of an IgG and capable of binding four antigen molecules has been described (see WO 0177342A1, and Miller, K., et al. (2003) J. Immunol. 170(9): 4854-61).

There is a need in the art for improved multivalent binding proteins capable of binding two or more antigens. U.S. Patent Application Serial No. 11/507,050 provides a novel family of binding proteins capable of binding two or more antigens with high affinity, which are called dual variable domain immunoglobulins (DVD-Ig™). The present invention provides further novel binding proteins capable of binding two or more antigens.

Summary of the Invention

This invention pertains to multivalent binding proteins capable of binding two or more antigens. The present invention provides a novel family of binding proteins capable of binding two or more antigens with high affinity.

In one embodiment, there is provided a binding protein comprising first and second polypeptide chains, each independently comprising VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first variable domain;

VD2 is a second variable domain;

C is a constant domain;

X1 is a linker;

X2 is an Fc region; and

n is 0 or 1;

wherein the VD1 domains on the first and second polypeptide chains form a first functional target binding site and the VD2 domains on the first and second polypeptide chains form a second functional target binding site, wherein the binding protein is capable of binding to PGE2, and wherein the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111.

In one embodiment, there is provided a binding protein conjugate comprising the binding protein as described herein, and an agent selected from the group consisting of an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent, wherein:

(a) the imaging agent is selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin, and wherein the radiolabel is optionally selected from the group consisting of ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm; or

(b) the therapeutic or cytotoxic agent is selected from the group consisting of an antimetabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

In one embodiment, there is an isolated nucleic acid encoding the binding protein amino acid sequence as described herein.

In one embodiment, there is provided a vector comprising the isolated nucleic acid as described herein, wherein the vector is optionally selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, and pBJ.

In one embodiment, there is provided an isolated host cell comprising the vector oas described herein, wherein the host cell is optionally a prokaryotic cell, an *Escherichia coli* cell, a eukaryotic cell, a protist cell, an animal cell, a plant cell, a fungal cell, a mammalian cell, an avian cell, an insect cell, a CHO cell, a COS cell, a yeast cell, a *Saccharomyces cerevisiae,* or an insect Sf9 cell.

In one embodiment, there is provided a method of producing a binding protein, comprising culturing the host cell as described herein in culture medium under conditions sufficient to produce the binding protein.

In one embodiment, there is provided a pharmaceutical composition comprising the binding protein or the binding protein conjugate as described herein, and a pharmaceutically acceptable carrier; wherein the pharmaceutical composition optionally further comprising at least one additional therapeutic agent; and wherein the additional therapeutic agent is optionally selected from the group consisting of: a therapeutic agent; an imaging agent; a cytotoxic agent, angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an antirheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

In one embodiment, there is provided a method of determining the presence, amount, or concentration of at least one target or fragment thereof in a test sample by an immunoassay,

wherein the immunoassay comprises contacting the test sample with at least one binding protein and at least one detectable label; and

wherein the at least one binding protein comprises the binding protein as described herein.

In one embodiment, there is provided a kit for assaying a test sample for the presence, amount, or concentration of a target or fragment thereof, the kit comprising:

(a) instructions for assaying the test sample for the target or fragment thereof; and

(b) at least one binding protein comprising the binding protein as described herein.

In one embodiment, there is provided the use of a binding protein as described herein or a binding protein conjugate as described herein for the manufacture of a medicament for the treatment of a disease or a disorder.

In one embodiment the invention provides a binding protein comprising a polypeptide chain, wherein the polypeptide chain comprises VDl-(Xl)n-VD2-C-(X2)n, wherein VDl is a first variable domain, VD2 is a second variable domain, C is a constant domain, Xl represents an amino acid or polypeptide, X2 represents an Fc region and n is 0 or 1. In an embodiment the VD 1 and VD2 in the binding protein are heavy chain variable domains. In another embodiment, the heavy chain variable domain is selected from the group consisting of a murine heavy chain variable domain, a human heavy chain variable domain, a CDR grafted heavy chain variable domain, and a humanized heavy chain variable domain. In yet another, embodiment VDl and VD2 are capable of binding the same antigen. In another embodiment VDl and VD2 are capable of binding different antigens. In still another embodiment, C is a heavy chain constant domain. For example, Xl is a linker with the proviso that Xl is not CHl. For example, Xl is a linker selected from the group consisting of AKTTPKLEEGEFSEAR (SEQ ID NO: 1); AKTTPKLEEGEFSEARV (SEQ ID NO: 2); AKTTPKLGG (SEQ ID NO: 3); SAKTTPKLGG (SEQ ID NO: 4); SAKTTP (SEQ ID NO: 5); RADAAP (SEQ ID NO: 6); RADAAPTVS (SEQ ID NO: 7); RADAAAAGGPGS (SEQ ID NO: 8); RADAAAA$(G_4S)_4$ (SEQ ID NO: 9), S AKTTPKLEEGEFSEARV (SEQ ID NO: 10); ADAAP (SEQ ID NO: 11); ADAAPTVSIFPP (SEQ ID NO: 12); TVAAP (SEQ ID NO: 13); TVAAPSVFIFPP (SEQ ID NO: 14); QPKAAP (SEQ ID NO: 15);

We claim:

1. A binding protein comprising first and second polypeptide chains, each independently comprising VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first variable domain;

VD2 is a second variable domain;

C is a constant domain;

X1 is a linker;

X2 is an Fc region; and

n is 0 or 1;

wherein the VD1 domains on the first and second polypeptide chains form a first functional target binding site and the VD2 domains on the first and second polypeptide chains form a second functional target binding site, wherein the binding protein is capable of binding to PGE2, and wherein the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111.

2. The binding protein of claim 1, comprising first and second polypeptide chains, each independently comprising VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first variable domain;

VD2 is a second variable domain;

C is a constant domain;

X1 is a linker;

X2 is an Fc region; and

n is 0 or 1;

wherein the VD1 domains on the first and second polypeptide chains form a first functional target binding site and the VD2 domains on the first and second polypeptide chains form a second functional target binding site; and wherein the binding protein is capable of binding

(a) TNF and PGE2, wherein

(1) the variable domains that form a functional binding site for TNF comprise CDRs 1-3 from SEQ ID NO: 112 and/or CDRs 1-3 from SEQ ID NO: 113; and

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111;

(b) NGF and PGE2, wherein

(1) the variable domains that form a functional binding site for NGF comprise comprise CDRs 1-3 from SEQ ID NO: 32 and/or CDRs 1-3 from SEQ ID NO: 33; and

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111;

(c) IL-17A and PGE2, wherein

(1) the variable domains that form a functional binding site for IL-17A comprise CDRs 1-3 from SEQ ID NO: 34 and/or CDRs 1-3 from SEQ ID NO: 35; and

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111;

(d) IL-1b and PGE2, wherein

(1) the variable domains that form a functional binding site for IL-1b comprise CDRs 1-3 from SEQ ID NO: 36 and/or CDRs 1-3 from SEQ ID NO: 37; and

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111;

(e) IL-6R and PGE2, wherein

(1) the variable domains that form a functional binding site for IL-6R comprise CDRs 1-3 from SEQ ID NO: 54 and/or CDRs 1-3 from SEQ ID NO: 55; and

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111;

(f) VEGF and PGE2, wherein

(1) the variable domains that form a functional binding site for VEGF comprise CDRs 1-3 from SEQ ID NO: 28 and/or CDRs 1-3 from SEQ ID NO: 29; and

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111;

(g) Abeta and PGE2, wherein

(1) the variable domains that form a functional binding site for Abeta comprise CDRs 1-3 from SEQ ID NO: 40 and/or CDRs 1-3 from SEQ ID NO: 41; and

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111;

or

(h) IL-15 and PGE2, wherein

(1) the variable domains that form a functional binding site for IL-15 comprise CDRs 1-3 from SEQ ID NO: 50 and/or CDRs 1-3 from SEQ ID NO: 51; and

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 110 and/or CDRs 1-3 from SEQ ID NO: 111.

