Claims

1. A binding protein comprising first and second polypeptide chains, wherein the first polypeptide chain comprises a first VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first heavy chain variable domain;
VD2 is a second heavy chain variable domain;
C is a heavy chain constant domain;
X1 is a linker;
X2 is an Fc region; and
wherein the second polypeptide chain comprises a second VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first light chain variable domain;
VD2 is a second light chain variable domain;
C is a light chain constant domain;
X1 is a linker;
X2 does not comprise an Fc region;
n is 0 or 1, and
wherein the binding protein is capable of binding a pair of antigens selected from the group consisting of IL-1alpha and IL-1beta,
wherein either the VD1 heavy and light chain variable domain or the VD2 heavy and light chain variable domain form an antigen binding domain that binds the IL-1beta antigen and comprises the amino acid sequences of SEQ ID NOs: 30 and 31 or SEQ ID NOs: 32 and 33, and
wherein the other of the VD1 or VD2 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.
2. The binding protein of claim 1, wherein the heavy chain variable domain of the antigen binding domain that binds the IL-1alpha comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, and 46 and wherein the light chain variable domain of the antigen binding domain that binds the IL-1alpha comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 33, 35, 37, 39, 41, 43, 45, and 47.
3. The binding protein of claim 1, wherein X1 or X2 is an amino acid sequence selected from the group consisting of SEQ ID NOs 1-29.
4. The binding protein of claim 1, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.
5. The binding protein according to claim 1, wherein the Fc region is a variant sequence Fc region.
6. A binding protein capable of binding two antigens comprising four polypeptide chains, wherein two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first heavy chain variable domain;
VD2 is a second heavy chain variable domain;
C is a heavy chain constant domain;
X1 is a linker;
X2 is an Fc region; and
wherein two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first light chain variable domain;
VD2 is a second light chain variable domain;
C is a light chain constant domain;
X1 is a linker;
X2 does not comprise an Fc region; and
n is 0 or 1;
wherein the VD1 heavy and light chain variable domains form an antigen binding domain that binds the IL-1beta antigen
and comprise the amino acid sequences of SEQ ID NOs 30 and 31 or SEQ ID NOs 32 and 33; and

wherein the VD2 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.

7. A binding protein capable of binding two antigens comprising four polypeptide chains, wherein two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first heavy chain variable domain;
VD2 is a second heavy chain variable domain;
C is a heavy chain constant domain;
X1 is a linker;
X2 is an Fc region; and
n is 0 or 1; and
wherein two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first light chain variable domain;
VD2 is a second light chain variable domain;
C is a light chain constant domain;
X1 is a linker;
X2 does not comprise an Fc region; and
n is 0 or 1;
wherein the VD2 heavy and light chain variable domains form an antigen binding domain that binds the IL-1beta antigen
and comprise the amino acid sequences of SEQ ID NOs 30 and 31 or SEQ ID NOs 32 and 33; and
wherein the VD1 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.

8. The binding protein of claim 1, 6, or 7, wherein the binding protein has an on rate constant (Kon) to IL-1beta antigen selected from the group consisting of: at least about $10^2 M^{-1}s^{-1}$; at least about $10^3 M^{-1}s^{-1}$; at least about $10^4 M^{-1}s^{-1}$; at least about $10^5 M^{-1}s^{-1}$; and at least about $10^6 M^{-1}s^{-1}$, as measured by surface plasmon resonance.

9. The binding protein of claim 1, 6, or 7, wherein the binding protein has an off rate constant (Koff) to IL-1beta antigen selected from the group consisting of: at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance.

10. The binding protein of claim 1, 6, or 7, wherein the binding protein has a dissociation constant (K_D) to IL-1beta antigen selected from the group consisting of: at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; and at most 10^{-13} M.

11. A binding protein conjugate comprising a binding protein according to any one of claims 1, 6, or 7, the 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 conjugate of claim 11, wherein the imaging agent is selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

13. The binding protein conjugate of claim 12, wherein the imaging agent is a radiolabel selected from the group consisting of: ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm.

