What is claimed is:

1. A binding protein comprising first and second polypeptide chains, wherein said 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 with the proviso that it is not CH1;

X2 is an Fc region; and

n is independently 0 or 1; and

wherein said 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 with the proviso that it is not CH1;

X2 does not comprise an Fc region; and

n is independently 0 or 1;

wherein, in said first polypeptide chain, VD1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 60-148, 196, 198, 200, 202, 204, 206, 208 and 210; and VD2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 213 and 227;

wherein, in said second polypeptide chain, VD1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 149-189, 197, 199, 201, 203, 205, 207, 209 and 211; and VD2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 216 and 229; and

wherein the binding protein binds human IL-1β and human IL-1α.

2. A binding protein comprising first and second polypeptide chains, wherein said 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 with the proviso that it is not CH1;

X2 is an Fc region; and

n is independently 0 or 1; and

wherein said 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 with the proviso that it is not CH1;

X2 does not comprise an Fc region; and

n is independently 0 or 1;

wherein, in said first polypeptide chain, VD1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 213 and 227; and VD2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 60-148, 196, 198, 200, 202, 204, 206, 208 and 210;

wherein, in said second polypeptide chain, VD1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 216 and 229; and VD2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 149-189, 197, 199, 201, 203, 205, 207, 209 and 211; and

wherein the binding protein binds human IL-1β and human IL-1α.

3. The binding protein according to Claim 1, wherein:
said first polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 212, 217, 226, 230, 232, 234, and 236.

4. The binding protein according to Claim 1, wherein:
said second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 215, 218, 228, 231, 233, 235, and 237.

5. The binding protein according to Claim 2, wherein:
said first polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 219 and 221.

6. The binding protein according to Claim 2, wherein:

said second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 220 and 222.

7. The binding protein according to Claim 1 or Claim 2, wherein:

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:212, then said second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 215, 228, 231, 233 and 235;

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:217, then said second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 218 and 237;

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:219, then said second polypeptide chain comprises the amino acid sequence of SEQ ID NO:220;

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:221, then said second polypeptide chain comprises SEQ ID NO:222;

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:226, then said second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 228, 215, 231, 233, and 235;

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:230, then said second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 231, 215, 228, 233, and 235;

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:232, then said second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 233, 215, 228, 231, and 235;

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:234, then said second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 235, 215, 228, 231, and 233; and

when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:236, then said second polypeptide chain comprises SEQ ID NO:237.

8. The binding protein according to Claim 1 or Claim 2, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.

9. The binding protein according to Claim 1 or Claim 2, wherein X1 or X2 is an amino acid sequence selected from the group consisting of SEQ ID NOs:26-57, 233, 224, and 225.

10. The binding protein according to Claim 1 or Claim 2, wherein the Fc region is selected from the group consisting of a native sequence Fc region and a variant sequence Fc region.

11. A binding protein conjugate comprising a binding protein as described in Claim 1 or Claim 2, said binding protein conjugate further comprising an agent selected from the group consisting of: an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

12. The binding protein according to Claim 1 or Claim 2, wherein said binding protein is a crystallized binding protein.

13. The crystallized binding protein according to Claim 12, wherein said crystallized binding protein is a carrier-free pharmaceutical controlled release crystallized IL-1β binding protein.

14. A composition for the release of a crystallized binding protein, said composition comprising:

(a) a formulation, wherein said formulation comprises a crystallized binding protein, described in Claim 12, and an ingredient; and

(b) at least one polymeric carrier.

15. A pharmaceutical composition comprising a binding protein as described in Claim 1 or Claim 2, a conjugate according to Claim 11, or a crystallized binding protein according to Claim 12 and a pharmaceutically acceptable carrier.

16. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide chain amino acid sequence of a binding protein described in Claim 1 or Claim 2.

17. A vector comprising one or more isolated nucleic acid molecules according to Claim 16.

18. A host cell comprising a vector according to Claim 17.

19. A method of producing a binding protein, comprising culturing a host cell described in Claim 34 in culture medium under conditions sufficient to produce the binding protein.

20. A method for reducing human IL-1 activity comprising contacting a human IL-1 protein with the binding protein as described in Claim 1 or Claim 2 such that human IL-1 protein activity is reduced.

21. Use of a binding protein as described in Claim 1 or Claim 2 or a crystal thereof in the manufacture of a medicament for reducing human IL-1 activity in a human subject suffering from a disorder in which IL-1 activity is detrimental.

22. Use of a binding protein as described in Claim 1 or Claim 2 or a crystal thereof in the manufacture of a medicament for treating a subject for a disorder in which IL-1 activity is detrimental.

23. The use of Claim 22, wherein said disorder is selected from the group consisting of: diabetes; uveitis; neuropathic pain; osteoarthritic pain; inflammatory pain; rheumatoid arthritis; osteoarthritis; juvenile chronic arthritis; septic arthritis; Lyme arthritis; psoriatic arthritis; reactive arthritis; spondyloarthropathy; systemic lupus erythematosus (SLE); Crohn's disease; ulcerative colitis; inflammatory bowel disease; autoimmune diabetes; insulin dependent diabetes mellitus; thyroiditis; asthma; allergic diseases; psoriasis; dermatitis; scleroderma; graft versus host disease; organ transplant rejection; acute immune disease associated with organ transplantation; chronic immune disease associated with organ transplantation; sarcoidosis; atherosclerosis; disseminated intravascular coagulation (DIC); 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; autoimmune uveitis; septic shock; toxic shock syndrome; sepsis syndrome; cachexia; infectious diseases; parasitic diseases; 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; polyglandular deficiency type II (Schmidt's syndrome); acute respiratory distress syndrome (ARDS); alopecia; alopecia areata; seronegative arthropathy; arthropathy; Reiter's disease; psoriatic arthropathy; ulcerative colitic arthropathy; enteropathic synovitis; chlamydia; *Yersinia* and *Salmonella* associated arthropathy; spondyloarthropathy; 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 (GCA); primary sclerosing hepatitis; cryptogenic autoimmune hepatitis; acquired immunodeficiency syndrome (AIDS); 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; 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; postinfectious 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; osteoarthrosis; primary sclerosing cholangitis; psoriasis type 1; psoriasis type 2; idiopathic leucopaenia; autoimmune neutropaenia; renal disease NOS; glomerulonephritides; microscopic vasculitis of the kidneys; Lyme disease; discoid lupus erythematosus; idiopathic male infertility; nitric oxide-associated male infertility; sperm autoimmunity; multiple sclerosis (all subtypes, including primary progressive, secondary progressive, relapsing remitting); 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 (AITP); 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; cholestasis; idiosyncratic liver disease; drug-induced hepatitis; non-alcoholic steatohepatitis; allergy; 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); cancer (such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate, and rectal cancer); hematopoietic

malignancies; leukemia; lymphoma; abetalipoproteinemia; acrocyanosis; acute and chronic parasitic or infectious processes; acute leukemia; acute lymphoblastic leukemia (ALL); T-cell ALL; FAB ALL; acute myeloid leukemia (AML); acute or chronic bacterial infection; acute pancreatitis; acute renal failure; adenocarcinomas; atrial 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; antiphospholipid syndrome; anti-receptor hypersensitivity reactions; aortic and peripheral aneurysms; 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 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 hemophagocytic 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; hemochromatosis; 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

(IPF); 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; lymphedema; malaria; malignant lymphoma; malignant histiocytosis; malignant melanoma; meningitis; meningococcemia; metabolic syndrome migraine headache; idiopathic migraine headache; mitochondrial multisystem disorder; mixed connective tissue disease; monoclonal gammopathy; multiple myeloma; multiple systems degenerations (Menzel; Dejerine-Thomas; Shy-Drager; and Machado-Joseph); myasthenia gravis; mycobacterium avium intracellulare; mycobacterium tuberculosis; myelodysplastic syndrome; myocardial infarction; myocardial ischemic disorders; nasopharyngeal carcinoma; neonatal chronic lung disease; nephritis; nephrosis; neurodegenerative diseases; neurogenic I muscular atrophies; neutropenic fever; non-Hodgkin's lymphoma; occlusion of the abdominal aorta and its branches; occlusive arterial disorders; OKT3® therapy; orchitis/epididymitis; 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; Raynaud's disease; Refsum's disease; regular narrow QRS tachycardia; renovascular hypertension; reperfusion injury; restrictive cardiomyopathy; sarcomas; 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; 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; viral encephalitis/aseptic meningitis; viral-associated hemophagocytic

