We claim:

1. A binding protein comprising a polypeptide chain, wherein said polypeptide chain comprises VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

(X1)n is a linker with the proviso that it is not CH1;

(X2)n is an Fc region;

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

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

wherein VD1 and VD2 independently comprise three CDRs from SEQ ID NO: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 323, 325, or and 327.

2. The binding protein according to claim 1, wherein the binding protein is capable of binding EGFR and CD-3; EGFR and IGF1R; EGFR and RON; EGFR and HGF; VEGF and EGFR; EGFR and ErbB3, EGFR and DLL-4, EGFR and PLGF, EGFR and EGFR, EGFR and RGMa, EGFR and tetanus toxoid; VEGF and tetanus toxoid; or tetanus toxoid and tetanus toxoid.

3. The binding protein of claim 1, wherein (X2)n is (X2)0.

4. A binding protein comprising a polypeptide chain, wherein said polypeptide chain comprises VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

(X1)n is a linker with the proviso that it is not CL;

(X2)n does not comprise an Fc region;

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

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

wherein VD1 and VD2 independently comprise three CDRs from SEQ ID NO: 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 324, 326, or 328.

5. The binding protein according to claim 4, wherein the binding protein is capable of binding EGFR and CD-3; EGFR and IGF1R; EGFR and RON; EGFR and HGF; VEGF and

EGFR; EGFR and ErbB3, EGFR and DLL-4, EGFR and PLGF, EGFR and EGFR, EGFR and RGMa, EGFR and tetanus toxoid; VEGF and tetanus toxoid; or tetanus toxoid and tetanus toxoid.

6. The binding protein of claim 4, wherein (X2)n is (X2)0.

7. 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)n is a first linker;

(X2)n is an Fc region; 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)n is a second linker;

(X2)n does not comprise an Fc region;

wherein said (X1)n is (X1)0 or (X1)1 and (X2)n is (X2)0 or (X2)1,

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

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

wherein the VD1 and VD2 heavy chain variable domains independently comprise three CDRs from SEQ ID NO: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 323, 325, or 327; and wherein the VD1 and VD2 light chain variable domains independently comprise three CDRs from SEQ ID NO: 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 324, 326, or 328.

8. The binding protein of claim 7, wherein the binding protein is capable of binding EGFR and CD-3; EGFR and IGF1R; EGFR and RON; EGFR and HGF; VEGF and EGFR; EGFR and ErbB3, EGFR and DLL-4, EGFR and PLGF, EGFR and EGFR, EGFR and RGMa, EGFR and tetanus toxoid; VEGF and tetanus toxoid; or tetanus toxoid and tetanus toxoid.

9. The binding protein of claim 8, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.

10. The binding protein of claim 8, wherein the Fc region is a variant sequence Fc region.

11. The binding protein of claim 8, wherein the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD.

12. The binding protein of claim 8, wherein said VD1 of the first polypeptide chain and said VD1 of the second polypeptide chain are obtained from a same parent antibody or antigen binding portion thereof.

13. The binding protein of claim 8, wherein said VD1 of the first polypeptide chain and said VD1 of the second polypeptide chain are obtained from different parent antibodies or antigen binding portions thereof.

14. The binding protein of claim 8, wherein said VD2 of the first polypeptide chain and said VD2 of the second polypeptide chain are obtained from a same parent antibody or antigen binding portion thereof.

15. The binding protein of claim 8, wherein said VD2 of the first polypeptide chain and said VD2 of the second polypeptide chain are obtained from different parent antibodies or antigen binding portions thereof.

16. The binding protein of claim 8, wherein said first and said second parent antibodies bind different epitopes on said antigen.

17. The binding protein of claim 8, wherein said first parent antibody or antigen binding portion thereof, binds said first antigen with a potency different from the potency with which said second parent antibody or antigen binding portion thereof, binds said second antigen.

18. The binding protein of claim 8, wherein said first parent antibody or antigen binding portion thereof, binds said first antigen with an affinity different from the affinity with which said second parent antibody or antigen binding portion thereof, binds said second antigen.

19. A binding protein capable of binding two antigens comprising four polypeptide chains, wherein first and third 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)n is a first linker;

(X2)n is an Fc region; and

wherein second and fourth 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)n is a second linker;

(X2)n does not comprise an Fc region;

wherein said (X1)n is (X1)0 or (X1)1 and (X2)n is (X2)0 or (X2)1,

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

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

wherein the VD1 and VD2 heavy chain variable domains independently comprise three CDRs from SEQ ID NOs: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 323, 325, or 327; and wherein the VD1 and VD2 light chain variable domains independently comprise three CDRs from SEQ ID NOs: 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 324, 326, or 328.