14. The binding protein conjugate of claim 12, wherein the 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, toxin, and an apoptotic agent.

15. The binding protein of claim 1, 6, or 7, wherein said binding protein is a crystallized binding protein.

16. The binding protein of claim 15, wherein the crystal is a carrier-free pharmaceutical controlled release crystal

17. The binding protein of claim 15, wherein the binding protein has a greater half life in vivo than the soluble counterpart of said binding protein.

18. The binding protein of claim 15, wherein the binding protein retains biological activity.

19. An isolated nucleic acid encoding a binding protein amino acid sequence according to any one of claims 1, 6, or 7.

20. A vector comprising an isolated nucleic acid according to claim 19.

21. The vector of claim 20, wherein the vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, and pBJ.

22. A host cell comprising a vector according to claim 20, wherein the host cell is not a human cell.

23. The host cell of claim 22, wherein host cell is a prokaryotic cell.

24. The host cell of claim 23, wherein the host cell is E.Coli.

25. The host cell of claim 22, wherein the host cell is a eukaryotic cell.

26. The host cell of claim 25, wherein the eukaryotic cell is selected from the group consisting of protist cell, animal cell, plant cell and fungal cell.

27. The host cell of claim 25, wherein the eukaryotic cell is an animal cell selected from the group consisting of: a mammalian cell, an avian cell, and an insect cell.

28. The host cell of claim 27, wherein the host cell is a CHO cell.

29. The host cell of claim 27, wherein the host cell is COS.

30. The host cell of claim 25, wherein the host cell is a yeast cell.

31. The host cell of claim 30, wherein the yeast cell is *Saccharomyces cerevisiae*.

32. The host cell of claim 27, wherein the host cell is an insect Sf9 cell.

33. A method of producing a binding protein, comprising culturing a host cell described in any one of claims 22-32 in culture medium under conditions sufficient to produce the binding protein.

34. The method of claim 33, wherein 50%-75% of the binding protein produced is a dual specific tetravalent binding protein.

35. The method of claim 33, wherein 75%-90% of the binding protein produced is a dual specific tetravalent binding protein.

36. The method of claim 33, wherein 90%-95% of the binding protein produced is a dual specific tetravalent binding protein.

37. A pharmaceutical composition comprising the binding protein of any one of claims 1-18, and a pharmaceutically acceptable carrier.

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

39. The pharmaceutical composition of claim 38, wherein the additional therapeutic agent is selected from the group consisting of: a cytotoxic agent, an angiogenesis inhibitor; a kinase inhibitor; a co-stimulation molecule blocker; an adhesion molecule blocker; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an antirheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

40. Use of the binding protein of any of claims 1-18 in the manufacture of a medicament or treating a subject for a disease or a disorder.

41. The use of claim 40, wherein the disorder is selected from the group comprising rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthopathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, spondyloarthopathy, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis B, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, 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, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthrosis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjörgren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo acute liver disease, chronic liver diseases, alcoholic cirrhosis, alcohol-induced liver injury, choleosatatis, idiosyncratic liver disease, Drug-Induced hepatitis, Non-alcoholic Steatohepatitis, allergy and asthma, group B streptococci (GBS) infection, mental disorders (*e.g.*, depression and schizophrenia), Th2 Type and Th1 Type mediated diseases, acute and chronic pain (different forms of pain), and cancers such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma) Abetalipoprotemia, Acrocyanosis, acute and chronic parasitic or infectious processes, acute leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute or chronic bacterial infection, acute pancreatitis, acute renal failure, adenocarcinomas, aerial ectopic beats, AIDS dementia complex, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allograft rejection, alpha-l-antitrypsin deficiency, amyotrophic lateral sclerosis, anemia, angina pectoris, anterior horn cell degeneration, anti cd3 therapy, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aordic and peripheral aneuryisms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, Burns, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chromic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, cor pulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, Dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic ateriosclerotic disease, Diffuse Lewy body disease, dilated congestive cardiomyopathy, disorders of the basal ganglia, Down's Syndrome in middle age, drug- induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, epiglottitis, epstein-barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hematophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, fungal sepsis, gas gangrene, gastric ulcer, glomerular nephritis, graft rejection of any organ or tissue, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, hairy cell leukemia, Hallerrorden-Spatz disease, hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, hepatitis (A), His

