE (SEQ ID NO:128)	53/54
Compound J	BAFF (4) VL (SEQ ID NO: 85)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF (4) VH (SEQ ID NO:84)	LGGGS G (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO:74)	55/56
Compound L	BAFF (5) VL (SEQ ID NO:87)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF (5) VH (SEQ ID NO:86)	LGGGS G (SEQ ID NO: 70)	IgG1KO-YTE (SEQ ID NO:128)	57/58
Compound N	BAFF (5) VL (SEQ ID NO:87)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF (5) VH (SEQ ID NO:86)	LGGGS G (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO:74)	59/60
Compound O	BAFF (6) VL (SEQ ID NO:89)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF (6) VH (SEQ ID NO:88)	LGGGS G (SEQ ID NO: 70)	IgG1KO-YTE (SEQ ID NO:128)	61/62
Compound P	BAFF (6) VL (SEQ ID NO:89)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF (6) VH (SEQ ID NO:88)	LGGGS G (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO:74)	63/64
Compound Q	BAFF 7) VL (SEQ ID NO:91)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF (7) VH (SEQ ID NO:90)	LGGGS G (SEQ ID NO: 70)	IgG1KO-YTE (SEQ ID NO:128)	65/66
Compound R	BAFF (7) VL (SEQ ID NO:91)	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)	BAFF (7) VH (SEQ ID NO:90)	LGGGS G (SEQ ID NO: 70)	IgG4-Pro-YTE (SEQ ID NO:74)	67/68

VL = variable domain light chain, VH = variable domain heavy chain, each chain comprises the linker GGGSGGG (SEQ ID NO:69) between the VL and VH.

Control antibodies were also used for comparison purposes. The controls were monoclonal antibodies that targeted either BAFF or IL23.

Table 2B. Control antibodies/antagonist

Control compounds	**Sequence**	
Control Antibody 1 (anti-BAFF monoclonal antibody) (BAFF (1))	BAFF(1) VH (SEQ ID NO:1)	BAFF(1) VL (SEQ ID NO:2)
Control Fusion Protein Antagonist 2 (non-antibody BAFF selective antagonist) (BAFF (2))	BAFF(2) (SEQ ID NO:131)	
Control Antibody 3 (anti-BAFF	BAFF(3) VH (SEQ ID NO:132)	BAFF(3) VL (SEQ ID NO:133)

monoclonal antibody) (BAFF (3))		
Control Antibody 4 (anti-IL-23A monoclonal antibody) (IL-23A (1))	IL23A(1) VH (SEQ ID NO:3)	IL23A(1) VL (SEQ ID NO:4)

Example 2: Thermal stability of compounds

Methods

Thermal unfolding and aggregation of 2 mg/ml solutions of the compounds in phosphate buffer were monitored from 20 °C to 110 °C at a scan rate of 60 °C/hr via an automated capillary DSC (MicroCal, LLC, Boston). Two scans with the corresponding buffer were performed to establish instrument thermal history and to obtain the instrument baseline for each sample, with the average of these scans subtracted from the subsequent protein thermogram to obtain the apparent heat capacity. Normalized scans were then analyzed with Origin 7.0. Pre-transition baselines were subtracted from each resulting heat capacity thermogram, to give the resulting excess heat capacity (Cp,ex) as a function of temperature. Reported values of transition temperatures (Tm) represent positions of peak maxima determined by visual inspection of the experimental thermograms.

Results

The results are shown in Table 3. The data show that exemplary compounds targeting IL23A and BAFF have a range of transition temperatures for the first peak (T_{m1}), ranging from 51.59 to 71.25°C. The results are surprising because the exemplary compounds all had the same overall structure and contained the same VH and VL gene sequences targeting IL-23A. Compounds with higher transition temperatures are more stable and predicted to have a long shelf-life.

Table 3. Thermal unfolding transition temperatures for compounds

Compound ID	**T_{m1} (°C)**	**T_{m2} (°C)**
Compound A	69.35	83.63
Compound B	65.87	--
Compound C	67.89	82.36

Compound D	64.93	--
Compound E	51.59	68.8
Compound F	52.75	64.48
Compound G	70.88	83.21
Compound H	71.25	83.62
Compound I	67.83	--
Compound J	68.26	--
Compound K	68.33	83.23
Compound L	68.3	82.58
Compound M	64.98	--
Compound N	65.52	--
Compound O	67.79	83.85
Compound P	65.09	--
Compound Q	69.19	81.9
Compound R	65.97	--
Compound X	52.36	64.53

Example 3. Surface Plasma Resonance (SPR) affinity of exemplary compounds

Test compounds were analyzed by SPR to determine affinity for BAFF and IL23A.

Materials and Methods:

SPR experiments were performed on a ProteOn XPR36 instrument (Bio Rad). A GLM chip was preconditioned with sequential injections of 60 sec of 0.5% SDS, 50 mM NaOH, and 100 mM HCl at a flow rate of 30 µl/min both vertical and horizontal directions.

The preconditioned GLM chip was then activated by an injection of EDC (76.7 mg/ml) and sulfo-NHS (21.7 mg/ml) mixture with ratio of 1:1 in 6 horizontal channels. Goat-anti-human IgG (GAHA) Fc gamma (Invitrogen) at a concentration of 30 µg/ml in 10 mM, pH 5.0 sodium acetate buffer was immobilized to 8,000 resonance units on the activated GLM chip in 6 horizontal channels. The chip was finally deactivated with 1 M ethanolamine HCl in 6 horizontal channels. The prepared GAHA chip was rotated to vertical direction to capture test compounds, over 5 vertical channels and the last channel was used as a column reference.

The captured chip was then rotated again to the horizontal direction for binding. Linked

human IL-23 (Boehringer Ingelheim Pharmaceuticals, Inc.) with five concentrations, 10.0 nM, 5.00 nM, 2.50 nM, 1.25 nM and 0.625 nM, were injected horizontally over the test compound surfaces for 10 minutes at a flow rate of 40 µl/min in the following running buffer (Bio Rad): phosphate buffer saline (pH 7.4), 0.005% Tween 20. The dissociation was allowed for 2 hour. The GAHA surface was regenerated using short pulse injection (18 seconds) of 0.85% phosphoric acid (Bio Rad) at a flow rate of 100 µl/min both horizontal and vertical directions after 10 min association and 2 hr dissociation. The regenerated GAHA was ready for another binding cycle. Binding of compounds to cynomolgus IL23, human BAFF or cynomolgus BAFF was done in similar way but the titration concentrations for binding to human BAFF or cynomolgus BAFF are 6.25 nM, 3.12 nM, 1.56 nM, 0.78 nM, and 0.39 nM.

Results:

The results in Table 4 show that both compounds tested were able to bind BAFF and IL23 with a dissociation constant (KD) in the picomolar range.

