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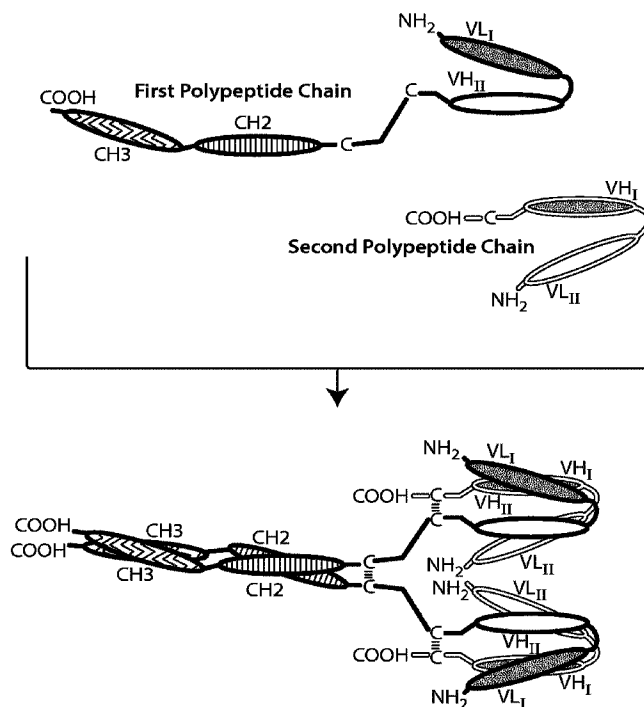
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(54) Title: COMPOUND TARGETING IL-23A AND TNF-ALPHA AND USES THEREOF



(57) Abrégé/Abstract:

The disclosure relates to compounds specific for IL23A and TNF-alpha, compositions comprising the compounds, and methods of use thereof. Nucleic acids, cells, and methods of production related to the compounds and compositions are also disclosed.

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(54) Title: COMPOUND TARGETING IL-23A AND TNF-ALPHA AND USES THEREOF

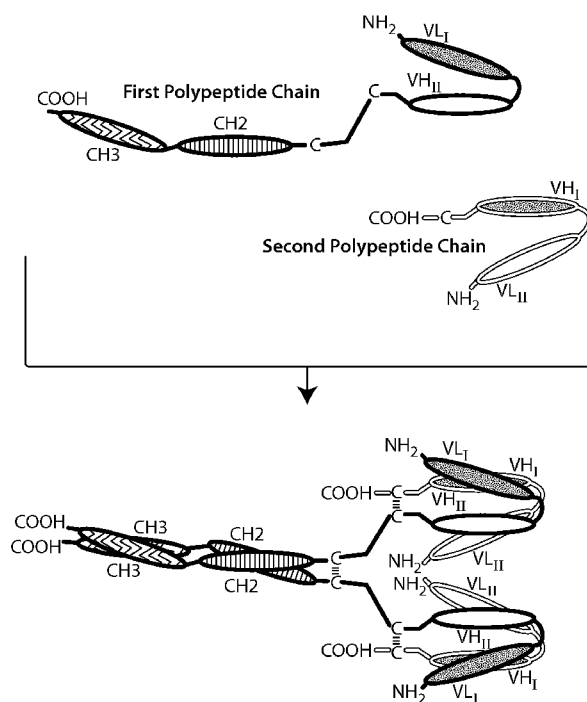


FIG. 1A

(57) Abstract: The disclosure relates to compounds specific for IL23A and TNF-alpha, compositions comprising the compounds, and methods of use thereof. Nucleic acids, cells, and methods of production related to the compounds and compositions are also disclosed.

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COMPOUND TARGETING IL-23A AND TNF-ALPHA AND USES THEREOF

RELATED APPLICATION

5 This application claims the benefit of the filing date under 35 U.S.C. §119 of United States Provisional Application Serial Number 62/045,498, filed September 3, 2014, and entitled Compound Targeting IL-23A and TNF-ALPHA and Uses Thereof.

BACKGROUND OF THE INVENTION

10 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.

15 It is well established that inhibiting activity of proinflammatory cytokines such as IL1, TNF-alpha, IL6, IL12, IL17, IL18, or IL23 reduces inflammation and suppresses specific pathways that activate immune cells.

20 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, $\gamma\delta$ 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 TGF-beta1, 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 IL12 β 1 subunit of IL12 receptor partnered with a unique IL23R subunit. Expression of the IL23R is restricted to specific populations of immune cells and is

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found primarily on subsets of T cells ($\alpha\beta$ and $\gamma\delta$ 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 IL12-beta1), 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. Invest.* 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).

The homotrimeric TNF- α cytokine is expressed predominantly by macrophages, lymphocytes, endothelial cells and fibroblasts and binds two distinct receptors: TNFRI, expressed on nearly all cell types and TNFRII, with more limited expression on immune cells (CD4+ T cells, NK cells). Like many TNF superfamily members, TNF- α exists as both membrane and soluble forms, the soluble form arising from cleavage of the membrane form by the ADAM12 metalloprotease (TACE, TNF α converting enzyme). Both membrane-bound and soluble forms of the cytokine are biologically active.

Tumor necrosis factor (TNF-alpha/ TNF- α) is a proinflammatory cytokine that stimulates the acute phase of inflammation. Tumor necrosis factor increases vascular permeability through induction of IL8, thereby recruiting macrophage and neutrophils to a site of infection. Once present, activated macrophages continue to produce TNF-alpha,

thereby maintaining and amplifying the inflammatory response. The primary role of TNF-alpha is the regulation of immune cells; however, TNF-alpha is also involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation. TNF-alpha is able to induce
 5 inflammation, induce apoptotic cell death, inhibit tumorigenesis and inhibit viral replication.

Dysregulation of TNF-alpha production has been implicated in a variety of human diseases, including autoimmune disease (e.g. rheumatoid arthritis (RA), Crohn's disease, multiple sclerosis), inflammatory bowel disease (IBD), ulcerative colitis, psoriasis, toxic shock, graft versus host disease, insulin resistance, Alzheimer's disease, cancer, and major
 10 depression (Swardfager W, et al. (2010) *Biol Psychiatry* 68 (10): 930–941; (Locksley RM, et al. (2001) *Cell* 104 (4): 487–501; Dowlati et al., (2010) *Biol Psychiatry* 67 (5): 446–457; Brynskov J. et al. (2002) *Gut* 51 (1): 37–43).

Antibodies have been used as biologic therapies for inhibition of TNF-alpha and IL23 in order to treat a variety of inflammatory diseases. Infliximab (Centocor, Malvern, Pa.)
 15 described in U.S. Pat. Nos. 6,277,969, 6,284,471, and 6,790,444, is a chimeric anti- TNF-alpha monoclonal IgG antibody bearing human IgG4 constant and mouse variable regions and is used clinically to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and plaque psoriasis. Monoclonal antibody adalimumab (clone D2E7; Abbott Laboratories, Abbott Park, Illinois) described in U.S. Pat. No.
 20 6,090,382, is an anti-TNF-alpha therapy used clinically to treat rheumatoid arthritis, Crohn's disease, psoriasis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis. Golimumab is a TNF-alpha blocker used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. In addition, human monoclonal antibody ustekinumab (Centocor, Inc, Malvern, Pa.), described in U.S. Pat. No. 6,902,734 and U.S.
 25 Pat. No. 7,166,285, is directed against interleukin 12 and interleukin 23 (specifically the p40 subunit), is clinically used to treat severe plaque psoriasis, and is further being investigated for the treatment of psoriatic arthritis, multiple sclerosis, and sarcoidosis. However, anti-TNF- α therapies have reported side effects [see for example: Keane J et al. (2001)].
 Tuberculosis is associated with infliximab, a tumor necrosis factor α -neutralizing agent. *N Engl J Med* 345 (15):1098–1104; Scheinfeld N. (2005) Adalimumab: a review of side effects.
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Expert Opin Drug Saf. 4(4):637-41; Chovel-Sella A et al. (2012) Clinical efficacy and adverse effects of golimumab in the treatment of rheumatoid arthritis. *Isr Med Assoc J.* 14(6):390-4]. Identification of more efficacious treatments should allow for administration of reduced dosages, as well as lower costs associated with the treatment.

- 5 There remains a need for compositions with increased efficacy for treating and preventing autoimmune or inflammatory diseases.

SUMMARY OF THE INVENTION

10 Provided herein are compounds specific for TNF-alpha 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:

- 15 (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

20 (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;

25 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;

- (iii) said heavy chain constant region 2 (CH2) comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256, numbered according to the EU index as in Kabat for a conventional antibody; and
- (iv) said first target protein is TNF-alpha and said second target protein is IL-23A or said first target protein is IL-23A and said second target protein is TNF-alpha,

wherein:

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

- In some embodiments, in (ii) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7.
- In some embodiments, in (ii) said VL1 comprises SEQ ID NO:6, said VH1 comprises SEQ ID NO:5, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7. In some embodiments, in (iv) said VL2 comprises SEQ ID NO:4, said VH2 comprises SEQ ID NO:3, said VL1 comprises SEQ ID NO:8 and said VH1 comprises SEQ ID NO:7. In some embodiments, in (iv) said VL2 comprises SEQ ID NO:6, said VH2 comprises SEQ ID NO:5, said VL1 comprises SEQ ID NO:8 and said VH1 comprises SEQ ID NO:7.

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 GGGSGGG (SEQ ID NO:9). In some

embodiments, said first linker and said second linker comprise the amino acid sequence GGGSGGG (SEQ ID NO:9).

In some embodiments, 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.

In some embodiments, 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. In some embodiments, said third linker comprises the amino acid sequence FNRGES (SEQ ID NO:11). In some embodiments, said fourth linker comprises the amino acid sequence VEPKSS (SEQ ID NO:12). In some embodiments, said third linker comprises the amino acid sequence FNRGES (SEQ ID NO:11) and said fourth linker comprises the amino acid sequence VEPKSS (SEQ ID NO:12). In some embodiments, third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:10). In some embodiments, said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:10).

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:40).

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 associate 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:13 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:14;
- (ii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:15 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:16;
- 5 (iii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:17 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:18;
- (iv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:19 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:20;
- (v) said first polypeptide comprises the amino acid sequence of SEQ ID NO:21 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:22;
- 10 (vi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:24;
- (vii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:26;
- 15 (viii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:28;
- (ix) said first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:30;
- (x) said first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:32;
- 20 (xi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:34; or
- (xi) 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.

25 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 CH2 and CH3, and CH1 if present, of one of the first polypeptides associates with the CH2 and CH3, and CH1 if present, of the other of the

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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 CH2 and a CH3 and each of said second polypeptides comprises a CL and wherein the CH2 and CH3 of one of the first polypeptides associates
5 with the CH2 and CH3 of the other of the first polypeptides and the CH1 of each said first polypeptides associates with the CL of one said second polypeptides to form a tetravalent molecule.

Other aspects of the disclosure relate to a first compound that competes with a second compound for binding to IL-23A and to TNF-alpha, wherein said first compound comprises a
10 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)
15 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
20 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
25 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 TNF-alpha and said second target protein is IL-23A or said first target protein is IL-23A and said second target protein is TNF-alpha,
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and wherein said second compound comprises a first polypeptide and a second polypeptide, wherein:

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

(ii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:15 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:16;

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

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

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

(vi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:24;

20 (vii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:26;

(viii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:28;

25 (ix) said first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:30;

(x) said first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:32;

5 (xi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:34; or

(xii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:35 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:36.

10 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
15 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
20 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 use of a compound described herein, such as a compound described above, in the manufacture of a medicament for use in medicine. In some embodiments, said use is the treatment of an autoimmune or an
25 inflammatory disease.

Other aspects of the disclosure relate to a use of a pharmaceutical composition described herein, such as a pharmaceutical composition described above, in the manufacture of a medicament 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 TNF-alpha and IL23A. The first polypeptide chain contains CH3, CH2, VH₂ (VH_{II}) and VL₁ (VL_I) domains. The second polypeptide chain contains VH₁ (VH_I) and VL₂ (VL_{II}) domains. VL₁ and VH₁ are specific for a first target protein (either TNF-alpha or IL23A) and VL₂ and VH₂ are specific for a second target protein (either IL23A or TNF-alpha). The upper panel shows each polypeptide chain separately. The lower panel shows a tetravalent compound 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 VH₁ and VL₁ and through association VH₂ and VL₂, respectively.

FIG. 1B is a diagram of another exemplary compound specific for TNF-alpha and IL23A. The first polypeptide chain contains CH3, CH2, CH1, VH₂ (VH_{II}) and VL₁ (VL_I) domains. The second polypeptide chain contains CL, VH₁ (VH_I) and VL₂ (VL_{II}) domains. VL₁ and VH₁ are specific for a first target protein (either TNF-alpha or IL23A) and VL₂ and VH₂ are specific for a second target protein (either IL23A or TNF-alpha). The upper panel shows each polypeptide chain separately. The lower panel shows a tetravalent compound 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 VH₁ and VL₁ and through association of VH₂ and VL₂, respectively. The compound is further associated through interactions between the CL and CH1 domains.

FIG. 2 is a graph showing the serum concentrations of Compound M and its YTE mutant Compound A in male cynomolgus monkey (mean±SD; N=3) after 1 mg/kg IV 10 minute infusion.

FIG. 3 is a graph show serum concentrations of Compound O and its corresponding YTE mutant Compound E in male cynomolgus monkey (mean±SD; N=3) after 1 mg/kg IV 10 minute infusion.

FIG. 4 is a series of graphs and a table showing that compound E maintained functional potency vs. IL23 in vivo. Mice were dosed equimolar with either control antibody 3 (IL23A monoclonal antibody) or compound E 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. Compound E maintained functional potency in vivo vs. control antibody 3 (IL23A monoclonal antibody) based on terminal exposure and level of efficacy. Control antibody 3: open squares, triangles and diamonds. Compound E: full squares, triangles and diamonds. MW: molecular weight.

FIG. 5 is a series of graphs and a table showing that Compound E maintained functional potency vs. TNF in vivo. Mice were dosed equimolar with either control antibody 2 (TNFa monoclonal antibody) or compound E and challenged with human TNF. Two hours after the challenge, whole blood was collected and serum analyzed for mouse KC and mouse

IL-6 as a measure of functional blockade of TNF. Compound E maintained functional potency *in vivo* vs. anti-TNF based on terminal exposure and level of efficacy. Control antibody 3: open squares, triangles and diamonds. Compound E: full squares, triangles and diamonds. MW: molecular weight.