bundle arrythmias, HIV infection/HIV neuropathy, Hodgkin's disease, hyperkinetic movement disorders, hypersensitity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, antibody mediated cytotoxicity, Asthenia, infantile spinal muscular atrophy, inflammation of the aorta, influenza a, ionizing radiation exposure, iridocyclitis/uveitis/optic neuritis, ischemia- reperfusion injury, ischemic stroke, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, lipedema, liver transplant rejection, lymphederma, malaria, malignamt Lymphoma, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, metabolic/idiopathic, migraine headache, mitochondrial multi.system disorder, mixed connective tissue disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel Dejerine- Thomas Shi-Drager and Machado-Joseph), myasthenia gravis, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodyplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, non- hodgkins lymphoma, occlusion of the abdominal aorta and its branches, occulsive arterial disorders, okt3 therapy, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoporosis, pancreas transplant rejection, pancreatic carcinoma, paraneoplastic syndrome/hypercalcemia of malignancy, parathyroid transplant rejection, pelvic inflammatory disease, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, preeclampsia, Progressive supranucleo Palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon and disease, Raynoud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, Senile Dementia of Lewy body type, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, Syncope, syphilis of the cardiovascular system, systemic anaphalaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T-cell or FAB ALL, Telangiectasia, thromboangitis obliterans, thrombocytopenia, toxicity, transplants, trauma/hemorrhage, type III hypersensitivity reactions, type IV hypersensitivity, unstable angina, uremia, urosepsis, urticaria, valvular heart diseases, varicose veins, ,vasculitis, venous diseases, venous thrombosis, ventricular fibrillation, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wernicke- Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, acute coronary syndromes, acute idiopathic polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, alopecia areata, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, arteriosclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic ischemia, cicatricial pemphigoid, clinically isolated syndrome (cis) with risk for multiple sclerosis, conjunctivitis, childhood onset psychiatric disorder, chronic obstructive pulmonary disease (COPD), dacryocystitis, dermatomyositis, diabetic retinopathy, diabetes mellitus, disk herniation, disk prolaps, 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, IPF/UIP, iritis, keratitis, keratojuntivitis sicca, Kussmaul disease or Kussmaul-Meier disease, Landry's paralysis, Langerhan's cell histiocytosis, livedo reticularis, macular degeneration, microscopic polyangiitis, morbus bechterev, motor neuron disorders, mucous membrane pemphigoid, multiple organ failure, myasthenia gravis, myelodysplastic syndrome, myocarditis, nerve root disorders, neuropathy, non-A non-B hepatitis, optic neuritis, osteolysis, ovarian cancer, pauciarticular JRA, peripheral artery occlusive disease (PAOD), peripheral vascular disease (PVD), peripheral artery, disease (PAD), phlebitis, polyarteritis nodosa (or periarteritis nodosa), polychondritis, polymyalgia rheumatica, poliosis, polyarticular JRA, polyendocrine deficiency syndrome, polymyositis, polymyalgia rheumatica (PMR), post-pump syndrome, primary Parkinsonism, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), prostatitis, pure red cell aplasia, primary adrenal insufficiency, recurrent neuromyelitis optica, restenosis, rheumatic heart disease, sapho (synovitis, acne, pustulosis, hyperostosis, and osteitis), scleroderma, secondary amyloidosis, shock lung, scleritis, sciatica, secondary adrenal insufficiency, silicone associated connective tissue disease, sneddon-wilkinson dermatosis, spondilitis ankylosans, Stevens-Johnson syndrome (SJS), systemic inflammatory response syndrome, temporal arteritis, toxoplasmic retinitis, toxic epidermal necrolysis, transverse myelitis, TRAPS (tumor necrosis factor receptor, type 1 allergic reaction, type II diabetes, urticaria, usual interstitial pneumonia (UIP), vasculitis, vernal conjunctivitis, viral retinitis, Vogt-Koyanagi-Harada syndrome (VKH syndrome), wet macular degeneration, wound healing, yersinia and salmonella associated arthropathy.

