We claim:

1. A humanized binding protein comprising an antigen binding domain capable of binding human tumor necrosis factor-alpha (TNF-α), the antigen binding domain comprising at least one CDR comprising an amino acid sequence of residues 31-35 of SEQ ID NO:22; residues 50-65 of SEQ ID NO:22; residues 98-106 of SEQ ID NO:22; residues 24-34 of SEQ ID NO:23; residues 50-56 of SEQ ID NO:23; or residues 89-97 of SEQ ID NO:23, wherein the binding protein comprises a human acceptor framework.

2. The binding protein of claim 1, wherein the binding protein comprises at least 3 CDRs.

3. The binding protein of claim 2, wherein the at least 3 CDRs comprises a variable domain CDR set is (a) residues 31-35 of SEQ ID NO:22; residues 50-65 of SEQ ID NO:22; and residues 98-106 of SEQ ID NO:22; and (b) residues 24-34 of SEQ ID NO:23; residues 50-56 of SEQ ID NO:23; or residues 89-97 of SEQ ID NO:23.

4. The binding protein of claim 3, wherein the antigen binding domain comprises an amino acid sequence comprising residues 31-35 of SEQ ID NO:22; residues 50-65 of SEQ ID NO:22; residues 98-106 of SEQ ID NO:22; residues 24-34 of SEQ ID NO:23; residues 50-56 of SEQ ID NO:23; and residues 89-97 of SEQ ID NO:23.

5. The binding protein of claim 1, wherein the antigen binding domain comprises a VH region.

6. The binding protein of claim 5, wherein the VH region comprises an amino acid sequence of SEQ ID NOs: 24, 25, 28, 29, 30, 31, 32, or 33.

7. The binding protein of claim 1, wherein the antigen binding domain comprises a VL region.

8. The binding protein of claim 7, wherein the VL region amino acid sequence is SEQ ID NOs: 26, 27, 34, 35, or 36.

9. The binding protein of claim 7, wherein the antigen binding domain comprises a VH region and a VL region.

10. The binding protein of claim 9, wherein the VH region comprises an amino acid sequence of SEQ ID NO: 24, 25, 28, 29, 30, 31, 32, or 33 and the VL region comprises an amino acid sequence of SEQ ID NO: 26, 27, 34, 35, or 36.

11. The binding protein of claim 1, wherein the human acceptor framework comprises at least one amino acid sequence of SEQ ID NOs: 6-21.

12. The binding protein of claim 11, wherein the human acceptor framework comprises an amino acid sequence of SEQ ID NOs 9, 10, 11, 12, 15, 16, 17, or 21.

13. The binding protein of claim 11 or 12, wherein the human acceptor framework comprises at least one framework region amino acid substitution, wherein the amino acid sequence of the framework is at least 65% identical to the sequence of the human acceptor framework and comprises at least 70 amino acid residues identical to the human acceptor framework.

14. The binding protein of claim 13, wherein the human acceptor framework comprises at least one framework region amino acid substitution at key residue that is a residue adjacent to a CDR; a glycosylation site residue; a rare residue; a residue capable of interacting with human TNF-α; a residue capable of interacting with a CDR; a canonical residue; a contact residue between heavy chain variable region and light chain variable region; a residue within a Vernier zone; a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 or a Kabat-defined first heavy chain framework.

15. The binding protein of claim 14, wherein the key residue is H1, H12, H24, H27, H29, H37, H48, H49, H67, H71, H73, H76, H78, L13, L43, L58, L70, or L80 .

16. The binding protein of claim 15, wherein the VH mutation is Q1E, I12V, A24V, G27F, I29L, V29F, F29L, I37V, I48L,V48L, S49G, V67L, F67L, V71K, R71K, T73N, N76S, L78I, or F78I.

17. The binding protein of claim 15, wherein the VL mutation is V13L, A43S, I58V, E70D, or S80P.

18. The binding protein of claim 1, wherein the binding protein comprises two variable domains that have amino acid sequences SEQ ID NO:24 and SEQ ID NO:26; SEQ ID NO:24 and SEQ ID NO:27; SEQ ID NO:25 and SEQ ID NO:26; SEQ ID NO:25 or SEQ ID NO:27.

19. The binding protein of claim 1, wherein the binding protein modulates a biological function of TNF-α.

20. The binding protein of claim 1, wherein the binding protein neutralizes TNF-α.

21. The binding protein of claim 1, wherein the binding protein diminishes the ability of TNF-α to bind to its receptor.

22. The binding protein of claim 21, wherein the binding protein diminishes the ability of pro-human TNF-α, mature-human TNF-α, or truncated-human TNF-α to bind to its receptor.

23. The binding protein of claim 1, wherein the binding protein of reduces one or more of TNF-dependent cytokine production; TNF-dependent cell killing; TNF-dependent inflammation; TNF-dependent bone erosion; and TNF-dependent cartilage damage.

