IL-7, IL-8, IL-12, IL-13, IL-15, IL-16, IL-18, IL-23, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD-19, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1β converting enzyme inhibitors, TNFα-converting enzyme inhibitors, T-cell signalling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, antiinflammatory cytokines, IL-4, IL-10, IL-11, IL-13, and TGFβ.

The present disclosure provides a binding protein that specifically binds at least two target proteins, wherein the target proteins comprise TNF-α and IL-17, and the binding protein comprises a polypeptide chain, wherein the polypeptide chain comprises 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 with the proviso that it is not CH1;

X2 is an Fc region;

(X1)n, wherein n is 0 or 1;

(X2)n, wherein n is 0 or 1; and

wherein the binding protein is capable of binding human IL-17 and TNF-α;

wherein the VD1 and the VD2 comprises either

a first CDR-H1 comprising NYGII,

a first CDR-H2 comprising WINTYTGKPTYAQKFQG, and

a first CDR-H3 comprising KLFTTMDVTDNAMDY; and.

or comprises

a second CDR-H1 comprising DYEIH,

a second CDR-H2 comprising VNDPESGGTFYNQKFDG, and

a second CDR-H3 comprising YSKWDSFDGMDY.

The present disclosure provides a binding protein that specifically binds at least two target proteins, wherein the target proteins comprise TNF-α and IL-17, and the binding protein comprises a polypeptide chain, wherein the polypeptide chain comprises 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 with the proviso that it is not CL;

X2 does not comprise an Fc region;

(X1)n, wherein n is 0 or 1;

(X2)n, wherein n is 0 or 1; and

wherein the binding protein is capable of binding human IL-17 and TNF-α;

wherein the VD1 and VD2 comprises either

a first CDR-L1 comprising RASQDISQYLN,

a first CDR-L2 comprising YTSRLQS, and

a first CDR-L3 comprising QQGNTWPPT;

or comprises

a second CDR-L1 comprising RASSGIISYID,

a second CDR-L2 comprising ATFDLAS, and

a second CDR-L3 comprising RQVGSYPET.

The present disclosure provides a binding protein that specifically binds at least two target proteins, wherein the target proteins comprise TNF-α and IL-17, and the binding protein comprises first and second polypeptide chains, wherein 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 first linker with the proviso that it is not CH1;

X2 is an Fc region; and

n is 0 or 1;

wherein the VD1 or VD2 of the first polypeptide chain comprises

a first CDR-H1comprising the amino acid sequence of NYGII;

a first CDR-H2 comprising the amino acid sequence of WINTYTGKPTYAQKFQG; and

a first CDR-H3 comprising the amino acid sequence of KLFTTMDVTDNAMDY;

or comprises

a second CDR-H1 comprising the amino acid sequence of DYEIH;

a second CDR-H2 comprising the amino acid sequence of VNDPESGGTFYNQKFDG; and

a second CDR-H3 comprising the amino acid sequence of YSKWDSFDGMDY; and

wherein 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 second linker with the proviso that it is not a light chain constant domain;

X2 does not comprise an Fc region;

n is 0 or 1; and

wherein the VD1 or VD2 of the second polypeptide chain comprises

a first CDR-L1 comprising the amino acid sequence of RASQDISQYLN;

a first CDR-L2 comprising the amino acid sequence of YTSRLQS; and

a first CDR-L3 comprising the amino acid sequence of QQGNTWPPT;

or comprises

a second CDR-L1 comprising the amino acid sequence of RASSGIISYID;

a second CDR-L2 comprising the amino acid sequence of ATFDLAS; and

a second CDR-L3 comprising the amino acid sequence of RQVGSYPET, wherein both VD1s bind the same target protein and both VD2s bind the same target protein.

The present disclosure provides a binding protein that specifically binds at least two target proteins, wherein the target proteins comprise TNF-α and IL-17, and the binding protein comprises four polypeptide chains, wherein two polypeptide chains comprise 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 first linker linker with the proviso that it is not CH1;

X2 is an Fc region; and

n is 0 or 1;

wherein two polypeptide chains comprise 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 second linker linker with the proviso that it is not a light chain constant domain;

X2 does not comprise an Fc region; and

n is 0 or 1;

wherein the VD1 and VD2 of the two first polypeptide chains comprises either

a first CDR-H1 comprising the amino acid sequence of NYGII;

a first CDR-H2 comprising the amino acid sequence of WINTYTGKPTYAQKFQG; and

a first CDR-H3 comprising the amino acid sequence of KLFTTMDVTDNAMDY;

or comprises

a second CDR-H1comprising the amino acid sequence of DYEIH;

a second CDR-H2 comprising the amino acid sequence of VNDPESGGTFYNQKFDG; and

a second CDR-H3-comprising the amino acid sequence of YSKWDSFDGMDY;

wherein the VD1 and VD2 of the two second polypeptide chains comprises either

a first CDR-L1 comprising the amino acid sequence of RASQDISQYLN;

a first CDR-L2 comprising the amino acid sequence of YTSRLQS; and

a first CDR-L3 comprising the amino acid sequence of QQGNTWPPT;

or comprises

a second CDR-L1 comprising the amino acid sequence of RASSGIISYID (SEQ ID NO: 822);

a second CDR-L2 comprising the amino acid sequence of ATFDLAS (SEQ ID NO: 823); and

a second CDR-L3 comprising the amino acid sequence of RQVGSYPET (SEQ ID NO: 824),

wherein all four VD1s bind the same target protein and all four VD2s bind the same target protein.

The present disclosure provides a binding protein comprising two first polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 660, and two second polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 665.

The present disclosure provides a binding protein conjugate comprising a binding protein as disclosed herein, the binding protein conjugate further comprising an agent selected from the group consisting of: an immunoadhension molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent.

The present disclosure provides the use of the binding protein as disclosed herein in the manufacture of a medicament for treating a subject for a disease or a disorder wherein the medicament is to be administered to the subject such that treatment is achieved.

Brief Description of the Drawings

Figure 1A is a schematic representation of Dual Variable Domain (DVD) constructs and shows the strategy for generation of a DVD-binding protein from two parent antibodies.

Figure 1B is a schematic representation of constructs DVD1-Ig, DVD2-Ig, and two chimeric mono-specific antibody clones.

Detailed Description of the Invention

Multivalent and/or multispecific binding proteins capable of binding two or more antigens are provided. Dual variable domain binding proteins (DVD-binding proteins), and pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors and host cells for making such DVD-binding proteins. Methods of using the DVD-binding proteins to detect specific antigens, either in vitro or in vivo are also provided.