20. A method for generating a binding protein 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 the polypeptide of any one of claims 1, 3, 7, or 24;

d) expressing the polypeptide chains

such that a binding protein capable of binding said first and said second antigen is generated;

wherein the VD1 and VD2 heavy chain variable domains independently comprise three CDRs from SEQ ID NO: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 323, 325, and 327; and wherein the VD1 and VD2 light chain variable domains independently comprise three CDRs from SEQ ID NO: 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 324, 326, and 328.

21. The method of claim 20, wherein the Fc region is a variant sequence Fc region.

22. The method of claim 20, wherein the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, and IgD.

23. The method of claim 20, wherein said first parent antibody or antigen binding portion thereof, binds said first antigen with a different affinity than the affinity with which said second parent antibody or antigen binding portion thereof, binds said second antigen.

24. The method of claim 20, wherein said first parent antibody or antigen binding portion thereof, binds said first antigen with a different potency than the potency with which said second parent antibody or antigen binding portion thereof, binds said second antigen.

25. The binding protein of claim 1, wherein the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NOs: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 323, 325, or 327.

26. The binding protein of claim 4, wherein the VD1 and VD2 light chain variable domains independently comprise SEQ ID NOs: 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 324, 326, or 328.

27. The binding protein of claim 7, wherein the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NOs: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 323, 325, or 327; and wherein the VD1 and VD2 light chain variable domains independently comprise SEQ ID NOs: 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 324, 326, or 328.

28. The binding protein of claim 19, wherein the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NOs: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 323, 325, or 327; and wherein the VD1 and VD2 light chain variable domains independently comprise SEQ ID NOs: 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 324, 326, or 328.

29. The method of claim 20, wherein the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NOs: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 323, 325, or 327; and wherein the VD1 and VD2 light chain variable domains independently comprise SEQ ID NOs: 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 324, 326, or 328.

30. A method of determining the presence of at least one antigen or fragment thereof in a test sample by an immunoassay,

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

wherein the at least one binding protein comprises the binding protein of claim 19.

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

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

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

and wherein the at least one binding protein comprises the binding protein of claim 19.

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

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

(b) at least one binding protein comprising the binding protein of claim 19.

33. A pharmaceutical composition comprising the binding protein of claim 19 and a pharmaceutically acceptable carrier.

34. The pharmaceutical composition of claim 33, wherein said additional therapeutic agent is an imaging agent, a cytotoxic agent, an angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof, methotrexate, cyclosporin, rapamycin, FK506, a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

35. The binding protein according to claims 1, 3, or 7, wherein X1 is any one of SEQ ID NO: 1-28.

36. The binding protein according to claims 1, 3, or 7 for use in treating a subject for a disease or disorder by administering to the subject said binding protein, such that treatment is achieved.

37. The binding protein of claim 36, wherein said disorder is rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthropathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, 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, 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, cholestasis, idiosyncratic liver disease, Drug-Induced hepatitis, Non-alcoholic Steatohepatitis, allergy and asthma, group B streptococci (GBS) infection, mental disorders (*e.g.*, such as depression and schizophrenia), Th2 Type and Th1 Type mediated diseases, acute and chronic pain, 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, aortic and peripheral aneuryisms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, burns, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chronic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, cor pulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic 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, Hallervorden-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, hypersensitivity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, antibody mediated cytotoxicity, asthenia, infantile spinal muscular atrophy, inflammation of the aorta, influenza a, ionizing radiation exposure, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, lipedema, liver transplant rejection, lymphedema, malaria, malignant 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 Shy-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-Hodgkin's 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 - arteriosclerotic 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 supranuclear 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, viral encephalitis/aseptic meningitis, viral-associated hemaphagocytic syndrome, Wernicke- Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, acute coronary syndromes, acute idiopathic polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, alopecia areata, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, arteriosclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss,

autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic ischemia, cicatricial pemphigoid, clinically isolated syndrome (cis) with risk for multiple sclerosis, conjunctivitis, childhood onset psychiatric disorder, chronic obstructive pulmonary disease (COPD), dacryocystitis, dermatomyositis, diabetic retinopathy, diabetes mellitus, disk herniation, disk prolapse, drug induced immune hemolytic anemia, endocarditis, endometriosis, endophthalmitis, episcleritis, erythema multiforme, erythema multiforme major, gestational pemphigoid, Guillain-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, keratoconjunctivitis 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, or wound healing.