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

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

26. The binding protein of claim 1, wherein the binding protein has a dissociation constant (K_D) of at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; or at most 10^{-13} M.

27. The binding protein of claim 1, wherein the binding protein comprises a heavy chain immunoglobulin constant domain of a human IgM constant domain, a human IgG1 constant domain, a human IgG2 constant domain, a human IgG3 constant domain, a human IgG4 constant domain, a human IgA constant domain, or a human IgE constant domain.

28. The binding protein of claim 27, wherein the heavy chain immunoglobulin constant region domain is a human IgG1 constant domain.

29. The binding protein of claim 1 or 27, wherein the binding protein further comprises a human Ig kappa constant domain or a human Ig lambda constant domain.

30. The binding protein of claim 28, wherein the human IgG1 constant domain comprises an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3.

31. The binding protein of claim 29, wherein the light chain immunoglobulin constant region domain is a human Ig kappa constant domain comprising an amino acid sequence of SEQ ID NO:4 or a human Ig lambda constant domain comprising an amino acid sequence SEQ ID NO:5.

32. A binding protein capable of binding human TNF-α, the binding protein comprising:
an Ig constant heavy region having an amino acid sequence of SEQ ID NO:2 or SEQ ID NO: 3;
an Ig constant light region having an amino acid sequence of SEQ ID NO:4 or SEQ ID NO: 5;
an Ig variable heavy region having an amino acid sequence of SEQ ID NO: 24, 25, 28, 29, 30, 31, 32, or 33; and
an Ig variable light region having an amino acid sequence of SEQ ID NO: 26, 27, 34, 35, or 36.

33. The binding protein of claim 1, wherein the binding protein is an immunoglobulin molecule, an Fv, a disulfide linked Fv, a monoclonal antibody, an scFv, a chimeric antibody, a single domain antibody, a CDR-grafted antibody, a diabody, a humanized antibody, a multispecific antibody, an Fab, a dual specific antibody, an Fab' fragment, a bispecific antibody, an F(ab')2 fragment, a DVD-Ig™, a bivalent fragment comprising

two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, a dAb fragment, an isolated complementarity determining region (CDR), or a single chain antibody.

34. A crystallized binding protein comprising a binding protein of claim 1, wherein the binding protein is in the form of a crystal.

35. The crystallized binding protein of claim 34, wherein the crystal is a carrier-free pharmaceutical controlled release crystal.

36. The crystallized binding protein of claim 34, wherein the binding protein has a greater half life *in vivo* than the soluble counterpart of the binding protein.

37. A composition for the release of a TNF-α binding protein, the composition comprising: (a) a formulation, wherein the formulation comprises the binding protein of claim 1 or 34 and an ingredient; and (b) at least one polymeric carrier.

38. The composition of claim 37, wherein the ingredient is selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β-cyclodextrin, methoxypolyethylene glycol, and polyethylene glycol.

39. The composition of claim 37, wherein the polymeric carrier is a polymer selected from one or more of the group consisting of: poly acrylic acid, poly cyanoacrylate, a poly amino acid, a poly anhydride, a poly depsipeptide, a poly ester, poly lactic acid, poly lactic-co-glycolic acid, poly b-hydroxybutryate, poly caprolactone, poly dioxanone; poly ethylene glycol, poly hydroxypropyl methacrylamide, poly organophosphazene, poly ortho esters, poly vinyl alcohol, poly vinylpyrrolidone, maleic anhydride-alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polysaccharides, and blends and copolymers thereof.

40. A TNF-α binding protein construct comprising the binding protein of claim 1 and a linker or an immunoglobulin constant domain.

41. The TNF-α binding protein construct of claim 40, wherein the binding protein possesses a human glycosylation pattern.

42. The TNF-α binding protein construct of claim 40, wherein the binding protein construct is a crystallized TNF-α binding protein construct.

43. The TNF-α binding protein construct of claim 42, wherein the crystallized TNF-α binding protein construct is a carrier-free pharmaceutical controlled release crystallized TNF-α binding protein construct.

44. The TNF-α binding protein construct of claim 40, wherein the binding protein construct has a greater half life *in vivo* than the soluble counterpart of the binding protein construct.

45. A TNF-α binding protein conjugate comprising a TNF-α binding protein construct of claim 40, the TNF-α binding protein conjugate further comprising an immunoadhesion molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent.

46. The TNF-α binding protein conjugate of claim 45, wherein the agent is an imaging agent that is a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

47. The TNF-α binding protein conjugate of claim 46, wherein radiolabel is ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm.

48. The TNF-α binding protein conjugate of claim 47, wherein the agent is a therapeutic or cytotoxic agent that is an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, or an apoptotic agent.