Table 4. Affinity of compounds binding to BAFF and IL23

Compound ID	KD to human BAFF (pM)	KD to cynomolgus BAFF (pM)	KD to human IL23 (pM)	KD to cynomolgus IL23 (pM)
Compound A	< 15	< 15	< 15	< 15
Compound B	< 15	< 15	< 15	< 15
Compound C	< 15	< 15	< 15	< 15
Compound D	< 15	< 15	< 15	< 15
Compound E	< 15	< 15	< 15	< 15
Compound F	< 15	< 15	< 15	< 15

Example 4. Inhibition of human and cynomolgus BAFF trimer-induced NFkB activation in BAFFR-CHO luciferase reporter cells

Materials/Methods:

Briefly, human BAFFR CHO NFkB luciferase reporter cells were harvested, washed, counted and resuspended at a concentration of 1.6 X 10^6 cells per ml in assay medium (AM) of (v/v) 1% Penicillin/Streptomycin in X-VIVO15, a chemically defined serum-free media (Lonza). Recombinant human or cynomolgus BAFF trimer (Boehringer Ingelheim Pharmaceuticals, Inc.) was prepared at a single concentration (52 pM) in AM and pre-

incubated with AM alone or with serial titrations of test compound for 30minutes at 37°C, 5% CO2 in a humidified incubator. After pre-incubation of BAFF + test compound, 50 ul of the mixture(s) was added to 50 ul of cells and the test plate was further incubated at 37°C (as described) for 24 hours. Control samples received either AM (unstimulated controls) or recombinant BAFF trimer diluted in AM (stimulated controls). After 24 hour incubation, the cell suspension was treated with 100ul STEADY-Glo reagent (Promega), following manufacturer's instruction, and assayed for luciferase expression. Resulting Relative Luminesence Units (RLU) were plotted versus Log10 nanamolar concentration of the test compound, where IC_{50} & IC_{90} values were calculated using a 4 Parameter Logistic Model, supported by Excel add-in Xlfit (ID Business Solutions Limited). The test compound IC_{50} & IC_{90} values were calculated as described above and Geomeans were calculated across multiple experiments and shown in Table 5 and Table 6.

Results:

The test compounds dose-dependently inhibited human and cynomolgus BAFF trimer -induced NFkB activation in BAFFR-CHO luciferase reporter cells. The results illustrated in Table 5 and 6 indicate that the IC_{50} & IC_{90} geomean values for the test compounds were comparable or more potent than control BAFF antagonists.

Table 5: IC_{50} and IC_{90} Geomean values for inhibiting human BAFF trimer in BAFFR-CHO report cells

Compound ID	**IC_{50} (pM)**	**IC_{90} (pM)**
Compound A	43	180
Compound B	39	256
Compound C	35	110
Compound D	34	172
Compound F	72	293
Compound O	27	119
Compound P	19	88
Compound Q	26	108
Compound R	30	139
Compound X	106	361
Control Antibody 1 (BAFF (1))	232	743
Control Fusion Protein Antagonist 2	173	914

(BAFF (2))		
Control Antibody 3 (BAFF (3))	70	417

Table 6: IC_{50} and IC_{90} Geomean values for inhibiting cynomolgus BAFF trimer BAFFR-CHO report cells

Compound ID	IC50 Geomean pM	IC90 Geomean pM
Compound A	132	191
Compound B	132	295
Compound D	118	248
Control Antibody 1 (BAFF (1))	288	635
Control Fusion Protein Antagonist 2 (BAFF (2))	602	1089
Control Antibody 3 (BAFF (3))	257	588

Example 5. Inhibition of human BAFF trimer-induced NFkB activation in TACI-CHO luciferase reporter cells

Materials/Methods:

Briefly, human TACI CHO NFkB luciferase reporter cells were harvested, washed, counted and resuspended at a concentration of 1.6 X 10^6 cells per ml in assay medium (AM) of (v/v) 1% Penicillin/Streptomycin in X-VIVO15, a chemically defined serum-free media (Lonza). Recombinant human BAFF trimer (Boehringer Ingelheim Pharmaceuticals, Inc.) was prepared at a single concentration (222 pM) in AM and pre-incubated with AM alone or with serial titrations of test compound for 30minutes at 37°C, 5% CO2 in a humidified incubator. After pre-incubation of BAFF + test compound, 50 ul of the mixture(s) was added to 50 ul of cells and the test plate was further incubated at 37°C (as described) for 24 hours. Control samples received either AM (unstimulated controls) or recombinant human BAFF trimer diluted in AM (stimulated controls). After 24 hour incubation, the cell suspension was treated with 100 ul STEADY-Glo reagent (Promega), following manufacturer's instruction, and assayed for luciferase expression. Resulting Relative Luminesence Units (RLU) were plotted versus Log10 nanamolar concentration of the test compound, where IC_{50} & IC_{90} values were calculated using a 4 Parameter Logistic Model, supported by Excel add-in Xlfit (ID Business Solutions Limited). The test compound IC_{50} & IC_{90} values were calculated as

described above and Geomeans were calculated across multiple experiments and shown in Table 7.

Results:

The test compounds dose-dependently inhibited human BAFF trimer -induced NFkB activation in TACI-CHO luciferase reporter cells. The results illustrated in Table 7 indicate that the IC_{50} & IC_{90} Geomean values for the test compound were comparable to or more potent than control BAFF antagonists.

Table 7: IC_{50} and IC_{90} Geomean values for inhibiting human BAFF trimer in TACI-CHO report cells

Compound ID	IC50 Geomean pM	IC90 Geomean pM
Compound A	159	417
Compound B	159	510
Compound D	163	436
Control Antibody 1 (BAFF (1))	273	576
Control Fusion Protein Antagonist 2 (BAFF (2))	829	1945
Control Antibody 3 (BAFF (3))	241	618

Example 6. Inhibition of BAFF 60mer-induced NFkB activation in BAFFR-CHO luciferase reporter cells

Materials/Methods:

Briefly, human BAFFR CHO NFkB luciferase reporter cells were harvested, washed, counted and resuspended at a concentration of 1.6 X 10^6 cells per ml in assay medium (AM) of (v/v) 1% Penicillin/Streptomycin in X-VIVO15, a chemically defined serum-free media (Lonza). Recombinant human BAFF 60mer (Boehringer Ingelheim Pharmaceuticals, Inc.) was prepared at a single concentration (4.2 pM) in AM and pre-incubated with AM alone or with serial titrations of test compound for 30 minutes at 37°C, 5% CO2 in a humidified incubator. After pre-incubation of BAFF + test compound, 50 ul of the mixture(s) was added to 50 ul of cells and the test plate was further incubated at 37°C (as described) for 24 hours.

Control samples received either AM (unstimulated controls) or recombinant human BAFF 60mer diluted in AM (stimulated controls). After 24 hour incubation, the cell suspension was treated with 100 ul STEADY-Glo reagent (Promega), following manufacturer's instruction, and assayed for luciferase expression. Resulting Relative Luminesence Units (RLU) were plotted versus Log10 nanamolar concentration of the test compound, where IC_{50} & IC_{90} values were calculated using a 4 Parameter Logistic Model, supported by Excel add-in Xlfit (ID Business Solutions Limited). The test compound IC_{50} & IC_{90} values were calculated as described above and Geomeans were calculated across multiple experiments and shown in Table 8.

Results:

The test compounds dose-dependently inhibited human BAFF 60 mer -induced NFkB activation in BAFFR-CHO luciferase reporter cells. The results illustrated in Table 8 indicate that the IC_{50} & IC_{90} Geomean values for the test compounds A, B, C, D, O, P, Q and R were more potent than all three control BAFF antagonists.

Table 8: IC_{50} and IC_{90} Geomean values for inhibiting human BAFF 60mer in BAFFR-CHO reporter cells

Compound ID	**IC_{50} (pM)**	**IC_{90} (pM)**
Compound A	6	19
Compound B	6	17
Compound C	6	14
Compound D	4	12
Compound F	1300	7388
Compound O	5	6
Compound P	2	9
Compound Q	5	13
Compound R	5	16
Compound X	1555	6839
Control Antibody 1 (BAFF (1))	24075	180053
Control Fusion Protein Antagonist 2 (BAFF (2))	43	107
Control Antibody 3 (BAFF (3))	15	38

Example 7: Neutralization of membrane bound BAFF-induced NFkB activation in BAFFR-

CHO luciferase reporter cells

Materials/Methods

CHO-K1 cells expressing human BAFF were counted and resuspended at a concentration of 2 X 10^6 cells per ml in standard growth medium. To stop cleavage of membrane-bound BAFF, cells were treated with 0.125% paraformaldehyde (Electron Microscopy) and incubated at room temperature for one hour. The fixed human BAFF CHO-K1 cells were then washed and resuspended at 2 X 10^6 cells per ml in standard growth media and incubated overnight at 37^{0}C, 5% CO_2. The fixed human BAFF CHO-K1 cells were then harvested and resuspended at a concentration of 3.2 X 10^6 cells per ml in X-VIVO15, a chemically defined serum-free (Lonza) assay medium (AM) containing 1% Penicillin/Streptomycin (v/v).