Unless otherwise defined herein, scientific and technical terms used herein have the meanings that are commonly understood by those of ordinary skill in the art. In the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of "or" means "and/or" unless stated otherwise. The use of the term "including", as well as other forms, such as "includes" and "included", is

Claims

We claim:

1. A binding protein comprising a polypeptide chain, wherein the polypeptide chain comprises 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 with the proviso that it is not CH1;

X2 is an Fc region;

(X1)n, wherein n is 0 or 1;

(X2)n, wherein n is 0 or 1; and

wherein

(a) VD1 or VD2 comprises three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the binding protein is capable of binding TNF;

(b) VD1 and VD2 independently comprise three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, or 809,or any one of 36-41, 48-72, or 88-97, and the binding protein is capable of binding TNF;

(c) VD1 comprises three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, or 809,or any one of 36-41, 48-72, or 88-97, and VD2 comprises three CDRs from SEQ ID NO: 30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; or

(d) VD2 comprises three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, or 809,or any one of 36-41, 48-72, or 88-97, and VD1 comprises three CDRs from SEQ ID NO: 30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811.

2. The binding protein of claim 1, wherein

(a) VD1 or VD2 comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, or 809, or any one of 36-41, 88-97, or 48-72, and the binding protein is capable of binding TNF;

(b) VD1 and VD2 independently comprise SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, or 809, or any one of 36-41, 88-97, or 48-72, and the binding protein is capable of binding TNF;

(c) VD1 comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, or 809, or any one of 36-41, 88-97, or 48-72, and VD2 comprises SEQ ID NO: 30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; or

(d) VD2 comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, or 809,or any one of 36-41, 88-97, or 48-72, and VD1 comprises SEQ ID NO: 30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811.

3. A binding protein comprising a polypeptide chain, wherein the polypeptide chain comprises 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 with the proviso that it is not CL;

X2 does not comprise an Fc region;

(X1)n, wherein n is 0 or 1;

(X2)n, wherein n is 0 or 1; and

wherein

(a) VD1 or VD2 comprises three CDRs from SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(b) VD1 and VD2 independently comprise three CDRs from SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(c) VD1 comprises three CDRs from SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and VD2 comprises three CDRs from SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766 or 812;

(d) VD2 comprises three CDRs from SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and VD1 comprises three CDRs from SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766 or 812.

4. The binding protein of claim 3, wherein

(a) VD1 or VD2 comprises SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107 and the binding protein is capable of binding TNF;

(b) VD1 and VD2 independently comprise SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(c) VD1 comprises SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and VD2 comprises SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766 or 812; or

(d) VD2 comprises SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and VD1 comprises SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766 or 812.

5. The binding protein of claim 1 or 3, wherein (X1)n is 0 and/or (X2)n is 0.

6. A binding protein comprising first and second polypeptide chains, wherein 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 first linker;

X2 is an Fc region;

(X1)n, wherein n is 0 or 1;

(X2)n, wherein n is 0 or 1; and

wherein 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 second linker;

X2 does not comprise an Fc region;

(X1)n, wherein n is 0 or 1;

(X2)n, wherein n is 0 or 1; and

wherein the first and second X1 linker are the same or different;

wherein the first X1 linker is not CH1 and/or the second X1 linker is not CL and

wherein

(a) the VD1 or VD2 heavy chain variable domain comprises three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 or VD2 light chain variable domain comprises three CDRs from SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(b) the VD1 and VD2 heavy chain variable domains independently comprise three CDRs from SEQ ID NO:541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 and VD2 light chain variable domains independently comprise three CDRs from SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(c) the VD1 heavy chain variable domain comprises three CDRs from SEQ ID NO:541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD2 heavy chain variable domain comprises three CDRs from SEQ ID NO:30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553,

563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD1 light chain variable domain comprises three CDRs from SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD2 light chain variable domain comprises three CDRs from SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, or 812; or

(d) the VD2 heavy chain variable domain comprises three CDRs from SEQ ID NO:541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD1 heavy chain variable domain comprises three CDRs from SEQ ID NO:30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD2 light chain variable domain comprises three CDRs from SEQ ID NO:546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD1 light chain variable domain comprises three CDRs from SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766 or 812.

7. The binding protein of claim 6, wherein

(a) the VD1 or VD2 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 or VD2 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(b) the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 and VD2 light chain variable domains independently comprise SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(c) the VD1 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741,

753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD2 heavy chain variable domain comprises SEQ ID NO: 30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD1 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD2 light chain variable domain comprises SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, or 812; or

(d) the VD2 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD1 heavy chain variable domain comprises SEQ ID NO:30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD2 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD1 light chain variable domain comprises SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, or 812.

8. The binding protein of claim 1, 3, or 6, wherein X1 and/or X2 is any one of SEQ ID NOs 1-29.

9. The binding protein of claim 6, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.

10. The binding protein of claim 1, 3, or 6, wherein the Fc region is a variant sequence Fc region.

11. The binding protein of claim 1, 3, or 6, wherein the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD.

12. The binding protein of claim 6, wherein the VD1 of the first polypeptide chain and the VD1 of the second polypeptide chain are obtained from a same first and second parent antibody, respectively, or antigen binding portion thereof.

13. The binding protein of claim 6, wherein the VD1 of the first polypeptide chain and the VD1 of the second polypeptide chain are from a different first and second parent antibody, respectively, or antigen binding portion thereof.

14. The binding protein of claim 6, wherein the VD2 of the first polypeptide chain and the VD2 of the second polypeptide chain are from a same first and second parent antibody, respectively, or antigen binding portion thereof.

15. The binding protein of claim 6, wherein the VD2 of the first polypeptide chain and the VD2 of the second polypeptide chain are from a different first and second parent antibody, respectively, or antigen binding portion thereof.

16. The binding protein of claim 13 or 15, wherein the first and the second parent antibodies bind different epitopes on the antigen.

17. The binding protein of any one of claims 12-16, wherein the first parent antibody or antigen binding portion thereof, binds the first antigen with a potency different from the potency with which the second parent antibody or antigen binding portion thereof, binds the second antigen.

18. The binding protein of any one of claims 12-16, wherein the first parent antibody or antigen binding portion thereof, binds the first antigen with an affinity different from the affinity with which the second parent antibody or antigen binding portion thereof, binds the second antigen.