5

DETAILED DESCRIPTION OF THE INVENTION

Described herein compounds that bind to both TNF-alpha (also referred to herein as TNF- α or TNFa) and IL23A (also referred to as IL23p19 or IL-23A). To date, there have been no approved compounds that target both TNF-alpha and IL23A. There are limited studies with simultaneous neutralization of two/more key inflammatory mediators using bio-therapeutics approach. While these studies failed to show improvement in clinical outcomes that were measured for rheumatoid arthritis (RA), a bi-functional therapeutic targeting the same combination has not been described to date. 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, the compounds described herein that bind to both TNF-alpha and IL23A have been found to have similar or improved properties compared to individual antibodies that target either IL23A or TNF-alpha. These 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 compounds had low aggregation. In one aspect, exemplary compounds showed particularly low aggregation. It was also shown that the linkers were optimized to improve stability and prevented cleavage and that the YTE mutation improved Fc Rn affinity. The

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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 (Fab).

5 Accordingly, aspects of the disclosure relate to compounds specific for both TNF-alpha and IL23A, as well as methods of use and production of such compounds.

Compounds

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

```
>NP_000585.2 - TNF-alpha [Homo sapiens]
MSTESMIRDVELAEALPKKTGGPQGSRRCLFSLFSFLIVAGATTLCLLHFGVIGPQREEFPRLSLI
15 SPLAQAVRSSSRTPSDKPVAVHVVANPQAEGLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYSQVLF
KGQGCPSTHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYEPIYLGGVFQLEKGDRLSA
EINRPDYLDFAESGQVYFGIIAL (SEQ ID NO: 144)

>NP_057668.1 - IL23A [Homo sapiens]
20 MLGSRVMLLLLLPWTAQGRAVPGGSSPAWTQCQQLSQKCLTLAWSAHPLVGHMDLREEGDEETTNVDPH
IQCGDGCDPQGLRDNQFCLQRIHQGLIFYEKLIGSDIFTGEPSSLPDSPVGQLHASLLGLSQLLQPEGH
HWETQQIPSLSPSQPWQRLRLRFKILRSIQAFVAVAAARVFAHGAATLSP (amino acids 1-19 are a
predicted signal sequence) (SEQ ID NO: 145)
```

25 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
30 (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 first 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

10 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

15 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 compound comprises the first polypeptide in configuration 1 and the second polypeptide in configuration 1. In some embodiments, the compound comprises the first polypeptide in configuration 3 and the second polypeptide in configuration 3.

20 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
25 embodiments, the first target protein is TNF-alpha and the second target protein is IL23A. In other embodiments, the first target protein is IL23A and the second target protein is TNF-alpha. 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 2A 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:8	SEQ ID NO:7
2	SEQ ID NO:8	SEQ ID NO:7	SEQ ID NO:2	SEQ ID NO:1
3	SEQ ID NO:8	SEQ ID NO:7	SEQ ID NO:4	SEQ ID NO:3
4	SEQ ID NO:8	SEQ ID NO:7	SEQ ID NO: 6	SEQ ID NO: 5
5	SEQ ID NO:8	SEQ ID NO:7	SEQ ID NO:4	SEQ ID NO: 5
6	SEQ ID NO:8	SEQ ID NO:7	SEQ ID NO: 6	SEQ ID NO: 3
7	SEQ ID NO:4	SEQ ID NO:3	SEQ ID NO:8	SEQ ID NO:7
8	SEQ ID NO:4	SEQ ID NO:5	SEQ ID NO:8	SEQ ID NO:7
9	SEQ ID NO:6	SEQ ID NO:3	SEQ ID NO:8	SEQ ID NO:7
10	SEQ ID NO:6	SEQ ID NO:5	SEQ ID NO:8	SEQ ID NO:7

- 5 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 or Table 2A. Exemplary light chain and heavy chain CDR sequences for the VL1, VH1, VL2, and VH2 sequences provided in Table 1 are shown below:

10 SEQ ID NO: 1 CDRs: DYAMH (SEQ ID NO: 146) (CDR1), AITWNSGHIDYADSV (SEQ ID NO: 147) (CDR2), VSYLSTASSLDY (SEQ ID NO: 148) (CDR3)

SEQ ID NO: 2 CDRs: RASQGIRNYLA (SEQ ID NO: 149) (CDR1), AASTLQS (SEQ ID NO: 150) (CDR2), QRYNRAPYT (SEQ ID NO: 151) (CDR3)

SEQ ID NO: 3 and SEQ ID NO: 5 CDRs: SYAMH (SEQ ID NO: 152) (CDR1), FMSYDGSNKKYADSVKG (SEQ ID NO: 153) (CDR2), NYYYYGMDV (SEQ ID NO: 154) (CDR3)

SEQ ID NO: 4 and SEQ ID NO: 6 CDRs: RASQSVYSYLA (SEQ ID NO: 155) (CDR1), DASNRAT (SEQ ID NO: 156) (CDR2), QQRSNWPPFT (SEQ ID NO: 157) (CDR3)

SEQ ID NO: 7 CDRs: DQTIH (SEQ ID NO: 158) (CDR1), YIYPRDDSPKYNENFKG (SEQ ID NO: 159) (CDR2), PDRSGYAWFIY (SEQ ID NO: 160) (CDR3)

SEQ ID NO: 8 CDRs: KASRDVAIAVA (SEQ ID NO: 161) (CDR1), WASTRHT (SEQ ID NO: 162) (CDR2), HQYSSYPFT (SEQ ID NO: 163) (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 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.

5 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.

10 In some embodiments, the amino acid sequences of the CH2 and CH3 are derived from an IgG1 or an IgG4 (e.g., SEQ ID NO: 39 or 37). 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:40).

15 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
20 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
25 Health and Human Services, 1991).

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
30 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. If the first polypeptide comprises a CH1, the first polypeptide may comprise a linker between the VL1 or VH2 (depending on the configuration 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. 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 discussed above) and the CL (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 GGGSGGG (SEQ ID NO:9), LGGGSG (SEQ ID NO:10), FNRGES (SEQ ID NO:11), VEPKSS (SEQ ID NO:12), 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 GGGSGGG (SEQ ID NO:9), LGGGSG (SEQ ID NO:10), FNRGES (SEQ ID NO:11), VEPKSS (SEQ ID NO:12), or a combination thereof.

In some embodiments, the compound comprises two first polypeptides and two
5 second polypeptides. In some embodiments, the CH2 and CH3 of one of the first polypeptides associates with the 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 CH2 and CH3 domains to form a tetravalent molecule comprising two
10 binding sites specific for the first target protein and two binding sites specific for the second target protein). If the first polypeptide further comprises a CH1 domain, the CH1 domain may also participate in formation of a tetravalent molecule (e.g., the two first polypeptides dimerize through associations between their respective CH1, CH2 and CH3 domains to form a tetravalent molecule comprising two binding sites for the first target protein and two
15 binding sites for the second target protein). In some embodiments, the two first polypeptides are associated together via at least one disulfide bond.

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 TNF-alpha and IL23A. In some embodiments, the test compound may have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence
20 identity 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 TNF-alpha and IL23A. A compound that “specifically binds” to an antigen or an epitope is a
25 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,
30 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., TNF-alpha 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
5 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
10 other antigens or other epitopes in the same antigen.

In some embodiments, a compound as described herein has a suitable binding affinity for TNF-alpha 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
15 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
20 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
25 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.,
30 using a fluorescence assay). Exemplary conditions for evaluating binding affinity are in HBS-

P buffer (10 mM HEPES pH7.4, 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:

$$[\text{Bound}] = [\text{N}][\text{Free}]/(\text{Kd} + [\text{Free}])$$

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) a first polypeptide comprises the amino acid sequence of SEQ ID NO:13 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:14;
- (ii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:15 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:16;
- (iii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:17 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:18;
- (iv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:19 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:20;
- (v) a first polypeptide comprises the amino acid sequence of SEQ ID NO:21 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:22;
- (vi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:24;

- (vii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:26;
- (viii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:28;
- 5 (ix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:30;
- (x) a first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and a
second polypeptide comprises the amino acid sequence of SEQ ID NO:32;
- (xi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and
10 a second polypeptide comprises the amino acid sequence of SEQ ID NO:34;
- (xii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:35 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:36;
- (xiii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:44 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:45;
- 15 (xiv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:46 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:47;
- (xv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:48 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:49;
- (xvi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:50 and
20 a second polypeptide comprises the amino acid sequence of SEQ ID NO:51;
- (xvii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:52
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:53;
- (xviii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:54
25 and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:55;
- (xix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:56 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:57;
- (xx) a first polypeptide comprises the amino acid sequence of SEQ ID NO:58 and
30 a second polypeptide comprises the amino acid sequence of SEQ ID NO:59;

- (xxi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:60 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:61;
- (xxii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:62
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:63;
- (xxiii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:64
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:65;
- (xxiv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:66
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:67;
- (xxv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:68
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:69;
- (xxvi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:70
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:71;
- (xxvii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:72
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:73;
- (xxviii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:74
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:75;
- (xxix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:76
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:77;
- (xxx) a first polypeptide comprises the amino acid sequence of SEQ ID NO:78
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:79;

- (xxxi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:80
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:81;
- 5 (xxxii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:82
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:83;
- (xxxiii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:84
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:85;
- 10 (xxxiv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:86
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:87;
- (xxxv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:88
and a second polypeptide comprises the amino acid sequence of SEQ ID
15 NO:89;
- (xxxvi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:90
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:91;
- (xxxvii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:92
and a second polypeptide comprises the amino acid sequence of SEQ ID
20 NO:93;
- (xxxviii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:94
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:95;
- 25 (xxxix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:96
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:97;
- (xl) a first polypeptide comprises the amino acid sequence of SEQ ID NO:98 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:99;

- (xli) a first polypeptide comprises the amino acid sequence of SEQ ID NO:100
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:101;
- 5 (xlii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:102
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:103;
- (xliii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:104
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:105;
- 10 (xliv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:106
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:107;
- (xlv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:108
and a second polypeptide comprises the amino acid sequence of SEQ ID
15 NO:109;
- (xlvi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:110
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:111;
- (xlvii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:112
and a second polypeptide comprises the amino acid sequence of SEQ ID
20 NO:113;
- (xlviii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:114
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:115;
- 25 (xlix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:116
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:117;
- (l) a first polypeptide comprises the amino acid sequence of SEQ ID NO:118 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:119;

- (li) a first polypeptide comprises the amino acid sequence of SEQ ID NO:120 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:121;
- (lii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:122 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:123;
- 5 (liii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:124
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:125;
- (liv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:126
and a second polypeptide comprises the amino acid sequence of SEQ ID
10 NO:127;
- (lv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:128 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:129;
- (lvi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:130
and a second polypeptide comprises the amino acid sequence of SEQ ID
15 NO:131;
- (lvii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:132
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:133;
- (lviii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:134
and a second polypeptide comprises the amino acid sequence of SEQ ID
20 NO:135;
- (lix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:136
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:137;
- 25 (lx) a first polypeptide comprises the amino acid sequence of SEQ ID NO:138 and
a second polypeptide comprises the amino acid sequence of SEQ ID NO:139;
- (lxi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:140
and a second polypeptide comprises the amino acid sequence of SEQ ID
NO:141; or

(lxii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:142 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:143.

5 In some embodiments, the compound comprises:

- (i) a first polypeptide comprises the amino acid sequence of SEQ ID NO:13 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:14;
- (ii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:15 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:16;
- 10 (iii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:17 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:18;
- (iv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:19 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:20;
- (v) a first polypeptide comprises the amino acid sequence of SEQ ID NO:21 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:22;
- 15 (vi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:24;
- (vii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:26;
- 20 (viii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:28;
- (ix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:30;
- (x) a first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:32;
- 25 (xi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:34; or
- (xii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:35 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:36.

30

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 estradiol, 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)).

5 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
10 ColeE1 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
15 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.

20 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
25 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
30 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., baculovirus) 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. 264:5503-5509); 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
5 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
10 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
15 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
20 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
25 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
30 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), 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), 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) 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
5 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, VERO, 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
10 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,
15 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
20 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
25 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
30 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
5 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
10 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 hygromycin, which confers resistance to hygromycin (Santerre et al. (1984) "Expression Of Prokaryotic Genes For
15 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),
20 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,
25 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
30 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
5 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.

10 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
15 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
20 some embodiments, the cell is 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
25 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
30 composition are those that comprise:

- (i) a first polypeptide comprises the amino acid sequence of SEQ ID NO:13 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:14;
- (ii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:15 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:16;
- 5 (iii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:17 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:18;
- (iv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:19 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:20;
- 10 (v) a first polypeptide comprises the amino acid sequence of SEQ ID NO:21 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:22;
- (vi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:24;
- (vii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:26;
- 15 (viii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:28;
- (ix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:30;
- (x) a first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:32;
- 20 (xi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:34; or
- (xii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:35 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:36.

25 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.

30 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
 5 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.

10 Non-limiting examples of autoimmune diseases include 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
 15 blistering skin diseases, Behcet's syndrome, multiple sclerosis, systemic 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,
 20 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
 25 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,
 30 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

5 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

10 the compounds of the invention. Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds of the invention 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

15 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

20 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.

25 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

30 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.

5 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.

10 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
15 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
20 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,
25 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 TNF-
30 alpha 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 TNF-alpha 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
5 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,
10 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

15 Yet other aspects of the disclosure relate to pharmaceutical compositions comprising a compound described herein. A composition comprising a compound of the invention (e.g., compounds specific for both TNF-alpha and IL23A) can be administered to a subject having or at risk of having an autoimmune or an inflammatory disease. The invention further provides for the use of a compound of the invention in the manufacture of a medicament for
20 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 invention for use in such pharmaceutical compositions are those that comprise:

- (i) a first polypeptide comprises the amino acid sequence of SEQ ID NO:13 and a
25 second polypeptide comprises the amino acid sequence of SEQ ID NO:14;
- (ii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:15 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:16;
- (iii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:17 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:18;

- (iv) a first polypeptide comprises the amino acid sequence of SEQ ID NO:19 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:20;
- (v) a first polypeptide comprises the amino acid sequence of SEQ ID NO:21 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:22;
- 5 (vi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:24;
- (vii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:26;
- (viii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:28;
- 10 (ix) a first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:30;
- (x) a first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:32;
- 15 (xi) a first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:34; or
- (xii) a first polypeptide comprises the amino acid sequence of SEQ ID NO:35 and a second polypeptide comprises the amino acid sequence of SEQ ID NO:36.

20 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

25 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

30 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 invention 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 invention does not absorb are used.

