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 a constant domain;

X1 is a linker;

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 DLL4 and VEGF, wherein the first polypeptide chain of the binding protein comprises SEQ ID NO: 56 and the second polypeptide chain of the binding protein comprises SEQ ID NO: 64.

2. The binding protein of claim 1, wherein the binding protein comprises a first polypeptide chain comprising a first VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

X1 is a linker;

X2 is an Fc region;

n is 0 or 1, and

wherein the binding protein comprises a second polypeptide chain comprising a second VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

X1 is a linker;

n is 0 or 1 for (X1)n;

n is 0 for (X2)n,

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.

3. The binding protein of claim 1 or 2, wherein the binding protein comprises two first and two second polypeptide chains and four functional target binding sites.

4. The binding protein of any one of claims 1-3, wherein the Fc region of the binding protein is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD, or a variant thereof.

5. The binding protein of any one of claims 1-3, wherein the Fc region of the binding protein is a variant sequence Fc region.

6. The binding protein of any one of claims 1-3, wherein the binding protein comprises the constant region sequences of SEQ ID NO: 74 and/or SEQ ID NO: 73.

7. The binding protein of any one of claims 1-3, wherein the first and second polypeptide chains of the binding protein comprise SEQ ID NOs: 74 and 73.

8. The binding protein of any one of claims 1-7, wherein the binding protein is capable of:

(a) binding to VEGF with a dissociation constant (K_D) of at most about 7.0×10^{-10} M, as measured by surface plasmon resonance, and/or blocking VEGF activity with an IC50 of at most about 3.8 nM, as measured in a VEGFR1 Competition ELISA; and/or

(b) binding to DLL4 with a dissociation constant (K_D) of at most about 1.0×10^{-8} M, as measured by surface plasmon resonance, and/or blocking DLL4 activity with an IC50 of at most about 1.09 nM, as measured in a Notch Competition ELISA.

9. A binding protein conjugate comprising a binding protein of any one of claims 1-8, the binding protein conjugate further comprising an agent, wherein the agent is an immunoadhension molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent.

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

11. The binding protein according to any one of claims 1-8, wherein the binding protein is a crystallized binding protein.

12. An isolated nucleic acid encoding the binding protein of any one of claims 1-8.

13. A vector comprising the isolated nucleic acid of claim 12.

14. The vector of claim 13 wherein said vector is selected from the group consisting of: pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6, pHybE, TOPO, and pBJ.

15. A host cell comprising the vector according to claim 13.

16. The host cell according to claim 15, wherein said host cell is a prokaryotic cell.

17. The host cell according to claim 16, wherein said host cell is *Escherichia coli*.

18. The host cell according to claim 15, wherein said host cell is a eukaryotic cell.

19. The host cell according to claim 18, wherein said eukaryotic cell is selected from the group consisting of: a protist cell, an animal cell, a plant cell, and a fungal cell.

20. The host cell according to claim 18, wherein said eukaryotic cell is an animal cell selected from the group consisting of: a mammalian cell, an avian cell, and an insect cell.

21. The host cell according to claim 20, wherein said mammalian cell is a CHO cell.

22. The host cell according to claim 20, wherein said mammalian cell is a COS cell.

23. The host cell according to claim 19, wherein said fungal cell is *Saccharomyces cerevisiae*.

24. The host cell according to claim 20, wherein said insect cell is an Sf9 cell.

25. A method of producing a binding protein comprising culturing the host cell according to any one of claims 15-24 in culture medium under conditions sufficient to produce the binding protein.

26. A protein produced by the method of claim 25.

27. A pharmaceutical composition comprising the binding protein of any one of claims 1-8 and at least one additional agent.