Human BAFFR CHO NFkB luciferase reporter cells were harvested, washed, and resuspended at a concentration of 1.6 X 10^6 cells per ml in assay medium. Fixed human BAFF CHO-K1 cells prepared at 3.2 x 10^6 cells per ml in AM and pre-incubated with serial titrations of test compounds for 30 minutes were then added to 50 ul of human BAFFR CHO NFkB luciferase reporter cells and further incubated at 37°C for 24 hours. Control reporter cells received either only AM (unstimulated controls) or fixed human BAFF CHO-K1 cells diluted in AM (stimulated controls). After 24 hour incubation, samples were treated with 100ul STEADY-Glo reagent (Promega), and assayed for luciferase expression. Relative Luminescence Units (RLU) were plotted versus Log_{10} nanamolar concentrations of the test compounds, where IC_{50} and IC_{90} values were calculated using a 4 Parameter Logistic Model, supported by Excel add-in Xlfit (ID Business Solutions Limited). The test compounds IC_{50} and IC_{90} values were calculated as described above and Geomeans were calculated across multiple experiments and shown in Table 9.

Results

The test compounds dose-dependently inhibited membrane-bound human BAFF-induced NFkB activation in BAFFR-CHO luciferase reporter cells. The results illustrated in Table 9 indicate that the IC_{50} and IC_{90} values for the test compounds were more potent than

all three control BAFF antagonists.

Table 9: IC_{50} and IC_{90} Geomean Values for inhibiting mbBAFF in BAFFR-CHO reporter cells

Compound ID	IC_{50} (pM)	IC_{90} (pM)
Compound A	118	1015
Compound B	125	1139
Compound D	104	938
Control Antibody 1 (BAFF (1))	553	10116
Control Fusion Protein Antagonist 2 (BAFF (2))	581	3678
Control Antibody 3 (BAFF (3))	250	2916

Example 8: Inhibition of human IL-23 activity in Lymphoblast B Cells (DB cells) with STAT3-luciferase reporter

Materials/Methods

Lymphoblast B cells (DB cells; ATCC catalog # CRL-2289) were stable transduced with a lenti-viral STAT-3/luciferase reporter gene (Qiagen). Transduced cells were kept under selection using puromycin (Life Technologies). The complete culture medium was RPMI-1640 medium (Life Technologies) supplemented with 10% FBS (Hyclone) and 2 µg/mL puromycin (Life Technologies). The assay medium was RPMI-1640 medium (Life Technologies) supplemented with 10% FBS (Hyclone).

Engineered DB-STAT3 cells were seeded at 20,000 cells/well in a white, flat-bottom 96-well plate at 80 µL/well in assay medium. Test compounds (10x) were prepared in polypropylene, round-bottom 96-well plates in assay medium, and diluted accordingly to create dose ranges from 1 µg/mL to 10 pg/mL. 10 µL of diluted test molecules or assay medium (for control wells) were added to each well in triplicate. 10 µL of 10x human IL-23 (to a final concentration of 75 ng/mL per plate) were added to each well. Alternatively, 10 µL of media was added to the control wells. The IL-23 dose selected for use in the assay represents the EC_{60} stimulant dose of human IL-23 for DB engineered cells as determined in

prior studies. The plates were incubated overnight at 37°C in 5% CO_2. The ONE-Glo™ luciferase assay reagent (Promega) was prepared and 100 µL was added to each well and mixed. The luminescence was measured on an Envision plate reader and then plotted (y-axis) against antibody concentration (x-axis). IC_{50} values of compounds were determined by applying the data to a 4-parmeter sigmoidal dose-response function using GraphPad Prism 6 software. IC_{90} values were determined by calculating the data with Find ECanything with GraphPad Prism 6 software. Geomeans were calculated across multiple experiments and shown in Table10.

Results

The results showed that the tested compounds were able to inhibit human IL-23 activity in DB cells with STAT3-luciferase reporter.

Table 10. IC_{50} and IC_{90} Geomean values for inhibiting human IL-23 in lymphoblast B cells

Compound ID	**IC_{50} (pM)**	**IC_{90} (pM)**
Compound A	145	1229
Compound B	161	1101
Compound C	189	2330
Compound D	128	3087
Control Antibody 4 (IL-23A (1))	79	634

Example 9: Inhibition of human and cynomolgus IL-23 activity in mouse splenocytes

Materials and Methods

Mononuclear cells from mouse spleens (female C57BL/6 less than 13 weeks of age; Jackson Laboratories) were isolated washed, counted, and resuspended to $4x10^6$ cells/ml in a standard T cell media (TCM). One hundred microliters of the mIL-2/splenocyte suspension was added to 96 well microtiter plates. Recombinant human IL-23 (Boehringer Ingelheim Pharmaceuticals, Inc.) or recombinant cynomolgus IL-23 (Boehringer Ingelheim Pharmaceuticals, Inc.) was diluted in TCM and pre-incubated for 2 hours at 37°C with TCM alone or with titrations of test samples. After the pre-incubation of test sample + IL-23, 100 ul of the mixture was added to the cells and the test plates were incubated at 37°C with 5% CO_2-

humidified air for 48 hours. Control samples received either TCM (unstimulated controls) or recombinant IL-23 diluted in TCM (stimulated controls). After the incubation, mouse IL-17 levels were determined from the supernatant using the Quantikine® Mouse IL-17 Immunoassay according to the manufacturer's instructions (R&D Systems). Interpolated mIL-17 pg/ml values were determined for each sample and converted to percent of control (POC). The POC was plotted versus concentration of the test sample and IC_{90} values were calculated using a 4 Parameter Logistic Model enabled by the Excel add-in XLfit (Activity Base software, ID Business Solutions, Ltd.). Test compounds were analyzed with respect to the IC_{50} and IC_{90} as described above, and Geomeans were calculated across multiple experiments for each test compound and shown in Table 11.

Results

The results showed that the tested compounds were able to inhibit both human and cynomolgus-IL23 induced mouse splenocyte release of mouse IL-17.

Table 11: IC_{50} and IC_{90} Geomean values for inhibiting human and cynomolgus IL-23 in mouse splenocytes

Compound ID	**Human IL23**		**Cyno IL23**	
	IC_{50} (pM)	**IC_{90} (pM)**	**IC_{50} (pM)**	**IC_{90} (pM)**
Compound A	146	1647	155	1309
Compound B	202	1360	200	1480
Compound C	133	761	110	880
Compound D	105	1700	97	1554
Control Antibody 4 (IL-23A (1))	84	366	64	331

Example 10. Pharmacokinetics of compounds in cynomolgus monkeys

Materials and Methods:

Single intravenous (IV) dose PK studies for test Compounds A, B, C, and D were conducted in male cynomolgus monkeys (n = 2 per molecule). Doses were administered as a slow 1 mg/kg IV bolus injection. Whole blood samples were collected pre-dose and 0.25, 2 and 6 h post-dose on the day of dosing and 1, 2, 3, 4, 7, 10, 14, 21, and 28 days post-dose.