49. An isolated nucleic acid encoding a binding protein comprising an amino acid sequence of claim 1.

50. An isolated nucleic acid encoding a TNF-α binding protein construct comprising an amino acid sequence of claim 40.

51. A vector comprising an isolated nucleic acid of claim 49 or 50.

52. The vector of claim 51, wherein the vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, and pBJ.

53. A host cell comprising a vector of claim 51.

54. The host cell of claim 53, wherein the host cell is a prokaryotic cell.

55. The host cell of claim 53, wherein the host cell is a eukaryotic cell.

56. The host cell of claim 55, wherein the eukaryotic cell is a protist cell, an animal cell, a plant cell, a fungal cell, a yeast cell, a mammalian cell, an avian cell, or an insect cell.

57. The host cell of claim 55, wherein the host cell is a CHO cell, a COS cell, or a *Saccharomyces cerevisiae* cell.

58. A method of producing a protein that binds TNF-α, the method comprising the steps of culturing a host cell of claim 53 in culture medium under conditions sufficient to produce a binding protein that binds TNF-α.

59. A TNF-α binding protein produced of the method of claim 58.

60. A pharmaceutical composition comprising the binding protein of claim 1, and a pharmaceutically acceptable carrier.

61. The pharmaceutical composition of claim 60, wherein the pharmaceutically acceptable carrier functions as an adjuvant.

62. The pharmaceutical composition of claim 601, wherein the adjuvant is hyaluronidase.

63. The pharmaceutical composition of claim 60, further comprising at least one additional therapeutic agent for treating a disorder in which TNF-α activity is detrimental.

64. The pharmaceutical composition of claim 63, wherein the additional agent is a therapeutic agent, an imaging agent, a cytotoxic agent, an angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof, methotrexate, cyclosporine, rapamycin, FK506, a detectable label, a detectable reporter, a TNF-α antagonist, an anti-rheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive agent, 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 oral steroid, an epinephrine or analog thereof, a cytokine, or a cytokine antagonist.

65. Use of the pharmaceutical composition of claim 60, in the manufacture of a medicament for treating a mammal..

66. Use of a binding protein of claim1, in the manufacture of a medicament for reducing human TNF-α activity, wherein said medicament is to be contacted with human TNF-α such that human TNF-α activity is reduced.

67. Use of the binding protein of claim 1 in the manufacture of a medicament for reducing human TNF-α activity in a human subject suffering from a disorder in which TNF-α activity is detrimentalsuch that human TNF-α activity in the human subject is reduced and/or treatment is achieved.

68. Use of the binding protein of claim 1, in the manufacture of a medicament for treating a patient suffering from a disorder in which TNF-α is detrimental wherein said medicament is to be administered before, concurrent, or after the administration of a second agent, wherein the second agent is an antibody, or fragment thereof, capable of binding human IL-12; PGE2; LPA; NGF; CGRP; SubP; RAGE; histamine; a histamine receptor blocker; bradykinin; IL-1alpha; IL-1beta; VEGF; PLGF; methotrexate; a corticosteroid, a

glucocorticoid receptor modulator; cyclosporin, rapamycin, FK506, or a non-steroidal anti-inflammatory agent.

69. The use of claim 68, wherein the disorder is a respiratory disorder; asthma; allergic and nonallergic asthma; asthma due to infection; asthma due to infection with respiratory

syncytial virus (RSV); chronic obstructive pulmonary disease (COPD); a condition involving airway inflammation; eosinophilia; fibrosis and excess mucus production; cystic fibrosis; pulmonary fibrosis; an atopic disorder; atopic dermatitis; urticaria; eczema; allergic rhinitis; allergic enterogastritis; an inflammatory and/or autoimmune condition of the skin; an inflammatory and/or autoimmune condition of gastrointestinal organs; inflammatory bowel diseases (IBD); ulcerative colitis; Crohn's disease; an inflammatory and/or autoimmune condition of the liver; liver cirrhosis; liver fibrosis; liver fibrosis caused by hepatitis B and/or C virus; scleroderma; tumors or cancers; hepatocellular carcinoma; glioblastoma; lymphoma; Hodgkin's lymphoma; a viral infection; a bacterial infection; a parasitic infection; HTLV-1 infection; suppression of expression of protective type 1 immune responses, and suppression of expression of a protective type 1 immune response during vaccination.