28. The pharmaceutical composition of claim 27, wherein the additional agent comprises at least one of an immunoadhesion molecule, an imaging agent, a therapeutic agent, a cytotoxic agent, a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, biotin, 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, a chemotherapeutic agent; an imaging agent, an angiogenesis inhibitor, a kinase inhibitor (including but not limited to a KDR and a TIE-2 inhibitor), a co-stimulation molecule modulator (including but not limited to anti-B7.1, anti-B7.2, CTLA4-Ig, anti-CD20), an adhesion molecule blocker (including but not limited to an anti-LFA-1 antibody, an anti-E/L selectin antibody, an anti-VEGF mAb; an anti-DLL4 mAb; a small molecule inhibitor), an anti-cytokine antibody or functional fragment thereof (including but not limited to an anti-IL-18, an anti-TNF, or an anti-IL-6/cytokine receptor antibody), 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, a cytokine antagonist, an anti-hypertensive agent, a diuretic, an adrenergic receptor antagonist, a calcium channel blocker, a renin inhibitor, an ACE inhibitor, an angiotensin II receptor antagonist, a vasodilator, an alpha-2 agonist, clonidine, methyldopa, hydralazine, prazosin, reserpine, moxonidine, guanfacine, perindopril/indapamide, lofexidine, metirosine, an anticoagulant, warfarin, heparin, low molecular weight heparin, dalteparin, argatroban, bivalirudin, lepirudin, and dextrose.

29. The pharmaceutical composition of claim 27, wherein the additional agent comprises one or more of a cytotoxic agent, a chemotherapeutic agent, an anti-angiogenic agent, an anti-CTLA4 antibody, a calcium channel blocker, an ACE inhibitor, FOLFIRI, paclitaxel, carboplatin, doxil, topotecan, and cisplatin.

30. Use of the binding protein of any one of claims 1-8, or the pharmaceutical composition of any one of claims 27-29, in the manufacture of a medicament for

treating a disease characterized by vascular overgrowth, edema, or aberrant DLL4 and/or VEGF expression or activity in a subject.

31. The use of claim 30, wherein the medicament further comprises at least one additional agent for treating a disease characterized by vascular overgrowth, edema, or aberrant DLL4 and/or VEGF expression or activity.

32. The use of claim 31, wherein the at least one additional agent comprises one or more of: irinotecan, leucovorin, 5-FU, temozolomide, capecitabine, gemcitabine, and paclitaxel.

33. The use of claim 31, wherein the at least one additional agent comprises one or more of: a cytotoxic agent, a chemotherapeutic agent, an anti-angiogenic agent, an anti-CTLA4 antibody, a calcium channel blocker, an ACE inhibitor, FOLFIRI, paclitaxel, carboplatin, doxil, topotecan, and cisplatin.

34. The use of any one of claims 30-33, wherein the disease is colorectal carcinoma, ovarian cancer, cervical cancer, breast cancer, lung cancer, or pancreatic cancer.

35. The use of any one of claims 30-33, wherein the disease is primary or metastatic cancer, breast cancer, colon cancer, rectum cancer, lung cancer, non-small cell lung cancer, adenocarcinoma, oropharynx cancer, hypopharynx cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, gallbladder cancer, bile duct cancer, small intestine cancer, urinary tract cancer, kidney cancer, bladder cancer, urothelium cancer, female genital tract cancer, cervical cancer, uterus cancer, ovarian cancer, choriocarcinoma, gestational trophoblastic disease, male genital tract cancer, prostate cancer, seminal vesicles cancer, testical cancer, germ cell tumors, endocrine gland cancer, thyroid cancer, adrenal gland cancer, pituitary gland cancer, skin cancer, hemangiomas, melanomas, sarcomas, bone sarcoma, soft tissue sarcoma, Kaposi's sarcoma, tumors of the brain, tumors of the nerves, tumors of the eyes, tumors of the meninges, astrocytomas, glioma, glioblastomas,

retinoblastomas, neuromas, neuroblastomas, Schwannomas, and meningiomas, solid tumors arising from hematopoietic malignancies, leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, stomach cancer, bladder cancer, prostate cancer, rectal cancer, hematopoietic malignancies, Abetalipoprotemia, acrocyanosis, acute leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), B cell lymphoma, Burkitt's lymphoma, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), colorectal carcinoma, hairy cell leukemia, malignant lymphoma, malignant histiocytosis, malignant melanoma, multiple myeloma, pancreatic carcinoma, paraneoplastic syndrome, hypercalcemia of malignancy, sarcomas, solid tumors, macular degeneration, diabetes mellitus type 1, diabetic retinopathy, or atherosclerosis.