19. A binding protein capable of binding two antigens, the binding protein comprising four polypeptide chains, wherein two polypeptide chains comprise 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 first linker;
X2 is an Fc region; and

wherein two polypeptide chains comprise 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 second linker;

X2 does not comprise an Fc region;

(X1)n, wherein n is 0 or 1; and

(X2)n, wherein n is 0 or 1;

wherein the first and second X1 linker are the same or different;

wherein the first X1 linker is not CH1 and/or the second X1 linker is not CL;

wherein

(a) the VD1 or VD2 heavy chain variable domain comprises three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 or VD2 light chain variable domain comprises three CDRs from SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(b) the VD1 and VD2 heavy chain variable domains independently comprise three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 and VD2 light chain variable domains independently comprise three CDRs from SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(c) the VD1 heavy chain variable domain comprises three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD2 heavy chain variable domain comprises three CDRs from SEQ ID NO:30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD1 light chain variable domain comprises three CDRs from SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD2 light chain variable domain comprises three CDRs from SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, or 812; or

(d) the VD2 heavy chain variable domain comprises three CDRs from SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD1 heavy chain variable domain comprises three CDRs from SEQ ID NO:30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD2 light chain variable domain comprises three CDRs from SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD1 light chain variable domain comprises three CDRs from SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766 or 812.

20. A binding protein capable of binding two antigens, the binding protein comprising four polypeptide chains, wherein two polypeptide chains comprise 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 first linker;
X2 is an Fc region;
(X1)n, wherein n is 0 or 1;
(X2)n, wherein n is 0 or 1; and

wherein two polypeptide chains comprise 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 second linker;
X2 does not comprise an Fc region;
(X1)n, wherein n is 0 or 1;
(X2)n, wherein n is 0 or 1; and

wherein the first and second X1 linker are the same or different;
wherein the first X1 linker is not CH1 and/or the second X1 linker is not CL
wherein
(a) the VD1 or VD2 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721,

731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 or VD2 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(b) the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 and VD2 light chain variable domains independently comprise SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(c) the VD1 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD2 heavy chain variable domain comprises SEQ ID NO: 30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD1 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD2 light chain variable domain comprises SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766 or 812; or

(d) the VD2 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD1 heavy chain variable domain comprises SEQ ID NO: 30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD2 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD1 light chain variable domain comprises SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, or 812.

21. The binding protein of claim 1, 3, 6, 19, or 20, wherein the binding protein has an on rate constant (K_{on}) to the one or more targets of at least about $10^2 M^{-1}s^{-1}$; at least about $10^3 M^{-1}s^{-1}$; at

least about $10^4 M^{-1}s^{-1}$; at least about $10^5 M^{-1}s^{-1}$; or at least about $10^6 M^{-1}s^{-1}$, as measured by surface plasmon resonance.

22. The binding protein of claim 1, 3, 6, 19, or 20, wherein the binding protein has an off rate constant (K_{off}) to the one or more targets of at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; or at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance.

23. The binding protein of claim 1, 3, 6, 19, or 20, wherein the binding protein has a dissociation constant (K_D) to the one or more targets of at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; or at most 10^{-13} M.

24. A binding protein conjugate comprising a binding protein of claim 1, 3, 6, 19, or 20, the binding protein conjugate further comprising an agent, wherein the agent is an immunoadhension molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent.

25. The binding protein conjugate of claim 24, wherein the imaging agent is a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

26. The binding protein of claim 1, 3, 6, 19, or 20, wherein the binding protein is a crystallized binding protein.

27. An isolated nucleic acid encoding a binding protein amino acid sequence of claim 1, 3, 6, 19, or 20.

28. A vector comprising an isolated nucleic acid of claim 27.

29. The vector of claim 28, wherein the vector is pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, pHybE, pBOS-hCγ1 or pBJ.

30. A host cell comprising a vector of claim 28.

31. The host cell of claim 30, wherein the host cell is a prokaryotic cell.

32. The host cell of claim 30, wherein the host cell is a eukaryotic cell.

33. The host cell of claim 32, wherein the eukaryotic cell is a protist cell, animal cell, plant cell, yeast cell, mammalian cell, avian cell, insect cell, or fungal cell.

34. A method of producing a binding protein, comprising culturing a host cell described in any one of claims 30-33 in culture medium under conditions sufficient to produce the binding protein.

35. A protein produced of the method of claim 34.

36. A pharmaceutical composition comprising the binding protein of claim 1, 3, 6, 19, 20, or 35, and a pharmaceutically acceptable carrier.

37. The pharmaceutical composition of claim 36, further comprising at least one additional therapeutic agent.

38. The pharmaceutical composition of claim 37, wherein the additional therapeutic agent is 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 (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, 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, or a cytokine antagonist.

39. The binding protein of claim 1, 3, 6, 19, 20, or 35 for use in treating a subject for a disease or a disorder by administering to the subject the binding protein such that treatment is achieved.

40. The binding protein of claim 39, wherein the disorder is autoimmune and inflammatory disorders, asthma, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, spondylosing arthropathy, psoriasis, gastrointestinal disorders, inflammatory bowel disease, ulcerative cholitis, Chrohn's disease, uveitis, and systemic lupus erythematosis.

41. The binding protein of claim 40, wherein the administering to the subject is 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.

42. A method for generating a binding protein capable of binding two antigens, the method comprising the steps of:

a) obtaining a first parent antibody or antigen binding portion thereof, capable of binding a first antigen;

b) obtaining a second parent antibody or antigen binding portion thereof, capable of binding a second antigen;

c) constructing the polypeptide of any one of claims 1, 3, 6, 19, or 20:

d) expressing the polypeptide chain(s);

such that a binding protein capable of binding the first and the second antigen is generated.

43. The method of claim 42, wherein

(a) the VD1 or VD2 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 or VD2 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(b) the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, the VD1 and VD2 light chain variable domains independently comprise SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the binding protein is capable of binding TNF;

(c) the VD1 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD2 heavy chain variable domain comprises SEQ ID NO: 30, 32, 34, 108, 109, 110,

111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD1 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD2 light chain variable domain comprises SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, or 812;

(d) the VD2 heavy chain variable domain comprises SEQ ID NO: 541, 551, 561, 571, 581, 591, 601, 606, 611, 616, 621, 626, 631, 636, 643, 653, 661, 671, 681, 691, 701, 711, 721, 731, 741, 753, 763, 771, 776, 781, 786, 791, 796, 801, 805, 807, 809, or any one of 36-41, 48-72, or 88-97, and the VD1 heavy chain variable domain comprises SEQ ID NO: 30, 32, 34, 108, 109, 110, 111, 112, 113, 114, 115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803 or 811; the VD2 light chain variable domain comprises SEQ ID NO: 546, 556, 566, 576, 586, 596, 648, 658, 666, 676, 686, 696, 706, 716, 726, 736, 746, 758, 768 or any one of 42-47, 73-87, or 98-107, and the VD1 light chain variable domain comprises SEQ ID NO: 31, 33, 35, 116, 117, 118, 119, 120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766 or 812.