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; dacryocystitis; dermatomyositis; diabetic retinopathy; disk herniation; disk prolapse; drug induced immune hemolytic anemia; endocarditis; endometriosis; endophthalmitis; episcleritis; erythema multiforme; erythema multiforme major; gestational pemphigoid; Guillain-Barré 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; iritis; keratitis; keratojunctivitis 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; 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; secondary 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; spondylitis ankylosans; Stevens-Johnson syndrome (SJS); systemic inflammatory response syndrome; temporal arteritis; toxoplasmic retinitis; toxic epidermal necrolysis; transverse myelitis; TRAPS (tumor necrosis factor receptor type 1 (TNFR)-associated periodic syndrome); type B insulin resistance with acanthosis nigricans; type 1 allergic reaction; type II

diabetes; urticaria; usual interstitial pneumonia (UIP); vernal conjunctivitis; viral retinitis; Vogt-Koyanagi-Harada syndrome (VKH syndrome); wet macular degeneration; wound healing; *Yersinia* and *Salmonella* associated arthropathy.

24. A binding protein comprising an antigen binding domain, said binding protein capable of binding human IL-1β, said antigen binding domain comprising six CDRs: CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, as defined below:

CDR-H1: $X_1$-Y-D-M-S (SEQ ID NO:190), wherein;

$X_1$ is S, K or R;

CDR-H2: Y-$X_2$-S-$X_4$-G-G-$X_7$-G-T-Y-Y-P-D-$X_{14}$-$X_{15}$-K-G (SEQ ID NO:191), wherein;

$X_2$ is I or V;

$X_4$ is S or H;

$X_7$ is G or A;

$X_{14}$ is T or S; and

$X_{15}$ is V or A;

CDR-H3: G-G-V-$X_4$-K-G-$X_7$-F-D-$X_{10}$ (SEQ ID NO:192), wherein;

$X_4$ is T or Y;

$X_7$ is Y or C; and

$X_{10}$ is V, E, L, M, Q, or Y;

CDR-L1: R-A-S-G-N-I-$X_7$-$X_8$-$X_9$-L-$X_{11}$ (SEQ ID NO:193), wherein;

$X_7$ is H, Y, or W;

$X_8$ is N, G, T, Q, E, H, D, or K;

$X_9$ is Y or W; and

$X_{11}$ is T, A, or N;

CDR-L2: $X_1$-A-K-$X_4$-L-$X_6$-$X_7$ (SEQ ID NO:194), wherein;

$X_1$ is N, Q, or D;

$X_4$ is T, N, I, E, or S;

$X_6$ is A, M, or E; and

$X_7$ is D, E, S, or A;

and

CDR-L3: Q-$X_2$-F-W-$X_5$-$X_6$-P-$X_8$-$X_9$ (SEQ ID NO:195), wherein;

$X_2$ is H or Q;

$X_5$ is S, N, T, K, R, or M;

$X_6$ is I or L;

$X_8$ is Y or A; and

$X_9$ is T, I, and N;

except that when CDR-H1 is S-Y-D-M-S (SEQ ID NO:17), then:

CDR-H2 cannot be Y-I-S-S-G-G-G-G-T-Y-Y-P-D-T-V-K-G (SEQ ID NO:18);

CDR-H3 cannot be G-G-V-T-K-G-Y-F-D-V (SEQ ID NO:19);

CDR-L1 cannot be R-A-S-G-N-I-H-N-Y-L-T (SEQ ID NO:20);

CDR-L2 cannot be N-A-K-T-L-A-D (SEQ ID NO:21); and

CDR-L3 cannot be Q-H-F-W-S-I-P-Y-T (SEQ ID NO:22).

25. The binding protein according to Claim 24, wherein at least three CDRs are from a set of CDRs selected from the group of CDR sets consisting of:

| CDR Set | SEQ ID NO. | CDR Set | SEQ ID NO. |
|---|---|---|---|
| 1 | residues 31-35 of SEQ ID NO:60 (CDR-H1); | 55 | residues 31-35 of SEQ ID NO:63 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:60 (CDR-H2); | | residues 50-66 of SEQ ID NO:63 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:60 (CDR-H3); | | residues 99-108 of SEQ ID NO:63 (CDR-H3); |
| 2 | residues 24-34 of SEQ ID NO:149 (CDR-L1); | 56 | residues 24-34 of SEQ ID NO:150 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:149 (CDR-L2); | | residues 50-56 of SEQ ID NO:150 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:149 (CDR-L3); | | residues 89-97 of SEQ ID NO:150 (CDR-L3); |
| 3 | residues 31-35 of SEQ ID NO:69 (CDR-H1); | 57 | residues 31-35 of SEQ ID NO:97 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:69 (CDR-H2); | | residues 50-66 of SEQ ID NO:97 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:69 (CDR-H3); | | residues 99-108 of SEQ ID NO:97 (CDR-H3); |
| 4 | residues 24-34 of SEQ ID NO:173 (CDR-L1); | 58 | residues 24-34 of SEQ ID NO:187 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:173 (CDR-L2); | | residues 50-56 of SEQ ID NO:187 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:173 (CDR-L3); | | residues 89-97 of SEQ ID NO:187 (CDR-L3); |

| | | | |
|---|---|---|---|
| 5 | residues 31-35 of SEQ ID NO:67 (CDR-H1); | 59 | residues 31-35 of SEQ ID NO:90 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:67 (CDR-H2) | | residues 50-66 of SEQ ID NO:90 (CDR-H2) |
| | residues 99-108 of SEQ ID NO:67 (CDR-H3); | | residues 99-108 of SEQ ID NO:90 (CDR-H3); |
| 6 | residues 24-34 of SEQ ID NO:151 (CDR-L1); | 60 | residues 24-34 of SEQ ID NO:156 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:151 (CDR-L2); | | residues 50-56 of SEQ ID NO:156 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:151 (CDR-L3); | | residues 89-97 of SEQ ID NO:156 (CDR-L3); |
| 7 | residues 31-35 of SEQ ID NO:88 (CDR-H1); | 61 | residues 31-35 of SEQ ID NO:92 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:88 (CDR-H2); | | residues 50-66 of SEQ ID NO:92 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:88 (CDR-H3); | | residues 99-108 of SEQ ID NO:92 (CDR-H3); |
| 8 | residues 24-34 of SEQ ID NO:159 (CDR-L1); | 62 | residues 24-34 of SEQ ID NO:153 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:159 (CDR-L2); | | residues 50-56 of SEQ ID NO:153 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:159 (CDR-L3); | | residues 89-97 of SEQ ID NO:153 (CDR-L3); |
| 9 | residues 31-35 of SEQ ID NO:96 (CDR-H1); | 63 | residues 31-35 of SEQ ID NO:94 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:96 (CDR-H2); | | residues 50-66 of SEQ ID NO:94 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:96 (CDR-H3); | | residues 99-108 of SEQ ID NO:94 (CDR-H3); |
| 10 | residues 24-34 of SEQ ID NO:155 (CDR-L1); | 64 | residues 24-34 of SEQ ID NO:166 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:155 (CDR-L2); | | residues 50-56 of SEQ ID NO:166 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:155 (CDR-L3); | | residues 89-97 of SEQ ID NO:166 (CDR-L3); |
| 11 | residues 31-35 of SEQ ID NO:90 (CDR-H1); | 65 | residues 31-35 of SEQ ID NO:82 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:90 (CDR-H2) | | residues 50-66 of SEQ ID NO:82 (CDR-H2) |
| | residues 99-108 of SEQ ID NO:90 (CDR-H3); | | residues 99-108 of SEQ ID NO:82 (CDR-H3); |
| 12 | residues 24-34 of SEQ ID NO:182 (CDR-L1); | 66 | residues 24-34 of SEQ ID NO:159 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:182 (CDR-L2); | | residues 50-56 of SEQ ID NO:159 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:182 | | residues 89-97 of SEQ ID NO:159 |