70. The use of claim 68, wherein the disorder is selected from the group consisting of: 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 vasculitis 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, choleostasis, 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) abetalipoproteinemia, 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 aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, burns, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chronic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, cor pulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic arteriosclerotic disease, Diffuse Lewy body disease, dilated congestive cardiomyopathy, disorders of the basal ganglia, Down's Syndrome in middle age, drug- induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hemophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, fungal sepsis, gas gangrene, gastric ulcer, glomerular nephritis, graft rejection of any organ or tissue, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, hairy cell leukemia, Hallervorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemochromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage,

hepatitis (A), His bundle arrhythmias, HIV infection/HIV neuropathy, Hodgkin's disease, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, 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 (JRA), 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 (Menzel, Dejerine-Thomas, Shy-Drager, and Machado-Joseph), myasthenia gravis, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodysplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, neurodegenerative diseases, neurogenic I muscular atrophies , neutropenic fever, non- 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/hypercalcemia of malignancy, parathyroid transplant rejection, pelvic inflammatory disease, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, preeclampsia, progressive supranucleo palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon and disease, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, senile dementia of Lewy body type, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrhythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, subacute sclerosing panencephalitis, syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic

inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T-cell or 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 hemophagocytic syndrome, Wernicke- Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, acute coronary syndromes, acute idiopathic polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, alopecia areata, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, arteriosclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic ischemia, cicatricial pemphigoid, clinically isolated syndrome (CIS) with risk for multiple sclerosis, conjunctivitis, childhood onset psychiatric disorder, 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, keratojunctivitis sicca, Kussmaul disease or Kussmaul-Meier disease, Landry's paralysis, Langerhan's cell histiocytosis, livedo reticularis, macular degeneration, microscopic polyangiitis, morbus bechterev, motor neuron disorders, mucous membrane pemphigoid, multiple organ failure, myasthenia gravis, myelodysplastic syndrome, myocarditis, nerve root disorders, neuropathy, non-A non-B hepatitis, optic neuritis, osteolysis, 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, spondylitis ankylosans, Stevens-Johnson syndrome (SJS), systemic inflammatory response syndrome, temporal arteritis, toxoplasmic retinitis, toxic epidermal necrolysis, transverse myelitis, TRAPS (tumor necrosis factor receptor associated periodic syndrome), type 1 allergic reaction, type II diabetes, urticaria, usual interstitial pneumonia (UIP), vasculitis, vernal conjunctivitis, viral retinitis, Vogt-Koyanagi-Harada syndrome (VKH syndrome), wet macular degeneration, wound healing, yersinia or salmonella associated arthropathy.

71. Use of the binding protein of claim1, in the manufacture of a medicament for treating a patient suffering from a disorder in which TNF-α is detrimental, wherein said medicament is to be administered before, concurrent, or after the administration of a second agent, wherein the second agent is an inhaled steroid; beta-agonist; short-acting or long-acting beta-agonist; antagonist of leukotrienes or leukotriene receptors; ADVAIR; IgE inhibitor; anti-IgE antibodies; XOLAIR; phosphodiesterase inhibitor; PDE4 inhibitor; xanthine; anticholinergic drug; mast cell-stabilizing agent; Cromolyn; IL-4 inhibitor; IL-5 inhibitor; eotaxin/CCR3 inhibitors antagonists of histamine or its receptors including H1, H2, H3, and H4; antagonists of prostaglandin D or its receptors DP1 and CRTH2; TNF antagonist; a soluble fragment of a TNF receptor; ENBREL; TNF enzyme antagonist; TNF converting enzyme (TACE) inhibitor; muscarinic receptor antagonist; TGF-beta antagonist; interferon gamma; perfenidone; chemotherapeutic agent, methotrexate; leflunomide; sirolimus (rapamycin) or an analog thereof, CCI-779; COX2 or cPLA2 inhibitor; NSAID; immunomodulator; p38 inhibitor; TPL-2, MK-2 and NFkB inhibitor; budenoside; epidermal growth factor; corticosteroid; cyclosporine; sulfasalazine; aminosalicylate; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitor; mesalamine; olsalazine; balsalazide; antioxidant; thromboxane inhibitor; IL-1 receptor antagonist; anti-IL-1β antibody; anti-IL-6 antibody; growth factor; elastase inhibitor; pyridinyl-imidazole compound; antibody or agonist of LT, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-

33, EMAP-II, GM-CSF, FGF, or PDGF; antibody of CD2, CD3, CD4, CD8, CD25, CD28, CD30,

CD40, CD45, CD69, CD90 or their ligand; FK506; rapamycin; mycophenolate mofetil; ibuprofen; prednisolone; phosphodiesterase inhibitor; adenosine agonist; antithrombotic agent; complement inhibitor; adrenergic agent; IRAK, NIK, IKK, p38, or MAP kinase inhibitor; IL-1β converting enzyme inhibitor; TNF-α□ converting enzyme inhibitor; T-cell signaling inhibitor; metalloproteinase inhibitor; 6-mercaptopurine; angiotensin converting enzyme inhibitor; soluble cytokine receptor; soluble p55 TNF receptor; soluble p75 TNF receptor; sIL-1RI; sIL-1RII; sIL-6R; anti-inflammatory cytokine; IL-4; IL-10; IL-11; or TGF-β.

72. The use of claim 67, wherein the administering to the subject is by at least one mode selected from the group consisting of parenteral, subcutaneous, intramuscular, intravenous, intra-articular, 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.