44. The method of claim 42, wherein the Fc region is a variant sequence Fc region.

45. The method of claim 42, wherein the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD.

46. The method of claim 42, wherein the first parent antibody or antigen binding portion thereof, if present, binds the first antigen with a different affinity and/or potency than the affinity and/or potency with which the second parent antibody or antigen binding portion thereof, if present, binds the second antigen.

47. A method of determining the presence of at least one antigen 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,-wherein the at least one binding protein comprises the binding protein of claim 1, 3, 9, 19, 20, or 35.

48. The method of claim 48, further comprising:

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

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

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

49. The method of claim 49, further comprising:

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

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

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

50. The method of any one of claims 48-50, wherein the test sample is from a patient and the method further comprises diagnosing, prognosticating, or assessing the efficiency of therapeutic/prophylactic treatment of the patient, and

wherein if the method further comprises assessing the efficacy of therapeutic/prophylactic treatment of the patient, the method optionally further comprises modifying the therapeutic/prophylactic treatment of the patient as needed to improve efficacy.

51. The method of any one of claims 48-51, wherein the method is adapted for use in an automated system or a semi-automated system.

52. The method of any one of claims 48-52, wherein the method determines the presence of more than one antigen in the sample.

53. A method of determining the amount or concentration of an antigen or fragment thereof in a test sample by an immunoassay,

wherein the immunoassay (a) employs at least one binding protein and at least one detectable label and (b) comprises comparing a signal generated by the detectable label with a control or calibrator comprising the antigen or fragment thereof,

wherein the calibrator is optionally part of a series of calibrators in which each calibrator differs from the other calibrators in the series by the concentration of the antigen or fragment thereof,

wherein the at least one binding protein comprises the binding protein of claim 1, 3, 9, 19, 20, or 35.

54. The method of claim 54, further comprising:

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

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

(iii) determining the amount or concentration of the antigen or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the amount or concentration of the antigen or fragment thereof is directly proportional to the signal generated by the detectable label.

55. The method of claim 55, further comprising:

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

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

(iii) determining the amount or concentration of the antigen or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence of the antigen or fragment thereof is indirectly proportional to the signal generated by the detectable label.

56. The method of any one of claims 54-56, wherein the test sample is from a patient and the method further comprises diagnosing, prognosticating, or assessing the efficiency of therapeutic/prophylactic treatment of the patient, and

wherein if the method further comprises assessing the efficacy of therapeutic/prophylactic treatment of the patient, the method optionally further comprises modifying the therapeutic/prophylactic treatment of the patient as needed to improve efficacy.

57. The method of any one of claims 54-57, wherein the method is adapted for use in an automated system or a semi-automated system.

58. The method of any one of claims 54-58, wherein the method determines the amount or concentration of more than one antigen in the sample.

59. A kit for assaying a test sample for the presence, amount, or concentration of an antigen or fragment thereof, the kit comprising

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

(b) at least one binding protein comprising the binding protein of claim 1, 3, 9, 19, 20, or 35.

60. An IL-17 binding protein comprising at least one heavy chain variable region (VH region) comprising:

(a) three complementarity determining regions (CDRs) from any one of SEQ ID NOS: 30, 32, 34, 108-115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803, and 811; or

(b) any one of SEQ ID NOS: 30, 32, 34, 108-115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803, and 811.

61. An IL-17 binding protein comprising at least one light chain variable regions (VL region) comprising:

(a) three complementarity determining regions (CDRs) from any one of SEQ ID NOS: 31, 33, 35, 116-120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, and 812; or

(b) any one of SEQ ID NOS: 31, 33, 35, 116-120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, and 812.

62. An IL-17 binding protein comprising at least one heavy chain variable region (VH region) and at least one light chain variable region (VL region), wherein the VH region comprises:

(a) three complementarity determining regions (CDRs) from any one of SEQ ID NOS: 30, 32, 34, 108-115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803, and 811; or

(b) any one of SEQ ID NOS: 30, 32, 34, 108-115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803, and 811; and

the VL region comprises:

(c) three CDRs from any one of SEQ ID NOS: 31, 33, 35, 116-120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, and 812; or

(d) any one of SEQ ID NOS: 31, 33, 35, 116-120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, and 812.

63. The binding protein of claim 62, wherein the binding protein comprises two VH regions and two VL regions.

64. The binding protein of claim 62, wherein the binding protein comprises at least one VH region and at least one VL region comprising a set of amino acid sequences selected from the group consisting of SEQ ID NOS: 30 and 31; 32 and 33; 34 and 35; 108 and 118; 108 and 119; 109 and 116; 110 and 117; 111 and 120; 112 and 117; 113 and 120; 114 and 117; 115 and 117; 527 and 537; 527 and 538; 528 and 535; 529 and 536; 530 and 539; 531 and 536; 532 and 539; 533 and 536; and 534 and 536.

65. The binding protein of claim 63, wherein the binding protein:

(a) modulates a biological function of IL-17;

(b) neutralizes IL-17;

(c) diminishes the ability of IL-17 to bind to its receptor;

(d) diminishes the ability of pro-human IL-17, mature-human IL-17, or truncated-human IL-17 to bind to its receptor; and/or

(e) reduces one or more of IL-17-dependent cytokine production, IL-17-dependent cell killing, IL-17-dependent inflammation, IL-17-dependent bone erosion, and IL-17-dependent cartilage damage.

66. The binding protein of claim 63, wherein the binding protein has an on rate constant (Kon) of at least about $10^2M^{-1}s^{-1}$; at least about $10^3M^{-1}s^{-1}$; at least about $10^4M^{-1}s^{-1}$; at least about $10^5M^{-1}s^{-1}$; or at least about $10^6M^{-1}s^{-1}$, as measured by surface plasmon resonance.

67. The binding protein of claim 63, wherein the binding protein has an off rate constant (Koff) of at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about 10^{-5}s-1; or at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance.

68. The binding protein of claim 63, wherein the binding protein has a dissociation constant (KD) of at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; or at most 10^{-13} M.