In other embodiments, the compounds of the invention 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 invention can be administered as pharmaceutical compositions comprising a therapeutically effective amount of a binding agent and one or more pharmaceutically compatible ingredients.

10 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
15 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
20 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
25 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
30 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-dioleoyloxy)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 invention 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 invention. 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.

5 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
10 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 invention. 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
15 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.

20 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.

25

EXAMPLES

Example 1. Construction of exemplary compounds targeting IL23A and TNF-alpha.

Table 2A below provides exemplary compounds that bind to both IL23A and TNF-alpha that were utilized in the Examples below. These compounds were produced by
30 recombinant methods known in the art (see, e.g., PCT Publications WO 2006/113665, WO

2008/157379, and WO 2010/080538.

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 TNF-alpha binding compounds

Compound ID	Large Chain vL	Large Chain vH	Small Chain vL	Small Chain vH	Linker types	Isotype	SEQ ID NO: (1st/2nd)
Compound A	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	GS	IgG1KO-YTE	13/14
Compound B	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	VF	IgG1KO-YTE	15/16
Compound C	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1KO-YTE	17/18
Compound D	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1KO-YTE	19/20
Compound E	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1KO-YTE	21/22
Compound F	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1KO-YTE	23/24
Compound G	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	GS	IgG1KO-YTE	25/26
Compound H	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	VF	IgG1KO-YTE	27/28

	ID NO: 4)	(SEQ ID NO: 7)	ID NO: 8)	ID NO: 3)			
Compound I	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	GS	IgG1KO- YTE	29/30
Compound J	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1KO- YTE	31/32
Compound K	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	VF	IgG1KO- YTE	33/34
Compound L	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1KO- YTE	35/36
Compound M	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	GS	IgG1KO	44/45
Compound N	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1KO	46/47
Compound O	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1KO	48/49
Compound P	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1KO	50/51
Compound Q	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	GS	IgG4Pro	52/53
Compound R	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	GS	IgG4Pro- YTE	54/55
Compound S	TNFa(2) VL (SEQ ID NO:	IL23A(1) VH (SEQ ID	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	GS	IgG4Pro	56/57

	4)	NO: 7)					
Compound T	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	GS	IgG4Pro- YTE	58/59
Compound U	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	VF	IgG1KO	60/61
Compound V	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	VF	IgG1WT	62/63
Compound W	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	VF	IgG4Pro	64/65
Compound X	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	VF	IgG4Pro- YTE	66/67
Compound Y	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1WT	68/69
Compound Z	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG4Pro	70/71
Compound AA	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG4Pro- YTE	72/73
Compound AB	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1WT	74/75
Compound AC	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG4Pro	76/77
Compound AD	IL23A(1) VL (SEQ ID NO: 8)	TNFA(2) VH (SEQ ID NO: 3)	TNFA(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG4Pro- YTE	78/79

Compound AE	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	GS	IgG1KO	80/81
Compound AF	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	GS	IgG1WT	82/83
Compound AG	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	GS	IgG4Pro	84/85
Compound AH	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	GS	IgG4Pro- YTE	86/87
Compound AI	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	VF	IgG1KO	88/89
Compound AJ	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	VF	IgG1WT	90/91
Compound AK	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	VF	IgG4Pro	92/93
Compound AL	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	VF	IgG4Pro- YTE	94/95
Compound AM	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1KO	96/97
Compound AN	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1WT	98/99
Compound AO	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG4Pro	100/101

Compound AP	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG4Pro- YTE	102/103
Compound AQ	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1KO	104/105
Compound AR	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1WT	106/107
Compound AS	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG4Pro	108/109
Compound AT	IL23A(1) VL (SEQ ID NO: 8)	TNFa(3) VH (SEQ ID NO: 5)	TNFa(3) VL (SEQ ID NO: 6)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG4Pro- YTE	110/111
Compound AU	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	GS	IgG1KO	112/113
Compound AV	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	GS	IgG1WT	114/115
Compound AW	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	GS	IgG4Pro	116/117
Compound AX	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	GS	IgG4Pro- YTE	118/119
Compound AY	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	VF	IgG1KO	120/121
Compound AZ	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	VF	IgG1WT	122/123

Compound BA	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	VF	IgG4Pro	124/125
Compound BB	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	VF	IgG4Pro- YTE	126/127
Compound BC	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1KO	128/129
Compound BD	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG1WT	130/131
Compound BE	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG4Pro	132/133
Compound BF	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	GS	IgG4Pro- YTE	134/135
Compound BG	TNFa(2) VL (SEQ ID NO: 4)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)	TNFa(2) VH (SEQ ID NO: 3)	GS	IgG1WT	136/137
Compound BH	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG1WT	138/139
Compound BI	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG4Pro	140/141
Compound BJ	IL23A(1) VL (SEQ ID NO: 8)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)	IL23A(1) VH (SEQ ID NO: 7)	VF	IgG4Pro- YTE	142/143

TNFa = TNF-alpha, VL = variable domain light chain, VH = variable domain heavy chain, GS = GGGSGGGG (SEQ ID NO: 9), LGGGSG (SEQ ID NO: 10), or both, VF = FNRGES (SEQ ID NO: 11), VEPKSS (SEQ ID NO: 12), or both, IgG1WT = IgG1 wild type; IgG1KO-

YTE = IgG1 with a M252Y/S254T/T256E triple mutation in the Fc region and also comprising L234A/L235A mutations, IgG4Pro-YTE = IgG4 with a M252Y/S254T/T256E triple mutation in the Fc region and also comprising S241P mutation, IgG1KO = truncated Fc region comprising L234A/L235A mutations, IgG4Pro = comprising S241P mutation. 1st = first polypeptide, 2nd = second polypeptide. The numbering of mutations is Kabat numbering for a conventional antibody starting with the antibody convention at CH1.

The below control antibodies were also used for comparison purposes. The controls were monoclonal antibodies that targeted either TNFa or IL23.

Table 2B.

Control compounds	VH sequence	VL sequence
Control antibody 1 (TNFa monoclonal antibody)	TNFa(1) VH (SEQ ID NO: 1)	TNFa(1) VL (SEQ ID NO: 2)
Control antibody 2 (TNFa monoclonal antibody)	TNFa(2) VH (SEQ ID NO: 3)	TNFa(2) VL (SEQ ID NO: 4)
Control Antibody 3 (IL23 monoclonal antibody)	IL23A(1) VH (SEQ ID NO: 7)	IL23A(1) VL (SEQ ID NO: 8)

Example 2. Surface Plasmon Resonance (SPR) affinity of exemplary compounds

Test compounds were analyzed by SPR to determine affinity for TNF-alpha 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. 5 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): 10 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 human TNF-alpha or cynomologus TNF-alpha was 15 done in similar way.

Results

The results in Table 3 show that both compounds tested were able to bind TNF-alpha and IL23 with a dissociation constant (KD) in the picomolar range.

20

Table 3.

Compound ID	KD to human TNF-alpha (pM)	KD to cynomologus TNF-alpha (pM)	KD to human IL23 (pM)
Compound A	2.14	7.71	4.28 ± 2.03
Compound E	4.11 ± 0.68	37.1 ± 16.2	7.00 ± 6.92

Example 3. Flow Cytometry Assessment of Binding to Membrane Bound TNF-alpha

Test compounds were assessed for their ability to dose dependently bind to cell lines transfected to express membrane bound TNF-alpha.

Material and methods

5 All reagents were prepared in flow cytometry staining buffer (BioLegend). Membrane expressed TNF-alpha transfected cell lines (Jurkat and CHO) and parental cell lines were harvested from tissue culture vessels, washed, counted and resuspended to 1×10^6 cells/ml in flow cytometry staining buffer. One hundred microliters of the cell suspension was added to 96 well microtiter plates and placed on ice. Titrations of test compounds were prepared
10 and 50uL was added to the cells. After sixty minute incubation on ice, the cell + test compounds were washed and 50uL of a secondary antibody (Jackson ImmunoResearch) was added. The samples were incubated in the dark, at 4C, for 60 minutes, followed by washes. After a final wash the cells were resuspended in 60uL of fixative (BD Bioscience). Median fluorescence was determined for each sample in a flow cytometer and plotted versus the
15 concentration of the test sample. EC₅₀ values were calculated using the 4 Parameter Logistic enabled by the Excel add-in XLfit (Activity Base software, ID Business Solutions, Ltd.). The EC₅₀ values shown below are Geomeans calculated across multiple experiments for each test sample and are shown in Table 4.

20 Results

The results shown in Table 4 below demonstrate that the compounds tested bound to membrane bound TNF-alpha in a dose dependent manner.

Table 4. EC50 values for membrane bound TNF-alpha.

Compound ID	mTNF-Jurkat Cell Binding EC ₅₀ pM (Geomean)	mTNF-CHO Cell Binding EC ₅₀ pM (Geomean)
Compound M	650	950
Compound A	910	890

Compound O	270	770
Compound E	200	450
Control antibody 1 (TNFa)	310	400
Control antibody 2 (TNFa)	230	310

Example 4. In vitro L929 Cytotoxicity Assay

The compounds were tested for their ability to inhibit TNF-alpha induced cytotoxicity.

5

Methods and Materials

This protocol used the PrestoBlue™ Cell Viability Reagent to determine cytotoxicity of recombinant human TNF- alpha. A more detailed protocol for the PrestoBlue Cell Viability Protocol can be downloaded from the Invitrogen website (Invitrogen.com). L929 cells were grown and harvested. 1.5×10^4 cells were transferred to each well of a 96-well plate for incubated overnight at 37°C . Serial dilutions of compounds were prepared starting at 5 nM in complete assay medium containing 10 µg/ml of actinomycin D and 1000 pg/ml of rhTNF-alpha. The positive controls contained 20 ng/ml rhTNF- alpha and 1 µg/ml actinomycin D. The negative control contained no TNF- alpha. 10 µL of the dilutions was added to corresponding wells and incubated overnight at 37°C in a 5% CO₂. PrestoBlue™ reagent was added to wells and the plate was incubated for 2 hour at 37°C in a 5% CO₂. The relative fluorescence unit of each well was measured using a Victor™x2 plate reader (excitation: 560 nm, emission: 590 nm). The fluorescent units (Y-axis) versus concentration of test compound (X-axis) were plotted and the IC₅₀ and IC₉₀ values of test compounds were calculated by using Graphpad software.

20

Results

The results in Table 5 show that the tested compounds were able to inhibit TNF-alpha

induced cytotoxicity in a dose-dependent manner.

Table 5.

Compound ID	IC₅₀ IC₉₀	L929 TNF Cytotox pM Geomean
Compound M	IC ₅₀	19
Compound M	IC ₉₀	55
Compound A	IC ₅₀	20
Compound A	IC ₉₀	67
Compound N	IC ₅₀	34
Compound N	IC ₉₀	
Compound D	IC ₅₀	
Compound D	IC ₉₀	
Compound O	IC ₅₀	4.2
Compound O	IC ₉₀	16
Compound E	IC ₅₀	4.1
Compound E	IC ₉₀	17
Compound P	IC ₅₀	3.4
Compound P	IC ₉₀	14
Compound F	IC ₅₀	2.5
Compound F	IC ₉₀	10
Control antibody 1 (TNFa)	IC ₅₀	62
Control antibody 1 (TNFa)	IC ₉₀	230
Control antibody 2 (TNFa)	IC ₅₀	20
Control antibody 2	IC ₉₀	95

(TNFa)		
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Example 5. Inhibition of TNF-alpha dependent IL-8 Release in HeLa Cells.

Anti-TNF test samples were assessed for their ability to inhibit the TNF dependent release of IL8 from the human cell line, HeLa. The samples were tested against a high and low concentration of recombinant human TNF-alpha and a single (high) concentration of recombinant cynomolgus TNF-alpha.

Materials and Methods

Briefly, HeLa cells (ATCC) were harvested, washed, counted and resuspended to 4×10^5 cells/ml in a standard complete media of (v/v) 10% Fetal Bovine Serum with 1% Penicillin & Streptomycin (CM). One hundred microliters of the HeLa cell suspension was added to 96 well microtiter plates. Recombinant human TNF-alpha (R&D Systems) at two concentrations (147nM or 4.4nM) as well as generated recombinant cynomolgus TNF-alpha (Boehringer Ingelheim Pharmaceuticals, Inc.) (147nM) were pre-incubated for 30 minutes at 37C with CM alone or with titrations of test samples. After the pre-incubation of test sample + TNF-alpha, 100 ul of the mixture(s) was added to the cells and the test plates were incubated at 37C with 5% CO₂-humidified air for 20 hours. Control samples received either CM (unstimulated controls) or recombinant TNF-alpha diluted in CM (stimulated controls). After the incubation, supernatants were assayed for IL8 in an ELISA kit (MesoScale Discovery) following the manufacturer's instructions. Interpolated IL8 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 IC₅₀ and IC₉₀ values were calculated using a 4 Parameter Logistic Model enabled by the Excel add-in XLfit (Activity Base software, ID Business Solutions, Ltd.).

The test compounds were analyzed with respect to the IC₅₀/IC₉₀ as described above, and Geomeans were calculated across multiple experiments for each test sample and shown in Table 6.

Results

The results in Tables 6 show that the IC₅₀ and IC₉₀ Geomean values for the tested compounds were similar to the IC₅₀ and IC₉₀ Geomean values for Control Antibody 1 and Control antibody 2. The data demonstrates that the test compounds dose dependently inhibited the TNF-alpha induced IL-8 secretion with either human (at two concentrations

5 tested) or cyno recombinant TNF-alpha.

Table 6.

Compound ID	IC ₅₀ IC ₉₀	HeLa IL8 Lo-Hu-TNF pM Geomean	HeLa IL8 Hi- Hu-TNF pM Geomean	HeLa IL8 Cyno-TNF pM Geomean
Compound M	IC ₅₀	7.9	260	150
Compound M	IC ₉₀	48	420	270
Compound A	IC ₅₀	8	280	120
Compound A	IC ₉₀	41	460	260
Compound N	IC ₅₀	9.2	350	170
Compound N	IC ₉₀	54	570	330
Compound D	IC ₅₀	11	380	190
Compound D	IC ₉₀	63	590	390
Compound O	IC ₅₀	9.9	430	300
Compound O	IC ₉₀	43	760	970
Compound E	IC ₅₀	9.2	320	180
Compound E	IC ₉₀	35	530	600
Compound P	IC ₅₀	9.2	410	210
Compound P	IC ₉₀	36	810	810
Compound F	IC ₅₀	7.9	350	190
Compound F	IC ₉₀	39	660	740
Control antibody 1 (TNFa)	IC ₅₀	34	330	170

Control antibody 1 (TNFa)	IC ₉₀	140	490	330
Control antibody 2 (TNFa)	IC ₅₀	11	290	280
Control antibody 2 (TNFa)	IC ₉₀	55	520	1200

Example 6. Inhibition of TNF-alpha dependent IL8 in whole blood

TNF is a potent inducer of IL8 release from human cells. Compounds were tested for their ability to inhibit TNF-alpha induced IL-8 release in whole blood samples.