3. The binding protein of claim 1 or 2, comprising first and second polypeptide chains, each independently comprising VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first variable domain;
VD2 is a second variable domain;
C is a constant domain;
X1 is a linker;
X2 is an Fc region; and
n is 0 or 1;

wherein the VD1 domains on the first and second polypeptide chains form a first functional target binding site and the VD2 domains on the first and second polypeptide chains form a second functional target binding site; and wherein the binding protein is capable of binding

(a) TNF and PGE2, wherein

(1) the variable domains that form a functional binding site for TNF comprise SEQ ID NOs: 112 and/or 113; and

(2) the variable domains that form a functional binding site for PGE2 comprise SEQ ID NOs: 110 and/or 111;

(b) NGF and PGE2, wherein

(1) the variable domains that form a functional binding site for NGF comprise SEQ ID NOs: 32 and/or 33; and

(2) the variable domains that form a functional binding site for PGE2 comprise SEQ ID NOs: 110 and/or 111;

(c) IL-17A and PGE2, wherein

(1) the variable domains that form a functional binding site for IL-17A comprise SEQ ID NOs: 34 and/or 35; and

(2) the variable domains that form a functional binding site for PGE2 comprise SEQ ID NOs: 110 and/or 111;

(d) IL-1b and PGE2, wherein

(1) the variable domains that form a functional binding site for IL-1b comprise SEQ ID NOs: 36 and/or 37; and

(2) the variable domains that form a functional binding site for PGE2 comprise SEQ ID NOs: 110 and/or 111;

(e) IL-6R and PGE2, wherein

(1) the variable domains that form a functional binding site for IL-6R comprise SEQ ID NOs: 54 and/or 55; and

(2) the variable domains that form a functional binding site for PGE2 comprise SEQ ID NOs: 110 and/or 111;

(f) VEGF and PGE2, wherein

(1) the variable domains that form a functional binding site for VEGF comprise SEQ ID NOs: 28 and/or 29; and

(2) the variable domains that form a functional binding site for PGE2 comprise SEQ ID NOs: 110 and/or 111;

(g) Abeta and PGE2, wherein

(1) the variable domains that form a functional binding site for Abeta comprise SEQ ID NOs: 40 and/or 41; and

(2) the variable domains that form a functional binding site for PGE2 comprise SEQ ID NOs: 110 and/or 111;

or

(h) IL-15 and PGE2, wherein

(1) the variable domains that form a functional binding site for IL-15 comprise SEQ ID NOs: 50 and/or 51; and

(2) the variable domains that form a functional binding site for PGE2 comprise SEQ ID NOs: 110 and/or 111.

4. The binding protein of any one of claims 1-3, wherein the binding protein that is capable of binding to

(a) TNF and PGE2

(1) inhibits TNF with an IC_{50} of at least 14 x 10^{-12} M, as measured by direct bind ELISA, and/or binds TNF with a dissociation constant (K_D) of at most 806 x 10^{-12} M, as measured by surface plasmon resonance;

and

(2) inhibits PGE2 with an IC_{50} of at least 45 x 10^{-12} M, as measured by direct bind ELISA, and/or binds PGE2 with a dissociation constant (K_D) of at most 261 x 10^{-12} M, as measured by surface plasmon resonance;

(b) NGF and PGE2

(1) inhibits NGF with an EC_{50} of at most 1.21 x 10^{-9} M, as measured by direct bind ELISA, and/or binds NGF with a dissociation constant (K_D) of at most 2.48 x 10^{-10} M, as measured by surface plasmon resonance;

and

(2) inhibits PGE2 with an EC_{50} of at most 1.3 x 10^{-9} M, as measured by direct bind ELISA, and/or neutralizes PGE2 with an EC_{50} of at most 0.079 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(c) IL-17A and PGE2

(1) inhibits IL-17A with an EC_{50} of at most 248.1 x 10^{-9} M, as measured by direct bind ELISA, and/or binds IL-17A with a dissociation constant (K_D) of at most 3.37 x 10^{-9} M, as measured by surface plasmon resonance;

and

(2) inhibits PGE2 with an EC_{50} of at most 1.55 x 10^{-9} M, as measured by direct bind ELISA, and/or neutralizes PGE2 with an EC_{50} of at most 0.025 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(d) IL-1b and PGE2

(1) inhibits IL-1b with an EC_{50} of at most 2480.71 x 10^{-9} M, as measured by direct bind ELISA; binds IL-1b with a dissociation constant (K_D) of at most 3.87 x 10^{-11} M, as measured by surface plasmon resonance; and/or neutralizes IL-1b with an EC_{50} of at most 3.22 x 10^{-9} M, as measured by an IL-1b neutralization assay;

and

(2) inhibits PGE2 with an EC_{50} of at most 1.23 x 10^{-9} M, as measured by direct bind ELISA, and/or neutralizes PGE2 with an EC_{50} of at most 0.217 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(e) IL-6R and PGE2

(1) inhibits IL-6R with an EC_{50} of at most 26,452.34 x 10^{-9} M, as measured by direct bind ELISA; binds IL-6R with a dissociation constant (K_D) of at most 4.48 x 10^{-10} M, as measured by surface plasmon resonance; and/or binds IL-6R with a FACS geometric mean of at least 0.21, as measured by flow cytometry;

and

(2) inhibits PGE2 with an EC_{50} of at most 1.65 x 10^{-9} M, as measured by direct bind ELISA, and/or neutralizes PGE2 with an EC_{50} of at most 0.036 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(f) VEGF and PGE2

(1) inhibits VEGF with an EC_{50} of at most 391.23 x 10^{-9} M, as measured by direct bind ELISA, and/or binds VEGF with a dissociation constant (K_D) of at most 7.55 x 10^{-10} M, as measured by surface plasmon resonance;

and

(2) inhibits PGE2 with an EC_{50} of at most 1.32 x 10^{-9} M, as measured by direct bind ELISA, and/or inhibits PGE2 with an EC_{50} of at most 0.245 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(g) Abeta and PGE2

inhibits PGE2 with an EC_{50} of at most 1.21 x 10^{-9} M, as measured by direct bind ELISA, and/or neutralizes PGE2 with an EC_{50} of at most 0.049 x 10^{-9} M, as measured by a PGE2 neutralization assay;

or

(h) IL-15 and PGE2

(1) binds IL-15 with a dissociation constant (K_D) of at most 4.89 x 10^{-9} M, as measured by surface plasmon resonance;

and

(2) inhibits PGE2 with an EC_{50} of at most 1.54 x 10^{-9} M, as measured by direct bind ELISA, and/or neutralizes PGE2 with an EC_{50} of at most 0.048 x 10^{-9} M, as measured by a PGE2 neutralization assay.