73. A method of determining the presence of TNF-α or fragment thereof in a test sample by an immunoassay, wherein the immunoassay comprises contacting the test sample with at least one binding protein or fragment thereof according to claim 1, and at least one detectable label.

74. The method of claim 73, wherein the method further comprises the steps of:

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

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

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

75. The method of claim 73, wherein the method further comprises the steps of:

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

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

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

76. The method of claim 73, wherein the method optionally further comprises diagnosing, prognosticating, or assessing the efficiency of therapeutic/prophylactic treatment of the patient.

Claims

1. A humanized binding protein or antigen binding fragment thereof comprising an antigen binding domain capable of binding human tumor necrosis factor-alpha (TNF-α), the antigen binding domain comprising three heavy chain complementarity determining regions (CDRs) and three light chain CDRs,

wherein the three heavy chain CDRs comprise:

CDR-H1, comprising amino acid residues 31-35 of SEQ ID NO:22;

CDR-H2, comprising amino acid residues 50-65 of SEQ ID NO:22;

CDR-H3, comprising amino acid residues 98-106 of SEQ ID NO:22;

wherein the three light chain CDRs comprise:

CDR-L1, comprising amino acid residues 24-34 of SEQ ID NO:23;

CDR-L2, comprising amino acid residues 50-56 of SEQ ID NO:23;

CDR-L3, comprising amino acid residues 89-97 of SEQ ID NO:23;

wherein the humanized binding protein or antigen binding fragment thereof comprises a human acceptor framework; and

wherein the humanized binding protein or antigen binding fragment thereof binds to human TNF-α with a dissociation constant (K_D) of at most 1.56 $x10^{-10}$ M, as measured by surface plasmon resonance.

2. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the antigen binding domain comprises a heavy chain variable (VH) region.

3. The humanized binding protein or antigen binding fragment thereof of claim 2, wherein the VH region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 25, 28, 29, 30, 31, 32, and 33.

4. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the antigen binding domain comprises a light chain variable (VL) region.

5. The humanized binding protein or antigen binding fragment thereof of claim 4, wherein the VL region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 27, 34, 35, and 36.

6. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the antigen binding domain comprises a heavy chain variable (VH) region and a light chain variable (VL) region.

7. The humanized binding protein or antigen binding fragment thereof of claim 6, wherein the VH region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 25, 28, 29, 30, 31, 32, and 33, and the VL region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 27, 34, 35, and 36.

8. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the human acceptor framework comprises at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 6-21.

9. The humanized binding protein or antigen binding fragment thereof of claim 8, wherein the human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 10, 11, 12, 15, 16, 17, and 21.

10. The humanized binding protein or antigen binding fragment thereof of claim 8 or 9, wherein the human acceptor framework comprises at least one amino acid substitution.

11. The humanized binding protein or antigen binding fragment thereof of claim 10, wherein the amino acid substitution is at a key residue selected from the group consisting of: a residue adjacent to a CDR; a glycosylation site residue; a residue capable of interacting with human TNF-α; a residue capable of interacting with a CDR; a contact residue between a heavy chain variable region and a light chain variable region; a residue within a Vernier zone; and a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework.

12. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the binding protein comprises two variable domains that have the amino acid

sequences of: SEQ ID NO:24 and SEQ ID NO:26; SEQ ID NO:24 and SEQ ID NO:27; SEQ ID NO:25 and SEQ ID NO:26; or SEQ ID NO:25 and SEQ ID NO:27.

13. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the binding protein or antigen binding fragment thereof inhibits a biological function of TNF-α.

14. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the binding protein or antigen binding fragment thereof neutralizes TNF-α.

15. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the binding protein or antigen binding fragment thereof diminishes the ability of TNF-α to bind to its receptor.

16. The humanized binding protein or antigen binding fragment thereof of claim 15, wherein the binding protein or antigen binding fragment thereof diminishes the ability of pro-human TNF-α, mature-human TNF-α, or truncated-human TNF-α to bind to its receptor.

17. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the binding protein or antigen binding fragment thereof reduces one or more of: TNF-dependent cytokine production; TNF-dependent cell killing; TNF-dependent inflammation; TNF-dependent bone erosion; and TNF-dependent cartilage damage.

18. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the binding protein or antigen binding fragment thereof comprises a heavy chain immunoglobulin constant domain of: a human IgM constant domain, a human IgG1 constant domain, a human IgG2 constant domain, a human IgG3 constant domain, a human IgG4 constant domain, a human IgA constant domain, or a human IgE constant domain.

19. The humanized binding protein or antigen binding fragment thereof of claim 18, wherein the heavy chain immunoglobulin constant domain is a human IgG1 constant domain.

20. The humanized binding protein or antigen binding fragment thereof of claim 1 or 18, wherein the binding protein or antigen binding fragment thereof further comprises a light chain immunoglobulin constant domain comprising a human Ig kappa constant domain or a human Ig lambda constant domain.