5

Methods and Materials

Briefly 120uL of heparinized human whole blood was added to each well in a 96 well microtiter plate. Assay reagents were prepared in a standard T cell media (TCM). Titrations of test samples were prepared at 10X concentrations and pre-incubated with a 10X concentration of human recombinant TNF (100ng/ml, R&D Systems) for 1 hour at 37C. After this pre-incubation, 30ul of the cytokine/test compound mixture was added to the whole blood along with 30uL of appropriate controls in TCM and incubated at 37C with 5% CO₂-humidified air for 48 hours. Control samples received either TCM (unstimulated controls) or recombinant human TNF-alpha diluted in TCM (stimulated controls). After the incubation, supernatants were assayed for IL8 in an ELISA kit (MesoScale Discovery) following manufacturer's instructions. Interpolated IL8 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 IC₅₀ and IC₉₀ values were calculated using a 4 Parameter Logistic Model enabled by the Excel add-in XLfit (Activity Base software, ID Business Solutions, Ltd.).

20

The test compounds were analyzed with respect to the IC₅₀/IC₉₀ as described above, and Geomeans were calculated across multiple experiments for each test sample and shown in Table 7.

Results

The results in Table 7 show that the IC₅₀ and IC₉₀ Geomean values for the tested compounds were similar to the IC₅₀ and IC₉₀ Geomean values for Control antibody 1 and control antibody 2. The data demonstrates that the test compounds dose dependently

5 inhibited the TNF-alpha induced IL8 release in human whole blood.

Table 7.

Compound ID	IC₅₀ IC₉₀	TNF-IL8 Whole Blood pM Geomean
Compound M	IC ₅₀	380
Compound M	IC ₉₀	790
Compound A	IC ₅₀	360
Compound A	IC ₉₀	490
Compound N	IC ₅₀	270
Compound N	IC ₉₀	520
Compound D	IC ₅₀	560
Compound D	IC ₉₀	1100
Compound O	IC ₅₀	320
Compound O	IC ₉₀	470
Compound E	IC ₅₀	340
Compound E	IC ₉₀	610
Compound P	IC ₅₀	290
Compound P	IC ₉₀	420
Compound F	IC ₅₀	310
Compound F	IC ₉₀	450
Control antibody 1 (TNFa)	IC ₅₀	320
Control antibody 1 (TNFa)	IC ₉₀	490

Control antibody 2 (TNFa)	IC ₅₀	330
Control antibody 2 (TNFa)	IC ₉₀	600

Example 7. NF-kappaB and STAT3 phosphorylation assays

IL23 engagement with its heterodimeric receptor complex (IL12R β 1-IL23R) results in the downstream phosphorylation of Signal transducer and activator of transcription 3 (STAT3). TNF engagement with its receptors (TNFR1/TNFR2) results in the downstream phosphorylation of nuclear factor of kappa light polypeptide gene enhancer in B-cells (NF- κ B). Compounds were assessed for their ability to inhibit TNF- dependent phosphorylation of NF- κ B in Jurkat cells, and IL23-dependent phosphorylation of STAT3 in DB cells.

10 **Methods and Materials:**

Briefly, cultures of Jurkat cells (ATCC) and DB cells (ATCC) growing in log phase were harvested, washed, counted and resuspended to 2×10^7 cells/mL in a standard complete media (CM; RPMI1640 with (v/v) 10% FCS and 1X Penicillin-Streptomycin (Invitrogen)). Titrations of test samples were prepared at 4X concentrations and pre-incubated with a mixture of 4X human recombinant IL23 (Boehringer Ingelheim Pharmaceuticals, Inc.) and recombinant human TNF (R&D Systems) for 1 hour at 37C. After the pre-incubation of the test reagent + cytokine mixture, 100 μ L of the mixture was added to wells containing 100 μ L of cells in duplicate. Controls were setup as follows: 100 μ L of the diluted TNF/IL23 + 100 μ L combined cells (stimulated control), or 100 μ L of CM + 100 μ L combined cells (unstimulated control). The assay plates were incubated for exactly 10 minutes at 37°C with 5% CO₂-humidified air. After the incubation, cell lysates were prepared and p-NF- κ B and p-STAT3 was assessed following the manufacturer's instructions (MesoScale Discovery). p-NF- κ B and p-STAT-3 raw values were determined for each sample and converted to percent of control (POC). The POC was plotted (Y-axis) versus concentration of the test agent (X-axis). IC₅₀ and IC₉₀ values were calculated using the 4 Parameter Logistic Model enabled by the Excel add-in XLfit (Activity Base software, ID Business Solutions, Ltd.).

The test compounds were analyzed with respect to the IC_{50}/IC_{90} as described above, and Geomeans were calculated across multiple experiments for each test sample and shown in Table 10. Note: this assay provides confidence that that the dual molecule is capable of neutralizing both downstream signaling events. The assay time point is optimal for the p-NF- κ B signal only and therefore the calculated IC_{50}/IC_{90} does not reflect the overall potencies in a quantitative manner.

Results

The results in Table 8 show that the test compounds were able to inhibit both TNF-alpha induced NF- κ B phosphorylation as well as IL23 induced phosphorylation of STAT3 in DB cells.

Table 8.

Compound ID	IC_{50} IC_{90}	Dual Phospho Jurkat-pNf-Kb pM Geomean*	Dual Phospho DB- pSTAT3 pM Geomean*
Compound M	IC_{50}	290	190
Compound M	IC_{90}	680	580
Compound A	IC_{50}	300	200
Compound A	IC_{90}	480	500
Compound N	IC_{50}	300	210
Compound N	IC_{90}	620	760
Compound D	IC_{50}	270	170
Compound D	IC_{90}	810	560
Compound O	IC_{50}	210	210
Compound O	IC_{90}	740	580
Compound E	IC_{50}	260	230
Compound E	IC_{90}	340	770

Compound P	IC ₅₀	290	340
Compound P	IC ₉₀	340	630
Compound F	IC ₅₀	280	360
Compound F	IC ₉₀	760	980
Control antibody 1 (TNFa)	IC ₅₀	360	NA
Control antibody 1 (TNFa)	IC ₉₀	660	NA
Control antibody 2 (TNFa)	IC ₅₀	260	NA
Control antibody 2 (TNFa)	IC ₉₀	420	NA
Control antibody 3(IL23A)	IC ₅₀	NA	89
Control antibody 3(IL23A)	IC ₉₀	NA	230

*Results are semi-quantitative and optimized more to the TNF readout. NA; No Activity

Example 8. Inhibition of IL23 induced STAT3 phosphorylation in DB cells

IL23 engagement with its heterodimeric receptor complex (IL12R β 1-IL23R) results
 5 in the downstream phosphorylation of Signal transducer and activator of transcription 3
 (STAT3). Anti-IL23 test samples were assessed for their ability to inhibit the IL23
 dependent phosphorylation in the human DB cell line.

Materials and Methods:

10 Briefly 100uL of the human DB cell line (ATCC) grown in log phase was added to
 each well in a 96 well microtiter plate at a concentration of 1×10^7 cells/ml. Assay reagents
 were prepared in a complete media (CM; RPMI1640 with (v/v) 10% Fetal Calf Serum and
 1X Penicillin-Streptomycin (Invitrogen)). Titrations of test samples were prepared at 4X
 concentrations and pre-incubated with a 4X concentration of human recombinant IL23

(Boehringer Ingelheim Pharmaceuticals, Inc.) for 1 hour at 37C. After this pre-incubation, 100ul of the cytokine/test sample mixture was added to the 100uL of DB cells and incubated at 37C with 5% CO₂-humidified air for 30 minutes. Control samples received either CM (unstimulated controls) or recombinant human IL23 diluted in CM (stimulated controls).

5 After the incubation, cell lysates were prepared and pSTAT3 was assessed following the manufacturer's instructions (MesoScale Discovery). Raw pSTAT3 values were determined for each sample and converted to percent of control (POC). The POC was plotted versus concentration of the test sample and IC₅₀ and IC₉₀ values were calculated using a 4 Parameter Logistic Model enabled by the Excel add-in XLfit (Activity Base software, ID Business

10 Solutions, Ltd.). The test compounds were analyzed with respect to the IC₅₀/IC₉₀ as described above, and Geomeans were calculated across multiple experiments for each test sample and shown in Table 9.

Results

15 The results in Table 9 show that the IC₅₀ and IC₉₀ Geomean values for the tested compounds were similar to the IC₅₀ and IC₉₀ Geomean values for an anti-IL23Ap19 control antibody. The data demonstrates that the test compounds dose dependently inhibited the IL23 induced phosphorylation of STAT3in DB cells.

20 Table 9.

Compound ID	IC ₅₀ IC ₉₀	hIL23 pSTAT3 DB assay pM Geomean
Compound M	IC ₅₀	190
Compound M	IC ₉₀	530
Compound A	IC ₅₀	210
Compound A	IC ₉₀	420
Compound N	IC ₅₀	240
Compound N	IC ₉₀	510

Compound D	IC ₅₀	280
Compound D	IC ₉₀	560
Compound O	IC ₅₀	300
Compound O	IC ₉₀	720
Compound E	IC ₅₀	300
Compound E	IC ₉₀	700
Compound P	IC ₅₀	300
Compound P	IC ₉₀	620
Compound F	IC ₅₀	260
Compound F	IC ₉₀	600
Control antibody 3(IL23A)	IC ₅₀	160
Control antibody 3(IL23A)	IC ₉₀	310

Example 9. Human IL-23 Dependent Mouse Splenocyte Assay (MSA)

A mouse splenocyte based assay was used to assess the ability of anti-human IL23 test samples to inhibit the induction of mouse IL17 by human recombinant IL23 and recombinant cynomolgus IL23 in mouse splenocyte cultures.

Materials and Methods:

Briefly, mononuclear cells from mouse spleens (female C57BL/6 less than 13weeks of age; JAX) were isolated washed, counted and resuspended to 4×10^6 cells/ml in a standard T cell media (TCM). One hundred microliters of the mIL2/splenocyte suspension was added to 96 well microtiter plates. Recombinant human IL23 (Boehringer Ingelheim Pharmaceuticals, Inc.) or recombinant cynomolgus IL23 (Boehringer Ingelheim Pharmaceuticals, Inc.) was diluted in TCM and pre-incubated for 2 hours at 37C with TCM alone or with titrations of test samples. After the pre-incubation of test sample + IL23, 100 ul of the mixture was added to the cells and the test plates were incubated at 37C with 5% CO₂-humidified air for 48 hr. Control samples received either TCM (unstimulated controls) or recombinant human IL23 diluted in TCM (stimulated controls) After the incubation, mouse

IL17 levels were determined from the supernatant using the Quantikine® Mouse IL-17 Immunoassay according to the manufacturer's instructions (R&D Systems). Interpolated mIL17 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 IC₅₀ and IC₉₀ values were calculated using a 4 Parameter Logistic Model enabled by the Excel add-in XLfit (Activity Base software, ID Business Solutions, Ltd.). The anti-IL23 test samples were analyzed with respect to the IC₅₀/IC₉₀ as described above and Geomeans were calculated across multiple experiments for each test sample and shown in Table 10.

10 Results

The results in Table 10 show that the tested compounds were able to inhibit both human and cynomolgus-IL23 induced mouse splenocyte release of IL17.

Table 10.

Compound ID	IC ₅₀ IC ₉₀	huIL23 MSA pM Geomean	CynoIL23 MSA pM Geomean
Compound M	IC ₅₀	140	120
Compound M	IC ₉₀	1600	890
Compound A	IC ₅₀	180	120
Compound A	IC ₉₀	1700	730
Compound N	IC ₅₀	230	140
Compound N	IC ₉₀	2000	940
Compound D	IC ₅₀	190	160
Compound D	IC ₉₀	2200	1100
Compound O	IC ₅₀	210	120
Compound O	IC ₉₀	2200	800
Compound E	IC ₅₀	200	77
Compound E	IC ₉₀	1700	1200
Compound P	IC ₅₀	200	97

Compound P	IC ₉₀	1400	1500
Compound F	IC ₅₀	170	69
Compound F	IC ₉₀	2300	1500
Control antibody 3(IL23A)	IC ₅₀	53	17
Control antibody 3(IL23A)	IC ₉₀	350	240

Example 10. Inhibition of IL23 induced phosphorylation of STAT3

IL23 engagement with its heterodimeric receptor complex (IL12R β 1-IL23R) results in the downstream phosphorylation of Signal transducer and activator of transcription 3 (STAT3). Compounds were tested for the ability to inhibit IL23 induced STAT3 activation in DB stable transfected cells

Materials and Methods

The cells were stimulated with a final concentration of 15ng/ml of IL23 protein. This dose was estimated to be the EC60 according to previous experiments, while allowing for inhibition with the tested compound. Cells were plated, compound dosed, and IL-23 added (in that order) and incubated overnight. If the compound inhibited cell stimulation, STAT3 was downregulated, leading to less luciferase activity.

Results

The results in Table 11 show that the tested compounds were able to inhibit IL23 induced phosphorylation of STAT3.

Table 11.

Compound ID	IC ₅₀	IL23A
	IC ₉₀	pSTAT3 (MG) pM

		Geomean
Compound M	IC ₅₀	120
Compound M	IC ₉₀	300
Compound A	IC ₅₀	130
Compound A	IC ₉₀	1100
Compound O	IC ₅₀	160
Compound O	IC ₉₀	650
Compound E	IC ₅₀	140
Compound E	IC ₉₀	830
Compound P	IC ₅₀	69
Compound P	IC ₉₀	480
Compound F	IC ₅₀	90
Compound F	IC ₉₀	650
Control antibody 3(IL23A)	IC ₅₀	35
Control antibody 3(IL23A)	IC ₉₀	140

Example 11. Further IL23-A Stat3 assays

Further experiments were run similarly to Example 8 to test for inhibition of IL23 induced activation of STAT3.