38. The binding protein of claim 36, wherein said administering to the subject is by parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

CLAIMS

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

VD1 is a first variable domain;

VD2 is a second variable domain;

C is constant domain;

X1 is a linker with the proviso that it is not CH1;

X2 is an Fc region;

n is 0 or 1,

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

a. EGFR and CD3, wherein:

the variable domains that form a functional target binding site for EGFR comprise

three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50,

three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324,

three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, or

three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328,

and

the binding protein is capable of binding to EGFR with an EC50 of at most 157.62 nM as measured by direct binding ELISA and/or with an IC50 of at most 16 pM as measured by rCTL activity, and

the variable domains that form a functional target binding site for CD3 comprise three CDRs from SEQ ID NO: 27 and three CDRs from SEQ ID NO: 28;

b. EGFR and IGF1R, wherein:

the variable domains that form a functional target binding site for EGFR comprise

three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50,

three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324,

three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, or

three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328,

and the binding protein is capable of binding to EGFR with an EC50 of at most 286.41 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for IGFR1 comprise three CDRs from SEQ ID NO: 31 and three CDRs from SEQ ID NO: 32 and the binding protein is capable of binding to IGF1R with an EC50 of at most 78.58 nM as measured by direct binding ELISA;

c. EGFR and RON, wherein:

the variable domains that form a functional target binding site for EGFR comprise

three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50,

three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324,

three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, or

three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328,

and

the binding protein is capable of binding to EGFR with an EC50 of at most 29.93 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for RON comprise three CDRs from SEQ ID NO: 29 and three CDRs from SEQ ID NO: 30 and the binding protein is capable of binding to RON with an EC50 of at most 24.99 nM as measured by direct binding ELISA;

d. EGFR and HGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise

three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50,

three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324,

three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, or

three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328,

and

the binding protein is capable of binding to EGFR with an EC50 of at most 332.05 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for HGF comprise three CDRs from SEQ ID NO: 33 and three CDRs from SEQ ID NO: 34 and the binding protein is capable of binding to HGF with an EC50 of at most 159.04 nM as measured by direct binding ELISA;

e. EGFR and VEGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise

three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50,

three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324,

three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, or three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328, and

the binding protein is capable of binding to EGFR with an EC50 of at most 561.59 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for VEGF comprise three CDRs from SEQ ID NO: 35 and three CDRs from SEQ ID NO: 36, three CDRs from SEQ ID NO: 53 and three CDRs from SEQ ID NO: 54, or three CDRs from SEQ ID NO: 55 and three CDRs from SEQ ID NO: 56, and the binding protein is capable of binding to VEGF with an EC50 of at most 528.26 nM as measured by direct binding ELISA;

f. EGFR and Erb33, wherein:

the variable domains that form a functional target binding site for EGFR comprise three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50, three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324, three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, or three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328, and

the binding protein is capable of binding to EGFR with an EC50 of at most 726.39 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for Erb33 comprise three CDRs from SEQ ID NO: 45 and three CDRs from SEQ ID NO: 46, three CDRs from SEQ ID NO: 47 and three CDRs from SEQ ID NO: 48, or three CDRs from SEQ ID NO: 51 and three CDRs from SEQ ID NO: 52, and the binding protein is capable of binding to Erb33 with an EC50 of at most 485.26 nM as measured by direct binding ELISA;

g. EGFR and DLL-4, wherein:

the variable domains that form a functional target binding site for EGFR comprise three CDRs from SEQ ID NO: 39 and three CDRs from SEQ ID NO: 40, three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50, three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324, three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, or three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328, and

the binding protein is capable of binding to EGFR with an EC50 of at most 189.14 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for DLL-4 comprise three CDRs from SEQ ID NO: 37 and three CDRs from SEQ ID NO: 38 and the binding protein is capable of binding to DLL-4 with an EC50 of at most 4.01 nM as measured by direct binding ELISA;

h. EGFR and PLGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise

three CDRs from SEQ ID NO: 39 and three CDRs from SEQ ID NO: 40,

three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50,

three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324,

three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, or

three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328, and

the binding protein is capable of binding to EGFR with an EC50 of at most 119.88 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for PLGF comprise three CDRs from SEQ ID NO: 41 and three CDRs from SEQ ID NO: 42 and the binding protein is capable of binding to PLGF with an EC50 of at most 0.74 nM as measured by direct binding ELISA;

or

i. EGFR and EGFR, wherein:

the variable domains that form functional target binding sites for EGFR each independently comprise

three CDRs from SEQ ID NO: 39 and three CDRs from SEQ ID NO: 40,

three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50,

three CDRs from SEQ ID NO: 323 and three CDRs from SEQ ID NO: 324

three CDRs from SEQ ID NO: 325 and three CDRs from SEQ ID NO: 326, and/or

three CDRs from SEQ ID NO: 327 and three CDRs from SEQ ID NO: 328, and

the binding protein is capable of binding to EGFR with an EC50 of at most 6.83 nM as measured by direct binding ELISA and/or with a KD of at most 4.20E-08 M as measured by surface plasmon resonance.