69. A binding protein capable of binding human IL-17, the binding protein comprising:

(a) a heavy chain constant region;

(b) a light chain constant region;

(c) a heavy chain variable region (VH region) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 30, 32, 34, 108-115, 121-317, 527-534, 543, 553, 563, 573, 583, 593, 603, 608, 613, 618, 623, 628, 633, 638, 641, 651, 663, 673, 683, 693, 703, 713, 723, 733, 743, 751, 761, 773, 778, 783, 788, 793, 798, 803, and 811; and

(d) a light chain variable region (VL region) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 31, 33, 35, 116-120, 318-526, 535-539, 548, 558, 568, 578, 588, 598, 646, 656, 668, 678, 688, 698, 708, 718, 728, 738, 748, 756, 766, and 812.

70. The binding protein of claim 62, wherein the binding protein comprises an immunoglobulin molecule, an Fv, a disulfide linked Fv, a monoclonal antibody, an scFv, a chimeric binding protein, a single domain binding protein, a CDR-grafted binding protein, a diabody, a humanized binding protein, a multispecific binding protein, an Fab, a dual specific binding protein, an Fab' fragment, a bispecific binding protein, an F(ab')2 fragment, a DVD-Ig™, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region, a Fd fragment consisting of the VH and CH1 domains, a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, a dAb fragment, an isolated complementarity determining region (CDR), or a single chain binding protein.

71. The binding protein of claim 63, wherein the binding protein is conjugated to an imaging agent selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

72. The binding protein of claim 63, wherein the binding protein further comprises a therapeutic or cytotoxic agent 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.

73. An isolated nucleic acid encoding a binding protein comprising the amino acid sequence of claim 62.

74. A vector comprising the isolated nucleic acid of claim 73.

75. A host cell comprising the vector of claim 74.

76. A method for producing a protein that binds IL-17, the method comprising the steps of culturing the host cell of claim 75 in a culture medium under conditions sufficient to produce a binding protein that binds IL-17.

77. A pharmaceutical composition comprising the binding protein of claim 62, and a pharmaceutically acceptable carrier.

78. Use of an effective amount of the pharmaceutical composition of claim 77, in the manufacture of a medicament for treating a mammal.

79. Use of the binding protein of claim 62, in the manufacture of a medicament for reducing human IL-17 activity, wherein IL-17 is to be contacted with such binding protein.

80. Use of the binding protein of claim 62, in the manufacture of a medicament for reducing human IL-17 activity in a human subject suffering from a disorder in which IL-17 activity is detrimental.

81. Use of the binding protein of claim 62 in the manufacture of a medicament for treating a patient suffering from a disorder in which IL-17 is detrimental wherein said binding protein is to be administered either before,

concurrent, or after the administration to the patient of a second agent, wherein the second agent is selected from the group consisting of budenoside, epidermal growth factor, corticosteroids, cyclosporin, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, lipoxygenase inhibitors, mesalamine, olsalazine, balsalazide, antioxidants, thromboxane inhibitors, IL-1 receptor antagonists, anti-IL-1β mAbs, anti-IL-6 or IL-6 receptor mAbs, growth factors, elastase inhibitors, pyridinyl-imidazole compounds, antibodies or agonists of TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-13, IL-15, IL-16, IL-18, IL-23, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD-19, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1β converting enzyme inhibitors, TNFα-converting enzyme inhibitors, T-cell signalling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, antiinflammatory cytokines, IL-4, IL-10, IL-11, IL-13, and TGFβ.

82. The use of claim 80 or 81, wherein the disorder is an autoimmune and/or inflammatory disorder.

83. The use of claims 82, wherein the disorder is selected from the group consisting of autoimmune and inflammatory disorders, asthma, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, spondylosing arthropathy, psoriasis, gastrointestinal disorders, inflammatory bowel disease, ulcerative cholitis, Chrohn's disease, uveitis, and systemic lupus erythematosis.

84. The use of claim 82, wherein the disorder is selected from the group consisting of immune and inflammatory diseases, autoimmune diseases, inflammation, Crohn's disease, psoriasis (including plaque psoriasis), arthritis (including rheumatoid arthritis, psoratic arthritis, osteoarthritis, or juvenile idiopathic arthritis), multiple sclerosis, ankylosing spondylitis, spondylosing arthropathy, systemic lupus erythematosus, uveitis, multiple sclerosis, sepsis, neurodegenerative diseases, neuronal regeneration, spinal cord injury, primary and metastatic cancers, a respiratory disorder; asthma; allergic and nonallergic asthma; asthma due to infection; asthma due to infection with respiratory syncytial virus (RSV); chronic obstructive pulmonary disease (COPD); a condition involving airway inflammation; eosinophilia; fibrosis and excess mucus production; cystic fibrosis; pulmonary fibrosis; an atopic disorder; atopic dermatitis; urticaria; eczema; allergic rhinitis; allergic enterogastritis; an inflammatory and/or autoimmune

condition of the skin; an inflammatory and/or autoimmune condition of gastrointestinal organs; inflammatory bowel diseases (IBD); ulcerative colitis; an inflammatory and/or autoimmune condition of the liver; liver cirrhosis; liver fibrosis; liver fibrosis caused by hepatitis B and/or C virus; scleroderma; tumors or cancers; hepatocellular carcinoma; glioblastoma; lymphoma; Hodgkin's lymphoma; a viral infection; a bacterial infection; a parasitic infection; HTLV-1 infection; suppression of expression of protective type 1 immune responses, and suppression of expression of a protective type 1 immune response during vaccination.

85. A method for determining the presence of IL-17 or a fragment thereof in a test sample by an immunoassay, wherein the immunoassay comprises contacting the test sample with at least one binding protein or fragment thereof according to claim 62, and at least one detectable label.

86. The method of claim 85, wherein the method further comprises:
(i) contacting the test sample with the at least one binding protein or fragment thereof, wherein the binding protein binds to an epitope on the IL-17 or fragment thereof so as to form a first complex;
(ii) contacting the complex with the at least one detectable label, wherein the detectable label binds to an epitope on the first complex, or on the IL-17 or fragment thereof, that is not bound by the binding protein or fragment thereof, to form a second complex; and
(iii) detecting the presence of the IL-17 or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence of the IL-17 or fragment thereof is directly correlated with the signal generated by the detectable label.