21. The humanized binding protein or antigen binding fragment thereof of claim 19, wherein the human IgG1 constant domain comprises an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3.

22. The humanized binding protein or antigen binding fragment thereof of claim 20, wherein the human Ig kappa constant domain comprises an amino acid sequence of SEQ ID NO:4, or the human Ig lambda constant domain comprises an amino acid sequence SEQ ID NO:5.

23. The humanized binding protein or antigen binding fragment thereof of claim 1, further comprising:

an immunoglobulin (Ig) constant heavy region comprising the amino acid sequence of SEQ ID NO:2 or SEQ ID NO: 3;

an Ig constant light region comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO: 5;

an Ig variable heavy region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 25, 28, 29, 30, 31, 32, and 33; and

an Ig variable light region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 27, 34, 35, and 36.

24. The humanized binding protein or antigen binding fragment thereof of claim 1, wherein the binding protein or antigen binding fragment thereof is selected from the group consisting of: an immunoglobulin molecule, an Fv, a disulfide linked Fv, a monoclonal antibody, an scFv, a chimeric antibody, a single domain antibody, a CDR-grafted antibody, a diabody, a humanized antibody, a multispecific antibody, an Fab, a dual specific antibody, an Fab' fragment, a bispecific antibody, an F(ab')2 fragment, a DVD-Ig™, a bivalent fragment comprising two Fab fragments linked by a

disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, a dAb fragment, and a single chain antibody.

25. A crystallized binding protein comprising the binding protein or antigen binding fragment thereof of claim 1, wherein the binding protein or antigen binding fragment thereof is in the form of a crystal.

26. The crystallized binding protein of claim 25, wherein the crystal is a carrier-free pharmaceutical controlled release crystal.

27. The crystallized binding protein of claim 25, wherein the binding protein or antigen binding fragment thereof has a greater half life *in vivo* than the soluble counterpart of the binding protein or antigen binding fragment thereof.

28. A composition for the release of a TNF-α binding protein comprising: (a) a formulation, wherein the formulation comprises the binding protein or antigen binding fragment thereof of claim 1 or 25, and an ingredient; and (b) at least one polymeric carrier.

29. The composition of claim 28, wherein the ingredient is selected from the group consisting of: albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β-cyclodextrin, methoxypolyethylene glycol, and polyethylene glycol.

30. The composition of claim 28, wherein the polymeric carrier is a polymer selected from the group consisting of: poly acrylic acid, poly cyanoacrylate, a poly amino acid, a poly anhydride, a poly depsipeptide, a poly ester, poly lactic acid, poly lactic-co-glycolic acid, poly b-hydroxybutryate, poly caprolactone, poly dioxanone, poly ethylene glycol, poly hydroxypropyl methacrylamide, poly organophosphazene, poly ortho esters, poly vinyl alcohol, poly vinylpyrrolidone, maleic anhydride-alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polysaccharides, and blends and copolymers thereof.

31. A tumor necrosis factor-alpha (TNF-α) binding protein construct comprising the humanized binding protein or antigen binding fragment thereof of claim 1, and a linker or an immunoglobulin constant domain.

32. The TNF-α binding protein construct of claim 31, wherein the binding protein or antigen binding fragment thereof is glycosylated.

33. The TNF-α binding protein construct of claim 31, wherein the binding protein construct is a crystallized TNF-α binding protein construct.

34. The TNF-α binding protein construct of claim 33, wherein the crystallized TNF-α binding protein construct is a carrier-free pharmaceutical controlled release crystallized TNF-α binding protein construct.

35. The TNF-α binding protein construct of claim 31, wherein the binding protein construct has a greater half life *in vivo* than the soluble counterpart of the binding protein construct.

36. A tumor necrosis factor-alpha (TNF-α) binding protein conjugate comprising the TNF-α binding protein construct of claim 31, and an immunoadhesion molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent.

37. The TNF-α binding protein conjugate of claim 36, wherein the -imaging agent -is a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

38. The TNF-α binding protein conjugate of claim 37, wherein the radiolabel is 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.

39. The TNF-α binding protein conjugate of claim 36, wherein the -therapeutic agent 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.

40. An isolated nucleic acid encoding a binding protein comprising an amino acid sequence of claim 1.

41. An isolated nucleic acid encoding a TNF-α binding protein construct comprising an amino acid sequence of claim 31.

42. A vector comprising an isolated nucleic acid of claim 40 or 41.

43. The vector of claim 42, wherein the vector is selected from the group consisting of: pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, and pBJ.

44. A host cell comprising a vector of claim 42, wherein the host cell is a prokaryotic cell.

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

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

47. The host cell of claim 46, wherein the eukaryotic cell is selected from the group consisting of a protist cell, an animal cell, a plant cell, a fungal cell, a yeast cell, a mammalian cell, an avian cell, and an insect cell.