36. The use of any one of claims 30-33, wherein the disease is colon cancer and/or the medicament further comprises one or more of irinotecan, leucovorin, temozolomide, gemcitabine, paclitaxel, capecitabine, and 5-FU.

37. The use of any one of claims 30-33, wherein the disease is glioblastoma and/or the medicament further comprises temozolomide.

38. The use of any one of claims 30-33, wherein the disease is pancreatic cancer and/or the medicament further comprises gemcitabine.

39. The use of any one of claims 30-33, wherein the disease is breast cancer and/or the medicament further comprises paclitaxel.

40. The use of any one of claims 30-39, wherein the medicament further comprises:
one or more amino acid,
one or more polysaccharide and/or polysorbate, and
the binding protein at a concentration of 0.1-100 mg/ml,
wherein the pharmaceutical composition is at a pH of 5.0-7.0.

41. The use of claim 40, wherein the one or more amino acid comprises histidine and is present at a concentration of 10-20 mM.

42. The use of claim 40 or 41, wherein the one or more polysaccharide comprises sucrose and is present at a concentration of 0-8.0% weight/volume (w/v).

43. The use of any one of claims 40-42, wherein the polysorbate is polysorbate 80 and is at a concentration of 0-0.06% w/v.

44. The use of any one of claims 40-43, wherein the one or more amino acid comprises arginine and is present at a concentration of 0-1.5% w/v.

45. The use of any one of claims 40-44, wherein the binding protein is present at a concentration of 0.1- 25 mg/ml.

46. The use of claim 40, wherein the composition comprises 15 mM histidine, 0.03% (w/v) polysorbate 80, 4% (w/v) sucrose, and 1-25 mg/ml of the binding protein, and is at a pH of 6.

47. A method of detecting the presence of at least one of VEGF or DLL4, or a fragment thereof, in a test sample by an immunoassay,

wherein the immunoassay comprises contacting the test sample with at least one binding protein and at least one detectable label, wherein the at least one binding protein comprises the binding protein of any one of claims 1-8.

48. The method according to claim 47, wherein the at least one detectable label comprises a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

49. The method according to claim 47, wherein the at least one detectable label is on the at least one binding protein.

50. The method according to claim 47, further comprising:

(i) contacting the test sample with the at least one binding protein, wherein the binding protein binds to an epitope on VEGF or DLL4 or fragment thereof in the test sample so as to form a first complex;
(ii) contacting the first complex with at least one detectable label to form a second complex, wherein the detectable label binds to the binding protein or to an epitope on VEGF or DLL4 or fragment thereof in the test sample that is not bound by the binding protein; and
(iii) detecting the presence of VEGF or DLL4 or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence of VEGF or DLL4 or fragment thereof is directly correlated with the signal generated by the detectable label.

51. The method according to any one of claims 47-50, wherein the test sample is from a patient and the method further comprises diagnosing, prognosticating, or assessing the efficacy of therapeutic or prophylactic treatment of the patient, and wherein if the method further comprises assessing the efficacy of therapeutic or prophylactic treatment of the patient, the method optionally further comprises modifying the therapeutic or prophylactic treatment of the patient as needed to improve efficacy.

52. The method according to any one of claims 47-51, wherein the method is adapted for use in an automated system or a semi-automated system.

53. The method according to any one of claims 47-52, wherein the method determines the amount or concentration of DLL4 and VEGF in the sample.

54. A kit for use in assaying a test sample for the presence, amount, or concentration of DLL4, VEGF, or both, the kit comprising

(a) instructions for assaying the test sample for VEGF and/or DLL4 or fragment(s) thereof; and

(b) at least one binding protein comprising the binding protein of any one of claims 1-8.

55. A pharmaceutical composition comprising the binding protein of any one of claims 1-8, further comprising:

one or more amino acid,

one or more polysaccharide and/or polysorbate, and

the binding protein at a concentration of 0.1-100 mg/ml,

wherein the pharmaceutical composition is at a pH of 5.0-7.0.

56. The pharmaceutical composition of claim 55, wherein the one or more amino acid comprises histidine and is present at a concentration of 10-20 mM.

57. The pharmaceutical composition of claim 55 or 56, wherein the one or more polysaccharide comprises sucrose and is present at a concentration of 0-8.0% weight/volume (w/v).