87. The method of claim 85, wherein the method further comprises:
(i) contacting the test sample with the at least one binding protein or fragment thereof, wherein the binding protein or fragment thereof binds to an epitope on the IL-17 or fragment thereof so as to form a first complex;
(ii) contacting the complex with the at least one detectable label, wherein the detectable label competes with the IL-17 or fragment thereof for binding to the binding protein or fragment thereof so as to form a second complex; and
(iii) detecting the presence of the IL-17 or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence of the IL-17 or fragment thereof is indirectly correlated with the signal generated by the detectable label.

88. The method of claim 85, wherein the method optionally further comprises diagnosing, prognosticating, or assessing the efficiency of therapeutic/prophylactic treatment of the patient.

Claims

1. A binding protein that specifically binds at least two target proteins, wherein the target proteins comprise TNF-α and IL-17, and the binding protein comprises a polypeptide chain, wherein the polypeptide chain comprises 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 with the proviso that it is not CH1;

X2 is an Fc region;

(X1)n, wherein n is 0 or 1;

(X2)n, wherein n is 0 or 1; and

wherein the binding protein is capable of binding human IL-17 and TNF-α;

wherein the VD1 and the VD2 comprises either

a first CDR-H1 comprising NYGII,

a first CDR-H2 comprising WINTYTGKPTYAQKFQG, and

a first CDR-H3 comprising KLFTTMDVTDNAMDY; and.

or comprises

a second CDR-H1 comprising DYEIH,

a second CDR-H2 comprising VNDPESGGTFYNQKFDG, and

a second CDR-H3 comprising YSKWDSFDGMDY.

2. The binding protein of claim 1, wherein the polypeptide chain comprises the amino acid sequence of SEQ ID NO: 660.

3. A binding protein that specifically binds at least two target proteins, wherein the target proteins comprise TNF-α and IL-17, and the binding protein comprises a polypeptide chain, wherein the polypeptide chain comprises 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 with the proviso that it is not CL;

X2 does not comprise an Fc region;

(X1)n, wherein n is 0 or 1;

(X2)n, wherein n is 0 or 1; and

wherein the binding protein is capable of binding human IL-17 and TNF-α;

wherein the VD1 and VD2 comprises either

a first CDR-L1 comprising RASQDISQYLN,

a first CDR-L2 comprising YTSRLQS, and

a first CDR-L3 comprising QQGNTWPPT;

or comprises

a second CDR-L1 comprising RASSGIISYID,

a second CDR-L2 comprising ATFDLAS, and

a second CDR-L3 comprising RQVGSYPET.

4. The binding protein of claim 3, wherein the polypeptide chain comprises the amino acid sequence of SEQ ID NO: 665.

5. The binding protein of claim 1 or 3, wherein the VD1 or VD2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 668 and 666.

6. A binding protein that specifically binds at least two target proteins, wherein the target proteins comprise TNF-α and IL-17, and the binding protein comprises first and second polypeptide chains, wherein 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 first linker with the proviso that it is not CH1;

X2 is an Fc region; and

n is 0 or 1;

wherein the VD1 or VD2 of the first polypeptide chain comprises

a first CDR-H1comprising the amino acid sequence of NYGII;

a first CDR-H2 comprising the amino acid sequence of WINTYTGKPTYAQKFQG; and

a first CDR-H3 comprising the amino acid sequence of KLFTTMDVTDNAMDY;

or comprises

a second CDR-H1 comprising the amino acid sequence of DYEIH;

a second CDR-H2 comprising the amino acid sequence of VNDPESGGTFYNQKFDG; and

a second CDR-H3 comprising the amino acid sequence of YSKWDSFDGMDY; and

wherein 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 second linker with the proviso that it is not a light chain constant domain;

X2 does not comprise an Fc region;

n is 0 or 1; and

wherein the VD1 or VD2 of the second polypeptide chain comprises

a first CDR-L1 comprising the amino acid sequence of RASQDISQYLN;

a first CDR-L2 comprising the amino acid sequence of YTSRLQS; and

a first CDR-L3 comprising the amino acid sequence of QQGNTWPPT;

or comprises

a second CDR-L1 comprising the amino acid sequence of RASSGIISYID;

a second CDR-L2 comprising the amino acid sequence of ATFDLAS; and

a second CDR-L3 comprising the amino acid sequence of RQVGSYPET, wherein both VD1s bind the same target protein and both VD2s bind the same target protein.

7. The binding protein of claim 6, wherein the VD1 or VD2 of the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 661, and the VD1 or VD2 of the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 666.

8. The binding protein of claim 1, 3, or 6, wherein X1 and/or X2 is any one of SEQ ID NOs 1-29, 662, and 667.

9. The binding protein of claim 6, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.

10. The binding protein of claim 1, 3, or 6, wherein the Fc region is a variant sequence Fc region.

11. The binding protein of claim 1, 3, or 6, wherein the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD.

12. The binding protein of claim 6, wherein the VD1 of the first polypeptide chain comprises the first CDR-H1 that comprises the amino acid sequence of NYGII, the first CDR-H2 that comprises the amino acid sequence of WINTYTGKPTYAQKFQG, and the first CDR-H3 that comprises the amino acid sequence of KLFTTMDVTDNAMDY;

wherein the VD2 of the first polypeptide chain comprises the second CDR-H1 that comprises the amino acid sequence of DYEIH, the second CDR-H2 that comprises the amino acid sequence of VNDPESGGTFYNQKFDG, and the second CDR-H3 that comprises the amino acid sequence of YSKWDSFDGMDY;

wherein the VD1 of the second polypeptide chain comprises the first CDR-L1 that comprises the amino acid sequence of RASQDISQYLN , the first CDR-L2 that comprises the amino acid sequence of YTSRLQS, and the first CDR-L3 that comprises the amino acid sequence of QQGNTWPPT; and

wherein the VD2 of the second polypeptide chain comprises the second CDR-L1 that comprises the amino acid sequence of RASSGIISYID, the second CDR-L2 that comprises the amino acid sequence of ATFDLAS, and the second CDR-L3 that comprises the amino acid sequence of RQVGSYPET.

13. The binding protein of claim 6, wherein the VD2 of the first polypeptide chain comprises the second CDR-H1 that comprises the amino acid sequence of DYEIH, the second CDR-H2 that comprises the amino acid sequence of VNDPESGGTFYNQKFDG, and the second CDR-H3 that comprises the amino acid sequence of YSKWDSFDGMDY; and wherein the VD2 of the second polypeptide chain the second CDR-L1 that comprises the amino acid sequence of RASSGIISYID, the second CDR-L2 that comprises the amino acid sequence of ATFDLAS, and the second CDR-L3 that comprises the amino acid sequence of RQVGSYPET.