5. The binding protein of any one of claims 1-4, wherein the binding protein is capable of binding:

(a) TNF and PGE2, wherein the binding protein comprises:

SEQ ID NOs: 114 and 115,

SEQ ID NOs: 116 and 117,

SEQ ID NOs: 118 and 119, or

SEQ ID NOs: 120 and 121;

(b) NGF and PGE2, wherein the binding protein comprises:

SEQ ID NOs: 132 and 133, or

SEQ ID NOs: 134 and 135;

(c) IL-17A and PGE2, wherein the binding protein comprises:

SEQ ID NOs: 136 and 137, or

SEQ ID NOs: 138 and 139;

(d) IL-1b and PGE2, wherein the binding protein comprises:

SEQ ID NOs: 140 and 141, or

SEQ ID NOs: 142 and 143;

(e) IL-6R and PGE2, wherein the binding protein comprises:

SEQ ID NOs: 172 and 173, or

SEQ ID NOs: 174 and 175;

(f) VEGF and PGE2, wherein the binding protein comprises:

SEQ ID NOs: 128 and 129, or

SEQ ID NOs: 130 and 131;

(g) Abeta and PGE2, wherein the binding protein comprises:

SEQ ID NOs: 148 and 149, or

SEQ ID NOs: 150 and 151;

or

(h) IL-15 and PGE2, wherein the binding protein comprises:

SEQ ID NOs: 164 and 165, or

SEQ ID NOs: 166 and 167.

6. The binding protein of any one of claims 1-5, wherein the binding protein is capable of binding:

(a) TNF and PGE2, wherein the binding protein comprises:

DVD HU2B5.7SLD2E7 (comprising SEQ ID NOs: 114 and 115),

DVD HU2B5.7LLD2E7 (comprising SEQ ID NOs: 116 and 117),

DVD D2E7SLHU2B5.7 (comprising SEQ ID NOs: 118 and 119), or

DVD D2E7LLHU2B5.7 (comprising SEQ ID NOs: 120 and 121);

(b) NGF and PGE2, wherein the binding protein comprises:

DVD 164 (comprising SEQ ID NOs: 132 and 133), or

DVD 163 (comprising SEQ ID NOs: 134 and 135);

(c) IL-17A and PGE2, wherein the binding protein comprises:

DVD 156 (comprising SEQ ID NOs: 136 and 137), or

DVD 155 (comprising SEQ ID NOs: 138 and 139);

(d) IL-1b and PGE2, wherein the binding protein comprises:

DVD 158 (comprising SEQ ID NOs: 140 and 141), or

DVD 157 (comprising SEQ ID NOs: 142 and 143);

(e) IL-6R and PGE2, wherein the binding protein comprises:

DVD 152 (comprising SEQ ID NOs: 172 and 173), or

DVD 151 (comprising SEQ ID NOs: 174 and 175);

(f) VEGF and PGE2, wherein the binding protein comprises:

DVD 162 (comprising SEQ ID NOs: 128 and 129), or

DVD 161 (comprising SEQ ID NOs: 130 and 131);

(g) Abeta and PGE2, wherein the binding protein comprises:

DVD 227 (comprising SEQ ID NOs: 148 and 149), or

DVD 228 (comprising SEQ ID NOs: 150 and 151);

or

(h) IL-15 and PGE2, wherein the binding protein comprises:

DVD 154 (comprising SEQ ID NOs: 164 and 165), or

DVD 153 (comprising SEQ ID NOs: 166 and 167).

7. The binding protein of any one of claims 1-4, wherein

(a) X1 is not CH1 or CL;

(b) X1 comprises one or more of SEQ ID NOs: 1-26;

(c) the binding protein is a crystalized binding protein;

(d) the Fc region is a native sequence Fc region or a variant sequence Fc region; and/or

(e) the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD.

8. The binding protein of any one of claims 1-7, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains, forming four functional target binding sites.

9. The binding protein of any one of claims 1-8, comprising first and second polypeptide chains, wherein the first polypeptide chain comprises a first VD1-(XI)n-VD2-C-(X2)n, wherein

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

X1 is a linker;

X2 is an Fc region; and

n is 0 or 1; and

wherein the second polypeptide chain comprises a second VD1-(XI)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

X1 is a linker;

n is 0 or 1 for (X1)n; and

n is 0 for (X2)n.

10. A binding protein conjugate comprising the binding protein of any one of claims 1-9, and an agent selected from the group consisting of an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent, wherein:

(a) the imaging agent is selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin, and wherein the radiolabel is optionally selected from the group consisting of ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm; or

(b) the therapeutic or cytotoxic agent is selected from the group consisting of an antimetabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

11. An isolated nucleic acid encoding the binding protein amino acid sequence of any one of claims 1-9.

12. A vector comprising the isolated nucleic acid of claim 11, wherein the vector is optionally selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, and pBJ.

13. An isolated host cell comprising the vector of claim 12, wherein the host cell is optionally a prokaryotic cell, an *Escherichia coli* cell, a eukaryotic cell, a protist cell, an animal cell, a plant cell, a fungal cell, a mammalian cell, an avian cell, an insect cell, a CHO cell, a COS cell, a yeast cell, a *Saccharomyces cerevisiae,* or an insect Sf9 cell.

14. A method of producing a binding protein, comprising culturing the host cell of claim 13 in culture medium under conditions sufficient to produce the binding protein.

15. A pharmaceutical composition comprising the binding protein of any one of claims 1-9 or the binding protein conjugate of claim 10, and a pharmaceutically acceptable carrier; wherein the pharmaceutical composition optionally further comprising at least one additional therapeutic agent; and wherein the additional therapeutic agent is optionally selected from the group consisting of: a therapeutic agent; an imaging agent; a cytotoxic agent, angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an antirheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

16. A method of determining the presence, amount, or concentration of at least one target or fragment thereof in a test sample by an immunoassay,

wherein the immunoassay comprises contacting the test sample with at least one binding protein and at least one detectable label; and

wherein the at least one binding protein comprises the binding protein of any one of claims 1-9.

17. The method of claim 16 further comprising:

(a) contacting the test sample with at least one binding protein, wherein the binding protein binds to an epitope on the target or fragment thereof so as to form a first complex;

(b) contacting the complex with at least one detectable label, wherein the detectable label binds to the binding protein or an epitope on the target or fragment thereof that is not bound by the binding protein to form a second complex; and

(c) detecting the presence, amount, or concentration of the target or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence, amount, or concentration of the target or fragment thereof is directly correlated with the signal generated by the detectable label.