58. The pharmaceutical composition of any one of claims 55-57, wherein the polysorbate is polysorbate 80 and is at a concentration of 0-0.06% w/v.

59. The pharmaceutical composition of any one of claims 55-58, wherein the one or more amino acid comprises arginine and is present at a concentration of 0-1.5% w/v.

60. The pharmaceutical composition of any one of claims 55-59, wherein the binding protein is present at a concentration of 0.1- 25 mg/ml.

61. The pharmaceutical composition of claim 55, wherein the composition comprises 15 mM histidine, 0.03% (w/v) polysorbate 80, 4% (w/v) sucrose, and 1-25 mg/ml of the binding protein, and is at a pH of 6.

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 a constant domain;

X1 is a linker;

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 DLL4 and VEGF, wherein:

(i) the variable domains that form a functional target binding site for DLL4 comprise:

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

(ii) the variable domains that form a functional target binding site for VEGF comprise:

three CDRs from SEQ ID NO: 41 and three CDRs from SEQ ID NO: 42.

2. The binding protein of claim 1, wherein the binding protein comprises a first polypeptide chain comprising a first VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

X1 is a linker;

X2 is an Fc region;

n is 0 or 1, and

wherein the binding protein comprises a second polypeptide chain comprising a second VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

X1 is a linker;

n is 0 or 1 for (X1)n;

n is 0 for (X2)n,

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.

3. The binding protein of claim 1 or 2, wherein the binding protein comprises:

(i) variable domains that form a functional target binding site for DLL4 comprising:

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

(ii) variable domains that form a functional target binding site for VEGF comprising:

SEQ ID NO: 41 and SEQ ID NO: 42.

4. The binding protein of any one of claims 1-3, wherein the binding protein comprises two first and two second polypeptide chains and four functional target binding sites.

5. The binding protein of any one of claims 1-4, wherein the linker X1 comprises any one of SEQ ID NOs 1-38 or a G/S based sequence.

6. The binding protein of any one of claims 1-4, wherein the linker X1 is SEQ ID NO: 2 on the first polypeptide chain and SEQ ID NO:6 on the second polypeptide chain.

7. The binding protein of any one of claims 1-6, wherein the Fc region of the binding protein is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD, or a variant thereof.

8. The binding protein of any one of claims 1-7, wherein the Fc region of the binding protein is a variant sequence Fc region.

9. The binding protein of any one of claims 1-6, wherein the binding protein comprises the constant region sequences of SEQ ID NO: 74 and/or SEQ ID NO: 73.

10. The binding protein of any one of claims 1-9, wherein the first polypeptide chain of the binding protein comprises SEQ ID NO: 56 and the second polypeptide chain of the binding protein comprises SEQ ID NO: 64.

11. The binding protein of any one of claims 1-9, wherein the first and second polypeptide chains of the binding protein comprise SEQ ID NOs: 74 and 73.

12. The binding protein of any one of claims 1-11, wherein the binding protein is capable of:

(a) binding to VEGF with a dissociation constant (K_D) of at most about 7.0 x 10^{-10} M, as measured by surface plasmon resonance, and/or blocking VEGF activity with an IC50 of at most about 3.8 nM, as measured in a VEGFR1 Competition ELISA; and/or

(b) binding to DLL4 with a dissociation constant (K_D) of at most about 1.0 x 10^{-8} M, as measured by surface plasmon resonance, and/or blocking DLL4 activity with an IC50 of at most about 1.09 nM, as measured in a Notch Competition ELISA.

13. A binding protein conjugate comprising a binding protein of claims 1-12, wherein the binding protein conjugate further comprising an agent, wherein the agent is an immunoadhesion molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent.

14. The binding protein conjugate according to claim 13, wherein the imaging agent is a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

15. The binding protein according to any one of claims 1-12, wherein the binding protein is a crystallized binding protein.

16. An isolated nucleic acid encoding the binding protein of any one of claims 1-12.

17. A vector comprising the isolated nucleic acid of claim 16.

18. The vector of claim 17 wherein said vector is selected from the group consisting of: pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6, pHybE, TOPO, and pBJ.