Serum concentrations of dosed molecules were measured by an MSD-based ligand binding assay.

Calibration standard curve and quality control (QC) samples were prepared in 100% pooled cynomolgus monkey serum. Each standard curve consisted of seven non-zero points starting at 512 ng/mL then serially diluted three-fold. A blank sample (matrix without analyte) was also included. Five QC samples at low, medium, and high ranges were prepared starting at 256 ng/mL, then serially diluted four-fold to 8 ng/mL, then a 2-fold dilution was used to prepare the lowest QC at 4 ng/mL. Standard curve and QC samples were included in duplicate during each analytical run. Lower and upper limits of quantification were defined as the lowest and highest QC points having reproducible back-calculated concentrations not exceeding 30 percent (%) of nominal concentrations. Acceptance criterion for standard curve points was 30 percent (%) of nominal concentrations.

To measure active drug concentration in serum samples a master mix was prepared, combining 0.5 µg/mL biotinylated recombinant human BAFF and 0.5 µg/mL sulfo-labeled goat anti-human IgG detection in binding buffer (5% BSA in 1x PBS with 0.05% Tween 20). Master mix was added to a 96-well non-binding and light-blocking plate at 50 µL per well. Twenty-five µL of standards and QCs (stock diluted 1:20 in binding buffer) were added per well in duplicate to the non-binding plate containing the master mix. Unknown serum samples were diluted 1:20 in binding buffer and 1:400 in binding buffer containing 5% serum. Twenty-five µL of diluted samples were added per well to non-binding plates containing master mix. Non-binding plates were incubated at room temperature on a plate shaker (500 rpm, 1.5 h). In parallel, an MSD streptavidin gold plate was blocked using 150 µL blocking buffer (5% BSA with 1X PBS with 0.05% Tween 20) and incubated at room temperature on a plate shaker (500 rpm, 1.5 h). After incubation, MSD plates were washed three times with 300 µL per well of wash buffer (0.05% Tween 20 in 1XPBS). Fifty µL of sample from non-binding plates were added to MSD plates and incubated at room temperature (1.5 h, 600 rpm). After incubation, plates were washed three times with wash buffer, and 150 µL of 2x Read Buffer T was added to each well and read immediately on an MSD Sector Imager 2400. Standard curves were fitted to a four-parameter logistics equation using MSD Discovery Workbench software. Pharmacokinetic parameters were calculated

using non-compartmental analysis in Phoenix WinNonlin 6.3 (Certara, MD, USA).

Results:

Mean (SD) serum concentration vs. time profiles for test compounds are illustrated in Figure 2. Mean (SD) pharmacokinetic parameters for test compounds are summarized in Table 12. Serum samples displaying a precipitous drop in drug concentration over time that were confirmed to be anti-drug antibody positive were excluded from pharmacokinetic parameter calculations.

Table 12: Mean (SD) pharmacokinetic parameters of test compounds in male cynomolgus monkeys following a single 1 mg/kg intravenous dose

Compound ID	$AUC_{0\text{-last}}$ (µg*d/mL)	$AUC_{0\text{-inf}}$ (µg*d/mL)	CL (mL/day/kg)	Vss (mL/kg)	$T_{½}$ (days)
Compound A	52.5 (6.6)	54.2 (7.1)	18.6 (2.4)	61.6 (4.3)	3.1 (0.3)
Compound B	102.7 (1.8)	127.0 (3.6)	7.9 (0.2)	64.4 (6.6)	6.2 (0.7)
Compound C	26.6 (1.4)	27.0 (1.3)	37.1 (1.8)	66.9 (13.2)	2.3 (0.4)
Compound D	33.8 (1.3)	34.5 (1.8)	29.0 (1.5)	55.7 (5.5)	2.8 (0.8)

Example 11. Predicting human PK and human dose of an exemplary Compound

Elementary Dedrick scaling was used to scale mean monkey serum concentrations of Compound B to human, using an allometric exponent of 1.0 for volume of distribution and 0.85 for clearance. The predicted human i.v. serum concentration-time profile was fitted to a linear two-compartment model. The human s.c. serum concentration-time profile was predicted by combining parameters from the two-compartment i.v. model with the mean s.c. absorption rate and bioavailability observed for marketed therapeutic mAbs. The clearance and terminal half-life are predicted to be 0.34 L/d and 9.9 d in healthy humans, respectively. The predicted human serum concentration-time profile of Compound B, following a 100 mg s.c. dose administered once every two-weeks, was shown in FIG. 3.

The predicted human efficacious dose is 1 mg/kg delivered s.c. once every two weeks. This dose regimen is predicted to maintain a Cmin ≥ 30 nM (6 µg/mL) with biweekly or less

frequent s.c. administration. The predicted efficacious dose may be based on concentration-PD biomarker responses observed for belimumab (Benlysta®), tabalumab and blisibimod in SLE and RA patients . In these studies, maximal inhibition of BAFF-related biomarkers was associated with a 30-40 nM steady-state Cmin. The concentration required to neutralize IL23 is much lower than that required to neutralize BAFF, and therefore does not impact the overall required Cmin for the dual antagonist.

Example 12. Purification of compounds

Methods:

Compounds were purified using Mab Select SuRe as an affinity purification step. Elution was performed using Sodium Acetate buffer pH 3.5. Following Mab Select SuRe purification the sample was neutralized and applied to a Poros 50 HS resin and eluted using a Sodium Chloride gradient in Sodium Citrate Buffer. Monomer peak elutes at 20 mM NaCitrate and 120 mM NaCl pH 6.0. Following ion exchange chromatography, the sample was consistently >95% monomer.

Sedimentation velocity (SV) experiment via Analytical ultracentrifugation (AUC) was used to provide information on sample purity and aggregation states. Samples were centrifuged in an optima XL-I (Beckman Coulter, Fullerton, CA) at 20 °C using an An60Ti four-hole rotor running at 40,000 rpm. The sedimentation process was monitored by ultraviolet absorbance at 280 nm, using corresponding dilution buffer as reference buffer. The variation in the concentration distribution in the ultracentrifuge cell with time was collected using XL-I operating software and was analyzed using the continuous c(S) distribution model in the SEDFIT software (version 14.1) to give the distribution of sedimentation coefficient. Monomer percentage was calculated based on the integrated peak area.

Results:

The results of purification of the compounds are shown in Table 13. The data show that the compounds have high purity and homogeneity, indicating good stability.

Table 13

Parameter Name	Compounds A, B, C, D
Percent Monomer (sedimentation velocity)	99% monomer 1% aggregate

Example 13: Mass Spectrometry profile of compounds

Methods:

Native Sample

This procedure yielded the intact mass of the compound or protein. 0.15ul of sample was injected onto an Agilent PoroShell 300SB-C3 column, 5um, (30x1.0mm). The column temperature was 80 °C and flow rate was 150ul/min. The compound or protein was eluted off the column with a gradient from 10%B at 0 minutes to 85%B at 6 minutes. Mobile phase A was Water/Acetonitrile/Formic Acid/Ammonium Acetate (99/1/0.1/2mM) and Mobile phase B was n-Propanol/Acetonitrile/Water/Formic Acid (70/20/10/0.1). The effluent was directed to an Agilent 6224 TOF mass spectrometer, which was scanned from mass 600 to mass 3200. The raw data was deconvoluted with the program MassHunter.