| | | | |
|---|---|---|---|
| | (CDR-L3); | | (CDR-L3); |

| | | | |
|---|---|---|---|
| 13 | residues 31-35 of SEQ ID NO:90 (CDR-H1); | 67 | residues 31-35 of SEQ ID NO:101 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:90 (CDR-H2); | | residues 50-66 of SEQ ID NO:101 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:90 (CDR-H3); | | residues 99-108 of SEQ ID NO:101 (CDR-H3); |
| 14 | residues 24-34 of SEQ ID NO:167 (CDR-L1); | 68 | residues 24-34 of SEQ ID NO:158 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:167 (CDR-L2); | | residues 50-56 of SEQ ID NO:158 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:167 (CDR-L3); | | residues 89-97 of SEQ ID NO:158 (CDR-L3); |
| 15 | residues 31-35 of SEQ ID NO:90 (CDR-H1); | 69 | residues 31-35 of SEQ ID NO:96 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:90 (CDR-H2); | | residues 50-66 of SEQ ID NO:96 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:90 (CDR-H3); | | residues 99-108 of SEQ ID NO:96 (CDR-H3); |
| 16 | residues 24-34 of SEQ ID NO:164 (CDR-L1); | 70 | residues 24-34 of SEQ ID NO:157 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:164 (CDR-L2); | | residues 50-56 of SEQ ID NO:157 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:164 (CDR-L3); | | residues 89-97 of SEQ ID NO:157 (CDR-L3); |
| 17 | residues 31-35 of SEQ ID NO:73 (CDR-H1); | 71 | residues 31-35 of SEQ ID NO:70 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:73 (CDR-H2); | | residues 50-66 of SEQ ID NO:70 (CDR-H2) |
| | residues 99-108 of SEQ ID NO:73 (CDR-H3); | | residues 99-108 of SEQ ID NO:70 (CDR-H3); |
| 18 | residues 24-34 of SEQ ID NO:174 (CDR-L1); | 72 | residues 24-34 of SEQ ID NO:161 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:174 (CDR-L2); | | residues 50-56 of SEQ ID NO:161 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:174 (CDR-L3); | | residues 89-97 of SEQ ID NO:161 (CDR-L3); |
| 19 | residues 31-35 of SEQ ID NO:86 (CDR-H1); | 73 | residues 31-35 of SEQ ID NO:83 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:86 (CDR-H2); | | residues 50-66 of SEQ ID NO:83 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:86 (CDR-H3); | | residues 99-108 of SEQ ID NO:83 (CDR-H3); |
| 20 | residues 24-34 of SEQ ID NO:159 (CDR-L1); | 74 | residues 24-34 of SEQ ID NO:158 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:159 (CDR-L2); | | residues 50-56 of SEQ ID NO:158 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:159 | | residues 89-97 of SEQ ID NO:158 |

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| | (CDR-L3); | | (CDR-L3); |

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| 21 | residues 31-35 of SEQ ID NO:90 (CDR-H1); | 75 | residues 31-35 of SEQ ID NO:102 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:90 (CDR-H2); | | residues 50-66 of SEQ ID NO:102 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:90 (CDR-H3); | | residues 99-108 of SEQ ID NO:102 (CDR-H3); |
| 22 | residues 24-34 of SEQ ID NO:169 (CDR-L1); | 76 | residues 24-34 of SEQ ID NO:185 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:169 (CDR-L2); | | residues 50-56 of SEQ ID NO:185 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:169 (CDR-L3); | | residues 89-97 of SEQ ID NO:185 (CDR-L3); |
| 23 | residues 31-35 of SEQ ID NO:91 (CDR-H1); | 77 | residues 31-35 of SEQ ID NO:98 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:91 (CDR-H2) | | residues 50-66 of SEQ ID NO:98 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:91 (CDR-H3); | | residues 99-108 of SEQ ID NO:98 (CDR-H3); |
| 24 | residues 24-34 of SEQ ID NO:165 (CDR-L1); | 78 | residues 24-34 of SEQ ID NO:160 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:165 (CDR-L2); | | residues 50-56 of SEQ ID NO:160 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:165 (CDR-L3); | | residues 89-97 of SEQ ID NO:160 (CDR-L3); |
| 25 | residues 31-35 of SEQ ID NO:76 (CDR-H1); | 79 | residues 31-35 of SEQ ID NO:74 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:76 (CDR-H2); | | residues 50-66 of SEQ ID NO:74 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:76 (CDR-H3); | | residues 99-108 of SEQ ID NO:74 (CDR-H3); |
| 26 | residues 24-34 of SEQ ID NO:175 (CDR-L1); | 80 | residues 24-34 of SEQ ID NO:186 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:175 (CDR-L2); | | residues 50-56 of SEQ ID NO:186 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:175 (CDR-L3); | | residues 89-97 of SEQ ID NO:186 (CDR-L3); |
| 27 | residues 31-35 of SEQ ID NO:99 (CDR-H1); | 81 | residues 31-35 of SEQ ID NO:95 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:99 (CDR-H2); | | residues 50-66 of SEQ ID NO:95 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:99 (CDR-H3); | | residues 99-108 of SEQ ID NO:95 (CDR-H3); |
| 28 | residues 24-34 of SEQ ID NO:189 (CDR-L1); | 82 | residues 24-34 of SEQ ID NO:157 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:189 (CDR-L2); | | residues 50-56 of SEQ ID NO:157 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:189 | | residues 89-97 of SEQ ID NO:157 |

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| | (CDR-L3); | | (CDR-L3); |

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| 29 | residues 31-35 of SEQ ID NO:100 (CDR-H1); | 83 | residues 31-35 of SEQ ID NO:72 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:100 (CDR-H2); | | residues 50-66 of SEQ ID NO:72 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:100 (CDR-H3); | | residues 99-108 of SEQ ID NO:72 (CDR-H3); |
| 30 | residues 24-34 of SEQ ID NO:168 (CDR-L1); | 84 | residues 24-34 of SEQ ID NO:178 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:168 (CDR-L2); | | residues 50-56 of SEQ ID NO:178 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:168 (CDR-L3); | | residues 89-97 of SEQ ID NO:178 (CDR-L3); |
| 31 | residues 31-35 of SEQ ID NO:71 (CDR-H1); | 85 | residues 31-35 of SEQ ID NO:96 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:71 (CDR-H2) | | residues 50-66 of SEQ ID NO:96 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:71 (CDR-H3); | | residues 99-108 of SEQ ID NO:96 (CDR-H3); |
| 32 | residues 24-34 of SEQ ID NO:170 (CDR-L1); | 86 | residues 24-34 of SEQ ID NO:163 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:170 (CDR-L2); | | residues 50-56 of SEQ ID NO:163 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:170 (CDR-L3); | | residues 89-97 of SEQ ID NO:163 (CDR-L3); |
| 33 | residues 31-35 of SEQ ID NO:84 (CDR-H1); | 87 | residues 31-35 of SEQ ID NO:77 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:84 (CDR-H2); | | residues 50-66 of SEQ ID NO:77 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:84 (CDR-H3); | | residues 99-108 of SEQ ID NO:77 (CDR-H3); |
| 34 | residues 24-34 of SEQ ID NO:188 (CDR-L1); | 88 | residues 24-34 of SEQ ID NO:183 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:188 (CDR-L2); | | residues 50-56 of SEQ ID NO:183 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:188 (CDR-L3); | | residues 89-97 of SEQ ID NO:183 (CDR-L3); |
| 35 | residues 31-35 of SEQ ID NO:78 (CDR-H1); | 89 | residues 31-35 of SEQ ID NO:90 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:78 (CDR-H2); | | residues 50-66 of SEQ ID NO:90 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:78 (CDR-H3); | | residues 99-108 of SEQ ID NO:90 (CDR-H3); |
| 36 | residues 24-34 of SEQ ID NO:179 (CDR-L1); | 90 | residues 24-34 of SEQ ID NO:171 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:179 (CDR-L2); | | residues 50-56 of SEQ ID NO:171 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:179 | | residues 89-97 of SEQ ID NO:171 |