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

VD1 is a first variable domain;

VD2 is a second variable domain;

C is constant domain;

X1 is a linker with the proviso that it is not CH1;

X2 is an Fc region;

n is 0 or 1,

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

a. EGFR and CD3, wherein:

the variable domains that form a functional target binding site for EGFR comprise a sequence selected from a group consisting of SEQ ID NOs: 49, 50, and 323-28 and the binding protein is capable of binding to EGFR with an EC50 of at most 6.83 nM as measured by direct binding ELISA and/or with a KD of at most 4.20E-08 M as measured by surface plasmon resonance, and

the variable domains that form a functional target binding site for CD3 comprise SEQ ID NO: 27 and/or SEQ ID NO: 28;

b. EGFR and IGF1R, wherein:

the variable domains that form a functional target binding site for EGFR comprise a sequence selected from a group consisting of SEQ ID NOs: 49, 50, and 323-28 and the binding protein is capable of binding to EGFR with an EC50 of at most 286.41 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for IGFR1 comprise SEQ ID NO: 31 and/or SEQ ID NO: 32 and the binding protein is capable of binding to IGF1R with an EC50 of at most 78.58 nM as measured by direct binding ELISA;

c. EGFR and RON, wherein:

the variable domains that form a functional target binding site for EGFR comprise a sequence selected from a group consisting of SEQ ID NOs: 49, 50, and 323-28 and the binding protein is capable of binding to EGFR with an EC50 of at most 29.93 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for RON comprise SEQ ID NO: 29 and/or SEQ ID NO: 30 and the binding protein is capable of binding to RON with an EC50 of at most 24.99 nM as measured by direct binding ELISA;

d. EGFR and HGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise a sequence selected from a group consisting of SEQ ID NOs: 49, 50, and 323-28 and the binding protein is capable of binding to EGFR with an EC50 of at most 332.05 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for HGF comprise SEQ ID NO: 33 and/or SEQ ID NO: 34 and the binding protein is capable of binding to HGF with an EC50 of at most 159.04 nM as measured by direct binding ELISA;

e. EGFR and VEGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise a sequence selected from a group consisting of SEQ ID NO: 49, 50, and 323-28 and the binding protein is capable of binding to EGFR with an EC50 of at most 561.59 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for VEGF comprise a sequence selected from a group consisting of SEQ ID NO: 35, 36, and 53-56 and the binding protein is capable of binding to VEGF with an EC50 of at most 528.26 nM as measured by direct binding ELISA;

f. EGFR and Erb33, wherein:

the variable domains that form a functional target binding site for EGFR comprise a sequence selected from a group consisting of SEQ ID NO: 49, 50, and 323-28 and the binding protein is capable of binding to EGFR with an EC50 of at most 726.39 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for Erb33 comprise a sequence selected from a group consisting of SEQ ID NO: 45-48 and 51-52 and the binding protein is capable of binding to Erb33 with an EC50 of at most 485.26 nM as measured by direct binding ELISA;

g. EGFR and DLL-4, wherein:

the variable domains that form a functional target binding site for EGFR comprise a sequence selected from a group consisting of SEQ ID NO: 39, 40, 49, 50, and 323-28 and the binding protein is capable of binding to EGFR with an EC50 of at most 189.14 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for DLL-4 comprise SEQ ID NO: 37 and/or SEQ ID NO: 38 and the binding protein is capable of binding to DLL-4 with an EC50 of at most 4.01 nM as measured by direct binding ELISA;

h. EGFR and PLGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise a sequence selected from a group consisting of SEQ ID NO: 39, 40, 49, 50, and 323-28 and the binding protein is capable of binding to EGFR with an EC50 of at most 119.88 nM as measured by direct binding ELISA, and

the variable domains that form a functional target binding site for PLGF comprise SEQ ID NO: 41 and/or SEQ ID NO: 42 and the binding protein is capable of binding to PLGF with an EC50 of at most 0.74 nM as measured by direct binding ELISA;

or

i. EGFR and EGFR, wherein:

the variable domains that form functional target binding sites for EGFR each independently comprise a sequence selected from a group consisting of SEQ ID NO: 39, 40, 49, 50, and 323-28 and is capable of binding to EGFR with an EC50 of at most 6.83 nM as measured by direct binding ELISA and/or with a KD of at most 4.20x10-08 M as measured by surface plasmon resonance.