5

Methods and Materials

DB-STAT3Luc10 Clone 10 suspension cells were grown in RPMI1640 + 10% FBS. 20,000 cells were added per well of 96 well plates at 80ul/well of cell suspension. 10ul of one of the serially diluted test compounds was added to each well. 15ng/mL of recombinant human IL-23 was added to each well , with certain wells contained only test compounds and no IL-23, for comparison. The plates were incubated overnight at 37°C / 5% CO₂. Luciferase activity was assayed using Steady-Glo (Promega and One-Glo (Promega and the

10

results were read on Envision Reader.

Results

The IC₅₀ and IC₉₀ for the tested compounds are shown in Table 12 and Table 13.

- 5 These tables show that the compounds inhibited IL-23-dependent STAT3 activation in a dose dependent manner.

Table 12.

Compound ID	IC ₅₀ (pM)	IC ₉₀ (pM)
Compound N	235.2	873.7
Control antibody 3(IL23A)	96.5	192.6
Compound D	185.6	871.6
Compound E	211.9	965.1
Control antibody 3(IL23A)	104.3	198.8
Compound G	220.2	1151.0
Compound C	162.7	620.4
Control antibody 3(IL23A)	80.3	181.3

10 Table 13.

Compound ID	First test		Second test		GEOMEAN	
	IC ₅₀ (pM)	IC ₉₀ (pM)	IC ₅₀ (pM)	IC ₉₀ (pM)	IC ₅₀ (pM)	IC ₉₀ (pM)
Control antibody 3(IL23A)			96.5	192.6	93.1	190.8
			104.3	198.8		
			80.3	181.3		
Compound N	178.6	856.4	235.2	873.7	205.0	865.0
Compound D	178.1	657.2	185.6	871.6	181.8	756.8
Compound E	170.2	764.9	211.9	965.1	189.9	859.2
Compound G	187.1	600.5	220.2	1151.0	203.0	831.4
Compound C	134.9	352.6	162.7	620.4	148.1	467.7

Example 12. Inhibition of Mouse IL17A and IL22 release induced by Human recombinant IL23

Test compounds were assessed for their ability to inhibit human IL23 induced

cytokine release in C57/Bl6 mice. IL17A and IL22 secretion are measured after intradermal injection of IL23

MATERIALS AND METHODS

5 Briefly, C57BL/6 female mice (7-10 weeks old, Charles River) were randomly divided into 8 groups, 8 animals/group and given a 100µl intraperitoneal 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
10 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);
15 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. Supernatants 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
20 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 are shown in FIG. 4.

RESULTS

25 The results in FIG. 4 show that treatment with a single intraperitoneal dose of test compound 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.

Example 13. Inhibition of Exogenous Human TNF-alpha Dependent Cytokine Release in
30 C57/Bl6 Mice

Test compounds were assessed for their ability to inhibit human TNF induced cytokine release in C57/Bl6 mice after exogenous exposure to human TNF. Serum KC and IL-6 secretion are measured following intraperitoneal administration of human TNF.

5 **Materials and Methods**

Briefly, C57BL/6 female mice (8-9 weeks old, Jackson Labs) were randomly divided into 8 groups, 8 animals/group and given a 200µl intraperitoneal injection of either phosphate buffered saline (Sigma) or test compound at equivalent molar dose of 13.3, 4 and 1.3 mg/kg vs. 10, 3 and 1 mg/kg respectively .

10 Two hour after test compound dosing mice were anesthetized via isoflurane (Butler Schein) and given a 200µl intraperitoneal injection of either 0.1%BSA control or 15µg/ml (3µg) rhTNF (R&D Systems) diluted in saline (Sigma). Two hours after the TNF challenge the mice were anesthetized via isoflurane, whole blood was collected and mice were then sacrificed via cervical dislocation. Whole blood was centrifuged at 12,000 rpm for 10
15 minutes and plasma collected. Plasma was assayed for the presence of mouse KC and IL-6, using the MultiPlex® Mouse KC and mouse IL-6 Immunoassays according to the manufacturer's instructions (MSD). 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
20 Dunnett's multiple comparisons test. Results are shown in Figure X.

Results

The results in FIG. 5 show that treatment with a single intraperitoneal dose of test compound was able to significantly inhibit the release of mouse KC and IL-6 in serum by
25 intraperitoneal injection of recombinant human TNF.

Example 14. Pharmacokinetics of compounds in cynomolgus monkeys

Materials and Methods

Single intravenous (IV) dose PK studies for two pairs of compounds (Compound M
30 and Compound A; and Compound O and Compound E) were conducted in male cynomolgus

monkeys (N=3 per group) naïve to biologics, and conducted according to the guidelines of Institutional Animal Care and Use Committee. IV doses were administered at 1 mg/kg as 10 min IV infusion. Serum samples were collected at pre-dose, 1, 4, 8 hr on the day of dosing, and 1, 2, 3, 4, 5, 7, 10, 14, 21, 28, 35, and 42 (1008 hr) days post dosing for Compound M and Compound A; and only up to Day 14 for Compound O and Compound E. Serum concentrations of the dosed molecules were measured by a ligand binding assay (ELISA).

Calibration standard curve and quality control (QC) samples were prepared in 100% serum for each analyte. Each standard curve consisted of seven non-zero points starting at 10240 ng/mL then serially diluted 3x. A blank sample (matrix without analyte) was also included. Four QC samples at low, medium, and high ranges were prepared starting at 2560 ng/mL then serially diluted four-fold. The standard curve and QC samples were stored frozen until sample analysis at which time they were diluted 20 times to mimic study samples. The standard curve and QC samples were included in duplicate during each analytical run. The lower and upper limits of quantification were defined as the lowest and highest standard curve points to reproducible have a back-calculated concentration that does not exceed 25 percent (%) of the nominal concentration. The acceptance criterion for the standard curve points and QC samples was 25 percent (%) of the nominal concentration.

Nunc ELISA plates were coated with 1 µL of monkey adsorbed goat anti-human IgG (Southern Biotech) as the capture reagent and incubated overnight at 2-8°C. After washing and blocking the plates with the wash buffer (0.05% (v/v) Tween 20 in phosphate buffered saline (PBS)) and blocking buffer (5% bovine serum albumin (BSA) in PBS), standard, QC, and unknown samples, diluted 1:20, 1:400 and 1:8000 with 5% monkey serum (monkey serum from Innovative Research) were added to the plate wells and incubated for 1 hour at room temperature. The plate wells were washed with the washing buffer and added with monkey adsorbed biotinylated goat anti-human IgG (Southern Biotech) as the secondary reagent and incubated at room temperature for 1 hour. The plates were washed 3 times and added with 100 µL of 1 µg/mL peroxidase-conjugated streptavidin for 15 min at room temperature, followed by further 3 times washing and the addition of 100 µL of 3,3',5,5'-Tetramethylbenzidine (TMB, BioFX) substrate for 3-4 min at room temperature. The reaction was stopped by adding 100 µL of stop solution (BioFX) and the absorbance was measured

using Molecular Devices plate reader with SoftmaxPro software, version 5.4.1.

Results

Single IV dose PK studies for two pairs of test compounds (Compound M and Compound A; and Compound O and Compound E) were conducted in male cynomolgus monkeys (N=3 per group) naïve to biologics. The test compounds were dosed at 1 mg/kg as 10 min IV infusion. Serum samples were collected at pre-dose, 1, 4, 8 hr on the day of dosing, and 1, 2, 3, 4, 5, 7, 10, 14, 21, 28, 35, and 42 (1008 hr) days post dosing for Compound M and Compound A; and only up to Day 14 for Compound O and Compound E. Serum concentrations of the dosed molecules were measured by a ligand binding assay (ELISA).

Serum concentrations (mean and SD) for each of the molecules are summarized in Table 14.

Table 14: Serum concentrations (mean±SD, N=3) for the test compounds in cynomolgus monkey

Time (day)	Compound M		Compound A		Compound O		Compound E	
	Mean (nM)	SD (nM)	Mean (nM)	SD (nM)	Mean (nM)	SD (nM)	Mean (nM)	SD (nM)
0	0	0	0	0	0	0	0	0
0.042	89.62	26.41	115.60	15.44	96.69	23.15	107.57	10.43
0.167	75.30	17.97	108.03	22.92	92.29	19.75	102.36	4.81
0.333	69.71	9.19	89.15	16.32	65.27	11.53	86.45	10.65
1	54.49	13.94	63.68	6.69	30.10	12.41	52.87	8.85
2	35.17	8.93	49.95	6.04	7.44	3.22	32.51	6.30
3	18.58	6.66	43.51	6.64	4.14	0.70	24.65	6.49
4	13.86	5.61	40.02	8.50	2.76	0.25	19.02	4.84
5	9.55	3.40	43.69	19.63	1.96	0.09	13.98	3.84
7	3.76	1.31	27.84	3.29	1.08	0.21	8.49	3.38

10	BQL	BQL	BQL	BQL	BQL	BQL	0.3797	NA
14	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
21	BQL	BQL	BQL	BQL				
28	BQL	BQL	BQL	BQL				
35	BQL	BQL	BQL	BQL				
42	BQL	BQL	BQL	BQL				

BQL: below quantitation limit

NC: not calculated, N=1

Pharmacokinetic (PK) parameters of these test compounds were calculated using the software Phoenix WinNonlin 6.1 (Certara, MD, USA) using non-compartmental approach for IV infusion dose. Serum samples that showed precipitous drop in the concentrations at any time point after dosing and all subsequent samples in that particular animal were excluded from the PK parameter estimation. Additional analysis showed that this sudden drop in the concentrations after the first few days was due to the development of anti-compound antibodies for a humanized biologic molecule in monkey. Only the first seven day data from individual animals were included in the PK analysis. Concentration-time plots are shown in FIGs. 2 and 3 for the two pairs of test compounds. Key PK parameters (mean $\pm$ SD) for the two pairs of test compounds are summarized in Table 15.

Table 15: Key PK parameters (mean $\pm$ SD; N=3) of the two test compound pairs in cynomolgus monkey after 1 mg/kg IV 10 min infusion dose

Compound ID	AUC (nM.day)	CL (mL/day/ kg)	Vss (mL/kg)	T1/2 (day)	MRT (day)
Compound M	186 $\pm$ 48.3	28.2 $\pm$ 7.8	62.4 $\pm$ 13.7	1.6 $\pm$ 0.04	2.2 $\pm$ 0.1
Compound A	592 $\pm$ 68.3	8.5 $\pm$ 1.1	71.5 $\pm$ 8.9	6.2 $\pm$ 0.5	8.4 $\pm$ 1.0
Compound O	98.0 $\pm$ 14.7	51.8 $\pm$ 7.8	76.1 $\pm$ 30.3	2.3 $\pm$ 0.8	1.4 $\pm$ 0.4
Compound E	244 $\pm$ 54.6	21.2 $\pm$ 4.5	65.0 $\pm$ 3.9	2.5 $\pm$ 0.3	3.1 $\pm$ 0.5

Compound A, the test compound with YTE mutation showed a 3.3-fold reduction in clearance (CL) and a 3.9-fold increase in terminal half-life (T_{1/2}) compared to the corresponding test compound not containing YTE mutation (Compound M). Compound E, the test compound with YTE mutation showed a 2.4-fold reduction in CL compared to the corresponding test compound not containing YTE mutation (Compound O).

Example 15. Predicting human PK and human dose of exemplary compound

Predicting Human PK:

Human PK prediction of Compound E was done by allometric scaling from the PK parameters obtained in cynomolgus monkey using a factor of 2-fold reduction in clearance in humans compared to monkey while maintaining same volume of distribution. Thus, predicted clearance in humans is 12.1 mL/day/kg with a terminal half-life of 7.4 days.

Predicting Human Dose:

Human dose prediction was done based on extensive exposure-efficacy data available from clinical trials of golimumab in diverse patient populations. Golimumab (Simponi®) is approved to treat rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) patients with 50 mg monthly subcutaneous (SC) doses, and ulcerative colitis (UC) patients with 100 mg monthly SC doses. Simponi® achieves a C_{trough} of approximately 3.2 nM in RA patients (50 mg monthly SC doses) and 9.7 nM (100 mg monthly SC doses) in UC patients (Simponi® BLA, 2009; Sandborn, 2013). These are used as benchmarks for therapeutic C_{troughs} for AS and CD, respectively. C_{trough} levels at the clinically approved doses of Stelara are about 6 nM. Based on the observation of a 3-fold higher potency of Compound E compared to ustekinumab (Stelara®) C_{trough} values of ~ 2 nM are needed for Compound E to cover IL23. As the C_{trough} concentration for covering TNF is greater than that for covering IL23, the 9.7 nM C_{trough} for Simponi® was used for dose projections.

Compartmental modeling of PK data in the cynomolgus monkey (2-compartment model) followed by Monte-Carlo simulations using a 2-fold reduction scaling of CL, 73%

bioavailability, and simultaneously varying clearance and distributional rate constants with a nominal 30% CV and log-normal distribution shows that 54 mg (90% confidence intervals 31 – 90 mg) SC doses administered every 2 weeks will maintain a C_{trough} of 9.7 nM.

5 Example 16. Purification of Compounds

Methods

Compounds were purified using Mab Select SuRe as an affinity purification step. High salt washes are avoided in order to prevent aggregation. Elution was performed using Sodium Acetate buffer pH 3.5. Following Mab Select SuRE purification the sample was
 10 neutralized and applied to a Hydroxyapatite Type I resin and eluted using various concentrations of phosphate buffer. Monomer peak elutes ~140 mM NaPhosphate 100 mM NaCl pH 7.0 and aggregate peak eluted at ~200 mM NaPhosphate 100 mM NaCl pH 7.0. Following hydroxyapatite, the sample was consistently >95% monomer.

Sedimentation velocity (SV) experiment via Analytical ultracentrifugation (AUC) was
 15 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
 20 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

25 The results of purification of the compounds are shown in Table 16. The data show that the compounds have high purity and homogeneity indicating good stability.

Table 16.

Parameter	Compound A	Compound E
-----------	------------	------------

Percent monomer (sedimentation velocity)	99.4	99.0
---	------	------

Example 17: Mass Spectrometry Profile of compounds

Methods

5 *Native Sample*

This procedure yielded the intact mass of the compound or protein. 2ul of sample was injected onto an Agilent Poroshell 300SB-C8 column, 5um, (75x1.0mm). The column temperature was 80 °C and flow rate was 50ul/min. The compound or protein was eluted off the column with a gradient from 20%B at 0 minutes to 85%B at 10 minutes. Mobile phase A was Water/Acetonitrile/Formic Acid (99/1/0.1) and Mobile phase B was
10 Acetonitrile/Water/Formic Acid (95/5/0.1). The effluent was directed to an Agilent 6210 TOF mass spectrometer, which was scanned from mass 600 to mass 3200. The raw data was deconvoluted with the program MassHunter.