Reduced Sample

This procedure yielded the mass of the protein or the light chain and the mass of the heavy chain. 5ul of sample was added to 5uL of a 20:1 mixture of 8M Guanadine HCL:TCEP and incubated for 15 minutes at room temperature. 0.15ul of this sample was injected as above, with the following differences: the compound or protein was eluted off the column with a gradient from 5%B at 0 minutes to 85%B at 6 minutes, the column temperature was 60 °C and the mass range was 600-2000.

Deglycosylated Sample

This procedure yielded the deglycosylated mass of the protein or the light chain and the heavy chain. 7.5ul of sample was added to 3.2uL of a 20:1 mixture of 400 mM Ammonium Bicarbonate:PNGase F and incubated for 3 hours at 37 °C. Then, 10ul of a 20:1 mixture of 8M Guanadine HCL:TCEP was added to the sample and incubated for 15 minutes at room temperature. This sample was injected as above for reduced sample.

Peptide Mapping by Mass Spectrometry

Samples were diluted into a denaturing buffer consisting of 6M GdHCl, 250 mM Tris-HCL pH 7.5 and 10 mM DTT and then incubated at 37°C for 30 minutes. Samples were then alkylated with iodoacetamide, and incubated in the dark at room temperature for 30 minutes. The reaction mixtures were purified and buffer exchanged into 100mM Tris-HCL pH 7.5 using Sephadex G-25 Superfine cartridges. Samples were then digested with trypsin during a 4 hour incubation at 37°C. The digested reaction mixtures were subsequently quenched by adding TFA.

The obtained tryptic digest was injected onto a Phenomenex Jupiter C18 reversed phase column via the autosampler of a Dionex Ultimate 3000 HPLC. A gradient solvent system consisting of solvent A: 0.1% Formic acid/99% water/1% acetonitrile and solvent B: 0.1% Formic acid/5% water/95% acetonitrile was utilized. The percentage of solvent B was increased from 0% to 38% over 140 minutes. The chromatographic separation took place at room temperature at a flow rate of 100 µl/min. Sample storage in the autosampler was at 4°C. After chromatographic separation the sample entered a Thermo Scientific Orbitrap Fusion mass spectrometer operated in positive electrospray ionization mode. The employed method included activation types of CID utilizing a resolution of 30,000, a minimum signal of 10,000, an isolation width of 1.0 and a normalized collision energy of 35.0V. The S-lens RF level was set at 20%. The data collection type is profile for the full MS scan and centroid for the CID MS/MS data. Data is collected over a mass range of 250-2000 Da at an acquisition rate of 1 spectra/second.

Collected raw LC-MS and LC-MS/MS fragmentation data from the enzymatic digest were analyzed utilizing Proteome Discover 1.4 (Thermo Scientific) against the given sequence. Identified peptides containing a consensus of N-X-S/T (X is not P) were then analyzed by manually extracting EIC for the glycosylated peptides. The MS intensities of the glycosylated peptides across the EIC were used to estimate their percentages of the total abundance of glycoforms.

Results:

The results are shown in Table 14. The data indicate the intended amino acid sequence and structure has been expressed and recovered without unexpected heterogeneity. The glycosylation pattern is typical of a conventional antibody expressed in CHO cells and does not show any atypical structures.

Table 14:

Parameter	**Compound B**
Mass Spectrometry: Intact Molecular Weight Profile	Intact/Matches Sequence
Mass Spectrometry: Glycosylation Profile	Similar to CHO expressed IgG

Example 14: Monomer content at high concentration

The purpose of this process description is to assess the inherent properties of compound B by evaluating aggregation with increased concentration. A standard buffer of 20 mM NaCitrate 120 mM NaCl pH 6 is used without formulation assessment to understand the molecules propensity to aggregate.

Methods:

The compound B was concentrated gradually to a concentration as high as possible without precipitation observed using Amicon Ultra centrifugal filter with cut-off molecular weight of 50,000 Dalton (Millipore, Billerica). The concentrated protein solutions were then subjected to analytical sec analysis to provide information on sample purity and aggregation states. Chromatography was run using an Agilent 1200 series HPLC system. The system was run at 1.0ml/min for 23 minutes. ~30ug of material was injected into a Tosoh Biosciences TSKgel G3000SWXL column (5um 250a 7.8x30 cm) and results were read at 280nm. Running buffer used was 50 mM NaPhosphate, 0.2 M L-arginine pH 6.8.

Results:

Summary of Analytical SEC data for compound B during concentration process is listed in Table 15 and FIG. 4. Data showing aggregation and sample purity at increasing

concentration is presented which demonstrates that compound B does not have a propensity to aggregate with increased concentration.

Table 15. Summary of Analytical SEC data for compound B during concentration process

Compound B concentration (mg/ml)	Analytical SEC data
10	99.6% monomer, 0.4% aggregate
20	99.5% monomer, 0.5% aggregate
40	99.6% monomer, 0.4% aggregate
75	99.5% monomer, 0.5% aggregate
100	99.5% monomer, 0.5% aggregate
121	99.5% monomer, 0.5% aggregate

M = monomer, A = aggregate

Example 15: Valence of compounds

Methods:

Analytical Membrane-Confined Electrophoresis was used to measure the valence of compounds which had previously been dialyzed into 10 mM Acetate 50 mM KCl pH 5.0 buffer overnight. In the experimental setup, 20 µL of sample at 1 mg/mL was loaded into a 2x2x4 mm3 quartz cuvette which both ends were sealed by 10 MWCO semi-permeable regenerated cellulose BioTech grade membranes. These membranes trap the macromolecule while allowing water and solvent components through. A 1 mA electric current was then applied through the cuvette, establishing an electric field along its length in which the charged macromolecule moved in the electric field with a continuous flow of fresh buffer. The real-time moving concentration boundary was detected using a linear photodiode array (LPDA) that provides intensity readings spaced along the cuvette. The velocity of the concentration boundary was used to calculate the electrophoretic mobility and subsequently the effective valence. Additional information such as the Stokes Radius (obtained from the sedimentation velocity run in the AUC), counterion radius (0.122 nm for chloride ion), buffer conductance (6.35 mS) and ionic strength (0.05 M) were then used to reveal the underlying valence of the macromolecule.

Results:

The valence data (see Table 16) indicate colloidal stability of the compounds in solution, i.e. net interaction of protein and protein in solution. The compounds with valence greater than 15 have strong net repulsive interaction and high potential to be formulated at high concentration.

Table 16. Valence data for compounds

Compound ID	Valence at pH 5.0
Compound A	24.4 ± 0.2
Compound B	21.5 ± 0.3
Compound D	21.8 ± 0.2

Example 16: Whole blood stability of compounds

Methods

A whole blood interference assay was developed on an Octet RED96 to detect the effects of non-specific binding or off-target binding for compounds in the presence of whole blood (WB). The compound solutions in whole blood and 1x kinetic running buffer (1xkb) were incubated at a temperature of 37 °C for 48 hours. Kinetic measurements for the incubated compound samples were performed with an Octet RED96 equipped with streptavidin (SA) biosensor tips (ForteBio, Menlo Park, CA) at 27 °C. The ratio of the on-rates/binding signals in buffer and whole blood were reported. A ratio < 2 was considered to show no interference.

Results

The results are shown in Table 17. No whole blood interference was observed for test compounds.

Table 17. Whole blood binding results for compounds

Parameters	Ratio of binding signal in WB/kinetic buffer to hu BAFF	Ratio of binding signal in WB/kinetic buffer to hu IL23
Compound A	1.2	1.1
Compound B	1.2	1.5
Compound C	1.1	1.3

Compound D	1.3	1.7
Compound E	1.0	1.1
Compound F	1.0	1.2

Example 17: Prediction of *in silico* Immunogenicity

Methods

Immunogenicity of protein therapeutics was predicted *in silico* by utilizing a computational tool, EpiMatrix that was developed by EpiVax, Inc. (Providence, RI).