18. The method of claim 16, further comprising:

(a) contacting the test sample with at least one binding protein, wherein the binding protein binds to an epitope on the target or fragment thereof so as to form a first complex;

(b) contacting the complex with at least one detectable label, wherein the detectable label competes with the target or fragment thereof for binding to the binding protein so as to form a second complex; and

(c) detecting the presence, amount, or concentration of the target or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence, amount, or concentration of the target or fragment thereof is indirectly correlated with the signal generated by the detectable label.

19. A kit for assaying a test sample for the presence, amount, or concentration of a target or fragment thereof, the kit comprising:

(a) instructions for assaying the test sample for the target or fragment thereof; and

(b) at least one binding protein comprising the binding protein of any one of claims 1-9.

20. Use of a binding protein of any one of claims 1-9 or a binding protein conjugate of claim 10 for the manufacture of a medicament for the treatment of a disease or a disorder.

21. The use according to claim 20 wherein said disorder is selected from the group comprising rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthropathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, spondyloarthopathy, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis B, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis

associated lung disease, Sjogren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, fibrosis, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, post-infectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-I autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycaemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthrosis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, Lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjorgren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo acute liver disease, chronic liver diseases, alcoholic cirrhosis, alcohol-induced liver injury, choleosatatis, idiosyncratic liver disease, drug-induced hepatitis, non-alcoholic steatohepatitis, allergy and asthma, group B streptococci (GBS) infection, mental disorders *(e.g.,* depression and schizophrenia), Th2 Type and Th1 Type mediated diseases, acute and chronic pain (different forms of pain), and cancers such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma) abetalipoprotemia, acrocyanosis, acute and chronic parasitic or infectious processes, acute leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute or chronic bacterial infection, acute pancreatitis, acute renal failure, adenocarcinomas, aerial ectopic beats, AIDS dementia complex, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allograft rejection, alpha-1-antitrypsin deficiency, amyotrophic lateral sclerosis, anemia, angina pectoris, anterior horn cell degeneration, anti cd3 therapy, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneuryisms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell

lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, Burns, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chronic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, cor pulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, Dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic arteriosclerotic disease, Diffuse Lewy body disease, dilated congestive cardiomyopathy, disorders of the basal ganglia, Down's Syndrome in middle age, drug- induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hematophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, fungal sepsis, gas gangrene, gastric ulcer, glomerular nephritis, graft rejection of any organ or tissue, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, hairy cell leukemia, Hallervorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, hepatitis (A), His bundle arrhythmias, HIV infection/HIV neuropathy, Hodgkin's disease, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, antibody mediated cytotoxicity, Asthenia, infantile spinal muscular atrophy, inflammation of the aorta, influenza a, ionizing radiation exposure, iridocyclitis/uveitis/optic neuritis, ischemia- reperfusion injury, ischemic stroke, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, lipedema, liver transplant rejection, lymphederma, malaria, malignant Lymphoma, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, metabolic/idiopathic, migraine headache, mitochondrial multisystem disorder, mixed connective tissue disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel Dejerine-Thomas Shi-Drager and Machado-Joseph), myasthenia gravis, mycobacterium avium

intracellulare, mycobacterium tuberculosis, myelodyplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, neurodegenerative diseases, neurogenic I muscular atrophies , neutropenic fever, non-Hodgkins lymphoma, occlusion of the abdominal aorta and its branches, occulsive arterial disorders, okt3 therapy, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoporosis, pancreas transplant rejection, pancreatic carcinoma, paraneoplastic syndrome/hypercalcemia of malignancy, parathyroid transplant rejection, pelvic inflammatory disease, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, preeclampsia, progressive supranucleo palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon and disease, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, senile dementia of Lewy body type, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrhythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, subacute sclerosing panencephalitis, Syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T -cell or F AB ALL, Telangiectasia, thromboangitis obliterans, thrombocytopenia, toxicity, transplants, trauma/hemorrhage, type III hypersensitivity reactions, type IV hypersensitivity, unstable angina, uremia, urosepsis, urticaria, valvular heart diseases, varicose veins, ,vasculitis, venous diseases, venous thrombosis, ventricular fibrillation, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, acute coronary syndromes, acute idiopathic polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, alopecia areata, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, arteriosclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic

ischemia, cicatricial pemphigoid, clinically isolated syndrome (cis) with risk for multiple sclerosis, conjunctivitis, childhood onset psychiatric disorder, chronic obstructive pulmonary disease (COPD), dacryocystitis, dermatomyositis, diabetic retinopathy, diabetes mellitus, disk herniation, disk prolapse, drug-induced immune hemolytic anemia, endocarditis, endometriosis, endophthalmitis, episcleritis, erythema multiforme, erythema multiforme major, gestational pemphigoid, Guillain-Barre syndrome (GBS), hay fever, Hughes syndrome, idiopathic Parkinson's disease, idiopathic interstitial pneumonia, IgE-mediated allergy, immune hemolytic anemia, inclusion body myositis, infectious ocular inflammatory disease, inflammatory demyelinating disease, inflammatory heart disease, inflammatory kidney disease, IPF/UIP, iritis, keratitis, keratojuntivitis sicca, Kussmaul disease or Kussmaul-Meier disease, Landry's paralysis, Langerhan's cell histiocytosis, livedo reticularis, macular degeneration, microscopic polyangiitis, morbus bechterev, motor neuron disorders, mucous membrane pemphigoid, multiple organ failure, myasthenia gravis, myelodysplastic syndrome, myocarditis, nerve root disorders, neuropathy, non-A non-B hepatitis, optic neuritis, osteolysis, ovarian cancer, pauciarticular JRA, peripheral artery occlusive disease (PAOD), peripheral vascular disease (PVD), peripheral artery, disease (PAD), phlebitis, polyarteritis nodosa (or periarteritis nodosa), polychondritis, polymyalgia rheumatica, poliosis, polyarticular JRA, polyendocrine deficiency syndrome, polymyositis, polymyalgia rheumatica (PMR), post-pump syndrome, primary Parkinsonism, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), prostatitis, pure red cell aplasia, primary adrenal insufficiency, recurrent neuromyelitis optica, restenosis, rheumatic heart disease, sapho (synovitis, acne, pustulosis, hyperostosis, and osteitis), scleroderma, secondary amyloidosis, shock lung, scleritis, sciatica, secondary adrenal insufficiency, silicone associated connective tissue disease, Sneddon-Wilkinson dermatosis, spondilitis ankylosans, Stevens-Johnson syndrome (SJS), systemic inflammatory response syndrome, temporal arteritis, toxoplasmic retinitis, toxic epidermal necrolysis, transverse myelitis, TRAPS (tumor necrosis factor receptor associated periodic syndrome), type 1 allergic reaction, type II diabetes, urticaria, usual interstitial pneumonia (UIP), vasculitis, vernal conjunctivitis, viral retinitis, Vogt-Koyanagi-Harada syndrome (VKH syndrome), wet macular degeneration, wound healing, yersinia and salmonella associated arthropathy.