15 *Reduced Sample*

This procedure yielded the mass of the protein or the light chain and the mass of the heavy chain. 2ul of 50mM TCEP was added to 10ul of sample and 10ul of 8M Guanidine and incubated for 15 minutes at 37 °C. 2ul of this sample was injected as above, with the following differences: the column temperature was 60 °C and the mass range was 600-2000.

20

Deglycosylated Sample

This procedure yielded the deglycosylated mass of the protein or the light chain and the heavy chain. 10ul of sample, 10ul of 200mM NH₄HCO₃, 2ul 50mM TCEP, and 1ul (1:10) PNGase F (or 1uL QA deglycosylation mix if O-linked glycosylations were present) were
25 incubated for 3 hours at 37 °C. The incubation was increased to overnight for heavily glycosylated samples. Then, 25ul 8M Guanidine and 4 ul of 50 mM TCEP were added and incubated for 15 minutes at 37 °C. This sample was injected as above for reduced sample.

Protein Peptide Mapping by Mass Spectrometry

25ul of sample was added to 25ul of 8M urea in 400mM ammonium bicarbonate. 5ul of 50mM TCEP was then added and the sample was incubated for 15 minutes at 60 °C. After cooling the sample to room temperature, 5ul of 150mM iodoacetamide was added and the sample was incubated at room temperature for 15 minutes. After adding 40ul of water, 5ul of trypsin in 1mM HCl was added to give a final enzyme: substrate ratio of 1:50. The sample was incubated at 37 °C overnight. 5ul was then injected onto a Thermo Hypurity C18 column, 100x1.0mm. Flow rate was 80ul/min. The protein was eluted off the column with a gradient from 0%B at 0 minutes to 40%B at 33 minutes. Mobile phase A was Water/Acetonitrile/Formic Acid (99/1/0.1) and Mobile phase B was Acetonitrile/Water/Formic Acid (95/5/0.1). The effluent was directed to a Thermo Orbitrap Velos mass spectrometer. The first scan event was in the FT, and scans from mass 300 to mass 2000 with a resolution of 30,000. The second through the seventh scan events were in the IT (ion trap) and fragmented the 6 most intense ions from the first scan event. Peptides containing glycosylation were profiled by manual extraction and percentages calculated based on peak heights.

Results

The results are shown in Table 17. 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 17.

Parameter	Compound A	Compound E
Mass Spectrometry: Intact Molecular Weight Profile	Intact/Matches Sequence	Intact/Matches Sequence
Mass Spectrometry: Glycosylation Profile	Not Determined	Similar to CHO

		expressed IgG
--	--	---------------

Example 18: 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 ($C_{p,ex}$) as a function of temperature. Reported values of transition temperatures (T_m) represent positions of peak maxima determined by visual inspection of the experimental thermograms.

Results

The results are shown in Table 18. The data show that the compounds are stable and would predict the ability to have a long shelf-life.

Table 18.

Parameter	Compound A	Compound E
Thermal Stability (°C)	57.9, 72.1, 82.9	67.6, 83.1

Example 19: Solubility of compounds

Methods

The compound samples were 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 analyzed in SV experiment via AUC to provide information on sample purity and

aggregation states (refer to Example 16 regarding purification for method details).

Results

The results are shown in Table 19. The data show that the compounds are soluble and
5 stable retaining a high percentage of monomer without formulation or added excipients.

Table 19.

Parameter	Compound A	Compound E
Solubility (Concentration)	48 mg/ml	51 mg/ml
Percent Monomer	98.6	97.0

Example 20: Valence of compounds

10 Methods

The valence measurement for the compound samples in 50 mM KCl and 10 mM sodium acetate buffer at pH 5.0 was performed on a Beckman Coulter (Fullerton, California) ProteomeLab PA800TM apparatus equipped with an ultraviolet (UV) absorbance detector, with a working wavelength of 214 nm. The system was maintained at 20 °C and an eCap
15 amine capillary with an inner diameter of 50 µm (Beckman Coulter, part #477431) was used. The capillary was rinsed with 100 mM NaOH, amine regeneration solution (Beckman Coulter, part # 477433) and running buffer before each sample injection. Migration times for the samples were measured at voltages of 10 kV, 14 kV, and 18 kV. Dimethylformamide (DMF) (0.005%) (Pierce) was used as an electroosmotic flow (EOF) marker. Data were
20 acquired using 32 KaratTM software (v7.0). Diffusion coefficient was determined from SV experiment via AUC.

Results

The valence data (see Table 20) indicate colloidal stability of the compounds in
25 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 20.

Parameter	Compound A	Compound E
Valence, pH 5.0	20.9	24.4

5 Example 21: Predicted 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-regitope, of which
 10 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
 15 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 together with other immunogenicity determinants helps to make an informed decision of the likelihood that the compounds will provoke an immune response in vivo.

20

Results

The results are shown in Table 21. The overall immunogenicity scores for these compounds are low and predict that these compounds are not likely to illicit a strong immune response in vivo.

25

Table 21.

Parameter	Compound A	Compound E
-----------	------------	------------

EpiVax	-37.7, -35.6	-31.1, -46.8
--------	--------------	--------------

Normalization of allele-specific scores

Example 22: Whole Blood Stability of Compounds

Methods

5 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
10 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

15 The results are shown in Table 22.

Table 22.

Parameter	Compound A	Compound E
Ration of binding signal in whole blood/kinetic buffer to hu TNFa	1.5	1.4
Ratio of binding signal in whole blood/kinetic buffer	1.8	1.3

Example 23: Summary of tested parameters

20 A summary of the parameter data for certain compounds is shown in Table 23 below.

Table 23.

Parameter	Compound A	Compound E
-----------	------------	------------

Percent Monomer after two-step purification process	99.4%	99%
Mass Spectrometry Profile	Intact	Intact
pI as determined by IEF (heterogeneity)	~8.8	~8.8
Thermal Stability (differential scanning calorimetry)	57.9, 72.1, 82.9	67.6, 83.1
Solubility	48 mg/ml	51 mg/ml
Valence at pH 5.0	20.9	24.4
Predicted Immunogenicity (EpiVax Score)	-37.69, -35.57	-31.1, -46.8
Whole Blood Stability (human WB, 48hrs at 37C); maintenance of binding to IL23 and TNFa	Maintained	Maintained

SEQUENCES

SEQ ID NO	Sequence
1	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHI DYADSVEGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGT LTVSS
2	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGQGTKVEIK
3	QVQLVESGGGVVQPGRSLRLSCAASGFISSYAMHWVRQAPGNGLWVAFMSYDGSNK KYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRGIAAGGNYYYYGMDV WGQGTITVTVSS
4	EIVLTQSPATLSLSPGERATLSCRASQSVSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIK
5	QVQLVESGGGVVQPGRSLRLSCAASGFISSYAMHWVRQAPGDGLEWVAFMSYDGSNK KYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRGIAAGGNYYYYGMDV WGQGTITVTVSS
6	EIVLTQSPATLSLSPGERATLSCRASQSVSYLAWYQQKPGQAPRLLIYDASNRATGIPAR

	FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIK
7	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPK YNENFKGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTV SS
8	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIK
9	GGGSGGG
10	LGGGSG
11	FNRGES
12	VEPKSS
13	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFSGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
14	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSLG GGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
15	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFSGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS

	RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
16	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGTLLTVSSVE PKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYFREAKVQWKVDNALQSGNSQESV TEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
17	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGTLLTVSSLG GGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
18	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFSGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGTLLTVSSLLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYFREAKVQWKVDNALQSGNSQESVT EQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
19	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGTLLTVSSFN RGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
20	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFSGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV

	QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
21	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSSGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
22	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
23	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSFNRGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
24	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE

	QDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
25	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLA WYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPCPAPEAA GGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
26	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSLGSGSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
27	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLA WYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPCPAPEAAG GPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
28	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
29	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLA WYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV

	QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
30	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
31	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
32	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASN RATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
33	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASN RATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ

	SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
34	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWVGQGT VTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
35	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWVGQGT VTVSSFNREGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
36	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
37	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLGLG
38	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFL

	FPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLGLG
39	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPG
40	EPKSCDKTHTCPPCP
41	RTVAAPSVFIFPPSDEQLKSGTASVVCCLNLFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
42	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEAAGG PSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
43	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEAAGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPG
44	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFLTITSLQPEDVATYYCQRYNRPYTFGGGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

45	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGTLLTVSSLG GGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPREAKVQWKVDNALQSGNSQES VTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
46	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGTLLTVSSFN RGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
47	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISLQPEDVATYYCQRYNRPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGTLLTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPREAKVQWKVDNALQSGNSQESVTE QDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
48	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTSSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
49	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF

	KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
50	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFISSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSFNREGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGGSFF LYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
51	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
52	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVTPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGGSFFLYSRLTVDKSR WQEGNVFCFSVMHEALHNHYTQKSLSLSLG
53	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFISSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSLGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

54	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDFAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLYITREPEVTCVVVDVSDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMEALHNHYTQKSLSLGLG
55	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARDRGIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
56	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDFAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMEALHNHYTQKSLSLGLG
57	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARDRGIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
58	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF

	KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCAPEFLGGP SVFLFPPKPKDTLYITREPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLGLG
59	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFISSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGRTVAAPS FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSK DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
60	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLA WYQQKPGQAPRLLIYDASN RATGIPAR FSGSGSGTDFTLTISSLQPEDFAVYYCQQR SNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHW MRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFN RG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
61	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFISSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSVEPKSSRTVAAPS FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSK DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
62	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLA WYQQKPGQAPRLLIYDASN RATGIPAR FSGSGSGTDFTLTISSLQPEDFAVYYCQQR SNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHW MRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFN RG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPPELLG

	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
63	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
64	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASN RATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGT LTVTVSSFN RG ESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVTPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
65	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
66	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASN RATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGT LTVTVSSFN RG ESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVTPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQ

	EGNVFSCSVMHEALHNHYTQKSLSLSLG
67	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
68	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
69	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
70	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPSNTKVDKRVEPKYGPCCPPC PAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
71	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV

	QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
72	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPCPPC PAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLG
73	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
74	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSFNRGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
75	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE

	QDSKDYSLSSSTLTLSKADYKHKVYACEVTHQGLSSPVTKSFNRGEC
76	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSGRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSFNREGESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVESKYGPPCPPCP APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLG
77	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSLSSSTLTLSKADYKHKVYACEVTHQGLSSPVTKSFNRGEC
78	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSGRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSFNREGESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVESKYGPPCPPCP APEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLG
79	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSLSSSTLTLSKADYKHKVYACEVTHQGLSSPVTKSFNRGEC
80	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV

	QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
81	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
82	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASN RATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
83	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
84	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASN RATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL

	QSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMHEALHNHYTQKSLSLGLG
85	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSLGGGSGRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
86	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLA WYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQR SNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKV SCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLYITREPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLGLG
87	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSLGGGSGRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
88	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLA WYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQR SNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKV SCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR

	EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
89	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
90	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGGGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGT LTVSSFNRG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
91	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
92	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGGGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGT LTVSSFNRG ESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVKFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSPG
93	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS

	RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
94	EIVLTQSPATLSLSPGERATLSCRASQSVSYLA WYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKV SCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVPSSSLG TKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLYITREPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSV MHEALHNHYTQKSLSLGLG
95	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSVEPKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
96	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSSLGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG
97	EIVLTQSPATLSLSPGERATLSCRASQSVSYLA WYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISLLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKV SCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG

	GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDYSLSTLTLSKADYKHKVYACEVTHQGLSSPVTKSFNRGEC
98	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSLGGGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
99	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDYSLSTLTLSKADYKHKVYACEVTHQGLSSPVTKSFNRGEC
100	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSLGGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
101	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLIYDASNRATGIPAR FSGSGSGTDFTLTISLQPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDYSLSTLTLSKADYKHKVYACEVTHQGLSSPVTKSFNRGEC
102	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS

	RFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSSLGGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPC PAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLG
103	EIVLTQSPATLSLSPGERATLSCRASQSVSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGT LTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
104	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSFNREGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG
105	EIVLTQSPATLSLSPGERATLSCRASQSVSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSED TAVYYCAIPDRSGYAWFIYWGQGT LTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
106	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT

	VTVSSFNRGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
107	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDYAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
108	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSFNRGESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNV DHKPSNTKVDKRVEPKYGPCCPPCP APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
109	EIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDYAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
110	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGDGLEWVAFMSYDGSNKKYADSV KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT VTVSSFNRGESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNV DHKPSNTKVDKRVEPKYGPCCPPCP APEFLGGPSVFLFPPKPKDTLYITREPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKT

	KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPG
111	EIVLTQSPATLSLSPGERATLSCRASQSVSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
112	EIVLTQSPATLSLSPGERATLSCRASQSVSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
113	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVP RFGSGSGRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLV SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLEWVAFMSYDGSNKKYADSV KGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRIAAGGNYYYYGMDVWGQGT TVTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
114	DIQMTQSPSSLSASVGDRVTITCRASQGIIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGSSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

115	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSLG GGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
116	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFSGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDYAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMEALHNHYTQKSLSLGLG
117	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSLG GGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
118	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFSGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDYAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLYITREPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMEALHNHYTQKSLSLGLG
119	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV

	EGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSLG GGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
120	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
121	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSVE PKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
122	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
123	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSVE PKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

124	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFSGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMEALHNHYTQKSLSLGLG
125	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNANKNSLYLQMNSLRSEDVAVYYCAKVSYLSTASSLDYWGQGLTVTVSSVE PKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
126	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFSGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSFNRG ESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLYITREPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMEALHNHYTQKSLSLGLG
127	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNANKNSLYLQMNSLRSEDVAVYYCAKVSYLSTASSLDYWGQGLTVTVSSVE PKSSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
128	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV

	EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSLG GGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYCKKVSNAKALPAIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
129	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
130	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSLG GGSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYCKKVSNAKALPAIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
131	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSKKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDVAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
132	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSLG GGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKYGPCCPPCPAPEFLGG

	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSR WQEGNVFSCSVMHEALHNHYTQKSLSLGLG
133	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGGGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
134	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSGRTDFTLTISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNLSRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSLG GGSGASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVTPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPCCPPCAPEFLGG PSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSR WQEGNVFSCSVMHEALHNHYTQKSLSLGLG
135	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGGGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
136	EIVLTQSPATLSLSPGERATLSCRASQSVSYLAWYQQKPGQAPRLLIYDASNRAITGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFDDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSLGG GSGASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVD

	KSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG
137	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGQVQLVE SGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLWVAFMSYDGSNKKYADSV KGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRGIAAGGNYYYYGMDVWGQGT VTVSSLGGGSGRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG GNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
138	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGTTLTVSSFN RGESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG
139	DIQMTQSPSSLSASVGDRVITITCRASQGIIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGTTLTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
140	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGTTLTVSSFN RGESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMEALHNHYTQKSLSLSLG
141	DIQMTQSPSSLSASVGDRVITITCRASQGIIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV

	QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
142	DIQMTQSPSSLSASVGDRVITITCKASRDVAIAVAWYQQKPGKVPKLLIYWASTRHTGVPS RFGSGSGRTDFTLTISLQPEDVADYFCHQYSSYPFTFGSGTKLEIKGGGSGGGGEVQLVE SGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSV EGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLDYWGQGLTVTVSSFN RGESASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLGL
143	DIQMTQSPSSLSASVGDRVITITCRASQGIRNYLAWYQQKPGKAPKLLIYAASTLQSGVPS RFGSGSGGTDFLTISLQPEDVATYYCQRYNRAPYTFGQGTKVEIKGGGSGGGGQVQLV QSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWGQGLTVTVSSVEPK SSRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
144	MSTESMIRDVELAEALPKKTGGPQGSRRCLFLSLFSLIVAGATTLFCLLHFGVIGPQREE FPRDLSLISPLAQAVRSSSRTPSDKPVAVHVVANPQAEGQLQWLNRRANALLANGVELRD NQLVVPSEGLYLIYSQVLFKGGQGPCSTHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRETPE GAEAKPWYEPIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIAL
145	MLGSRAVMLLLLPWTAQGRAVPGGSSPAWTQCQQLSQKLCTLAWSAHLVGHMDLR EEGDEETTNDVPHIQCGDGDGPQGLRDNSQFCLQRIHQGLIFYEKLLGSDIFTGEPSSLPDS PVGQLHASLLGLSLLQPEGHHWETQQIPSLSPSQPWQRLLLRFKILRSLQAFVAVAAARV FAHGAATLSP
146	DYAMH
147	AITWNSGHIDYADSV
148	VSYLSTASSLDY
149	RASQGIRNYLA
150	AASTLQS
151	QRYNRAPYT
152	SYAMH
153	FMSYDGSNKKYADSVKG
154	NYYYYGMDV

155	RASQSVYSYLA
156	DASNRAT
157	QQRSNWPPFT
158	DQTIH
159	YIYPRDDSPKYNENFKG
160	PDRSGYAWFIY
161	KASRDVAIAVA
162	WASTRHT
163	HQYSSYPFT

OTHER EMBODIMENTS

5 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.

10 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

What is claimed is:

1. A compound comprising a first polypeptide and a second polypeptide, wherein:
 - 5 (A) said first polypeptide comprises in the direction from the N-terminus to the C-terminus:
 - (i) a light chain variable domain of a first immunoglobulin (VL1) specific for a first target protein;
 - (ii) a heavy chain variable domain of a second immunoglobulin (VH2) specific for a
10 second target protein;
 - (iii) a heavy chain constant region 1 (CH1);
 - (iv) a hinge region from an IgG1 or from an IgG4;
 - (v) a heavy chain constant region 2 (CH2); and
 - (vi) a heavy chain constant region 3 (CH3); and
 - 15 (B) said second polypeptide comprises in the direction from the N-terminus to the C-terminus:
 - (i) a light chain variable domain of the second immunoglobulin (VL2) specific for said second target protein;
 - (ii) a heavy chain variable domain of the first immunoglobulin (VH1) specific for said
20 first target protein; and
 - (iii) a light chain constant region (CL),
 - (C) further wherein:
 - (i) said VL1 and VH1 associate to form a binding site that binds said first target protein;
 - 25 (ii) said VL2 and VH2 associate to form a binding site that binds said second target protein;
 - (iii) said heavy chain constant region 2 (CH2) comprises a tyrosine at position 252, a threonine at position 254 and a glutamic acid a position 256, numbered according to the EU index as in Kabat;

- (iv) said heavy chain constant region 1 domain (CH1) of the first polypeptide and the light chain constant region domain (CL) of the second polypeptide are associated together via a disulfide bond to form a C1 domain;
- (v) said first target protein is TNF-alpha and said second target protein is IL-23A or said first target protein is IL-23A and said second target protein is TNF-alpha,
- (D) and wherein:
- (i) said VL1 comprises SEQ ID NO:2, said VH1 comprises SEQ ID NO:1, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7; or
- (ii) said VL1 comprises SEQ ID NO:4 or 6, said VH1 comprises SEQ ID NO:3 or 5, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7; or
- (iii) said VL1 comprises SEQ ID NO:8, said VH1 comprises SEQ ID NO:7, said VL2 comprises SEQ ID NO:2 and said VH2 comprises SEQ ID NO:1; or
- (iv) said VL1 comprises SEQ ID NO:8, said VH1 comprises SEQ ID NO:7, said VL2 comprises SEQ ID NO:4 or 6 and said VH2 comprises SEQ ID NO:3 or 5.
2. The compound according to claim 1, wherein in (ii) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7.
3. The compound according to claim 1, wherein in (ii) said VL1 comprises SEQ ID NO:4, said VH1 comprises SEQ ID NO:5, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7.
4. The compound according to claim 1, wherein in (ii) said VL1 comprises SEQ ID NO:6, said VH1 comprises SEQ ID NO:5, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7.
5. The compound according to claim 1, wherein in (ii) said VL1 comprises SEQ ID NO:6, said VH1 comprises SEQ ID NO:3, said VL2 comprises SEQ ID NO:8 and said VH2 comprises SEQ ID NO:7.

6. The compound according to claim 1, wherein in (iv) said VL2 comprises SEQ ID NO:4, said VH2 comprises SEQ ID NO:3, said VL1 comprises SEQ ID NO:8 and said VH1 comprises SEQ ID NO:7.
- 5 7. The compound according to claim 1, wherein in (iv) said VL2 comprises SEQ ID NO:4, said VH2 comprises SEQ ID NO:5, said VL1 comprises SEQ ID NO:8 and said VH1 comprises SEQ ID NO:7.
8. The compound according to claim 1, wherein in (iv) said VL2 comprises SEQ ID NO:6, said VH2 comprises SEQ ID NO:5, said VL1 comprises SEQ ID NO:8 and said VH1 comprises SEQ ID NO:7.
- 10 9. The compound according to claim 1, wherein in (iv) said VL2 comprises SEQ ID NO:6, said VH2 comprises SEQ ID NO:3, said VL1 comprises SEQ ID NO:8 and said VH1 comprises SEQ ID NO:7.
- 15 10. 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.
- 20 11. The compound according to claim 10, wherein said first linker or said second linker comprises the amino acid sequence GGGSGGG (SEQ ID NO:9).
12. The compound according to claim 10, wherein said first linker and said second linker comprise the amino acid sequence GGGSGGG (SEQ ID NO:9).
- 25 13. The compound according to claim 1, 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.
- 30 14. The compound according to claim 13, wherein said third linker comprises the amino acid sequence FNRGES (SEQ ID NO:11).

15. The compound according to claim 13, wherein said fourth linker comprises the amino acid sequence VEPKSS (SEQ ID NO:12).
- 5 16. The compound according to claim 13, wherein said third linker comprises the amino acid sequence FNRGES (SEQ ID NO:11) and said fourth linker comprises the amino acid sequence VEPKSS (SEQ ID NO:12).
- 10 17. The compound according to claim 13, wherein said third linker or said fourth linker comprises the amino acid sequence LGGGSG (SEQ ID NO:10).
18. The compound according to claim 13, wherein said third linker and said fourth linker comprise the amino acid sequence LGGGSG (SEQ ID NO:10).
- 15 19. The compound according to any one of claims 1 to 18, 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.
- 20 20. The compound according to any one of claims 1 to 19, wherein the amino acid sequence of said heavy chain constant region 2 (CH2) or said heavy chain constant region 3 (CH3) is from a IgG1 or from a IgG4.
21. The compound according to any one of claims 1 to 20, wherein said hinge region comprises the amino acid sequence EPKSCDKTHTCPPCP (SEQ ID NO:40).
- 25 22. The compound according to any one of claims 1 to 21, 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.
- 30 23. The compound according to claim 1, wherein:
(i) said first polypeptide comprises the amino acid sequence of SEQ ID NO:13 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:14;

- (ii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:15 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:16;
- (iii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:17 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:18;
- 5 (iv) said first polypeptide comprises the amino acid sequence of SEQ ID NO:19 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:20;
- (v) said first polypeptide comprises the amino acid sequence of SEQ ID NO:21 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:22;
- (vi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:23 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:24;
- 10 (vii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:25 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:26;
- (viii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:27 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:28;
- 15 (ix) said first polypeptide comprises the amino acid sequence of SEQ ID NO:29 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:30;
- (x) said first polypeptide comprises the amino acid sequence of SEQ ID NO:31 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:32;
- (xi) said first polypeptide comprises the amino acid sequence of SEQ ID NO:33 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:34; or
- 20 (xii) said first polypeptide comprises the amino acid sequence of SEQ ID NO:35 and said second polypeptide comprises the amino acid sequence of SEQ ID NO:36.

24. The compound according to claim 23, 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.

25. The compound according to claim 23 or 24, wherein said compound comprises two said first polypeptides and two said second polypeptides, wherein each of said first polypeptides comprises a CH1, a CH2 and a CH3 and each of said second polypeptides comprises a CL and wherein the CH2 and CH3 of one of the first polypeptides associates with the CH2 and CH3 of

the other of the first polypeptides and the CH1 of each said first polypeptides associates with the CL of one said second polypeptides to form a tetravalent molecule.

26. A pharmaceutical composition comprising the compound according to any one of claims
5 1 to 25 and a pharmaceutically acceptable carrier.

27. Use of the compound according to any one of claims 1 to 25 or a pharmaceutical
composition comprising said compound and a pharmaceutically acceptable carrier, for treating an
autoimmune or an inflammatory disease in a subject.

10

28. The compound according to any one of claims 1 to 25 for use in human therapy.

29. The compound according to claim 28, wherein said use is the treatment of an autoimmune
or an inflammatory disease.

15

30. A pharmaceutical composition comprising the compound according to any one of claims
1 to 25 and a pharmaceutically acceptable carrier, for use in human therapy.

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

32. A nucleic acid comprising a nucleotide sequence encoding the compound according to
any one of claims 1 to 25.

25 33. A vector comprising the nucleic acid according to claim 32.

34. The vector according to claim 33, further comprising a promoter operably linked to said
nucleic acid.

30 35. An isolated cell comprising the nucleic acid according to claim 32 or the vector according
to claim 33 or claim 34.

36. A method of producing the compound according to any one of claims 1 to 25 comprising obtaining the isolated cell according to claim 35 and expressing said nucleic acid in said cell.
37. The method according to claim 36, further comprising isolating and purifying said
5 compound.
38. Use of the compound according to any one of claims 1 to 25 or a pharmaceutical composition comprising said compound and a pharmaceutically acceptable carrier, for the manufacture of a medicament for treating an autoimmune or an inflammatory disease in a
10 subject.

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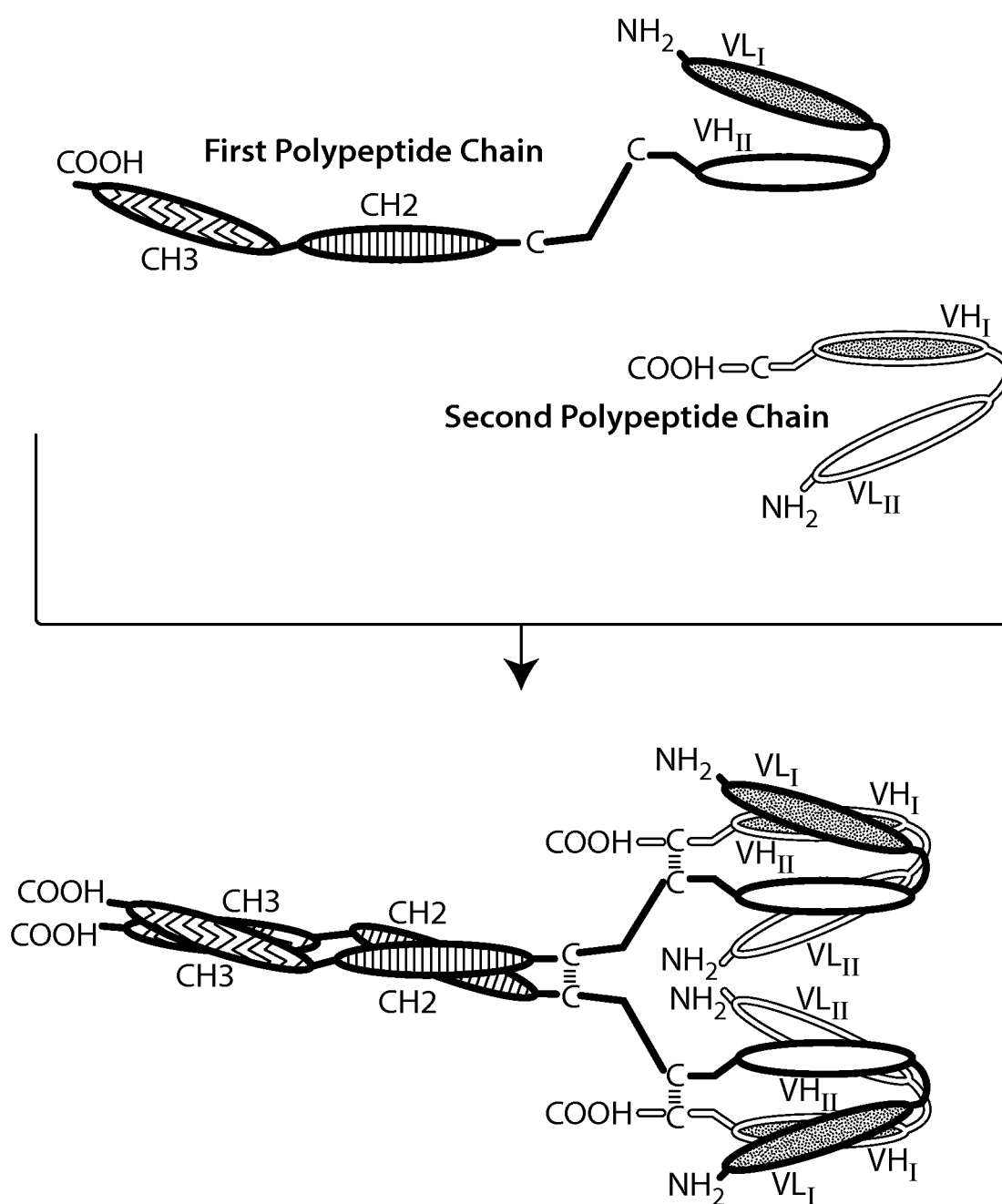