3. The binding protein according to any one of claim 1 or claim 2, comprising first and second polypeptide chains, wherein

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

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

X1 is a first linker with the proviso that it is not CH1;

X2 is an Fc region;

n is 0 or 1; and

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

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

X1 is a second linker with the proviso that it is not CH1;

X2 does not comprise an Fc region;

n is 0 or 1.

4. A binding protein according to any one of claims 1-3, wherein the binding protein comprises variable domains that form functional binding sites for

a. EGFR and CD3, wherein the variable domains that form a functional target binding site for EGFR comprise

SEQ ID NO: 49 and SEQ ID NO: 50,

SEQ ID NO: 323 and SEQ ID NO: 324,

SEQ ID NO: 325 and SEQ ID NO: 326, or

SEQ ID NO: 327 and SEQ ID NO: 328, and

the variable domains that form a functional target binding site for CD3 comprise SEQ ID NO: 27 and SEQ ID NO: 28;

b. EGFR and IGF1R, wherein:

the variable domains that form a functional target binding site for EGFR comprise

SEQ ID NO: 49 and SEQ ID NO: 50,

SEQ ID NO: 323 and SEQ ID NO: 324,

SEQ ID NO: 325 and SEQ ID NO: 326, or

SEQ ID NO: 327 and SEQ ID NO: 328, and

the variable domains that form a functional target binding site for IGFR1 comprise SEQ ID NO: 31 and SEQ ID NO: 32;

c. EGFR and RON, wherein:

the variable domains that form a functional target binding site for EGFR comprise

SEQ ID NO: 49 and SEQ ID NO: 50,

SEQ ID NO: 323 and SEQ ID NO: 324,

SEQ ID NO: 325 and SEQ ID NO: 326, or

SEQ ID NO: 327 and SEQ ID NO: 328, and

the variable domains that form a functional target binding site for RON comprise SEQ ID NO: 29 and SEQ ID NO: 30;

d. EGFR and HGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise

SEQ ID NO: 49 and SEQ ID NO: 50,

SEQ ID NO: 323 and SEQ ID NO: 324,

SEQ ID NO: 325 and SEQ ID NO: 326, or

SEQ ID NO: 327 and SEQ ID NO: 328, and

the variable domains that form a functional target binding site for HGF comprise SEQ ID NO: 33 and SEQ ID NO: 34;

e. EGFR and VEGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise

SEQ ID NO: 49 and SEQ ID NO: 50,

SEQ ID NO: 323 and SEQ ID NO: 324,

SEQ ID NO: 325 and SEQ ID NO: 326, or

SEQ ID NO: 327 and SEQ ID NO: 328, and

the variable domains that form a functional target binding site for VEGF comprise

SEQ ID NO: 35 and SEQ ID NO: 36,

SEQ ID NO: 53 and SEQ ID NO: 54, or

SEQ ID NO: 55 and SEQ ID NO: 56;

f. EGFR and Erb33, wherein:

the variable domains that form a functional target binding site for EGFR comprise

SEQ ID NO: 49 and SEQ ID NO: 50,

SEQ ID NO: 323 and SEQ ID NO: 324,

SEQ ID NO: 325 and SEQ ID NO: 326, or

SEQ ID NO: 327 and SEQ ID NO: 328, and

the variable domains that form a functional target binding site for Erb33 comprise

SEQ ID NO: 45 and SEQ ID NO: 46,

SEQ ID NO: 47 and SEQ ID NO: 48, or

SEQ ID NO: 51 and SEQ ID NO: 52;

g. EGFR and DLL-4, wherein:

the variable domains that form a functional target binding site for EGFR comprise

SEQ ID NO: 39 and SEQ ID NO: 40,

SEQ ID NO: 49 and SEQ ID NO: 50,

SEQ ID NO: 323 and SEQ ID NO: 324,

SEQ ID NO: 325 and SEQ ID NO: 326, or

SEQ ID NO: 327 and SEQ ID NO: 328, and

the variable domains that form a functional target binding site for DLL-4 comprise SEQ ID NO: 37 and SEQ ID NO: 38;

h. EGFR and PLGF, wherein:

the variable domains that form a functional target binding site for EGFR comprise

SEQ ID NO: 39 and SEQ ID NO: 40,
SEQ ID NO: 49 and SEQ ID NO: 50,
SEQ ID NO: 323 and SEQ ID NO: 324,
SEQ ID NO: 325 and SEQ ID NO: 326, or
SEQ ID NO: 327 and SEQ ID NO: 328, and

the variable domains that form a functional target binding site for PLGF comprise SEQ ID NO: 41 and SEQ ID NO: 42;

or

i. EGFR and EGFR, wherein:

the variable domains that form functional target binding sites for EGFR each independently comprise

SEQ ID NO: 39 and SEQ ID NO: 40,
SEQ ID NO: 49 and SEQ ID NO: 50,
SEQ ID NO: 323 and SEQ ID NO: 324,
SEQ ID NO: 325 and SEQ ID NO: 326, or
SEQ ID NO: 327 and SEQ ID NO: 328.