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| | (CDR-L3); | | (CDR-L3); |

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| 37 | residues 31-35 of SEQ ID NO:93 (CDR-H1); | 91 | residues 31-35 of SEQ ID NO:79 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:93 (CDR-H2); | | residues 50-66 of SEQ ID NO:79 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:93 (CDR-H3); | | residues 99-108 of SEQ ID NO:79 (CDR-H3); |
| 38 | residues 24-34 of SEQ ID NO:176 (CDR-L1); | 92 | residues 24-34 of SEQ ID NO:180 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:176 (CDR-L2); | | residues 50-56 of SEQ ID NO:180 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:176 (CDR-L3); | | residues 89-97 of SEQ ID NO:180 (CDR-L3); |
| 39 | residues 31-35 of SEQ ID NO:87 (CDR-H1); | 93 | residues 31-35 of SEQ ID NO:381 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:87 (CDR-H2) | | residues 50-66 of SEQ ID NO:381 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:87 (CDR-H3); | | residues 99-108 of SEQ ID NO:381 (CDR-H3); |
| 40 | residues 24-34 of SEQ ID NO:154 (CDR-L1); | 94 | residues 24-34 of SEQ ID NO:152 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:154 (CDR-L2); | | residues 50-56 of SEQ ID NO:152 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:154 (CDR-L3); | | residues 89-97 of SEQ ID NO:152 (CDR-L3); |
| 41 | residues 31-35 of SEQ ID NO:85 (CDR-H1); | 95 | residues 31-35 of SEQ ID NO:81 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:85 (CDR-H2); | | residues 50-66 of SEQ ID NO:81 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:85 (CDR-H3); | | residues 99-108 of SEQ ID NO:81 (CDR-H3); |
| 42 | residues 24-34 of SEQ ID NO:162 (CDR-L1); | 96 | residues 24-34 of SEQ ID NO:177 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:162 (CDR-L2); | | residues 50-56 of SEQ ID NO:177 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:162 (CDR-L3); | | residues 89-97 of SEQ ID NO:177 (CDR-L3); |
| 43 | residues 31-35 of SEQ ID NO:89 (CDR-H1); | 97 | residues 31-35 of SEQ ID NO:80 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:89 (CDR-H2); | | residues 50-66 of SEQ ID NO:80 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:89 (CDR-H3); | | residues 99-108 of SEQ ID NO:80 (CDR-H3); |
| 44 | residues 24-34 of SEQ ID NO:170 (CDR-L1); | 98 | residues 24-34 of SEQ ID NO:172 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:170 (CDR-L2); | | residues 50-56 of SEQ ID NO:172 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:170 | | residues 89-97 of SEQ ID NO:172 |

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| | (CDR-L3); | | (CDR-L3); |

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| 45 | residues 31-35 of SEQ ID NO:75 (CDR-H1); | 99 | residues 31-35 of SEQ ID NO:196 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:75 (CDR-H2) | | residues 50-66 of SEQ ID NO:196 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:75 (CDR-H3); | | residues 99-108 of SEQ ID NO:196 (CDR-H3); |
| 46 | residues 24-34 of SEQ ID NO:181 (CDR-L1); | 100 | residues 24-34 of SEQ ID NO:197 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:181 (CDR-L2); | | residues 50-56 of SEQ ID NO:197 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:181 (CDR-L3); | | residues 89-97 of SEQ ID NO:197 (CDR-L3); |
| 47 | residues 31-35 of SEQ ID NO:92 (CDR-H1); | 101 | residues 31-35 of SEQ ID NO:198 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:92 (CDR-H2); | | residues 50-66 of SEQ ID NO:198 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:92 (CDR-H3); | | residues 99-108 of SEQ ID NO:198 (CDR-H3); |
| 48 | residues 24-34 of SEQ ID NO:184 (CDR-L1); | 102 | residues 24-34 of SEQ ID NO:199 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:184 (CDR-L2); | | residues 50-56 of SEQ ID NO:199 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:184 (CDR-L3); | | residues 89-97 of SEQ ID NO:199 (CDR-L3); |
| 49 | residues 31-35 of SEQ ID NO:200 (CDR-H1); | 103 | residues 31-35 of SEQ ID NO:202 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:200 (CDR-H2); | | residues 50-66 of SEQ ID NO:202 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:200 (CDR-H3); | | residues 99-108 of SEQ ID NO:202 (CDR-H3); |
| 50 | residues 24-34 of SEQ ID NO:201 (CDR-L1); | 104 | residues 24-34 of SEQ ID NO:203 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:201 (CDR-L2); | | residues 50-56 of SEQ ID NO:203 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:201 (CDR-L3); | | residues 89-97 of SEQ ID NO:203 (CDR-L3); |
| 51 | residues 31-35 of SEQ ID NO:204 (CDR-H1); | 105 | residues 31-35 of SEQ ID NO:206 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:204 (CDR-H2); | | residues 50-66 of SEQ ID NO:206 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:204 (CDR-H3); | | residues 99-108 of SEQ ID NO:206 (CDR-H3); |
| 52 | residues 24-34 of SEQ ID NO:205 (CDR-L1); | 106 | residues 24-34 of SEQ ID NO:207 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:205 (CDR-L2); | | residues 50-56 of SEQ ID NO:207 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:205 | | residues 89-97 of SEQ ID NO:207 |

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| | (CDR-L3); | | (CDR-L3); |

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| 53 | residues 31-35 of SEQ ID NO:208 (CDR-H1); | 107 | residues 31-35 of SEQ ID NO:210 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:208 (CDR-H2); | | residues 50-66 of SEQ ID NO:210 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:208 (CDR-H3); | | residues 99-108 of SEQ ID NO:210 (CDR-H3); |
| 54 | residues 24-34 of SEQ ID NO:209 (CDR-L1); | 108 | residues 24-34 of SEQ ID NO:211 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:209 (CDR-L2); | | residues 50-56 of SEQ ID NO:211 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:209 (CDR-L3); | | residues 89-97 of SEQ ID NO:211 (CDR-L3); |
| 109 | residues 31-35 of SEQ ID NO:103 (CDR-H1); | 155 | residues 31-35 of SEQ ID NO:126 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:103 (CDR-H2); | | residues 50-66 of SEQ ID NO:126 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:103 (CDR-H3); | | residues 99-108 of SEQ ID NO:126 (CDR-H3); |
| 110 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 156 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 111 | residues 31-35 of SEQ ID NO:104 (CDR-H1); | 157 | residues 31-35 of SEQ ID NO:127 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:104 (CDR-H2); | | residues 50-66 of SEQ ID NO:127 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:104 (CDR-H3); | | residues 99-108 of SEQ ID NO:127 (CDR-H3); |
| 112 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 158 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 113 | residues 31-35 of SEQ ID NO:105 (CDR-H1); | 159 | residues 31-35 of SEQ ID NO:128 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:105 (CDR-H2); | | residues 50-66 of SEQ ID NO:128 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:105 (CDR-H3); | | residues 99-108 of SEQ ID NO:128 (CDR-H3); |
| 114 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 160 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 | | residues 89-97 of SEQ ID NO:59 |

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| | (CDR-L3); | | (CDR-L3); |
| 115 | residues 31-35 of SEQ ID NO:106 (CDR-H1); | 161 | residues 31-35 of SEQ ID NO:129 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:106 (CDR-H2); | | residues 50-66 of SEQ ID NO:129 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:106 (CDR-H3); | | residues 99-108 of SEQ ID NO:129 (CDR-H3); |
| 116 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 162 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 117 | residues 31-35 of SEQ ID NO:107 (CDR-H1); | 163 | residues 31-35 of SEQ ID NO:130 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:107 (CDR-H2); | | residues 50-66 of SEQ ID NO:130 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:107 (CDR-H3); | | residues 99-108 of SEQ ID NO:130 (CDR-H3); |
| 118 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 164 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 119 | residues 31-35 of SEQ ID NO:108 (CDR-H1); | 165 | residues 31-35 of SEQ ID NO:131 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:108 (CDR-H2); | | residues 50-66 of SEQ ID NO:131 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:108 (CDR-H3); | | residues 99-108 of SEQ ID NO:131 (CDR-H3); |
| 120 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 166 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 121 | residues 31-35 of SEQ ID NO:109 (CDR-H1); | 167 | residues 31-35 of SEQ ID NO:132 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:109 (CDR-H2); | | residues 50-66 of SEQ ID NO:132 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:109 (CDR-H3); | | residues 99-108 of SEQ ID NO:132 (CDR-H3); |
| 122 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 168 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |

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| 123 | residues 31-35 of SEQ ID NO:110 (CDR-H1); | 169 | residues 31-35 of SEQ ID NO:133 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:110 (CDR-H2); | | residues 50-66 of SEQ ID NO:133 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:110 (CDR-H3); | | residues 99-108 of SEQ ID NO:133 (CDR-H3); |
| 124 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 170 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 125 | residues 31-35 of SEQ ID NO:111 (CDR-H1); | 171 | residues 31-35 of SEQ ID NO:134 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:111 (CDR-H2); | | residues 50-66 of SEQ ID NO:134 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:111 (CDR-H3); | | residues 99-108 of SEQ ID NO:134 (CDR-H3); |
| 126 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 172 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 127 | residues 31-35 of SEQ ID NO:112 (CDR-H1); | 173 | residues 31-35 of SEQ ID NO:135 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:112 (CDR-H2); | | residues 50-66 of SEQ ID NO:135 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:112 (CDR-H3); | | residues 99-108 of SEQ ID NO:135 (CDR-H3); |
| 128 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 174 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 129 | residues 31-35 of SEQ ID NO:113 (CDR-H1); | 175 | residues 31-35 of SEQ ID NO:136 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:113 (CDR-H2); | | residues 50-66 of SEQ ID NO:136 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:113 (CDR-H3); | | residues 99-108 of SEQ ID NO:136 (CDR-H3); |
| 130 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 176 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 | | residues 89-97 of SEQ ID NO:59 |

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| | (CDR-L3); | | (CDR-L3); |
| 131 | residues 31-35 of SEQ ID NO:114 (CDR-H1); | 177 | residues 31-35 of SEQ ID NO:137 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:114 (CDR-H2); | | residues 50-66 of SEQ ID NO:137 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:114 (CDR-H3); | | residues 99-108 of SEQ ID NO:137 (CDR-H3); |
| 132 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 178 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 133 | residues 31-35 of SEQ ID NO:115 (CDR-H1); | 179 | residues 31-35 of SEQ ID NO:138 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:115 (CDR-H2); | | residues 50-66 of SEQ ID NO:138 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:115 (CDR-H3); | | residues 99-108 of SEQ ID NO:138 (CDR-H3); |
| 134 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 180 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 135 | residues 31-35 of SEQ ID NO:116 (CDR-H1); | 181 | residues 31-35 of SEQ ID NO:139 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:116 (CDR-H2); | | residues 50-66 of SEQ ID NO:139 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:116 (CDR-H3); | | residues 99-108 of SEQ ID NO:139 (CDR-H3); |
| 136 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 182 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 137 | residues 31-35 of SEQ ID NO:117 (CDR-H1); | 183 | residues 31-35 of SEQ ID NO:140 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:117 (CDR-H2); | | residues 50-66 of SEQ ID NO:140 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:117 (CDR-H3); | | residues 99-108 of SEQ ID NO:140 (CDR-H3); |
| 138 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 184 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |

| | | | |
|---|---|---|---|
| 139 | residues 31-35 of SEQ ID NO:118 (CDR-H1); | 185 | residues 31-35 of SEQ ID NO:141 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:118 (CDR-H2); | | residues 50-66 of SEQ ID NO:141 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:118 (CDR-H3); | | residues 99-108 of SEQ ID NO:141 (CDR-H3); |
| 140 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 186 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 141 | residues 31-35 of SEQ ID NO:119 (CDR-H1); | 187 | residues 31-35 of SEQ ID NO:142 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:119 (CDR-H2); | | residues 50-66 of SEQ ID NO:142 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:119 (CDR-H3); | | residues 99-108 of SEQ ID NO:142 (CDR-H3); |
| 142 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 188 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 143 | residues 31-35 of SEQ ID NO:120 (CDR-H1); | 189 | residues 31-35 of SEQ ID NO:143 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:120 (CDR-H2); | | residues 50-66 of SEQ ID NO:143 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:120 (CDR-H3); | | residues 99-108 of SEQ ID NO:143 (CDR-H3); |
| 144 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 190 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 145 | residues 31-35 of SEQ ID NO:121 (CDR-H1); | 191 | residues 31-35 of SEQ ID NO:144 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:121 (CDR-H2); | | residues 50-66 of SEQ ID NO:144 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:121 (CDR-H3); | | residues 99-108 of SEQ ID NO:144 (CDR-H3); |
| 146 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 192 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 | | residues 89-97 of SEQ ID NO:59 |

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|---|---|---|---|
| | (CDR-L3); | | (CDR-L3); |
| 147 | residues 31-35 of SEQ ID NO:122 (CDR-H1); | 193 | residues 31-35 of SEQ ID NO:145 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:122 (CDR-H2); | | residues 50-66 of SEQ ID NO:145 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:122 (CDR-H3); | | residues 99-108 of SEQ ID NO:145 (CDR-H3); |
| 148 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 194 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 149 | residues 31-35 of SEQ ID NO:123 (CDR-H1); | 195 | residues 31-35 of SEQ ID NO:146 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:123 (CDR-H2); | | residues 50-66 of SEQ ID NO:146 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:123 (CDR-H3); | | residues 99-108 of SEQ ID NO:146 (CDR-H3); |
| 150 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 196 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 151 | residues 31-35 of SEQ ID NO:124 (CDR-H1); | 197 | residues 31-35 of SEQ ID NO:147 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:124 (CDR-H2); | | residues 50-66 of SEQ ID NO:147 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:124 (CDR-H3); | | residues 99-108 of SEQ ID NO:147 (CDR-H3); |
| 152 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 198 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3); |
| 153 | residues 31-35 of SEQ ID NO:125 (CDR-H1); | 199 | residues 31-35 of SEQ ID NO:148 (CDR-H1); |
| | residues 50-66 of SEQ ID NO:125 (CDR-H2); | | residues 50-66 of SEQ ID NO:148 (CDR-H2); |
| | residues 99-108 of SEQ ID NO:125 (CDR-H3); | | residues 99-108 of SEQ ID NO:148 (CDR-H3); |
| 154 | residues 24-34 of SEQ ID NO:59 (CDR-L1); | 200 | residues 24-34 of SEQ ID NO:59 (CDR-L1); |
| | residues 50-56 of SEQ ID NO:59 (CDR-L2); | | residues 50-56 of SEQ ID NO:59 (CDR-L2); |
| | residues 89-97 of SEQ ID NO:59 (CDR-L3); | | residues 89-97 of SEQ ID NO:59 (CDR-L3). |