We claim:

1. A binding protein comprising first and second polypeptide chains, each independently comprising VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first variable domain;

VD2 is a second variable domain;

C is a constant domain;

X1 is a linker;

X2 is an Fc region; and

n is 0 or 1;

wherein the VD1 domains on the first and second polypeptide chains form a first functional target binding site and the VD2 domains on the first and second polypeptide chains form a second functional target binding site, and wherein the binding protein is capable of binding:

(a) TNF and PGE2, wherein:

(1) the variable domains that form a functional binding site for TNF comprise

CDRs 1-3 from SEQ ID NO: 112 and CDRs 1-3 from SEQ ID NO: 113, or

CDRs 1-3 from SEQ ID NO: 87 and CDRs 1-3 from SEQ ID NO: 90,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(b) NGF and PGE2, wherein:

(1) the variable domains that form a functional binding site for NGF comprise

CDRs 1-3 from SEQ ID NO: 32 and CDRs 1-3 from SEQ ID NO: 33,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(c) IL-17A and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-17A comprise

CDRs 1-3 from SEQ ID NO: 34 and CDRs 1-3 from SEQ ID NO: 35,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(d) IL-1b and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-1b comprise

CDRs 1-3 from SEQ ID NO: 36 and CDRs 1-3 from SEQ ID NO: 37,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(e) IL-6R and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-6R comprise

CDRs 1-3 from SEQ ID NO: 54 and CDRs 1-3 from SEQ ID NO: 55,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(f) VEGF and PGE2, wherein:

(1) the variable domains that form a functional binding site for VEGF comprise

CDRs 1-3 from SEQ ID NO: 28 and CDRs 1-3 from SEQ ID NO: 29,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(g) Abeta and PGE2, wherein:

(1) the variable domains that form a functional binding site for Abeta comprise

CDRs 1-3 from SEQ ID NO: 40 and CDRs 1-3 from SEQ ID NO: 41,

CDRs 1-3 from SEQ ID NO: 42 and CDRs 1-3 from SEQ ID NO: 43, or

CDRs 1-3 from SEQ ID NO: 44 and CDRs 1-3 from SEQ ID NO: 45,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(h) IL-15 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-15 comprise CDRs 1-3 from SEQ ID NO: 50 and CDRs 1-3 from SEQ ID NO: 51,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49, CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111, CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81, CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(i) IL-6 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-6 comprise CDRs 1-3 from SEQ ID NO: 38 and CDRs 1-3 from SEQ ID NO: 39,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49, CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111, CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81, CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(j) IL-18 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-18 comprise CDRs 1-3 from SEQ ID NO: 46 and CDRs 1-3 from SEQ ID NO: 47,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49, CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111, CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(k) PGE2 and PGE2, wherein the variable domains that form each functional target binding site independently comprise:

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(l) S1P and PGE2, wherein:

(1) the variable domains that form a functional binding site for S1P comprise

CDRs 1-3 from SEQ ID NO: 52 and CDRs 1-3 from SEQ ID NO: 53,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

(m) EGFR and PGE2, wherein:

(1) the variable domains that form a functional binding site for EGFR comprise

CDRs 1-3 from SEQ ID NO: 56 and CDRs 1-3 from SEQ ID NO: 57, or

CDRs 1-3 from SEQ ID NO: 58 and CDRs 1-3 from SEQ ID NO: 59,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85;

or

(n) IGFR and PGE2, wherein:

(1) the variable domains that form a functional binding site for IGFR comprise

CDRs 1-3 from SEQ ID NO: 60 and CDRs 1-3 from SEQ ID NO: 61,

and/or

(2) the variable domains that form a functional binding site for PGE2 comprise

CDRs 1-3 from SEQ ID NO: 48 and CDRs 1-3 from SEQ ID NO: 49,

CDRs 1-3 from SEQ ID NO: 110 and CDRs 1-3 from SEQ ID NO: 111,

CDRs 1-3 from SEQ ID NO: 80 and CDRs 1-3 from SEQ ID NO: 81,

CDRs 1-3 from SEQ ID NO: 82 and CDRs 1-3 from SEQ ID NO: 83, or

CDRs 1-3 from SEQ ID NO: 84 and CDRs 1-3 from SEQ ID NO: 85.

2. A binding protein comprising first and second polypeptide chains, each independently comprising VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first variable domain;

VD2 is a second variable domain;

C is constant domain;

X1 is a linker;

X2 is an Fc region; and

n is 0 or 1;

wherein the VD1 domains on the first and second polypeptide chains form a first functional target binding site and the VD2 domains on the first and second polypeptide chains form a second functional target binding site, and wherein the binding protein is capable of binding:

(a) TNF and PGE2, wherein:

(1) the variable domains that form a functional binding site for TNF comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 112, 113, 87, and 90;

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(b) NGF and PGE2, wherein:

(1) the variable domains that form a functional binding site for NGF comprise SEQ ID NOs: 32 and/or 33,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(c) IL-17A and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-17A comprise SEQ ID NOs: 34 and/or 35,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(d) IL-1b and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-1b comprise SEQ ID NOs: 36 and/or 37,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(e) IL-6R and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-6R comprise SEQ ID NOs: 54 and/or 55,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(f) VEGF and PGE2, wherein:

(1) the variable domains that form a functional binding site for VEGF comprise SEQ ID NOs: 28 and/or 29,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(g) Abeta and PGE2, wherein:

(1) the variable domains that form a functional binding site for Abeta comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 40, 41, 42, 43, 44, and 45

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(h) IL-15 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-15 comprise SEQ ID NOs: 50 and/or 51,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(i) IL-6 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-6 comprise SEQ ID NOs: 38 and/or 39,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(j) IL-18 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-18 comprise SEQ ID NOs: 46 and/or 47,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(k) PGE2 and PGE2, wherein

the variable domains that form each functional target binding site independently comprise amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(l) S1P and PGE2, wherein:

(1) the variable domains that form a functional binding site for S1P comprise SEQ ID NOs: 52 and/or 53,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

(m) EGFR and PGE2, wherein:

(1) the variable domains that form a functional binding site for EGFR an amino acid sequence selected from the group consisting of SEQ ID NOs: 56, 57, 58, and 59,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85;

or

(n) IGFR and PGE2, wherein:

(1) the variable domains that form a functional binding site for IGFR comprise CDRs 1-3 from SEQ ID NO: 60 and CDRs 1-3 from SEQ ID NO: 61,

and

(2) the variable domains that form a functional binding site for PGE2 comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 49, 110, 111, 80, 81, 82, 83, 84, and 85.