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

a. EGFR and CD3, and comprises

DVD331 (comprising SEQ ID NO: 123 and SEQ ID NO: 124),
DVD332 (comprising SEQ ID NO: 125 and SEQ ID NO: 126),
DVD773 (comprising SEQ ID NO: 127 and SEQ ID NO: 128),
DVD774 (comprising SEQ ID NO: 129 and SEQ ID NO: 130),
DVD803 (comprising SEQ ID NO: 131 and SEQ ID NO: 132),
DVD804 (comprising SEQ ID NO: 133 and SEQ ID NO: 134),
DVD833 (comprising SEQ ID NO: 135 and SEQ ID NO: 136), or
DVD834 (comprising SEQ ID NO: 137 and SEQ ID NO: 138);

b. EGFR and IGF1R, and comprises

DVD333 (comprising SEQ ID NO: 139 and SEQ ID NO: 140),
DVD334 (comprising SEQ ID NO: 141 and SEQ ID NO: 142),
DVD775 (comprising SEQ ID NO: 143 and SEQ ID NO: 144),
DVD776 (comprising SEQ ID NO: 145 and SEQ ID NO: 146),
DVD805 (comprising SEQ ID NO: 147 and SEQ ID NO: 148),

DVD806 (comprising SEQ ID NO: 149 and SEQ ID NO: 150),
DVD835 (comprising SEQ ID NO: 151 and SEQ ID NO: 152), or
DVD836 (comprising SEQ ID NO: 153 and SEQ ID NO: 154);

c. EGFR and RON, and comprises

DVD325 (comprising SEQ ID NO: 75 and SEQ ID NO: 76),
DVD326 (comprising SEQ ID NO: 77 and SEQ ID NO: 78),
DVD767 (comprising SEQ ID NO: 79 and SEQ ID NO: 80),
DVD768 (comprising SEQ ID NO: 81 and SEQ ID NO: 82),
DVD797 (comprising SEQ ID NO: 83 and SEQ ID NO: 84),
DVD798 (comprising SEQ ID NO: 85 and SEQ ID NO: 86),
DVD827 (comprising SEQ ID NO: 87 and SEQ ID NO: 88), or
DVD828 (comprising SEQ ID NO: 89 and SEQ ID NO: 90);

d. EGFR and HGF, and comprises

DVD335 (comprising SEQ ID NO: 155 and SEQ ID NO: 156),
DVD336 (comprising SEQ ID NO: 157 and SEQ ID NO: 158),
DVD777 (comprising SEQ ID NO: 159 and SEQ ID NO: 160),
DVD778 (comprising SEQ ID NO: 161 and SEQ ID NO: 162),
DVD807 (comprising SEQ ID NO: 163 and SEQ ID NO: 164),
DVD808 (comprising SEQ ID NO: 165 and SEQ ID NO: 166),
DVD837 (comprising SEQ ID NO: 167 and SEQ ID NO: 168), or
DVD838 (comprising SEQ ID NO: 169 and SEQ ID NO: 170);

e. EGFR and VEGF, and comprises

DVD337 (comprising SEQ ID NO: 171 and SEQ ID NO: 172),
DVD338 (comprising SEQ ID NO: 173 and SEQ ID NO: 174),
DVD779 (comprising SEQ ID NO: 175 and SEQ ID NO: 176),
DVD780 (comprising SEQ ID NO: 177 and SEQ ID NO: 178),
DVD809 (comprising SEQ ID NO: 179 and SEQ ID NO: 180),
DVD810 (comprising SEQ ID NO: 181 and SEQ ID NO: 182),
DVD839 (comprising SEQ ID NO: 183 and SEQ ID NO: 184),
DVD840 (comprising SEQ ID NO: 185 and SEQ ID NO: 186),
DVD757 (comprising SEQ ID NO: 235 and SEQ ID NO: 236),
DVD758 (comprising SEQ ID NO: 237 and SEQ ID NO: 238),
DVD789 (comprising SEQ ID NO: 239 and SEQ ID NO: 240),
DVD790 (comprising SEQ ID NO: 241 and SEQ ID NO: 242),