26. The binding protein according to Claim 25, comprising CDRs from two CDR sets.

27. The binding protein according to Claim 26, wherein said two CDR sets are selected from the group consisting of:

| | |
|---|---|
| CDR Set 1 and CDR Set 2 | CDR Set 101 and CDR Set 102 |
| CDR Set 3 and CDR Set 4 | CDR Set 103 and CDR Set 104 |
| CDR Set 5 and CDR Set 6 | CDR Set 105 and CDR Set 106 |
| CDR Set 7 and CDR Set 8 | CDR Set 107 and CDR Set 108 |
| CDR Set 9 and CDR Set 10 | CDR Set 109 and CDR Set 110 |
| CDR Set 11 and CDR Set 12 | CDR Set 111 and CDR Set 112 |
| CDR Set 13 and CDR Set 14 | CDR Set 113 and CDR Set 114 |
| CDR Set 15 and CDR Set 16 | CDR Set 115 and CDR Set 116 |
| CDR Set 17 and CDR Set 18 | CDR Set 117 and CDR Set 118 |
| CDR Set 19 and CDR Set 20 | CDR Set 119 and CDR Set 120 |
| CDR Set 21 and CDR Set 22 | CDR Set 121 and CDR Set 122 |
| CDR Set 23 and CDR Set 24 | CDR Set 123 and CDR Set 124 |
| CDR Set 25 and CDR Set 26 | CDR Set 125 and CDR Set 126 |
| CDR Set 27 and CDR Set 28 | CDR Set 127 and CDR Set 128 |
| CDR Set 29 and CDR Set 30 | CDR Set 129 and CDR Set 130 |
| CDR Set 31 and CDR Set 32 | CDR Set 131 and CDR Set 132 |
| CDR Set 33 and CDR Set 34 | CDR Set 133 and CDR Set 134 |
| CDR Set 35 and CDR Set 36 | CDR Set 135 and CDR Set 136 |
| CDR Set 37 and CDR Set 38 | CDR Set 137 and CDR Set 138 |
| CDR Set 39 and CDR Set 40 | CDR Set 139 and CDR Set 140 |
| CDR Set 41 and CDR Set 42 | CDR Set 141 and CDR Set 142 |
| CDR Set 43 and CDR Set 44 | CDR Set 143 and CDR Set 144 |
| CDR Set 45 and CDR Set 46 | CDR Set 145 and CDR Set 146 |
| CDR Set 47 and CDR Set 48 | CDR Set 147 and CDR Set 148 |
| CDR Set 49 and CDR Set 50 | CDR Set 149 and CDR Set 150 |
| CDR Set 51 and CDR Set 52 | CDR Set 151 and CDR Set 152 |
| CDR Set 53 and CDR Set 54 | CDR Set 153 and CDR Set 154 |

| | |
|---|---|
| CDR Set 55 and CDR Set 56 | CDR Set 155 and CDR Set 156 |
| CDR Set 57 and CDR Set 58 | CDR Set 157 and CDR Set 158 |
| CDR Set 59 and CDR Set 60 | CDR Set 159 and CDR Set 160 |
| CDR Set 61 and CDR Set 62 | CDR Set 161 and CDR Set 162 |
| CDR Set 63 and CDR Set 64 | CDR Set 163 and CDR Set 164 |
| CDR Set 65 and CDR Set 66 | CDR Set 165 and CDR Set 166 |
| CDR Set 67 and CDR Set 68 | CDR Set 167 and CDR Set 168 |
| CDR Set 69 and CDR Set 70 | CDR Set 169 and CDR Set 170 |
| CDR Set 71 and CDR Set 72 | CDR Set 171 and CDR Set 172 |
| CDR Set 73 and CDR Set 74 | CDR Set 173 and CDR Set 174 |
| CDR Set 75 and CDR Set 76 | CDR Set 175 and CDR Set 176 |
| CDR Set 77 and CDR Set 78 | CDR Set 177 and CDR Set 178 |
| CDR Set 79 and CDR Set 80 | CDR Set 179 and CDR Set 180 |
| CDR Set 81 and CDR Set 82 | CDR Set 181 and CDR Set 182 |
| CDR Set 83 and CDR Set 84 | CDR Set 183 and CDR Set 184 |
| CDR Set 85 and CDR Set 86 | CDR Set 185 and CDR Set 186 |
| CDR Set 87 and CDR Set 88 | CDR Set 187 and CDR Set 188 |
| CDR Set 89 and CDR Set 90 | CDR Set 189 and CDR Set 190 |
| CDR Set 91 and CDR Set 92 | CDR Set 191 and CDR Set 192 |
| CDR Set 93 and CDR Set 94 | CDR Set 193 and CDR Set 194 |
| CDR Set 95 and CDR Set 96 | CDR Set 195 and CDR Set 196 |
| CDR Set 97 and CDR Set 98 | CDR Set 197 and CDR Set 198 |
| CDR Set 99 and CDR Set 100 | CDR Set 199 and CDR Set 200 |

28. The binding protein according to any one of Claims 24-27, further comprising a human acceptor framework.

29. The binding protein according to Claim 28, wherein said human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 7-10, 13-16, 25, 240-316, and 317-381.

30. The binding protein according to any one of Claims 24-27, wherein said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO:60-SEQ ID NO:189.

31. The binding protein according to Claim 30, wherein said binding protein comprises two variable domains, wherein said two variable domains comprise amino acid sequences selected from the group consisting of:

| | |
|---|---|
| SEQ ID NO:60 and SEQ ID NO:149 | SEQ ID NO:198 and SEQ ID NO:199 |
| SEQ ID NO:69 and SEQ ID NO:173 | SEQ ID NO:202 and SEQ ID NO:203 |
| SEQ ID NO:67 and SEQ ID NO:151 | SEQ ID NO:206 and SEQ ID NO:207 |
| SEQ ID NO:88 and SEQ ID NO:159 | SEQ ID NO:210 and SEQ ID NO:211 |
| SEQ ID NO:96 and SEQ ID NO:155 | SEQ ID NO:103 and SEQ ID NO:59 |
| SEQ ID NO:90 and SEQ ID NO:182 | SEQ ID NO:104 and SEQ ID NO:59 |
| SEQ ID NO:90 and SEQ ID NO:167 | SEQ ID NO:105 and SEQ ID NO:59 |
| SEQ ID NO:90 and SEQ ID NO:164 | SEQ ID NO:106 and SEQ ID NO:59 |
| SEQ ID NO:73 and SEQ ID NO:174 | SEQ ID NO:107 and SEQ ID NO:59 |
| SEQ ID NO:86 and SEQ ID NO:159 | SEQ ID NO:108 and SEQ ID NO:59 |
| SEQ ID NO:90 and SEQ ID NO:169 | SEQ ID NO:109 and SEQ ID NO:59 |
| SEQ ID NO:91 and SEQ ID NO:165 | SEQ ID NO:110 and SEQ ID NO:59 |
| SEQ ID NO:76 and SEQ ID NO:175 | SEQ ID NO:111 and SEQ ID NO:59 |
| SEQ ID NO:99 and SEQ ID NO:189 | SEQ ID NO:112 and SEQ ID NO:59 |
| SEQ ID NO:100 and SEQ ID NO:168 | SEQ ID NO:113 and SEQ ID NO:59 |
| SEQ ID NO:71 and SEQ ID NO:170 | SEQ ID NO:114 and SEQ ID NO:59 |
| SEQ ID NO:84 and SEQ ID NO:188 | SEQ ID NO:115 and SEQ ID NO:59 |
| SEQ ID NO:78 and SEQ ID NO:179 | SEQ ID NO:116 and SEQ ID NO:59 |
| SEQ ID NO:93 and SEQ ID NO:176 | SEQ ID NO:117 and SEQ ID NO:59 |
| SEQ ID NO:87 and SEQ ID NO:154 | SEQ ID NO:118 and SEQ ID NO:59 |
| SEQ ID NO:85 and SEQ ID NO:162 | SEQ ID NO:119 and SEQ ID NO:59 |
| SEQ ID NO:89 and SEQ ID NO:170 | SEQ ID NO:120 and SEQ ID NO:59 |
| SEQ ID NO:75 and SEQ ID NO:181 | SEQ ID NO:121 and SEQ ID NO:59 |
| SEQ ID NO:92 and SEQ ID NO:184 | SEQ ID NO:122 and SEQ ID NO:59 |
| SEQ ID NO:200 and SEQ ID NO:201 | SEQ ID NO:123 and SEQ ID NO:59 |
| SEQ ID NO:204 and SEQ ID NO:205 | SEQ ID NO:124 and SEQ ID NO:59 |
| SEQ ID NO:208 and SEQ ID NO:209 | SEQ ID NO:125 and SEQ ID NO:59 |
| SEQ ID NO:63 and SEQ ID NO:150 | SEQ ID NO:126 and SEQ ID NO:59 |