EpiMatrix incorporates the prediction of T-helper epitope as well as the T-reg epitope, of which the former is to provoke an immune response while the latter is inhibitory. Briefly, the protein sequence was first parsed into overlapping 9-mer peptide frames that has been proven the core of class II HLA binding. The binding potential of 9-mer peptides to each of eight common class II HLA alleles are evaluated based on experimental data or computational prediction. A score is generated to reflect the binding potential of the 9-mer peptide to each HLA allele and normalization is performed to make it possible to compare any 9-mer across multiple HLA alleles and enable immunogenicity prediction on a global scale. In the end the program generates an overall 'immunogenicity score', tReg Adjusted Epx Score, that likelihood that the compounds will provoke an immune response *in vivo*.

Results

The results are shown in Table 18. The overall immunogenicity scores for test compounds are low and predict that these compounds are not likely to illicit a strong immune response *in vivo*.

Table 18 EpiVax Scores

Parameter	**EpiVax (Chain 1, Chain 2)**
Compound A	-46.13, -28.39
Compound B	-45.77, -28.39
Compound C	-41.40, -28.42
Compound D	-41.01, -28.42
Compound E	-39.81, -41.43

Compound F	-42.15, -36.94
Compound G	-43.75, -29.30
Compound H	-35.19, -43.44
Compound I	-43.38, -29.30
Compound J	-34.78, -43.44
Compound K	-43.75, -33.61
Compound L	-37.80, -43.44
Compound M	-43.38, -33.61
Compound N	-37.40, -43.44
Compound O	-34.66, -39.56
Compound P	-34.24, -39.56
Compound Q	-34.64, -47.37
Compound R	-34.22, -47.37
Compound S	-40.96, -40.09
Compound T	-43.91, -40.09
Compound U	-41.31, -44.98
Compound V	-42.53, -36.94
Compound W	-38.33, -44.98
Compound X	-39.42, -41.43

Example 18: Inhibition of human BAFF in primary human B-cell proliferation assay

Materials and Methods

The normal healthy blood samples (n = 3 donors) used in this study were purchased from Biological Specialty Corporation, Philadelphia, PA.The complete culture medium was IMDM (Life Technologies) supplemented with 10% FBS (Life Technologies) plus Pen/Strep (Life Technologies). The B-cell isolation buffer consisted of sterile Mg^{++} and Ca^{++} free DPBS (Life Technologies) plus 2% FBS plus 2 mM EDTA (Life Technologies).

Isolation of Human B Cells from Healthy Human Whole Blood

Four hundred mL of heparinized whole blood was transferred to a 1000 mL sterile polystyrene bottle and an equal volume of DPBS was added. Thirty-five 35 mL of PBS-diluted blood was placed on the top of a 15 mL Ficoll-Paque™ Plus (GE Healthcare) gradient preloaded in a 50 mL polystyrene round-bottom tube. The tubes were centrifuged at 2000 rpm at room temperature for 20 minutes without brake. Next, two-thirds of the top supernatant was aspirated, and the middle gray layer containing peripheral blood

mononuclear cells (PBMC) was transferred to a 50 mL conical tube. DPBS (Ca++ and Mg++ free) + 2% FBS was added, up to a volume of 50 mL. The tubes were spun down at 1200 rpm for 10 minutes. The resulting cell pellet was resuspended with DPBS (Ca++ and Mg++ free) + 2% FBS (wash buffer), and the centrifugation step (1200 rpm for 10 minutes) was repeated. The cell pellet was again resuspended in wash buffer up to 50 mL. Cell viability and cell concentration were measured at this point.

The tube was then spun down at 1200 rpm for 10 minutes, and the supernatant was discarded. The cell pellet was resuspended with complete culture medium and the cell concentration was adjusted to 5×10^6 cells/mL. The suspended cells were placed into a 75 cm^2 tissue culture flask and incubated in a 5% CO_2 incubator (at 37°C) overnight. The B cells were then isolated by using Dynabeads® Untouched™ Human B Cells Kit (Life Technologies) following the manufacturer's protocol. The cell concentration was adjusted to be suitable for the downstream procedure after measuring cell concentration and viability.

Evaluation of B-cell Proliferation Using ^{3}H-thymidine Incorporation Assay

B cells were seeded in a Falcon tissue culture 96–well, round-bottom plate (1×10^5 cells/100 µL culture medium per well). Then, test articles were prepared at 4x serial concentrations ranging from 0.028 to 20 nM and B cell stimuli (anti-IgM antibody and human BAFF) at 4x concentrations (8 µg/mL and 20 ng/mL, respectively) with complete culture medium. 50 µL of prediluted test articles were added to the respective wells (0.007 to 5 nM, final concentration). Then, 50 µL of prediluted goat anti-human IgM (2 µg/mL, final concentration) and hBAFF (5 ng/mL or 98 pM, final concentration) were added to the corresponding wells (see Figure 6). The B cells were cultivated in a 5% CO_2 37°C humidified incubator for 72 hours. Eighteen hours prior to the end of the incubation, 20 µL of 1 µCi ^{3}H-thymidine (Pelkin Elmer) was added to each well. A cell harvester was used to transfer ^{3}H-thymidine incorporated DNA/well to a microfiber glass filter plate, where 30 µL scintillation enhancer was added to the wells after air-drying the plate for at least 4 hours. The counts per minute (cpm) value of each well was measured using a MicroBeta Topcount, and the cpm value (y-axis) versus concentration of test articles (x-axis) was plotted.

Statistical Analyses

IC_{50} and IC_{90} were determined by curve fitting the data to a 4-parmeter sigmoidal dose-response function using GraphPad Prism 6 software. Geomeans were calculated across three experiments and shown in Table 19.

Results

The results showed that Compound B appeared to be approximately 2-fold more potent as compared to Control Antibody 3 when comparing IC_{50} and IC_{90} values.

Table 19. IC50 and IC90 Geomean values for inhibiting human BAFF in primary human B-cell proliferation assay

Compound ID	**IC_{50} (pM)**	**IC_{90} (pM)**
Compound B	33.7	160.2
Control Antibody 3 (BAFF (3))	87.3	370.8

Example 19. Inhibition of B220+ B cell numbers induced by human BAFF overexpression in B10.RIII mice

Materials and Methods

Briefly, on day 1 B10.RIII female mice (6-8 weeks old, Jackson Laboratory) were randomly divided into 10 groups, 10 animals/group and given a 100µl intraperiotoneal injection of either citrate buffer (20mM NaCitrate, 115mM NaCl, pH 6.0) or test compounds at equivalent molar dose of 1.3, 0.4 and 0.13 mg/kg vs. 1, 3 and 0.1 mg/kg respectively. Naïve untreated mice were an additional control. Immediately following treatment day 1, mice were administered a single 3 mg dose (1.5 mg/mL) of human BAFF minicircle DNA (System Biosciences) via hydrodynamic injection versus empty vector (EV) control group. Intraperiotoneal treatment with either citrate buffer or test compounds was repeated every 72 hours on days 3, 6, 9 and 12.

On day 14 mice were anesthetized via isoflurane (Butler Schein) and sacrificed via cervical dislocation. Spleens were removed and a cell suspension analyzed by flow cytometry for B220+ B cells. The mean numbers for each treatment group were determined and significance compared to control calculated using the One-way ANOVA followed by

Dunnett's multiple comparisons test. Results are shown in FIG. 5.