42. The use according to claim 41 by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

43. A method for generating a Dual Variable Domain Immunoglobulin capable of binding two antigens comprising the steps of

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

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

c) constructing first and third polypeptide chains comprising VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first heavy chain variable domain obtained from the first parent antibody or antigen binding portion thereof;

VD2 is a second heavy chain variable domain obtained from the second parent antibody or antigen binding portion thereof;

C is a heavy chain constant domain;

X1 is a linker;

X2 is an Fc region;

n is 0 or 1; and

d) constructing second and fourth polypeptide chains comprising VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain obtained from said first parent antibody or antigen binding portion thereof;

VD2 is a second light chain variable domain obtained from said second parent antibody or antigen binding thereof;

C is a light chain constant domain;

X1 is a linker;

X2 does not comprise an Fc region; and

n is 0 or 1; and

e) expressing the first, second, third and fourth polypeptide chains;

such that a Dual Variable Domain Immunoglobulin capable of binding the first and the second antigen is generated, wherein the binding protein is capable of binding a pair of antigens selected from the group consisting of of IL-1alpha and IL-1beta,

wherein the VD1 heavy and light chain variable domains form an antigen binding domain that binds the IL-1beta antigen

and comprise the amino acid sequences of SEQ ID NOs 30 and 31 or SEQ ID NOs 32 and 33; and

wherein the VD2 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.

44. The method of claim 43, wherein the heavy chain variable domain of the antigen binding domain that binds the IL-1alpha comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, and 46 and wherein the light chain variable domain of the antigen binding domain that binds the IL-1alpha comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 33, 35, 37, 39, 41, 43, 45, and 47.

45. A method for generating a Dual Variable Domain Immunoglobulin binding protein capable of binding two antigens with desired properties comprising the steps of

a) obtaining a first parent antibody or antigen binding portion thereof, capable of binding a first antigen and possessing at least one desired property exhibited by the Dual Variable Domain Immunoglobulin;

b) obtaining a second parent antibody or antigen binding portion thereof, capable of binding a second antigen and possessing at least one desired property exhibited by the Dual Variable Domain Immunoglobulin;

c) constructing first and third polypeptide chains comprising VD1-(X1)n-VD2-C-(X2)n, wherein;

VD1 is a first heavy chain variable domain obtained from the first parent antibody or antigen binding portion thereof;

VD2 is a second heavy chain variable domain obtained from the second parent antibody or antigen binding portion thereof;

C is a heavy chain constant domain;

X1 is a linker;

X2 is an Fc region; and

n is 0 or 1;

d) constructing second and fourth polypeptide chains comprising VD1-(X1)n-VD2-C-(X2)n, wherein;

VD1 is a first light chain variable domain obtained from the first parent antibody or antigen binding portion thereof;

VD2 is a second light chain variable domain obtained from the second parent antibody or antigen binding portion thereof;

C is a light chain constant domain;

X1 is a linker;

X2 does not comprise an Fc region; and

n is 0 or 1;

e) expressing the first, second, third and fourth polypeptide chains;

such that a Dual Variable Domain Immunoglobulin binding protein capable of binding the first and the second antigen with desired properties is generated, wherein the binding protein is capable of binding a pair of antigens selected from the group consisting of IL-1alpha and IL-1beta,

wherein the VD1 heavy and light chain variable domains form an antigen binding domain that binds the IL-1beta antigen

and comprise the amino acid sequences of SEQ ID NOs 30 and 31 or SEQ ID NOs 32 and 33; and

wherein the VD2 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.