3. The binding protein according to claim 1 or 2, wherein the binding protein is capable of binding:

(a) TNF and PGE2, wherein:

(1) the variable domains that form a functional binding site for TNF comprise

SEQ ID NO: 112 and SEQ ID NO: 113, or

SEQ ID NO: 87 and SEQ ID NO: 90,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(b) NGF and PGE2, wherein:

(1) the variable domains that form a functional binding site for NGF comprise

SEQ ID NO: 32 and SEQ ID NO: 33,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(c) IL-17A and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-17A comprise

SEQ ID NO: 34 and SEQ ID NO: 35,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(d) IL-1b and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-1b comprise

SEQ ID NO: 36 and SEQ ID NO: 37,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(e) IL-6R and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-6R comprise

SEQ ID NO: 54 and SEQ ID NO: 55,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(f) VEGF and PGE2, wherein:

(1) the variable domains that form a functional binding site for VEGF comprise

SEQ ID NO: 28 and SEQ ID NO: 29,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(g) Abeta and PGE2, wherein:

(1) the variable domains that form a functional binding site for Abeta comprise

SEQ ID NO: 40 and SEQ ID NO: 41,

SEQ ID NO: 42 and SEQ ID NO: 43, or

SEQ ID NO: 44 and SEQ ID NO: 45,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(h) IL-15 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-15 comprise

SEQ ID NO: 50 and SEQ ID NO: 51,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(i) IL-6 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-6 comprise

SEQ ID NO: 38 and SEQ ID NO: 39,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(j) IL-18 and PGE2, wherein:

(1) the variable domains that form a functional binding site for IL-18 comprise

SEQ ID NO: 46 and SEQ ID NO: 47,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(k) PGE2 and PGE2, wherein the variable domains that form each functional target binding site independently comprise:

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(l) S1P and PGE2, wherein:

(1) the variable domains that form a functional binding site for S1P comprise

SEQ ID NO: 52 and SEQ ID NO: 53,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

(m) EGFR and PGE2, wherein:

(1) the variable domains that form a functional binding site for EGFR comprise

SEQ ID NO: 56 and SEQ ID NO: 57, or

SEQ ID NO: 58 and SEQ ID NO: 59,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85;

or

(n) IGFR and PGE2, wherein:

(1) the variable domains that form a functional binding site for IGFR comprise

SEQ ID NO: 60 and SEQ ID NO: 61,

and

(2) the variable domains that form a functional binding site for PGE2 comprise

SEQ ID NO: 48 and SEQ ID NO: 49,

SEQ ID NO: 110 and SEQ ID NO: 111,

SEQ ID NO: 80 and SEQ ID NO: 81,

SEQ ID NO: 82 and SEQ ID NO: 83, or

SEQ ID NO: 84 and SEQ ID NO: 85.

4. The binding protein according to any one of claims 1-3, wherein:

(a) the first polypeptide chain comprises a first VD1-(X1)n-VD2-C-(X2)n, wherein:

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

X1 is a linker;

X2 is an Fc region; and

n is 0 or 1; and

(b) the second polypeptide chain comprises a second VD1-(X1)n-VD2-C-(X2)n, wherein:

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

X1 is a linker;

n is 1 for (X1)n; and

n is 0 for (X2)n.

5. The binding protein according to any one of claims 1-4, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains, forming four functional target binding sites.

6. A binding protein capable of binding:

(a) TNF and PGE2, wherein the binding protein comprises any one of:

DVD HU2B5.7SLD2E7 (comprising SEQ ID NOs: 114 and 115),

DVD HU2B5.7LLD2E7 (comprising SEQ ID NOs: 116 and 117),

DVD D2E7SLHU2B5.7 (comprising SEQ ID NOs: 118 and 119),

DVD D2E7LLHU2B5.7 (comprising SEQ ID NOs: 120 and 121),

DVD 8C11-mNL-2B5 (comprising SEQ ID NOs: 86 and 89),

DVD 8C11-mSL-2B5 (comprising SEQ ID NOs: 92 and 93),

DVD 8C11-mLL-2B5 (comprising SEQ ID NOs: 94 and 95),

DVD 2B5-mNL-8C11 (comprising SEQ ID NOs: 96 and 97),

DVD 2B5-mSL-8C11 (comprising SEQ ID NOs: 98 and 99),

DVD 2B5-mLL-8C11 (comprising SEQ ID NOs: 100 and 101),

DVD 8C11-hSL-2B5 (comprising SEQ ID NOs: 102 and 103),

DVD 8C11-hLL-2B5 (comprising SEQ ID NOs: 104 and 105),

DVD 2B5-hSL-8C11 (comprising SEQ ID NOs: 106 and 107),

DVD 2B5-hLL-8C11 (comprising SEQ ID NOs: 108 and 109);

(b) NGF and PGE2, wherein the binding protein comprises any one of:

DVD 164 (comprising SEQ ID NOs: 132 and 133), and

DVD 163 (comprising SEQ ID NOs: 134 and 135);

(c) IL-17A and PGE2, wherein the binding protein comprises any one of:

DVD 156 (comprising SEQ ID NOs: 136 and 137), and

DVD 155 (comprising SEQ ID NOs: 138 and 139);

(d) IL-1b and PGE2, wherein the binding protein comprises any one of:

DVD 158 (comprising SEQ ID NOs: 140 and 141), and

DVD 157 (comprising SEQ ID NOs: 142 and 143);

(e) IL-6R and PGE2, wherein the binding protein comprises any one of:

DVD 250 (comprising SEQ ID NOs: 144 and 145), and

DVD 249 (comprising SEQ ID NOs: 146 and 147);

(f) VEGF and PGE2, wherein the binding protein comprises any one of:

DVD 162 (comprising SEQ ID NOs: 128 and 129), and

DVD 161 (comprising SEQ ID NOs: 130 and 131);

(g) Abeta and PGE2, wherein the binding protein comprises any one of:

DVD 227 (comprising SEQ ID NOs: 148 and 149),

DVD 228 (comprising SEQ ID NOs: 150 and 151),

DVD 199 (comprising SEQ ID NOs: 152 and 153),

DVD 200 (comprising SEQ ID NOs: 154 and 155),

DVD 213 (comprising SEQ ID NOs: 156 and 157), and

DVD 214 (comprising SEQ ID NOs: 158 and 159);

(h) IL-15 and PGE2, wherein the binding protein comprises any one of:

DVD 154 (comprising SEQ ID NOs: 164 and 165), and

DVD 153 (comprising SEQ ID NOs: 166 and 167);

(i) IL-6 and PGE2, wherein the binding protein comprises any one of:

DVD 250 (comprising SEQ ID NOs: 144 and 145), and

DVD 249 (comprising SEQ ID NOs: 146 and 147);

(j) IL-18 and PGE2, wherein the binding protein comprises any one of:

DVD 241 (comprising SEQ ID NOs: 160 and 161), and

DVD 242 (comprising SEQ ID NOs: 162 and 163);

or

(k) S1P and PGE2, wherein the binding protein comprises any one of:

DVD 252 (comprising SEQ ID NOs: 168 and 169), and

DVD 251 (comprising SEQ ID NOs: 170 and 171).