Results

The results showed that treatment for 14 days with Compound B was able to significantly inhibit the expansion of B220+ B cells induced by human BAFF minicircle DNA.

Example 20. Inhibition of human IL23 induced mouse IL17A and IL22 release in C57/Bl6 mice

Materials and Methods

Briefly, C57BL/6 female mice (7-10 weeks old, Charles River) were randomly divided into 8 groups, 8 animals/group and given a 100µl intraperiotoneal injection of either citrate buffer (20mM NaCitrate, 115mM NaCl, pH 6.0) or test compounds at equivalent molar dose of 1.3, 0.4 and 0.13 mg/kg vs. 1, 3 and 0.1 mg/kg respectively.

One hour after test compound dosing mice were anesthetized via isoflurane (Butler Schein) and given a 20µl intradermal injection of either 0.1%BSA (Sigma) control or 15µg/ml (0.3µg) rhIL23 (generated in-house) diluted in saline (Invitrogen) to both ears. Intradermal challenges were repeated daily for 2 consecutive days. Twenty-four hours after the second challenge the mice were sacrificed via cervical dislocation and each ear was removed. Ear tissue was homogenized in 1ml of homogenization buffer (HBSS (Gibco); 0.4% Triton X-100 (Sigma); 1X SigmaFast Protease Inhibitor (Sigma)) using a MP Biomedicals Fast-Prep 24 homogenizer. Homogenized samples are centrifuged at 4C for 10 min and supernatant collected. Supernantants were assayed for the presence of mouse IL17A and IL22, using the Quantikine® Mouse IL-17 and mouse IL-22 Immunoassays according to the manufacturer's instructions (R&D Systems). Interpolated cytokine pg/ml values were determined for each sample. The mean pg/ml levels for each treatment group were determined and significance compared to control calculated using the One-way ANOVA followed by Dunnett's multiple comparisons test.

Results

The results in FIG.6 showed that treatment with a single intraperitoneal dose of Compound B was able to significantly inhibit the release of mouse IL17 and IL22 in the skin induced by two daily consecutive intra dermal injections of recombinant human IL23.

SEQUENCES

SEQ ID NO	Sequence
1	QVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMGGIIP MFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLFPHH ALSPWGRGTMVTVSS
2	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVL
3	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPR DDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIY WGQGTLVTVSS
4	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIK
5	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVLG GGSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLE WIGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRS GYAWFIYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG
6	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMG GIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLF PHHALSPWGRGTMVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
7	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH

	TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMG GIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLF PHHALSPWGRGTMVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG
8	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVLG GGSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLE WIGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRS GYAWFIYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
9	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVLG GGSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLE WIGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRS GYAWFIYWGQGTLVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKL EPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG
10	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMG GIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLF PHHALSPWGRGTMVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
11	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMG GIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLF PHHALSPWGRGTMVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKL

	EPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG
12	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVLG GGSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLE WIGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRS GYAWFIYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
13	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVLG GGSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLE WIGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRS GYAWFIYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLSLG
14	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMG GIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLF PHHALSPWGRGTMVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
15	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMG GIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLF PHHALSPWGRGTMVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK

	GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLSLG
16	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVLG GGSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLE WIGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRS GYAWFIYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
17	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVLG GGSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLE WIGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRS GYAWFIYWGQGTLVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKE SKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLG
18	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMG GIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLF PHHALSPWGRGTMVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
19	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLQQSGAEVKKPGSSVRVSCKASGGTFNNNAINWVRQAPGQGLEWMG GIIPMFGTAKYSQNFQGRVAITADESTGTASMELSSLRSEDTAVYYCARSRDLLLF PHHALSPWGRGTMVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKE SKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLG
20	SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRP SGIPDRFSGSSSGNTASLTITGAQAEDEADYYCSSRDSSGNHWVFGGGTELTVLG GGSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLE

	WIGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRS GYAWFIYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
21	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPG
22	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLSWLQQEPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC
23	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKLEPKSSDKTH TCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG
24	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLSWLQQEPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
25	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG

	GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG
26	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLSWLQQEPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC
27	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKESKYGPPCPP CPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
28	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLSWLQQEPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
29	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSH

	EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPG
30	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLNWYQQKPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC
31	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKLEPKSSDKTH TCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG
32	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLNWYQQKPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
33	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG

34	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLNWYQQKPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC
35	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKESKYGPPCPP CPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
36	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLNWYQQKPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
37	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQRPGQGLEWIGRI DPNSGATKYNEKFESKVTLTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG
38	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFADYYCLQYRSYPRTFGGGTKLEIKGGGS GGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIG YIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGY AWFIYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY

	PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
39	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQRPGQGLEWIGRI DPNSGATKYNEKFESKVTLTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKLEP KSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG
40	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFADYYCLQYRSYPRTFGGGTKLEIKGGGS GGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIG YIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGY AWFIYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
41	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQRPGQGLEWIGRI DPNSGATKYNEKFESKVTLTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLG
42	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFADYYCLQYRSYPRTFGGGTKLEIKGGGS GGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIG YIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGY AWFIYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
43	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG

	GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQRPGQGLEWIGRI DPNSGATKYNEKFESKVTLTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKESK YGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLG
44	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFADYYCLQYRSYPRTFGGGTKLEIKGGGS GGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIG YIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGY AWFIYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
45	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQAPGQGLEWIGRI DPNSGATKYNEKFESRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG
46	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYRSYPRTFGQGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYI YPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAW FIYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC
47	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQAPGQGLEWIGRI DPNSGATKYNEKFESRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKLEP KSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEV

	KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG
48	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYRSYPRTFGQGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYI YPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAW FIYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
49	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQAPGQGLEWIGRI DPNSGATKYNEKFESRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLG
50	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYRSYPRTFGQGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYI YPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAW FIYWGQGTLVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC
51	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQAPGQGLEWIGRI DPNSGATKYNEKFESRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSGGCGGGEVAACEKEVAALEKEVAALEKEVAALEKESK YGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLG

52	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYRSYPRTFGQGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYI YPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAW FIYWGQGTLVTVSSGGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
53	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLSWLQQEPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG
54	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
55	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLSWLQQEPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEA LHNHYTQKSLSLSLG
56	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG

	EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
57	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLNWYQQKPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG
58	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW GQGTTVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
59	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLNWYQQKPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIKGGGSGG GGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIY PRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWF IYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEA LHNHYTQKSLSLSLG
60	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMG EIFPGSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYW

	GQGTTVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
61	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFADYYCLQYRSYPRTFGGGTKLEIKGGGS GGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIG YIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGY AWFIYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG
62	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQRPGQGLEWIGRI DPNSGATKYNEKFESKVTLTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
63	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFADYYCLQYRSYPRTFGGGTKLEIKGGGS GGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIG YIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGY AWFIYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLG
64	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQRPGQGLEWIGRI DPNSGATKYNEKFESKVTLTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY

	PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
65	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYRSYPRTFGQGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYI YPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAW FIYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG
66	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQAPGQGLEWIGRI DPNSGATKYNEKFESRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
67	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYRSYPRTFGQGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYI YPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAW FIYWGQGTLVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSN TKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLG
68	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRH TGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSG GGGQVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQAPGQGLEWIGRI DPNSGATKYNEKFESRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRT DALDYWGQGTSVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC

	EVTHQGLSSPVTKSFNRGEC
69	GGGSGGGG
70	LGGGSG
71	FNRGEC
72	VEPKSC
73	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
74	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
75	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G
76	EPKSCDKTHTCPPCP
77	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
78	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
79	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE

	VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G
80	MDDSTEREQSRLTSCLKKREEMKLKECVSILPRKESPSVRSSKDGKLLAATLLLAL LSCCLTVVSFYQVAALQGDLASLRAELQGHHAEKLPAGAGAPKAGLEEAPAVTA GLKIFEPPAPGEGNSSQNSRNKRAVQGPEETVTQDCLQLIADSETPTIQKGSYTFVP WLLSFKRGSALEEKENKILVKETGYFFIYGQVLYTDKTYAMGHLIQRKKVHVFG DELSLVTLFRCIQNMPETLPNNSCYSAGIAKLEEGDELQLAIPRENAQISLDGDVTF FGALKLL
81	MLGSRAVMLLLLLPWTAQGRAVPGGSSPAWTQCQQLSQKLCTLAWSAHPLVGH MDLREEGDEETTNDVPHIQCGDGCDPQGLRDNSQFCLQRIHQGLIFYEKLLGSDIF TGEPSLLPDSPVGQLHASLLGLSQLLQPEGHHWETQQIPSLSPSQPWQRLLLRFKIL RSLQAFVAVAARVFAHGAATLSP
82	GGCGGGEVAACEKEVAALEKEVAALEKEVAALEK
83	GGCGGGKVAACKEKVAALKEKVAALKEKVAALKE
84	QVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMGEIFP GSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYWGQG TTVTVSS
85	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLSWLQQEPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIK
86	QVQLVQSGAEVKKPGSSVKVSCKAPDHIFSIHWMQWVRQAPGQGLEWMGEIFP GSGTTDYNEKFKGKVTITVDKSTSTAYMELSSLRSEDTAVYYCASGAFDYWGQG TTVTVSS
87	DIQMTQSPSSLSASVGDRVTITCRASQDIGNRLNWYQQKPGKAPKRLIYATSSLDS GVPSRFSGSRSGTEFTLTISSLQPEDFVTYYCLQYASSPFTFGQGTKLEIK
88	QVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQRPGQGLEWIGRIDPNS GATKYNEKFESKVTLTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRTDALD YWGQGTSVTVSS
89	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFADYYCLQYRSYPRTFGGGTKLEIK
90	QVQLVQSGAEVKKPGASVKVSCKASGYSFSTFFIHWVRQAPGQGLEWIGRIDPNS GATKYNEKFESRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGEDLLIRTDALD YWGQGTSVTVSS
91	DIQMTQSPSSLSASVGDRVSITCKASQNAGIDVAWFQQKPGKAPKLLIYSKSNRY TGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYRSYPRTFGQGTKLEIK
92	GGTFNNNAIN

93	GIIPMFGTAKYSQNFQG
94	SRDLLLFPHHALSP
95	QGDSLRSYYAS
96	GKNNRPS
97	SSRDSSGNHWV
98	GYTFTDQTIH
99	YIYPRDDSPKYNENFKG
100	PDRSGYAWFIY
101	KASRDVAIAVA
102	WASTRHT
103	HQYSSYPFT
104	DHIFSIHWMQ
105	EIFPGSGTTDYNEKFKG
106	GAFDY
107	RASQDIGNRLS
108	ATSSLDS
109	LQYASSPFT
110	DHIFSIHWMQ
111	EIFPGSGTTDYNEKFKG
112	GAFDY
113	RASQDIGNRLN
114	ATSSLDS
115	GYSFSTFFIH
116	RIDPNSGATKYNEKFES
117	GEDLLIRTDALDY
118	KASQNAGIDVA
119	SKSNRYT
120	LQYRSYPRT
121	GYSFSTFFIH
122	GRIDPNSGATKYNEKFES
123	GEDLLIRTDALDY
124	KASQNAGIDVA
125	SKSNRYT
126	LQYRSYPRT
127	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG

	LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLG
128	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G
129	LEPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPG
130	LEPKSSDKTHTCPPCP
131	GCKWDLLIKQWVCDPLGSGSATGGSGSTASSGSGSATHMLPGCKWDLLIKQWV CDPLGGGGGVDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
132	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHS GSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGYYDILTGYYYY FDYWGQGTLVTVSS
133	EIVLTQSPATLSLSPGERATLSCRASQSVSRYLAWYQQKPGQAPRLLIYDASNRAT GIPARFSGSGSGTDSTLTISSLEPEDFAVYYCQQRSNWPRTFGQGTKVEIK
134	ESKYGPPCPPCP
135	GGCGGG
136	LGGCGGGS

OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or

similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present disclosure, and without departing from the spirit and scope thereof, can make various changes and modifications of the disclosure to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

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

(ii) 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

(iii) 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

(iv) 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

(v) 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; or

(vi) 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.

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 C1 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 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. 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.

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

13. 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

(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.

14. The compound according to claim 13, 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 and wherein each of said first polypeptide is associated to one said second polypeptide via at least one disulfide bond.

15. The compound according to claim 13 or 14, wherein said compound comprises two said first polypeptides and two 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 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.

16. 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 sad 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.

17. 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:2, said VH1 comprises SEQ ID NO:1, said VL2 comprises SEQ ID NO:4 and said VH2 comprises SEQ ID NO:3; or

(ii) 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

(iii) 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

(iv) 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

(v) 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; or

(vi) 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.

18. The compound according to claim 17, 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.

19. The compound according to claim 18, wherein said first linker or said second linker comprises the amino acid sequence GGGSGGGG (SEQ ID NO:69).

20. The compound according to claim 18, wherein said first linker and said second linker comprise the amino acid sequence GGGSGGGG (SEQ ID NO:69).

21. The compound according to claim 18, wherein each of said first polypeptides further comprises a third linker between said VH2 and said CH1, and each of said second polypeptides further comprises a fourth linker between said VH1 and said CL.

22. The compound according to claim 21, wherein said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:70).

23. The compound according to claim 21, wherein said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:70).

24. The compound according to claim 17, 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.

25. The compound according to claim 17, 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.

26. The compound according to claim 17, 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).

27. The compound according to claim 17, wherein:

(i) 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

(ii) 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
(iii) 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
(iv) 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
(v) 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
(vi) 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
(vii) 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
(viii) 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
(ix) 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
(x) 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
(xi) 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
(xii) 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.

28. A pharmaceutical composition comprising a compound according to any one of claims 1 to 27.

29. A method of treating an autoimmune or an inflammatory disease comprising administering a compound according to any one of claims 1 to 27 or a pharmaceutical composition comprising said compound to a subject.

30. A compound according to any one of claims 1 to 27 for use in medicine.

31. The compound according to claim 30, wherein said use is the treatment of an autoimmune or an inflammatory disease.

32. A pharmaceutical composition comprising a compound according to any one of claims 1 to 27 for use in medicine.

33. The pharmaceutical composition according to claim 32, wherein said use is the treatment of an autoimmune or an inflammatory disease.

34. A nucleic acid comprising a nucleotide sequence encoding a polypeptide according to any one of claims 1 to 27.

35. A vector comprising a nucleic acid according to claim 34.

36. The vector according to claim 35, further comprising a promoter operably linked to said nucleic acid.

37. A cell comprising a nucleic acid according to claim 34 or a vector according to 35 or 36.

38. A method of producing a polypeptide according to any one of claims 1 to 27 comprising obtaining a cell according to claim 37 and expressing said nucleic acid in said cell.

39. The method according to claim 38, further comprising isolating and purifying said polypeptide.

40. The method according to claim 29, the compound according to claim 31 or the composition according to claim 32, 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 Sjogren's syndrome (pSS), chronic graft versus host disease (cGVHD), systemic sclerosis (SSc), Rheumatoid Arthritis (RA), Psoriasis (Ps), Ankylosing Spondylitis (AS) or Psoriatic Arthritis (PA).