Claims

1. A binding protein comprising first and second polypeptide chains, wherein the first polypeptide chain comprises a first VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first heavy chain variable domain;
VD2 is a second heavy chain variable domain;
C is a heavy chain constant domain;
X1 is a linker;
X2 is an Fc region; and
wherein the second polypeptide chain comprises a second VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first light chain variable domain;
VD2 is a second light chain variable domain;
C is a light chain constant domain;
X1 is a linker;
X2 does not comprise an Fc region;
n is 0 or 1, and
wherein the binding protein is capable of binding a pair of antigens selected from the group consisting of IL-1alpha and IL-1beta,
wherein either the VD1 heavy and light chain variable domain or the VD2 heavy and light chain variable domain form an antigen binding domain that binds the IL-1beta antigen and comprises the amino acid sequences of SEQ ID NOs: 30 and 31 or SEQ ID NOs: 32 and 33, and
wherein the other of the VD1 or VD2 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.

2. The binding protein of claim 1, wherein the heavy chain variable domain of the antigen binding domain that binds the IL-1alpha comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, and 46 and wherein the light chain variable domain of the antigen binding domain that binds the IL-1alpha comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 33, 35, 37, 39, 41, 43, 45, and 47.

3. The binding protein of claim 1, wherein X1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-29.

4. The binding protein of claim 1, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.

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

6. A binding protein capable of binding two antigens comprising four polypeptide chains, wherein two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first heavy chain variable domain;
VD2 is a second heavy chain variable domain;
C is a heavy chain constant domain;
X1 is a linker;
X2 is an Fc region; and
wherein two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain;
VD2 is a second light chain variable domain;
C is a light chain constant domain;
X1 is a linker;
X2 does not comprise an Fc region; and
n is 0 or 1;

wherein the VD1 heavy and light chain variable domains form an antigen binding domain that binds the IL-1beta antigen

and comprise the amino acid sequences of SEQ ID NOs: 30 and 31 or SEQ ID NOs: 32 and 33; and

wherein the VD2 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.

7. A binding protein capable of binding two antigens comprising four polypeptide chains, wherein two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, wherein

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

wherein two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain;
VD2 is a second light chain variable domain;
C is a light chain constant domain;
X1 is a linker;
X2 does not comprise an Fc region; and
n is 0 or 1;

wherein the VD2 heavy and light chain variable domains form an antigen binding domain that binds the IL-1beta antigen

and comprise the amino acid sequences of SEQ ID NOs: 30 and 31 or SEQ ID NOs: 32 and 33; and

wherein the VD1 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.

8. The binding protein of claim 1, 6, or 7, wherein the binding protein has an on rate constant (Kon) to IL-1beta antigen selected from the group consisting of: at least about $10^2 M^{-1}s^{-1}$; at least about $10^3 M^{-1}s^{-1}$; at least about $10^4 M^{-1}s^{-1}$; at least about $10^5 M^{-1}s^{-1}$; and at least about $10^6 M^{-1}s^{-1}$, as measured by surface plasmon resonance.

9. The binding protein of claim 1, 6, or 7, wherein the binding protein has an off rate constant (Koff) to IL-1beta antigen selected from the group consisting of: at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance.

10. The binding protein of claim 1, 6, or 7, wherein the binding protein has a dissociation constant (K_D) to IL-1beta antigen selected from the group consisting of: at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; and at most 10^{-13} M.

11. A binding protein conjugate comprising a binding protein according to any one of claims 1, 6, or 7, the binding protein conjugate further comprising at least one selected from the group consisting of an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

12. The binding protein conjugate of claim 11, wherein the imaging agent is selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

13. The binding protein conjugate of claim 12, wherein the imaging agent is a radiolabel selected from the group consisting of: ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm.

14. The binding protein conjugate of claim 12, wherein the therapeutic or cytotoxic agent is selected from the group consisting of an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

15. The binding protein of claim 1, 6, or 7, wherein said binding protein is a crystallized binding protein.

16. The binding protein of claim 15, wherein the crystal is a carrier-free pharmaceutical controlled release crystal.

17. The binding protein of claim 15, wherein the binding protein has a greater half life in vivo than the soluble counterpart of said binding protein.