48. The host cell of claim 46, wherein the host cell is selected from the group consisting of a CHO cell, a COS cell, and a *Saccharomyces cerevisiae* cell.

49. A method of producing a protein that binds TNF-α, the method comprising the steps of culturing a host cell of claim 44 in culture medium under conditions sufficient to produce a binding protein that binds TNF-α.

50. A TNF-α binding protein produced of the method of claim 49.

51. A pharmaceutical composition for treating a disorder in which TNF-α activity is detrimental comprising the binding protein or antigen binding fragment thereof of claim 1, and a pharmaceutically acceptable carrier.

52. The pharmaceutical composition of claim 51, wherein the pharmaceutically acceptable carrier functions as an adjuvant.

53. The pharmaceutical composition of claim 52, wherein the adjuvant is hyaluronidase.

54. The pharmaceutical composition of claim 51, wherein the composition further comprises at least one additional agent for treating a disorder in which TNF-α activity is detrimental.

55. The pharmaceutical composition of claim 54, wherein the additional agent is a therapeutic agent, an imaging agent, a cytotoxic agent, an angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof, methotrexate, cyclosporine, rapamycin, FK506, a detectable label, a detectable reporter, a TNF-α antagonist, an anti-rheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive agent, 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 oral steroid, an epinephrine or analog thereof, a cytokine, or a cytokine antagonist.

56. Use of the pharmaceutical composition of claim 51, in the manufacture of a medicament for treating a mammal.

57. Use of a binding protein of claim 1, in the manufacture of a medicament for reducing human TNF-α activity, wherein said medicament is to be contacted with human TNF-α such that human TNF-α is reduced.

58. Use of the binding protein of claim 1 in the manufacture of a medicament for reducing human TNF-α activity in a human subject suffering from a disorder in which

TNF-α activity is detrimental such that human TNF-α activity in the human subject is reduced and/or treatment is achieved.

59. Use of the binding protein of claim 1, in the manufacture of a medicament for treating a patient suffering from a disorder in which TNF-α is detrimental wherein said medicament is to be administered before, concurrent, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an antibody, or fragment thereof, capable of binding human IL-12; PGE2; LPA; NGF; CGRP; SubP; RAGE; histamine; a histamine receptor blocker; bradykinin; IL-1alpha; IL-1beta; VEGF; PLGF; methotrexate; a corticosteroid, a glucocorticoid receptor modulator; cyclosporin, rapamycin, FK506, and a non-steroidal anti-inflammatory agent.

60. The use of claim 59, wherein the disorder is selected from the group consisting of a respiratory disorder; asthma; allergic and nonallergic asthma; asthma due to infection; asthma due to infection with respiratory syncytial virus (RSV); chronic obstructive pulmonary disease (COPD); a condition involving airway inflammation; eosinophilia; fibrosis and excess mucus production; cystic fibrosis; pulmonary fibrosis; an atopic disorder; atopic dermatitis; urticaria; eczema; allergic rhinitis; allergic enterogastritis; an inflammatory and/or autoimmune condition of the skin; an inflammatory and/or autoimmune condition of gastrointestinal organs; inflammatory bowel diseases (IBD); ulcerative colitis; Crohn's disease; an inflammatory and/or autoimmune condition of the liver; liver cirrhosis; liver fibrosis; liver fibrosis caused by hepatitis B and/or C virus; scleroderma; tumors or cancers; hepatocellular carcinoma; glioblastoma; lymphoma; Hodgkin's lymphoma; a viral infection; a bacterial infection; a parasitic infection; HTLV-1 infection; suppression of expression of protective type 1 immune responses, and suppression of expression of a protective type 1 immune response during vaccination.

61. The use of claim 59, wherein the disorder is selected from the group consisting of 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 vasculitis 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, choleostasis, 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) abetalipoproteinemia, 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 aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, burns, cardiac

arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chronic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, cor pulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic arteriosclerotic disease, Diffuse Lewy body disease, dilated congestive cardiomyopathy, disorders of the basal ganglia, Down's Syndrome in middle age, drug-induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hemophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, fungal sepsis, gas gangrene, gastric ulcer, glomerular nephritis, graft rejection of any organ or tissue, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, hairy cell leukemia, Hallervorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemochromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, hepatitis (A), His bundle arrhythmias, HIV infection/HIV neuropathy, Hodgkin's disease, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, 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 (JRA), 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 (Menzel, Dejerine-Thomas, Shy-Drager, and Machado-Joseph), myasthenia gravis, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodysplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, neurodegenerative diseases, neurogenic I muscular atrophies , neutropenic fever, non-Hodgkins lymphoma, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, muromonab-CD3 therapy, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoporosis, pancreas transplant rejection, pancreatic carcinoma, paraneoplastic syndrome/hypercalcemia of malignancy, parathyroid transplant rejection, pelvic inflammatory disease, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, preeclampsia, progressive supranucleo palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon and disease, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, senile dementia of Lewy body type, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrhythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, subacute sclerosing panencephalitis, syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T-cell or 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 hemophagocytic syndrome, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, acute coronary syndromes, acute idiopathic

polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, alopecia areata, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, arteriosclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic ischemia, cicatricial pemphigoid, clinically isolated syndrome (CIS) with risk for multiple sclerosis, conjunctivitis, childhood onset psychiatric disorder, 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, keratojunctivitis sicca, Kussmaul disease or Kussmaul-Meier disease, Landry's paralysis, Langerhan's cell histiocytosis, livedo reticularis, macular degeneration, microscopic polyangiitis, morbus bechterev, motor neuron disorders, mucous membrane pemphigoid, multiple organ failure, myasthenia gravis, myelodysplastic syndrome, myocarditis, nerve root disorders, neuropathy, non-A non-B hepatitis, optic neuritis, osteolysis, 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, spondylitis

ankylosans, Stevens-Johnson syndrome (SJS), systemic inflammatory response syndrome, temporal arteritis, toxoplasmic retinitis, toxic epidermal necrolysis, transverse myelitis, TRAPS (tumor necrosis factor receptor associated periodic syndrome), type 1 allergic reaction, type II diabetes, urticaria, usual interstitial pneumonia (UIP), vasculitis, vernal conjunctivitis, viral retinitis, Vogt-Koyanagi-Harada syndrome (VKH syndrome), wet macular degeneration, wound healing, and yersinia or salmonella associated arthropathy.

62. Use of the binding protein of claim 1, in the manufacture of a medicament for treating a patient suffering from a disorder in which TNF-α is detrimental, wherein said medicament is to be administered before, concurrent, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an inhaled steroid; beta-agonist; short-acting or long-acting beta-agonist; antagonist of leukotrienes or leukotriene receptors; fluticasone propionate and salmeterol xinafoate; IgE inhibitor; anti-IgE antibodies; omalizumab; phosphodiesterase inhibitor; PDE4 inhibitor; xanthine; anticholinergic drug; mast cell-stabilizing agent; Cromolyn; IL-4 inhibitor; IL-5 inhibitor; eotaxin/CCR3 inhibitors antagonists of histamine or its receptors including H1, H2, H3, and H4; antagonists of prostaglandin D or its receptors DP1 and CRTH2; TNF antagonist; a soluble fragment of a TNF receptor; etanercept; TNF enzyme antagonist; TNF converting enzyme (TACE) inhibitor; muscarinic receptor antagonist; TGF-beta antagonist; interferon gamma; perfenidone; chemotherapeutic agent, methotrexate; leflunomide; sirolimus (rapamycin) or an analog thereof, CCI-779; COX2 or cPLA2 inhibitor; NSAID; immunomodulator; p38 inhibitor; TPL-2, MK-2 and NFkB inhibitor; budenoside; epidermal growth factor; corticosteroid; cyclosporine; sulfasalazine; aminosalicylate; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitor; mesalamine; olsalazine; balsalazide; antioxidant; thromboxane inhibitor; IL-1 receptor antagonist; anti-IL-1β antibody; anti-IL-6 antibody; growth factor; elastase inhibitor; pyridinyl-imidazole compound; antibody or agonist of LT, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, EMAP-II, GM-CSF, FGF, or PDGF; antibody of CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligand; FK506; rapamycin; mycophenolate mofetil; ibuprofen; prednisolone; phosphodiesterase inhibitor;

adensosine agonist; antithrombotic agent; complement inhibitor; adrenergic agent; IRAK, NIK, IKK, p38, or MAP kinase inhibitor; IL-1β converting enzyme inhibitor; TNF-α converting enzyme inhibitor; T-cell signaling inhibitor; metalloproteinase inhibitor; 6-mercaptopurine; angiotensin converting enzyme inhibitor; soluble cytokine receptor; soluble p55 TNF receptor; soluble p75 TNF receptor; sIL-1RI; sIL-1RII; sIL-6R; anti-inflammatory cytokine; IL-4; IL-10; IL-11; and TGF-β.

63. The use of claim 58, wherein the administering to the subject is by at least one mode selected from the group consisting of parenteral, subcutaneous, intramuscular, intravenous, intra-articular, 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.

64. A method of determining the presence of TNF-α or fragment thereof in a test sample by an immunoassay, wherein the immunoassay comprises contacting the test sample with at least one binding protein or fragment thereof according to claim 1, and at least one detectable label.

65. The method of claim 64, wherein the method further comprises the steps of:

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

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

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

66. The method of claim 64, wherein the method further comprises the steps of:

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

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

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

67. The method of claim 64, wherein the method optionally further comprises diagnosing, prognosticating, or assessing the efficiency of therapeutic/prophylactic treatment of the patient.