14. The binding protein of claim 6, wherein the VD1 of the first polypeptide chain comprises the first CDR-H1 that comprises the amino acid sequence of NYGII, the first CDR-H2 that comprises the amino acid sequence of WINTYTGKPTYAQKFQG, and the first CDR-H3 that comprises the amino acid sequence of KLFTTMDVTDNAMDY (SEQ ID NO: 815); and

wherein the VD1 of the second polypeptide chain comprises the first CDR-L1 that comprises the amino acid sequence of RASQDISQYLN, the first CDR-L2 that comprises the amino acid sequence of YTSRLQS, and the first CDR-L3 that comprises the amino acid sequence of QQGNTWPPT.

15. The binding protein of claim 6, wherein the VD1 of the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 661, the VD2 of the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 663, the VD1 of the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 666, and the VD2 of the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 668.

16. The binding protein of claim 6, wherein wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 660.

17. The binding protein of claim 6, wherein the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 665.

18. The binding protein of claim 6, wherein the first polypeptide chain comprise the amino acid sequence of SEQ ID NO: 660, wherein heavy chain constant domain comprises the amino acid sequence of SEQ ID NO: 774, the second polypeptide chain comprise the amino acid sequence of SEQ ID NO: 665, and the light chain constant domain comprises the amino acid sequence of SEQ ID NO: 669.

19. A binding protein that specifically binds at least two target proteins, wherein the target proteins comprise TNF-α and IL-17, and the binding protein comprises four polypeptide chains, wherein two polypeptide chains comprise 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 first linker linker with the proviso that it is not CH1;
X2 is an Fc region; and
n is 0 or 1;

wherein two polypeptide chains comprise 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 second linker linker with the proviso that it is not a light chain constant domain;
X2 does not comprise an Fc region; and
n is 0 or 1;

wherein the VD1 and VD2 of the two first polypeptide chains comprises either

a first CDR-H1 comprising the amino acid sequence of NYGII;
a first CDR-H2 comprising the amino acid sequence of WINTYTGKPTYAQKFQG; and
a first CDR-H3 comprising the amino acid sequence of KLFTTMDVTDNAMDY;

or comprises

a second CDR-H1comprising the amino acid sequence of DYEIH;

a second CDR-H2 comprising the amino acid sequence of VNDPESGGTFYNQKFDG; and

a second CDR-H3-comprising the amino acid sequence of YSKWDSFDGMDY;

wherein the VD1 and VD2 of the two second polypeptide chains comprises either

a first CDR-L1 comprising the amino acid sequence of RASQDISQYLN;

a first CDR-L2 comprising the amino acid sequence of YTSRLQS; and

a first CDR-L3 comprising the amino acid sequence of QQGNTWPPT;

or comprises

a second CDR-L1 comprising the amino acid sequence of RASSGIISYID (SEQ ID NO: 822);

a second CDR-L2 comprising the amino acid sequence of ATFDLAS (SEQ ID NO: 823); and

a second CDR-L3 comprising the amino acid sequence of RQVGSYPET (SEQ ID NO: 824),

wherein all four VD1s bind the same target protein and all four VD2s bind the same target protein.

20. The binding protein of claim 19, wherein the VD1 or VD2 of the two first polypeptide chains comprises the amino acid sequence of SEQ ID NO: 661 or SEQ ID NO: 663, and the VD1 or VD2 of the two second polypeptide chains comprises the amino acid sequence of SEQ ID NO: 666 or SEQ ID NO: 668.

21. The binding protein of claim 19, the VD1 of the two first polypeptide chains the first CDR-H1 that comprises the amino acid sequence of NYGII, the first CDR-H2 that comprises the amino acid sequence of WINTYTGKPTYAQKFQG, and the first CDR-H3 that comprises the amino acid sequence of KLFTTMDVTDNAMDY;

wherein the VD2 of the two first polypeptide chains comprises the second CDR-H1 that comprises the amino acid sequence of DYEIH, the second CDR-H2 that comprises the amino acid sequence of VNDPESGGTFYNQKFDG, and the second CDR-H3 that comprises the amino acid sequence of YSKWDSFDGMDY;

wherein the VD1 of the two second polypeptide chains comprises the first CDR-L1 that comprises the amino acid sequence of RASQDISQYLN, the first CDR-L2 that comprises the amino acid sequence of YTSRLQS, and the first CDR-L3 that comprises the amino acid sequence of QQGNTWPPT; and

wherein the VD2 of the two second polypeptide chains comprises the second CDR-L1 that comprises the amino acid sequence of RASSGIISYID, the second CDR-L2 that

comprises the amino acid sequence of ATFDLAS, and the second CDR-L3 that comprises the amino acid sequence of RQVGSYPET.

22. The binding protein of claim 2, 7, or 20, wherein VD1 of the first polypeptide chain(s) comprises the amino acid sequence of SEQ ID NO: 661.

23. The binding protein of claim 2, 7, or 20, wherein VD2 of the first polypeptide chain(s) comprises the amino acid sequence of SEQ ID NO: 661.

24. The binding protein of claim 2, 7, or 20, wherein VD1 of the second polypeptide chain(s) comprises the amino acid sequence of SEQ ID NO: 666.

25. The binding protein of claim 2, 7, or 20, wherein VD2 of the second polypeptide chain(s) comprises the amino acid sequence of SEQ ID NO: 666.

26. The binding protein of claim 20, wherein the VD1 of the two first polypeptide chains comprises the amino acid sequence of SEQ ID NO: 661, and the VD1 of the two second polypeptide chains comprises the amino acid sequence of SEQ ID NO: 666.

27. The binding protein of claim 20, wherein the VD2 of the two first polypeptide chains comprises the amino acid sequence of SEQ ID NO: 661, and the VD2 of the two second polypeptide chains comprises the amino acid sequence of SEQ ID NO: 666.

28. The binding protein of claim 20, wherein the VD1 of the two first polypeptide chains comprises the amino acid sequence of SEQ ID NO: 663, and the VD1 of the two second polypeptide chains comprises the amino acid sequence selected of SEQ ID NO: 668.

29. The binding protein of claim 20, wherein the VD2 of the two first-polypeptide chains comprises the amino acid sequence of SEQ ID NO: 663, and the VD2 of the two second polypeptide chains comprises the amino acid sequence of SEQ ID NO: 668.