18. The binding protein of claim 15, wherein the binding protein retains biological activity.

19. An isolated nucleic acid encoding a binding protein amino acid sequence according to any one of claims 1, 6, or 7.

20. A vector comprising an isolated nucleic acid according to claim 19.

21. The vector of claim 20, wherein the vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, and pBJ.

22. A host cell comprising a vector according to claim 20, wherein the host cell is not a human cell.

23. The host cell of claim 22, wherein host cell is a prokaryotic cell.

24. The host cell of claim 23, wherein the host cell is E.Coli.

25. The host cell of claim 22, wherein the host cell is a eukaryotic cell.

26. The host cell of claim 25, wherein the eukaryotic cell is selected from the group consisting of protist cell, animal cell, plant cell and fungal cell.

27. The host cell of claim 25, wherein the eukaryotic cell is an animal cell selected from the group consisting of: a mammalian cell, an avian cell, and an insect cell.

28. The host cell of claim 27, wherein the host cell is a CHO cell.

29. The host cell of claim 27, wherein the host cell is a COS cell.

30. The host cell of claim 25, wherein the host cell is a yeast cell.

31. The host cell of claim 30, wherein the yeast cell is *Saccharomyces cerevisiae.*

32. The host cell of claim 27, wherein the host cell is an insect Sf9 cell.

33. A method of producing a binding protein, comprising culturing a host cell described in any one of claims 22-32 in culture medium under conditions sufficient to produce the binding protein.

34. The method of claim 33, wherein 50%-75% of the binding protein produced is a dual specific tetravalent binding protein.

35. The method of claim 33, wherein 75%-90% of the binding protein produced is a dual specific tetravalent binding protein.

36. The method of claim 33, wherein 90%-95% of the binding protein produced is a dual specific tetravalent binding protein.

37. A pharmaceutical composition comprising the binding protein of any one of claims 1-18, and a pharmaceutically acceptable carrier.

38. The pharmaceutical composition of claim 37, further comprising at least one additional therapeutic agent selected from the group consisting of: a cytotoxic agent, an angiogenesis inhibitor; a kinase inhibitor; a co-stimulation molecule blocker; an adhesion molecule blocker; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an antirheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

39. Use of the binding protein of any of claims 1-18 in the manufacture of a medicament for treating a subject for an autoimmune or inflammatory disease or disorder.

40. Use of the binding protein of any of claims 1-18 in the manufacture of a medicament for treating a subject for a disease or a disorder, wherein the disorder is selected from the group comprising rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy,

systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthopathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, spondyloarthopathy, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis B, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, 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, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthrosis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjörgren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic

autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo acute liver disease, chronic liver diseases, alcoholic cirrhosis, alcohol-induced liver injury, choleosatatis, idiosyncratic liver disease, Drug-Induced hepatitis, Non-alcoholic Steatohepatitis, allergy and asthma, group B streptococci (GBS) infection, mental disorders (*e.g.*, depression and schizophrenia), Th2 Type and Th1 Type mediated diseases, acute and chronic pain (different forms of pain), and cancers such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma) Abetalipoprotemia, Acrocyanosis, acute and chronic parasitic or infectious processes, acute leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute or chronic bacterial infection, acute pancreatitis, acute renal failure, adenocarcinomas, aerial ectopic beats, AIDS dementia complex, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allograft rejection, alpha-l- antitrypsin deficiency, amyotrophic lateral sclerosis, anemia, angina pectoris, anterior horn cell degeneration, anti cd3 therapy, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aordic and peripheral aneuryisms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, Burns, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chronic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, cor pulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, Dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic ateriosclerotic disease, Diffuse Lewy body disease, dilated congestive cardiomyopathy, disorders of the basal ganglia, Down's Syndrome in middle age, drug- induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, epiglottitis, epstein-barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hematophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, fungal sepsis, gas gangrene, gastric ulcer, glomerular nephritis, graft rejection of any organ or tissue, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, hairy cell leukemia, Hallerrorden-Spatz disease, hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, hepatitis (A), His bundle arrythmias, HIV infection/HIV neuropathy, Hodgkin's disease, hyperkinetic movement disorders, hypersensitity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, antibody mediated cytotoxicity, Asthenia, infantile spinal muscular atrophy, inflammation of the aorta, influenza a, ionizing radiation exposure, iridocyclitis/uveitis/optic neuritis, ischemia- reperfusion injury, ischemic stroke, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions

of the corticospinal system, lipedema, liver transplant rejection, lymphederma, malaria, malignamt Lymphoma, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, metabolic/idiopathic, migraine headache, mitochondrial multi.system disorder, mixed connective tissue disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel Dejerine- Thomas Shi-Drager and Machado-Joseph), myasthenia gravis, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodyplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, neurodegenerative diseases, neurogenic I muscular atrophies , neutropenic fever, non- hodgkins lymphoma, occlusion of the abdominal aorta and its branches, occulsive arterial disorders, okt3 therapy, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoporosis, pancreas transplant rejection, pancreatic carcinoma, paraneoplastic syndrome/hypercalcemia of malignancy, parathyroid transplant rejection, pelvic inflammatory disease, perennial rhinitis, pericardial disease, peripheral atherlosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, preeclampsia, Progressive supranucleo Palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon and disease, Raynoud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, Senile Dementia of Lewy body type, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, Syncope, syphilis of the cardiovascular system, systemic anaphalaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T-cell or FAB ALL, Telangiectasia, thromboangitis obliterans, thrombocytopenia, toxicity, transplants, trauma/hemorrhage, type III hypersensitivity reactions, type IV hypersensitivity, unstable angina, uremia, urosepsis, urticaria, valvular heart diseases, varicose veins, ,vasculitis, venous diseases, venous thrombosis, ventricular fibrillation, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wernicke- Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, acute coronary syndromes, acute idiopathic polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, alopecia areata, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, arteriosclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic ischemia, cicatricial pemphigoid, clinically isolated syndrome (cis) with risk for multiple sclerosis, conjunctivitis, childhood onset psychiatric disorder, chronic obstructive pulmonary disease (COPD), dacryocystitis, dermatomyositis, diabetic retinopathy, diabetes mellitus, disk herniation, disk prolaps, 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, IPF/UIP, iritis, keratitis, keratojuntivitis sicca, Kussmaul disease or Kussmaul-Meier disease, Landry's paralysis, Langerhan's cell histiocytosis, livedo reticularis, macular degeneration, microscopic polyangiitis, morbus bechterev, motor neuron disorders, mucous membrane pemphigoid, multiple organ failure, myasthenia gravis, myelodysplastic syndrome, myocarditis, nerve root disorders, neuropathy, non-A non-B hepatitis, optic neuritis, osteolysis, ovarian cancer, pauciarticular JRA, peripheral artery occlusive disease (PAOD), peripheral vascular disease (PVD), peripheral artery, disease (PAD), phlebitis, polyarteritis nodosa (or periarteritis nodosa), polychondritis, polymyalgia rheumatica, poliosis, polyarticular JRA, polyendocrine deficiency syndrome, polymyositis, polymyalgia rheumatica (PMR), post-pump syndrome, primary Parkinsonism, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), prostatitis, pure red cell aplasia, primary adrenal insufficiency, recurrent neuromyelitis optica, restenosis, rheumatic heart disease, sapho (synovitis, acne, pustulosis, hyperostosis, and osteitis), scleroderma, secondary amyloidosis, shock lung, scleritis, sciatica, secondary adrenal insufficiency, silicone associated connective tissue disease, sneddon-wilkinson dermatosis, spondilitis ankylosans, Stevens-Johnson syndrome (SJS), systemic inflammatory response syndrome, temporal arteritis, toxoplasmic retinitis, toxic epidermal necrolysis, transverse myelitis, TRAPS (tumor necrosis factor receptor, type 1 allergic reaction, type II diabetes, urticaria, usual interstitial pneumonia (UIP), vasculitis, vernal conjunctivitis, viral retinitis, Vogt-Koyanagi-Harada syndrome (VKH syndrome), wet macular degeneration, wound healing, yersinia and salmonella associated arthropathy.