| | |
|---|---|
| SEQ ID NO:97 and SEQ ID NO:187 | SEQ ID NO:127 and SEQ ID NO:59 |
| SEQ ID NO:90 and SEQ ID NO:156 | SEQ ID NO:128 and SEQ ID NO:59 |
| SEQ ID NO:92 and SEQ ID NO:153 | SEQ ID NO:129 and SEQ ID NO:59 |
| SEQ ID NO:94 and SEQ ID NO:166 | SEQ ID NO:130 and SEQ ID NO:59 |
| SEQ ID NO:82 and SEQ ID NO:159 | SEQ ID NO:131 and SEQ ID NO:59 |
| SEQ ID NO:101 and SEQ ID NO:158 | SEQ ID NO:132 and SEQ ID NO:59 |
| SEQ ID NO:96 and SEQ ID NO:157 | SEQ ID NO:133 and SEQ ID NO:59 |
| SEQ ID NO:70 and SEQ ID NO:161 | SEQ ID NO:134 and SEQ ID NO:59 |
| SEQ ID NO:83 and SEQ ID NO:158 | SEQ ID NO:135 and SEQ ID NO:59 |
| SEQ ID NO:102 and SEQ ID NO:185 | SEQ ID NO:136 and SEQ ID NO:59 |
| SEQ ID NO:98 and SEQ ID NO:160 | SEQ ID NO:137 and SEQ ID NO:59 |
| SEQ ID NO:74 and SEQ ID NO:186 | SEQ ID NO:138 and SEQ ID NO:59 |
| SEQ ID NO:95 and SEQ ID NO:157 | SEQ ID NO:139 and SEQ ID NO:59 |
| SEQ ID NO:72 and SEQ ID NO:178 | SEQ ID NO:140 and SEQ ID NO:59 |
| SEQ ID NO:96 and SEQ ID NO:163 | SEQ ID NO:141 and SEQ ID NO:59 |
| SEQ ID NO:77 and SEQ ID NO:183 | SEQ ID NO:142 and SEQ ID NO:59 |
| SEQ ID NO:90 and SEQ ID NO:171 | SEQ ID NO:143 and SEQ ID NO:59 |
| SEQ ID NO:79 and SEQ ID NO:180 | SEQ ID NO:144 and SEQ ID NO:59 |
| SEQ ID NO:381 and SEQ ID NO:152 | SEQ ID NO:145 and SEQ ID NO:59 |
| SEQ ID NO:81 and SEQ ID NO:177 | SEQ ID NO:146 and SEQ ID NO:59 |
| SEQ ID NO:80 and SEQ ID NO:172 | SEQ ID NO:147 and SEQ ID NO:59 |
| SEQ ID NO:196 and SEQ ID NO:197 | SEQ ID NO:148 and SEQ ID NO:59 |

32. The IL-1β binding protein according to Claim 23, wherein said IL-1β binding protein is selected from the group consisting of: an immunoglobulin molecule, a disulfide linked Fv, a monoclonal antibody, an scFv, a chimeric antibody, a CDR-grafted antibody, a diabody, a humanized antibody, a multispecific antibody, an Fab, a dual specific antibody, a Fab', a bispecific antibody, and a $F(ab')_2$, a DVD-Ig™, and an Fv.

33. The IL-1β binding protein according to Claim 32, wherein said binding protein comprises an immunoglobulin constant domain having an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

34. An IL-1β binding protein conjugate comprising an IL-1β binding protein as described in Claim 32, said IL-1β binding protein conjugate further comprising an agent selected from the group consisting of an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

35. The IL-1β binding protein according to Claim 23, or the IL-1β binding protein conjugate of Claim 34, wherein said binding protein is a crystallized binding protein.

36. A pharmaceutical composition comprising a binding protein as described in Claim 24, or the IL-1β binding protein conjugate of Claim 34, and a pharmaceutically acceptable carrier.

37. An isolated nucleic acid encoding an amino acid sequence of an IL-1β binding protein as described in Claim 24.

38. A vector comprising an isolated nucleic acid according to Claim 37.

39. A host cell comprising a vector according to Claim 38.

40. A method of producing an IL-1β binding protein, comprising culturing a host cell described in Claim 39 in culture medium under conditions sufficient to produce the IL-1β binding protein.

41. Use of a binding protein as described in Claim 24 or a crystal thereof in the manufacture of a medicament for reducing human IL-1 activity in a human subject suffering from a disorder in which IL-1 activity is detrimental.

42. Use of a binding protein as described in Claim 24 or a crystal thereof in the manufacure of a medicament for treating a subject for a disorder in which IL-1 activity is detrimental.

43. The use of Claim 42, wherein said disorder is selected from the group consisting of: diabetes; uveitis; neuropathic pain; osteoarthritic pain; inflammatory pain; rheumatoid arthritis; osteoarthritis; juvenile chronic arthritis; septic arthritis; Lyme arthritis; psoriatic arthritis; reactive arthritis; spondyloarthropathy; systemic lupus erythematosus (SLE); Crohn's disease; ulcerative colitis; inflammatory bowel disease; autoimmune diabetes; insulin dependent diabetes

ulcerative colitis; inflammatory bowel disease; autoimmune diabetes; insulin dependent diabetes mellitus; thyroiditis; asthma; allergic diseases; psoriasis; dermatitis; scleroderma; graft versus host disease; organ transplant rejection; acute immune disease associated with organ transplantation; chronic immune disease associated with organ transplantation; sarcoidosis; atherosclerosis; disseminated intravascular coagulation (DIC); 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; autoimmune uveitis; septic shock; toxic shock syndrome; sepsis syndrome; cachexia; infectious diseases; parasitic diseases; 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; polyglandular deficiency type II (Schmidt's syndrome); acute respiratory distress syndrome (ARDS); alopecia; alopecia areata; seronegative arthropathy; arthropathy; Reiter's disease; psoriatic arthropathy; ulcerative colitic arthropathy; enteropathic synovitis; chlamydia; *Yersinia* and *Salmonella* associated arthropathy; spondyloarthropathy; 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 (GCA); primary sclerosing hepatitis; cryptogenic autoimmune hepatitis; acquired immunodeficiency syndrome (AIDS); 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; 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; postinfectious 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; osteoarthrosis; primary sclerosing cholangitis; psoriasis type 1; psoriasis type 2; idiopathic leucopaenia; autoimmune neutropaenia; renal disease NOS; glomerulonephritides; microscopic vasculitis of the kidneys; Lyme disease; discoid lupus erythematosus; idiopathic male infertility; nitric oxide-associated male infertility; sperm autoimmunity; multiple sclerosis (all subtypes, including primary progressive, secondary progressive, relapsing remitting); 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 (AITP); 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; cholestasis; idiosyncratic liver disease; drug-induced hepatitis; non-alcoholic steatohepatitis; allergy; 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); cancer (such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate, and rectal cancer); hematopoietic malignancies; leukemia; lymphoma; abetalipoproteinemia; acrocyanosis; acute and chronic parasitic or infectious processes; acute leukemia; acute lymphoblastic leukemia (ALL); T-cell ALL; FAB ALL; acute myeloid leukemia (AML); acute or chronic bacterial infection; acute pancreatitis; acute renal failure; adenocarcinomas; atrial 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; antiphospholipid syndrome; anti-receptor hypersensitivity reactions; aortic and peripheral aneurysms; 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 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 hemophagocytic 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; hemochromatosis; 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 (IPF); 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; lymphedema; malaria; malignant lymphoma; malignant histiocytosis; malignant melanoma; meningitis; meningococcemia; metabolic syndrome migraine headache; idiopathic migraine headache; mitochondrial multisystem disorder; mixed connective tissue disease; monoclonal gammopathy; multiple myeloma; multiple systems degenerations (Menzel; Dejerine-Thomas; Shy-Drager; and Machado-Joseph); myasthenia gravis; mycobacterium avium intracellulare; mycobacterium tuberculosis; myelodysplastic syndrome; myocardial infarction; myocardial ischemic disorders; nasopharyngeal carcinoma; neonatal chronic lung disease; nephritis; nephrosis; neurodegenerative diseases; neurogenic I muscular atrophies; neutropenic fever; non-Hodgkin's lymphoma; occlusion of the abdominal aorta and its branches; occlusive arterial disorders; OKT3® therapy; orchitis/epididymitis; 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; Raynaud's disease; Refsum's disease; regular narrow QRS tachycardia; renovascular hypertension; reperfusion injury; restrictive cardiomyopathy; sarcomas; 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; 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; viral encephalitis/aseptic meningitis; viral-associated hemophagocytic 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; dacryocystitis; dermatomyositis; diabetic retinopathy; disk herniation; disk prolapse; drug induced immune hemolytic anemia; endocarditis; endometriosis; endophthalmitis; episcleritis; erythema multiforme; erythema multiforme major; gestational pemphigoid; Guillain-Barré 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; iritis; keratitis;

keratojunctivitis 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; 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; secondary 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; spondylitis ankylosans; Stevens-Johnson syndrome (SJS); systemic inflammatory response syndrome; temporal arteritis; toxoplasmic retinitis; toxic epidermal necrolysis; transverse myelitis; TRAPS (tumor necrosis factor receptor type 1 (TNFR)-associated periodic syndrome); type B insulin resistance with acanthosis nigricans; type 1 allergic reaction; type II diabetes; urticaria; usual interstitial pneumonia (UIP); vernal conjunctivitis; viral retinitis; Vogt-Koyanagi-Harada syndrome (VKH syndrome); wet macular degeneration; wound healing; *Yersinia* and *Salmonella* associated arthropathy.