7. The binding protein according to any one of claims 1-6 wherein the binding protein is capable of binding:

(a) TNF and PGE2, wherein the binding protein:

(1) inhibits TNF with an IC_{50} of at least 14×10^{-12} M, as measured by direct bind ELISA, and/or

binds TNF with a dissociation constant (K_D) of at most 806×10^{-12} M, as measured by surface plasmon resonance;

and/or

(2) inhibits PGE2 with an IC_{50} of at least 45×10^{-12} M, as measured by direct bind ELISA, and/or

binds PGE2 with a dissociation constant (K_D) of at most 261 x 10^{-12} M, as measured by surface plasmon resonance;

(b) NGF and PGE2, wherein the binding protein:

(1) inhibits NGF with an EC_{50} of at most 1.21 x 10^{-9} M, as measured by direct bind ELISA, and/or

binds NGF with a dissociation constant (K_D) of at most 2.48 x 10^{-10} M, as measured by surface plasmon resonance;

and/or

(2) inhibits PGE2 with an EC_{50} of at most 1.3 x 10^{-9} M, as measured by direct bind ELISA, and/or

neutralizes PGE2 with an EC_{50} of at most 0.079 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(c) IL-17A and PGE2, wherein the binding protein:

(1) inhibits IL-17A with an EC_{50} of at most 248.1 x 10^{-9} M, as measured by direct bind ELISA, and/or

binds IL-17A with a dissociation constant (K_D) of at most 3.37 x 10^{-9} M, as measured by surface plasmon resonance;

and/or

(2) inhibits PGE2 with an EC_{50} of at most 1.55 x 10^{-9} M, as measured by direct bind ELISA, and/or

neutralizes PGE2 with an EC_{50} of at most 0.025 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(d) IL-1b and PGE2, wherein the binding protein:

(1) inhibits IL-1b with an EC_{50} of at most 2480.71 x 10^{-9} M, as measured by direct bind ELISA,

binds IL-1b with a dissociation constant (K_D) of at most 3.87 x 10^{-11} M, as measured by surface plasmon resonance, and/or

neutralizes IL-1b with an EC_{50} of at most 3.22 x 10^{-9} M, as measured by an IL-1b neutralization assay;

and/or

(2) inhibits PGE2 with an EC_{50} of at most 1.23 x 10^{-9} M, as measured by direct bind ELISA, and/or

neutralizes PGE2 with an EC_{50} of at most 0.217 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(e) IL-6R and PGE2, wherein the binding protein:

(1) inhibits IL-6R with an EC_{50} of at most 26,452.34 x 10^{-9} M, as measured by direct bind ELISA,

binds IL-6R with a dissociation constant (K_D) of at most 4.48 x 10^{-10} M, as measured by surface plasmon resonance, and/or

binds IL-6R with a FACS geometric mean of at least 0.21, as measured by flow cytometry;

and/or

(2) inhibits PGE2 with an EC_{50} of at most 1.65 x 10^{-9} M, as measured by direct bind ELISA, and/or

neutralizes PGE2 with an EC_{50} of at most 0.036 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(f) VEGF and PGE2, wherein the binding protein:

(1) inhibits VEGF with an EC_{50} of at most 391.23 x 10^{-9} M, as measured by direct bind ELISA, and/or

binds VEGF with a dissociation constant (K_D) of at most 7.55 x 10^{-10} M, as measured by surface plasmon resonance;

and/or

(2) inhibits PGE2 with an EC_{50} of at most 1.32 x 10^{-9} M, as measured by direct bind ELISA, and/or

inhibits PGE2 with an EC_{50} of at most 0.245 x 10^{-9} M, as measured by a PGE2 neutralization assay;

(g) Abeta and PGE2, wherein the binding protein:

(1) inhibits PGE2 with an EC_{50} of at most 1.21 x 10^{-9} M, as measured by direct bind ELISA; and/or

neutralizes PGE2 with an EC_{50} of at most 0.049 x 10^{-9} M, as measured by a PGE2 neutralization assay;

or

(h) IL-15 and PGE2, wherein the binding protein:

(1) binds IL-15 with a dissociation constant (K_D) of at most 4.89 x 10^{-9} M, as measured by surface plasmon resonance;

and/or

(2) inhibits PGE2 with an EC_{50} of at most 1.54 x 10^{-9} M, as measured by direct bind ELISA, and/or

neutralizes PGE2 with an EC_{50} of at most 0.048 x 10^{-9} M, as measured by a PGE2 neutralization assay.

8. The binding protein according to any one of claims 1-7, wherein:

(a) X1 is not CH or CL;

(b) X1 comprises any one of SEQ ID NOs: 1-27;

(c) the binding protein is a crystallized binding protein;

(d) the Fc region is a variant sequence Fc region;

and/or

(e) the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD.

9. A binding protein conjugate comprising a binding protein according to any one of claims 1-8, the binding protein conjugate further comprising an immunoadhesion molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent, wherein:

(a) the imaging agent is optionally selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin, and wherein said radiolabel is optionally selected from the group consisting of ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm;

or

(b) the therapeutic or cytotoxic agent is optionally selected from the group consisting of an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

10. A pharmaceutical composition comprising the binding protein of any one of claims 1-8, or the binding protein conjugate of claim 9, and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, further comprising at least one additional therapeutic agent, wherein the additional therapeutic agent is optionally selected from the group consisting of an imaging agent, a cytotoxic agent, an angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof, methotrexate, cyclosporin, rapamycin, FK506, a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

12. Use of a binding protein according to any one of claims 1-8 or a binding protein conjugate of claim 9 in the manufacture of a medicament for treating a subject for a disease or disorder.

13. The use according to claim 12, wherein the disease or disorder is rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure,

Addison's disease, sporadic, polyglandular deficiency type I, polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia associated arthropathy, salmonella associated arthropathy, atheromatous disease, arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, acquired immunodeficiency related diseases, hepatitis B, hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis associated lung disease, polymyositis associated lung disease, Sjögren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, fibrosis, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, post-infectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycaemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthrosis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, Lyme disease, discoid lupus erythematosus, male infertility idiopathic, male infertility NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjörgren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis,

vitiligo acute liver disease, chronic liver disease, alcoholic cirrhosis, alcohol-induced liver injury, choleosatatis, idiosyncratic liver disease, drug-induced hepatitis, non-alcoholic steatohepatitis, allergy, asthma, group B streptococci (GBS) infection, mental disorders, depression, schizophrenia, Th2 type mediated disease, Th1 type mediated disease, acute pain, chronic pain, different forms of pain, cancer, lung cancer, breast cancer, stomach cancer, bladder cancer, colon cancer, pancreatic cancer, ovarian cancer, prostate cancer, rectal cancer, hematopoietic malignancies, leukemia, lymphoma, Abetalipoprotemia, acrocyanosis, acute and chronic parasitic or infectious processes, acute leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute bacterial infection, chronic bacterial infection, acute pancreatitis, acute renal failure, adenocarcinomas, aerial ectopic beats, AIDS dementia complex, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allograft rejection, alpha-l-antitrypsin deficiency, amyotrophic lateral sclerosis, anemia, angina pectoris, anterior horn cell degeneration, anti cd3 therapy, anti-phospholipid syndrome, anti-receptor hypersensitivity reactions, aortic aneurysm, peripheral aneurysm, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, sustained atrial fibrillation, paroxysmal atrial fibrillation, atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, burns, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chronic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, cor pulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic arteriosclerotic disease, diffuse Lewy body disease, dilated congestive cardiomyopathy, disorders of the basal ganglia, Down's syndrome in middle age, drug-induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hematophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, fungal sepsis, gas gangrene, gastric ulcer, glomerular nephritis, graft rejection of any organ, graft rejection of any tissue, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, hairy cell leukemia, Hallervorden-Spatz disease, Hashimoto's thyroiditis, hay