41. The use according to claim 39 or claim 40 by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

42. A method for generating a Dual Variable Domain Immunoglobulin capable of binding two antigens comprising the steps of
    a) obtaining a first parent antibody or antigen binding portion thereof, capable of binding a first antigen;
    b) obtaining a second parent antibody or antigen binding portion thereof, capable of binding a second antigen;
    c) constructing first and third polypeptide chains comprising VD1-(X1)n-VD2-C-(X2)n, wherein
        VD1 is a first heavy chain variable domain obtained from the first parent antibody or antigen binding portion thereof;
        VD2 is a second heavy chain variable domain obtained from the second parent antibody or antigen binding portion thereof;
        C is a heavy chain constant domain;
        X1 is a linker;

X2 is an Fc region;
n is 0 or 1; and
d) constructing second and fourth polypeptide chains comprising VD1-(X1)n-VD2-C-(X2)n, wherein
VD1 is a first light chain variable domain obtained from said first parent antibody or antigen binding portion thereof;
VD2 is a second light chain variable domain obtained from said second parent antibody or antigen binding thereof;
C is a light chain constant domain;
X1 is a linker;
X2 does not comprise an Fc region; and
n is 0 or 1; and
e) expressing the first, second, third and fourth polypeptide chains;
such that a Dual Variable Domain Immunoglobulin capable of binding the first and the second antigen is generated, wherein the binding protein is capable of binding a pair of antigens selected from the group consisting of IL-1alpha and IL-1beta,
wherein the VD1 heavy and light chain variable domains form an antigen binding domain that binds the IL-1beta antigen
and comprise the amino acid sequences of SEQ ID NOs: 30 and 31 or SEQ ID NOs: 32 and 33; and
wherein the VD2 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.

43. The method of claim 42, wherein the heavy chain variable domain of the antigen binding domain that binds the IL-1alpha comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, and 46 and wherein the light chain variable domain of the antigen binding domain that binds the IL-1alpha comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 33, 35, 37, 39, 41, 43, 45, and 47.

44. A method for generating a Dual Variable Domain Immunoglobulin binding protein capable of binding two antigens with desired properties comprising the steps of
a) obtaining a first parent antibody or antigen binding portion thereof, capable of binding a first antigen and possessing at least one desired property exhibited by the Dual Variable Domain Immunoglobulin;
b) obtaining a second parent antibody or antigen binding portion thereof, capable of binding a second antigen and possessing at least one desired property exhibited by the Dual Variable Domain Immunoglobulin;
c) constructing first and third polypeptide chains comprising VD1-(X1)n-VD2-C-(X2)n, wherein;
VD1 is a first heavy chain variable domain obtained from the first parent antibody or antigen binding portion thereof;
VD2 is a second heavy chain variable domain obtained from the second parent antibody or antigen binding portion thereof;
C is a heavy chain constant domain;
X1 is a linker;
X2 is an Fc region; and
n is 0 or 1;

d) constructing second and fourth polypeptide chains comprising VD1-(X1)n-VD2-C-(X2)n, wherein;
VD1 is a first light chain variable domain obtained from the first parent antibody or antigen binding portion thereof;
VD2 is a second light chain variable domain obtained from the second parent antibody or antigen binding portion thereof;
C is a light chain constant domain;
X1 is a linker;
X2 does not comprise an Fc region; and
n is 0 or 1;

e) expressing the first, second, third and fourth polypeptide chains;

such that a Dual Variable Domain Immunoglobulin binding protein capable of binding the first and the second antigen with desired properties is generated, wherein the binding protein is capable of binding a pair of antigens selected from the group consisting of IL-1alpha and IL-1beta,

wherein the VD1 heavy and light chain variable domains form an antigen binding domain that binds the IL-1beta antigen

and comprise the amino acid sequences of SEQ ID NOs: 30 and 31 or SEQ ID NOs: 32 and 33; and

wherein the VD2 heavy and light chain variable domains forms an antigen binding domain that binds the IL-1alpha antigen.