FIG. 1A

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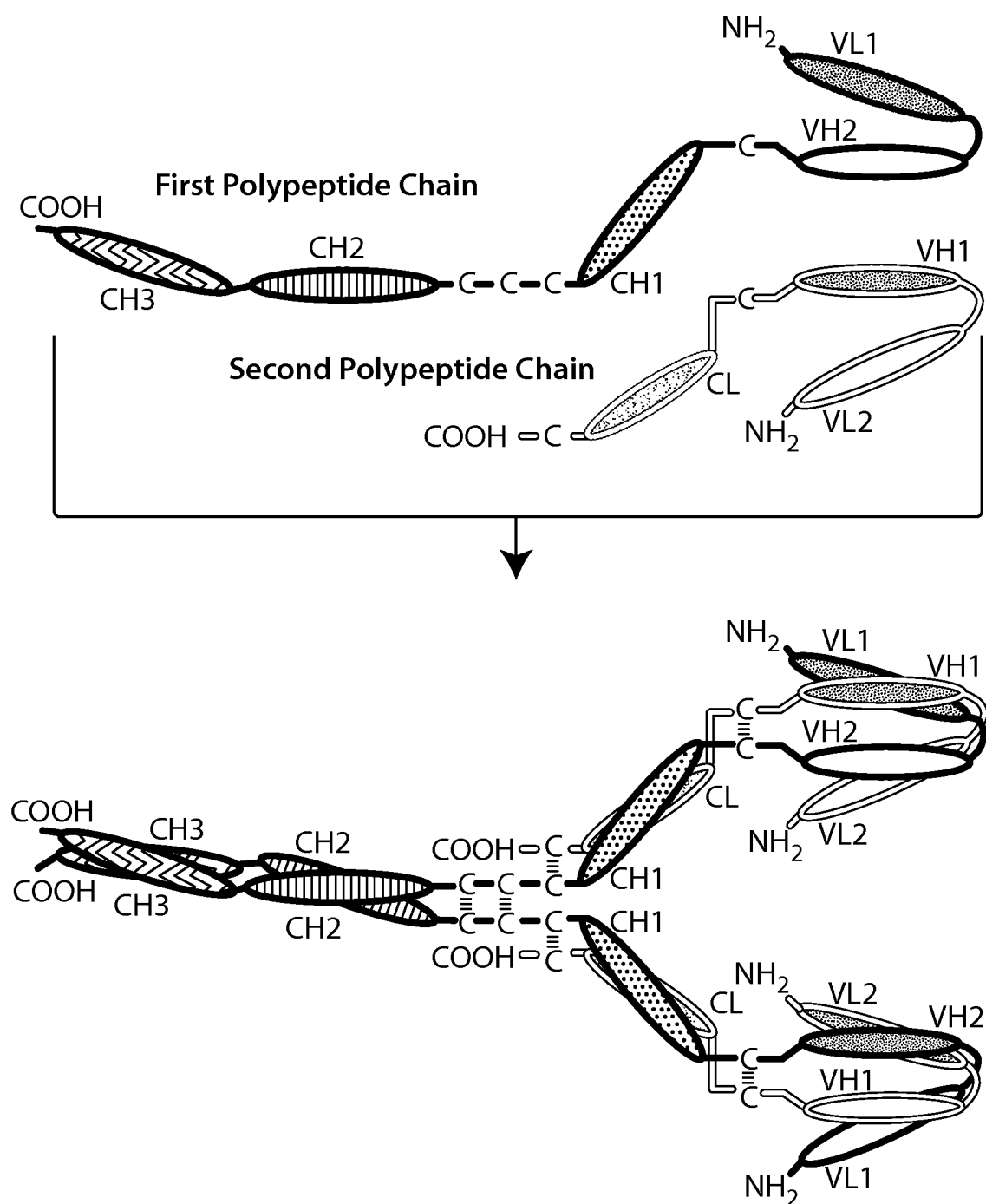


FIG. 1B

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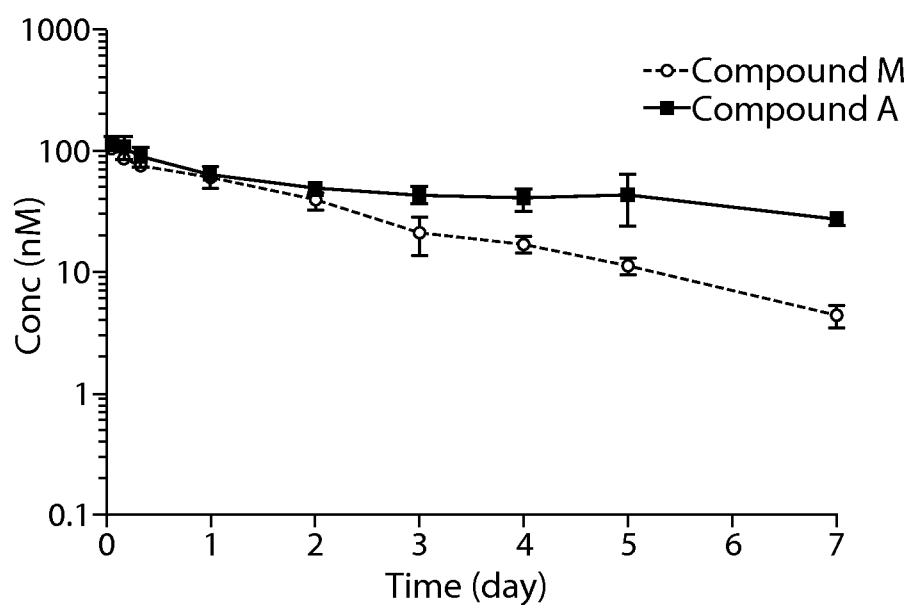


FIG. 2

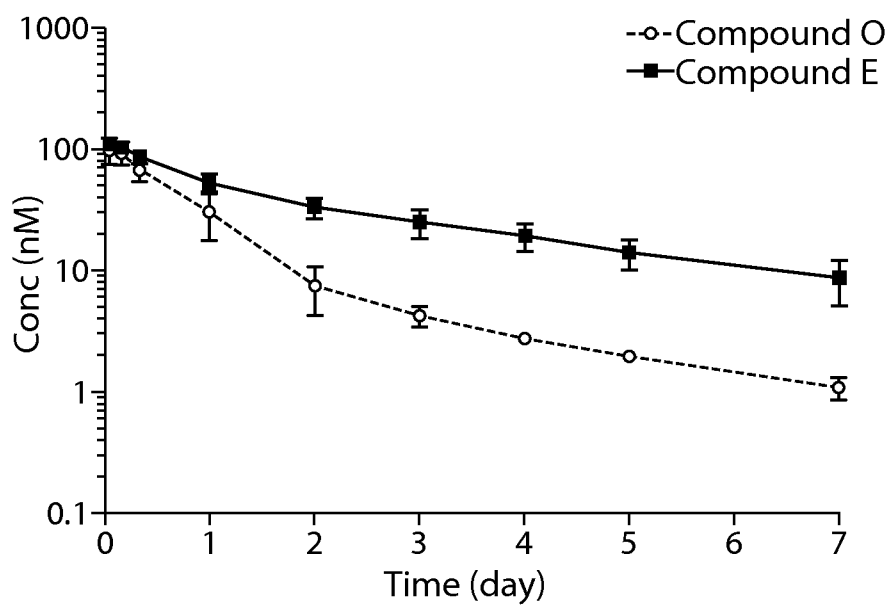
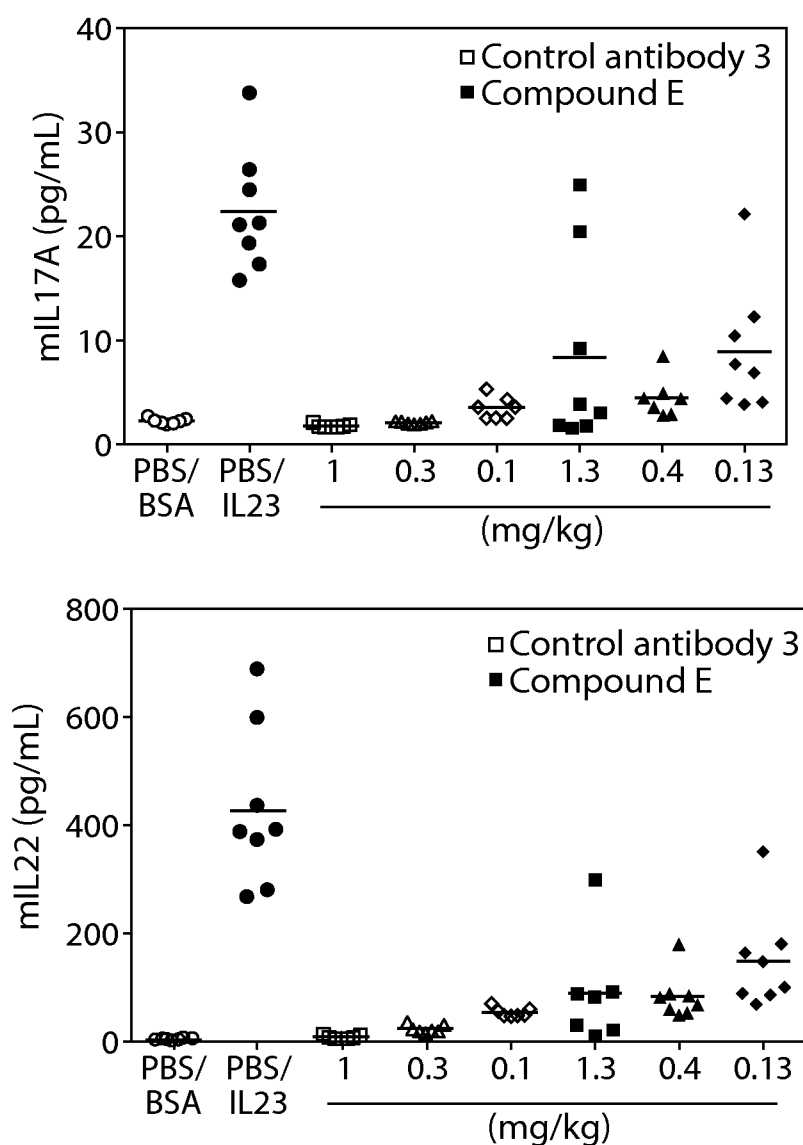


FIG. 3

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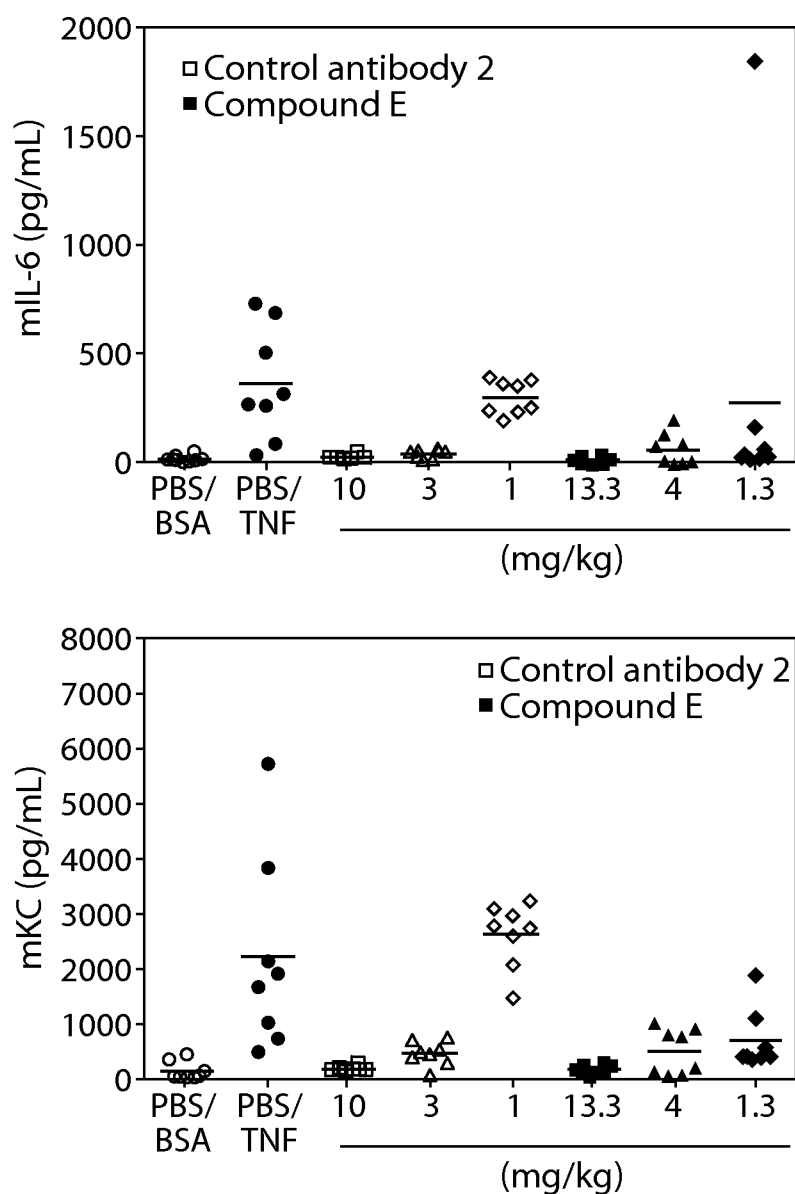


Mean serum levels (nM +SD) at 49hr post IP dosing
(doses are MW normalized)

Dose (mg/kg)	Control antibody 3	SD	Compound E	SD
0.1	4	1	3	1
0.3	19	4	16	6
1	62	20	42	6

FIG. 4

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Mean serum levels (nM +SD) at 4hr post IP dosing
(doses are MW normalized)

Dose (mg/kg)	Control antibody 2	SD	Compound E	SD
1	26	8	33	15
3	81	27	229	100
10	1103	296	497	256

FIG. 5