fever, heart transplant rejection, hemachromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, hepatitis A, His bundle arrhythmias, HIV infection, HIV neuropathy, Hodgkin's disease, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, antibody mediated cytotoxicity, Asthenia, infantile spinal muscular atrophy, inflammation of the aorta, influenza A, ionizing radiation exposure, iridocyclitis, uveitis, optic neuritis, ischemia- reperfusion injury, ischemic stroke, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, lipedema, liver transplant rejection, lymphederma, malaria, malignant lymphoma, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, metabolic/idiopathic, migraine headache, mitochondrial multisystem disorder, mixed connective tissue disease, monoclonal gammopathy, multiple myeloma, multiple systems degeneration, Mencel degeneration, Dejerine-Thomas degeneration, Shi-Drager degeneration, Machado-Joseph degeneration, myasthenia gravis, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodyplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, neurodegenerative diseases, neurogenic muscular atrophies, neutropenic fever, non-Hodgkin's lymphoma, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, okt3 therapy, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoporosis, pancreas transplant rejection, pancreatic carcinoma, paraneoplastic syndrome/hypercalcemia of malignancy, parathyroid transplant rejection, pelvic inflammatory disease, perennial rhinitis, pericardial disease, peripheral atherlosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, preeclampsia, progressive supranucleo palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon and disease, Raynoud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, senile dementia of Lewy body type, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrhythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, subacute sclerosing panencephalitis, syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile

rheumatoid arthritis, T-cell or FAB ALL, telangiectasia, thromboangitis obliterans, thrombocytopenia, toxicity, transplants, trauma, hemorrhage, type III hypersensitivity reactions, type IV hypersensitivity, unstable angina, uremia, urosepsis, urticaria, valvular heart diseases, varicose veins, vasculitis, venous diseases, venous thrombosis, ventricular fibrillation, viral infections, fungal infections, vital encephalitis, aseptic meningitis, vital-associated hemaphagocytic syndrome, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ, xenograft rejection of any tissue, acute coronary syndromes, acute idiopathic polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic ischemia, cicatricial pemphigoid, clinically isolated syndrome (cis) with risk for multiple sclerosis, childhood onset psychiatric disorder, dacryocystitis, dermatomyositis, diabetic retinopathy, disk herniation, disk prolapse, drug induced immune hemolytic anemia, endometriosis, endophthalmitis, episcleritis, erythema multiforme, erythema multiforme major, gestational pemphigoid, Guillain-Barré syndrome (GBS), Hughes syndrome, idiopathic Parkinson's disease, idiopathic interstitial pneumonia, IgE-mediated allergy, immune hemolytic anemia, inclusion body myositis, infectious ocular inflammatory disease, inflammatory demyelinating disease, inflammatory heart disease, inflammatory kidney disease, IPF/UIP, iritis, keratitis, keratojuntivitis sicca, Kussmaul disease or Kussmaul-Meier disease, Landry's paralysis, Langerhan's cell histiocytosis, livedo reticularis, macular degeneration, microscopic polyangiitis, morbus bechterev, motor neuron disorders, mucous membrane pemphigoid, multiple organ failure, myelodysplastic syndrome, myocarditis, nerve root disorders, neuropathy, non-A non-B hepatitis, optic neuritis, osteolysis, pauciarticular JRA, peripheral artery occlusive disease (PAOD), peripheral vascular disease (PVD), peripheral artery disease (PAD), phlebitis, polyarteritis nodosa, periarteritis nodosa, polychondritis, polymyalgia rheumatica, poliosis, polyarticular JRA, polyendocrine deficiency syndrome, polymyositis, polymyalgia rheumatica (PMR), primary Parkinsonism, prostatitis, pure red cell aplasia, primary adrenal insufficiency, recurrent neuromyelitis optica, restenosis, rheumatic heart disease, sapho (synovitis, acne, pustulosis, hyperostosis, and osteitis), secondary amyloidosis, shock lung, scleritis, sciatica, secondary adrenal insufficiency, silicone associated connective tissue disease, Sneddon-Wilkinson dermatosis, spondilitis ankylosans, Stevens-Johnson syndrome (SJS), temporal arteritis, toxoplasmic retinitis, toxic epidermal necrolysis, transverse myelitis, TRAPS (tumor

necrosis factor receptor-associated periodic syndrome), type 1 allergic reaction, type II diabetes, usual interstitial pneumonia (UIP), vasculitis, vernal conjunctivitis, viral retinitis, Vogt-Koyanagi-Harada syndrome (VKH syndrome), wet macular degeneration, or wound healing.

14. The use according to claim 12 or 13, wherein the medicament is formulated for parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal administration.

15. An isolated nucleic acid encoding a binding protein amino acid sequence according to any one of claims 1-8.

16. A vector comprising an isolated nucleic acid according to claim 15, wherein the vector is optionally selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, pHybE, and pBJ.

17. An isolated host cell comprising a vector according to claim 16, wherein the host cell is optionally selected from the group consisting of a prokaryotic cell, an *E. coli* cell, a eukaryotic cell, a protist cell, an animal cell, a plant cell, a fungal cell, a mammalian cell, a yeast cell, an avian cell, an insect cell, a CHO cell, a COS cell, a *S. cerevisiae* cell, and an Sf9 cell.

18. A method of producing a binding protein, comprising culturing a host cell of claim 17 in culture medium under conditions sufficient to produce the binding protein.

19. A method of determining the presence, amount, or concentration of at least one target or fragment thereof in a test sample by an immunoassay,

wherein the immunoassay comprises contacting the test sample with at least one binding protein and at least one detectable label; and

wherein the at least one binding protein comprises the binding protein of any one of claims 1-8, or the conjugate of claim 9.

20. The method of claim 19, further comprising:

(a) contacting the test sample with the at least one binding protein, wherein the binding protein binds to an epitope on the target or fragment thereof so as to form a first complex;

(b) contacting the complex with the at least one detectable label, wherein the detectable label binds to the binding protein or an epitope on the target or fragment thereof that is not bound by the binding protein to form a second complex; and

(c) detecting the presence, amount, or concentration of the target or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence, amount, or concentration of the target or fragment thereof is directly correlated with the signal generated by the detectable label.

21. The method of claim 19, further comprising:

(a) contacting the test sample with the at least one binding protein, wherein the binding protein binds to an epitope on the target or fragment thereof so as to form a first complex;

(b) contacting the complex with the at least one detectable label, wherein the detectable label competes with the target or fragment thereof for binding to the binding protein so as to form a second complex; and

(c) detecting the presence, amount, or concentration of the target or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence, amount, or concentration of the target or fragment thereof is indirectly correlated with the signal generated by the detectable label.

22. A kit for assaying a test sample for the presence, amount, or concentration of a target or fragment thereof, the kit comprising instructions for assaying the test sample for the target or fragment thereof and at least one binding protein comprising the binding protein of any one of claims 1-8, or the binding protein conjugate of claim 9.