DVD819 (comprising SEQ ID NO: 243 and SEQ ID NO: 244),
DVD820 (comprising SEQ ID NO: 245 and SEQ ID NO: 246),
DVD849 (comprising SEQ ID NO: 247 and SEQ ID NO: 248),
DVD850 (comprising SEQ ID NO: 249 and SEQ ID NO: 250),
DVD759 (comprising SEQ ID NO: 251 and SEQ ID NO: 252),
DVD760 (comprising SEQ ID NO: 253 and SEQ ID NO: 254),
DVD791 (comprising SEQ ID NO: 255 and SEQ ID NO: 256),
DVD792 (comprising SEQ ID NO: 257 and SEQ ID NO: 258),
DVD821 (comprising SEQ ID NO: 259 and SEQ ID NO: 260),
DVD822 (comprising SEQ ID NO: 261 and SEQ ID NO: 262),
DVD851 (comprising SEQ ID NO: 263 and SEQ ID NO: 264), or
DVD852 (comprising SEQ ID NO: 265 and SEQ ID NO: 266);

f. EGFR and Erb33, and comprises

DVD327 (comprising SEQ ID NO: 91 and SEQ ID NO: 92),
DVD328 (comprising SEQ ID NO: 93 and SEQ ID NO: 94),
DVD769 (comprising SEQ ID NO: 95 and SEQ ID NO: 96),
DVD770 (comprising SEQ ID NO: 97 and SEQ ID NO: 98),
DVD799 (comprising SEQ ID NO: 99 and SEQ ID NO: 100),
DVD800 (comprising SEQ ID NO: 101 and SEQ ID NO: 102),
DVD829 (comprising SEQ ID NO: 103 and SEQ ID NO: 104),
DVD830 (comprising SEQ ID NO: 105 and SEQ ID NO: 106),
DVD329 (comprising SEQ ID NO: 107 and SEQ ID NO: 108),
DVD330 (comprising SEQ ID NO: 109 and SEQ ID NO: 110),
DVD771 (comprising SEQ ID NO: 111 and SEQ ID NO: 112),
DVD772 (comprising SEQ ID NO: 113 and SEQ ID NO: 114),
DVD801 (comprising SEQ ID NO: 115 and SEQ ID NO: 116),
DVD802 (comprising SEQ ID NO: 117 and SEQ ID NO: 118),
DVD831 (comprising SEQ ID NO: 119 and SEQ ID NO: 120),
DVD832 (comprising SEQ ID NO: 121 and SEQ ID NO: 122),
DVD755 (comprising SEQ ID NO: 219 and SEQ ID NO: 220),
DVD756 (comprising SEQ ID NO: 221 and SEQ ID NO: 222),
DVD787 (comprising SEQ ID NO: 223 and SEQ ID NO: 224),
DVD788 (comprising SEQ ID NO: 225 and SEQ ID NO: 226),
DVD817 (comprising SEQ ID NO: 227 and SEQ ID NO: 228),

DVD818 (comprising SEQ ID NO: 229 and SEQ ID NO: 230),

DVD847 (comprising SEQ ID NO: 231 and SEQ ID NO: 232), or

DVD848 (comprising SEQ ID NO: 233 and SEQ ID NO: 234);

g. EGFR and DLL-4, and comprises

DVD339 (comprising SEQ ID NO: 187 and SEQ ID NO: 188),

DVD340 (comprising SEQ ID NO: 189 and SEQ ID NO: 190),

DVD781 (comprising SEQ ID NO: 191 and SEQ ID NO: 192),

DVD782 (comprising SEQ ID NO: 193 and SEQ ID NO: 194),

DVD811 (comprising SEQ ID NO: 195 and SEQ ID NO: 196),

DVD812 (comprising SEQ ID NO: 197 and SEQ ID NO: 198),

DVD841 (comprising SEQ ID NO: 199 and SEQ ID NO: 200), or

DVD842 (comprising SEQ ID NO: 201 and SEQ ID NO: 202);

h. EGFR and PLGF, and comprises

DVD341 (comprising SEQ ID NO: 203 and SEQ ID NO: 204),

DVD342 (comprising SEQ ID NO: 205 and SEQ ID NO: 206),

DVD783 (comprising SEQ ID NO: 207 and SEQ ID NO: 208),

DVD784 (comprising SEQ ID NO: 209 and SEQ ID NO: 210),

DVD813 (comprising SEQ ID NO: 211 and SEQ ID NO: 212),

DVD814 (comprising SEQ ID NO: 213 and SEQ ID NO: 214),

DVD843 (comprising SEQ ID NO: 215 and SEQ ID NO: 216), or

DVD844 (comprising SEQ ID NO: 217 and SEQ ID NO: 218);

or

i. EGFR and EGFR, and comprises

DVD321 (comprising SEQ ID NO: 59 and SEQ ID NO: 60),

DVD322 (comprising SEQ ID NO: 61 and SEQ ID NO: 62),

DVD765 (comprising SEQ ID NO: 63 and SEQ ID NO: 64),

DVD766 (comprising SEQ ID NO: 65 and SEQ ID NO: 66),

DVD795 (comprising SEQ ID NO: 67 and SEQ ID NO: 68),

DVD796 (comprising SEQ ID NO: 69 and SEQ ID NO: 70),

DVD825 (comprising SEQ ID NO: 71 and SEQ ID NO: 72), or

DVD826 (comprising SEQ ID NO: 73 and SEQ ID NO: 74).