30. The binding protein of claim 20, wherein the VD2 of the two first polypeptide chains comprises the amino acid sequence of SEQ ID NO: 663, and the VD2 of the two second polypeptide chains comprises the amino acid sequence of SEQ ID NO: 668, and wherein the VD1 of the two first polypeptide chains comprises the amino acid sequence of SEQ ID NO: 661, and the VD1 of the two second polypeptide chains comprises the amino acid sequence of SEQ ID NO: 666.

31. The binding protein of claim 20, wherein the two first polypeptide chains comprise the amino acid sequence of SEQ ID NO: 660.

32. The binding protein of claim 20, wherein the two second polypeptide chains comprise the amino acid sequence of SEQ ID NO: 665.

33. A binding protein comprising two first polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 660, and two second polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 665.

34. The binding protein of claim 33, wherein the two first polypeptide chains comprise the amino acid sequence of SEQ ID NO: 774, and wherein the two second polypeptide chains comprise the amino acid sequence of SEQ ID NO: 669.

35. The binding protein of claim 1, 3, 6, 19, or 20, wherein the binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 554, 559, 734, 774, and 779.

36. The binding protein of claim 19, wherein the X1 in the two first polypeptide chains and the two second polypeptide chains independently comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-29, 662, and 667.

37. The binding protein of claim 19, wherein the Fc region comprises a variant Fc region.

38. A binding protein conjugate comprising a binding protein of claim 1, 3, 6, 19, or 20-37, the binding protein conjugate further comprising an agent selected from the group consisting of: an immunoadhension molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent.

39. The binding protein conjugate of claim 38, wherein the imaging agent is a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

40. The binding protein of claim 1, 3, 6, 19, or 20-37, wherein the binding protein is a crystallized binding protein.

41. An isolated nucleic acid encoding a binding protein amino acid sequence of claim 1, 3, 6, 19, or 20-37.

42. A vector comprising the isolated nucleic acid of claim 41.

43. The vector of claim 42, wherein the vector is pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, pHybE, pBOS-hCγ1 or pBJ.

44. A host cell comprising the vector of claim 42 or 43.

45. The host cell of claim 44, wherein the host cell is a prokaryotic cell.

46. The host cell of claim 44, wherein the host cell is a eukaryotic cell.

47. The host cell of claim 46, wherein the eukaryotic cell is a protist cell, animal cell, plant cell, yeast cell, mammalian cell, avian cell, insect cell, or fungal cell.

48. A method of producing a binding protein, comprising culturing the host cell described in any one of claims 44-47 in culture medium under conditions sufficient to produce the binding protein.

49. A pharmaceutical composition comprising the binding protein of claim 1, 3, 6, 19, or 20-37, and a pharmaceutically acceptable carrier.

50. The pharmaceutical composition of claim 49, further comprising at least one additional agent.

51. The pharmaceutical composition of claim 50, wherein the additional agent is 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 (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, 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, or a cytokine antagonist.

52. Use of the binding protein of any of claims 1, 3, 6, 19, or 20-37 in the manufacture of a medicament for treating a subject for a disease or a disorder wherein the medicament is to be administered to the subject such that treatment is achieved.

53. The use of claim 52, wherein the disorder is autoimmune and inflammatory disorders, asthma, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, spondylosing arthropathy, psoriasis, gastrointestinal disorders, inflammatory bowel disease, ulcerative cholitis, Chrohn's disease, uveitis, and systemic lupus erythematosis.

54. The use of claim 53, wherein the administration to the subject is 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.

55. A method for generating a binding protein capable of binding two antigens, the method comprising the steps of:

a) obtaining a first parent antibody or antigen binding portion thereof, capable of binding a first antigen;

b) obtaining a second parent antibody or antigen binding portion thereof, capable of binding a second antigen;

c) constructing the polypeptide of any one of claims 1, 3, 6, 19, or 20-37:

d) expressing the polypeptide chain(s);

such that a binding protein capable of binding the first and the second antigen is generated.

56. A method of determining the presence of at least one antigen 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,-wherein the at least one binding protein comprises the binding protein of claim 1, 3, 9, 19, or 20-37.

57. The method of claim 56, further comprising:

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

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

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

58. The method of claim 56, further comprising:

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

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

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

59. The method of any one of claims 56-58, wherein the test sample is from a patient and the method further comprises diagnosing, prognosticating, or assessing the efficiency of therapeutic/prophylactic treatment of the patient, and

wherein if the method further comprises assessing the efficacy of therapeutic/prophylactic treatment of the patient, the method optionally further comprises modifying the therapeutic/prophylactic treatment of the patient as needed to improve efficacy.

60. The method of any one of claims 56-59, wherein the method is adapted for use in an automated system or a semi-automated system.

61. The method of any one of claims 56-59, wherein the method determines the presence of more than one antigen in the sample.

62. A method of determining the amount or concentration of an antigen or fragment thereof in a test sample by an immunoassay,

wherein the immunoassay (a) employs at least one binding protein and at least one detectable label and (b) comprises comparing a signal generated by the detectable label with a control or calibrator comprising the antigen or fragment thereof,

wherein the calibrator is optionally part of a series of calibrators in which each calibrator differs from the other calibrators in the series by the concentration of the antigen or fragment thereof,

wherein the at least one binding protein comprises the binding protein of claim 1, 3, 9, 19, or 20-37.

63. The method of claim 62, further comprising:

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

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

(iii) determining the amount or concentration of the antigen or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the amount or concentration of the antigen or fragment thereof is directly proportional to the signal generated by the detectable label.

64. The method of claim 62, further comprising:

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

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

(iii) determining the amount or concentration of the antigen or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence of the antigen or fragment thereof is indirectly proportional to the signal generated by the detectable label.

65. The method of any one of claims 62-64, wherein the test sample is from a patient and the method further comprises diagnosing, prognosticating, or assessing the efficiency of therapeutic/prophylactic treatment of the patient, and

wherein if the method further comprises assessing the efficacy of therapeutic/prophylactic treatment of the patient, the method optionally further comprises modifying the therapeutic/prophylactic treatment of the patient as needed to improve efficacy.

66. The method of any one of claims 62-65, wherein the method is adapted for use in an automated system or a semi-automated system.

67. The method of any one of claims 62-66, wherein the method determines the amount or concentration of more than one antigen in the sample.

68. A kit for assaying a test sample for the presence, amount, or concentration of an antigen or fragment thereof, the kit comprising

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

(b) at least one binding protein comprising the binding protein of claim 1, 3, 9, 19, or 20-37.