## CLAIMS

1. A binding protein comprising first and second polypeptide chains, wherein said 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 with the proviso that it is not CH1;

X2 is an Fc region; and

n is independently 0 or 1; and

wherein said 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 with the proviso that it is not CH1;

X2 does not comprise an Fc region; and

n is independently 0 or 1;

wherein, in said first polypeptide chain,

VD1 comprises the amino acid sequence of SEQ ID NO: 204; and VD2 comprises the amino acid sequence of SEQ ID NO: 213;

wherein, in said second polypeptide chain,

VD1 comprises the amino acid sequence of SEQ ID NO: 238; and

VD2 comprises the amino acid sequence of SEQ ID NO: 216; and

wherein the binding protein binds human IL-1β and human IL-1α.

2. A binding protein comprising first and second polypeptide chains, wherein said 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 with the proviso that it is not CH1;

X2 is an Fc region; and

n is independently 0 or 1; and

wherein said 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 with the proviso that it is not CH1;

X2 does not comprise an Fc region; and

n is independently 0 or 1;

wherein, in said first polypeptide chain,

VD1 comprises the amino acid sequence of SEQ ID NO: 213; and

VD2 comprises the amino acid sequence of SEQ ID NO: 204;

wherein, in said second polypeptide chain,

VD1 comprises the amino acid sequence of SEQ ID NO: 216; and

VD2 comprises the amino acid sequence of SEQ ID NO: 238; and

wherein the binding protein binds human IL-1β and human IL-1α.

3. The binding protein according to Claim 1, wherein:
said first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 212.

4. The binding protein according to Claim 1, wherein:
said second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 215.

5. The binding protein according to Claim 2, wherein:
said first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 219.

6. The binding protein according to Claim 2, wherein:
said second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 220.

7. The binding protein according to Claim 1, wherein:
when said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:212,
then said second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 215.

8. The binding protein according to Claim 2, wherein said first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 219, and said second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 220.

9. The binding protein according to Claim 1, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.

10. The binding protein according to Claim 1, wherein X1 is an amino acid sequence selected from the group consisting of SEQ ID NOs: 26-57, 223 224, and 225.

11. The binding protein according to Claim 1, wherein the Fc region is a variant sequence Fc region.

12. The binding protein according to any of Claims 1, 3, 4, 7, 9, 10 or 11, wherein the Fc region is selected from the group consisting of an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, and IgD.

13. The binding protein according to Claim 12, wherein the IgG1 heavy chain constant region comprises L234A and L235A hinge-region mutations.

14. A binding protein conjugate comprising a binding protein as described in any of Claims 1, 3, 4, 7, 9, 10, 11, 12 or 13, said binding protein conjugate further comprising an agent selected from the group consisting of: an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

15. The binding protein conjugate according to Claim 14, wherein said agent is 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, a toxin, and an apoptotic agent.

16. A pharmaceutical composition comprising a binding protein as described in any of Claims 1, 3, 4, 7, 9, 10, 11, 12 or 13, and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition according to Claim 16, further comprising at least one additional agent.

18. The pharmaceutical composition according to Claim 17, wherein said additional agent is selected from the group consisting of: a therapeutic agent; 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 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 thereof; a cytokine; and a cytokine antagonist.

19. A pharmaceutical composition comprising a binding protein conjugate as described in Claim 14, and a pharmaceutically acceptable carrier.

20. The pharmaceutical composition according to Claim 19, wherein said binding protein conjugate 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, a toxin, and an apoptotic agent.

21. The binding protein according to Claim 2, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.

22. The binding protein according to Claim 2, wherein X1 or X2 is an amino acid sequence selected from the group consisting of SEQ ID NOs:26-57, 223, 224, and 225.

23. The binding protein according to Claim 2, wherein the Fc region is a variant sequence Fc region.

24. A binding protein conjugate comprising a binding protein as described in any of claims 2, 5, 6, 8, 21, 22, or 23, said binding protein conjugate further comprising an agent selected from the group consisting of: an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

25. The binding protein conjugate according to Caim 24, wherein said agent is 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, a toxin, and an apoptotic agent.

26. A pharmaceutical composition comprising a binding protein as described in any of claims 2, 5, 6, 8, 21, 22, or 23, and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition according to Claim 26, further comprising at least one additional agent.

28. The pharmaceutical composition according to Claim 27, wherein said additional agent is selected from the group consisting of: a therapeutic agent; 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 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 thereof; a cytokine; and a cytokine antagonist.

29. A pharmaceutical composition comprising a binding protein conjugate as described in Claim 24, and a pharmaceutically acceptable carrier.

30. The pharmaceutical composition according to Claim 29, wherein said agent is 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, a toxin, and an apoptotic agent.

31. A binding protein comprising first and second polypeptide chains, wherein said 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 with the proviso that it is not CH1;
X2 is an Fc region; and
n is independently 0 or 1; and
wherein said 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 with the proviso that it is not CH1;
X2 does not comprise an Fc region; and
n is independently 0 or 1;
wherein, in said first polypeptide chain,
VD1 comprises the amino acid sequence of SEQ ID NO: 204; and
VD2 comprises the amino acid sequence of SEQ ID NO: 213;
wherein, in said second polypeptide chain,
VD1 comprises the amino acid sequence of SEQ ID NO: 238; and
VD2 comprises the amino acid sequence of SEQ ID NO: 216; and
wherein said first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 212, and said second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 215; and
wherein the binding protein binds human IL-1β and human IL-1α.

32. A binding protein comprising first and second polypeptide chains, wherein said 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 with the proviso that it is not CH1;
X2 is an Fc region; and n is independently 0 or 1; and
wherein said 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 with the proviso that it is not CH1;
X2 does not comprise an Fc region; and n is independently 0 or 1;
wherein, in said first polypeptide chain,
VD1 comprises the amino acid sequence of SEQ ID NO: 213; and
VD2 comprises the amino acid sequence of SEQ ID NO: 204;
wherein, in said second polypeptide chain,
VD1 comprises the amino acid sequence of SEQ ID NO: 216; and
VD2 comprises the amino acid sequence of SEQ ID NO: 238; and

wherein said first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 219, and said second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 220; and

wherein the binding protein binds human IL-1β and human IL-1α.

33. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide chain amino acid sequence of a binding protein described in any of Claims 1-13 or 21-23.

34. A vector comprising one or more isolated nucleic acid molecules according to Claim 33.

35. A host cell comprising a vector according to Claim 34.

36. A method of producing a binding protein, comprising culturing the host cell described in Claim 35 in culture medium under conditions sufficient to produce the binding protein.

37. Use of the binding protein as described in any of Claims 1-13 or 21-23 in the manufacture of a medicament for reducing human IL-1α activity such that human IL-1 protein activity is reduced.

38. Use of the binding protein as described in any of Claims 1-13 or 21-23 or a crystal thereof, in the manufacture of a medicament for reducing human IL-1 activity in a human subject suffering from a disorder in which IL-1 activity is detrimental, such that human IL-1 activity in the human subject is reduced.

39. Use of the binding protein as described in any of Claims 1-13 or 21-23 or a crystal thereof in the manufacture of a medicament for treating a disorder in which IL-1 activity is detrimental, such that treatment is achieved in a human subject.