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

7. The binding protein according to any one of claims 1-6, wherein

a. X1 is not CL;

b. X1 is at least one of SEQ ID NO: 1-26 or a G/S based sequence;

c. the binding protein is a crystallized binding protein;

d. the Fc region is a variant sequence Fc region; and/or

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

8. A binding protein conjugate comprising a binding protein according to any one of claims 1-7, the binding protein conjugate further comprising an immunoadhesion molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent.

9. The binding protein conjugate according to claim 8, wherein the imaging agent is a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

10. The binding protein conjugate according to claim 9, wherein the radiolabel is 3H, 14C, 35S, 90Y, 99Tc, 111In, 125I, 131I, 177Lu, 166Ho, or 153Sm.

11. The binding protein conjugate according to claim 8, wherein the therapeutic or cytotoxic agent is 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, or an apoptotic agent.

12. A pharmaceutical composition comprising the binding protein of any one of claims 1-7 or the binding protein conjugate of claims 8-11, and a pharmaceutically acceptable carrier, optionally comprising at least one additional therapeutic agent selected from the group consisting of an imaging agent, a cytotoxic agent, an angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof, methotrexate, cyclosporin, rapamycin, FK506, a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a 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.

13. Use of the binding protein according to claims 1-7 or the binding protein conjugate according to any one of claims 8-11 in the manufacture of a medicament for treating a disease or disorder.

14. The use of claim 13, wherein the disorder is 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 ofthe 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, Sjogren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, fibrosis, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-l 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 I, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjorgren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo acute liver disease, chronic liver diseases, alcoholic cirrhosis, alcohol-induced liver injury, choleosatatis, idiosyncratic liver disease, Drug-Induced hepatitis, Non-alcoholic Steatohepatitis, allergy and asthma, group B streptococci (GBS) infection, mental disorders (e.g., depression and schizophrenia), Th2 Type and Thl 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 hom cell degeneration, anti cd3 therapy, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneuryisms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, Bums, 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 ofthe corticospinal system, lipedema, liver

transplant rejection, lymphederma, malaria, malignamt Lymphoma, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, metabolic/idiopathic diseases, migraine headache, mitochondrial multi.system disorder, mixed connective tissue disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel DejerineThomas 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, occlusive arterial disorders, okt3 therapy, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoporosis, pancreas transplant rejection, pancreatic carcinoma, paraneoplastic syndrome l, 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 ofLewy 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 ofthe 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, traumalhemorrhage, 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, carcinomas of breast, colon, rectum, lung, oropharynx, hypopharynx, esophagus, stomach, pancreas, liver, gallbladder and bile ducts, small intestine, urinary tract (including kidney, bladder and urothelium), female genital tract (including cervix, uterus, and ovaries as

well as choriocarcinoma and gestational trophoblastic disease), male genital tract (including prostate, seminal vesicles, testes and germ cell tumors), endocrine glands (including the thyroid, adrenal, and pituitary glands), and skin, as well as hemangiomas, melanomas, sarcomas (including those arising from bone and soft tissues as well as Kaposi's sarcoma), tumors ofthe brain, nerves, eyes, and meninges (including astrocytomas, gliomas, glioblastomas, retinoblastomas, neuromas, neuroblastomas, Schwannomas, and meningiomas), solid tumors arising from hematopoietic malignancies such as leukemias, and lymphomas (both Hodgkin's and non-Hodgkin's lymphomas).

15. The use of claim 13 or 14, wherein the medicament is administered parenterally, subcutaneously, intramuscularly, intravenously, intrarticularly, intrabronchially, intraabdominally, intracapsularly, intracartilaginously, intracavitarily, intracelially, intracerebellarly, intracerebroventricularly, intracolically, intracervically, intragastrically, intrahepatically, intramyocardially, intraosteally, intrapelvically, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrapulmonarily, intrarectally, intrarenally, intraretinally, intraspinally, intrasynovially, intrathoracically intrauterine, intravesically, bolusly, vaginally, rectally, buccally, sublingually, intranasally, and/or transdermally.

16. An isolated nucleic acid encoding a binding protein according to any one of claims 1-7.

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

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

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