19. A host cell comprising the vector according to claim 17.

20. The host cell according to claim 19, wherein said host cell is a prokaryotic cell.

21. The host cell according to claim 20, wherein said host cell is *Escherichia coli*.

22. The host cell according to claim 19, wherein said host cell is a eukaryotic cell.

23. The host cell according to claim 22, wherein said eukaryotic cell is selected from the group consisting of: a protist cell, an animal cell, a plant cell, and a fungal cell.

24. The host cell according to claim 22, wherein said eukaryotic cell is an animal cell selected from the group consisting of: a mammalian cell, an avian cell, and an insect cell.

25. The host cell according to claim 24, wherein said mammalian cell is a CHO cell.

26. The host cell according to claim 24, wherein said mammalian cell is a COS cell.

27. The host cell according to claim 23, wherein said fungal cell is *Saccharomyces cerevisiae*.

28. The host cell according to claim 24, wherein said insect cell is an Sf9 cell.

29. A method of producing a binding protein comprising culturing the host cell according to any one of claims 19-28 in culture medium under conditions sufficient to produce the binding protein.

30. A protein produced by the method of claim 29.

31. A composition comprising the binding protein of any one of claims 1-12 and at least one additional agent.

32. The composition of claim 31, wherein the additional agent comprises at least one of an immunoadhesion molecule, an imaging agent, a therapeutic agent, a cytotoxic agent, a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, biotin, 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, a chemotherapeutic agent; an imaging agent, an angiogenesis inhibitor, a kinase inhibitor (including but not limited to a KDR and a TIE-2 inhibitor), a co-stimulation molecule modulator (including but not limited to anti-B7.1, anti-B7.2, CTLA4-Ig, anti-CD20), an adhesion molecule blocker (including but not limited to an anti-LFA-1 antibody, an anti-E/L selectin antibody, an anti-VEGF mAb; an anti-DLL4 mAb; a small molecule inhibitor), an anti-cytokine antibody or functional fragment thereof (including but not limited to an anti-IL-18, an anti-TNF, or an anti-IL-6/cytokine receptor antibody), 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, a cytokine antagonist, an anti-hypertensive agent, a diuretic, an adrenergic receptor

antagonist, a calcium channel blocker, a renin inhibitor, an ACE inhibitor, an angiotensin II receptor antagonist, a vasodilator, an alpha-2 agonist, clonidine, methyldopa, hydralazine, prazosin, reserpine, moxonidine, guanfacine, perindopril/indapamide, lofexidine, metirosine, an anticoagulant, warfarin, heparin, low molecular weight heparin, dalteparin, argatroban, bivalirudin, lepirudin, and dextrose.

33. The composition of claim 31, wherein the additional agent comprises one or more of a cytotoxic agent, a chemotherapeutic agent, an anti-angiogenic agent, an anti-CTLA4 antibody, a calcium channel blocker, an ACE inhibitor, FOLFIRI, paclitaxel, carboplatin, doxil, topotecan, and cisplatin.

34. Use of the binding protein of any one of claims 1-12, or the pharmaceutical composition of any one of claims 31-33, in the manufacture of a medicament for treating a disease characterized by vascular overgrowth, edema, or aberrant DLL4 and/or VEGF expression or activity in a subject.

35. The use of claim 34, wherein the medicament further comprises at least one additional agent for treating a disease characterized by vascular overgrowth, edema, or aberrant DLL4 and/or VEGF expression or activity.

36. The use of claim 35, wherein the at least one additional agent comprises one or more of: irinotecan, leucovorin, 5-FU, temozolomide, capecitabine, gemcitabine, and paclitaxel.

37. The use of claim 35, wherein the at least one additional agent comprises one or more of: a cytotoxic agent, a chemotherapeutic agent, an anti-angiogenic agent, an anti-CTLA4 antibody, a calcium channel blocker, an ACE inhibitor, FOLFIRI, paclitaxel, carboplatin, doxil, topotecan, and cisplatin.

38. The use of any one of claims 34-37, wherein the disease is colorectal carcinoma, ovarian cancer, cervical cancer, breast cancer, lung cancer, or pancreatic cancer.

39. The use of any one of claims 34-37, wherein the disease is primary or metastatic cancer, breast cancer, colon cancer, rectum cancer, lung cancer, non-small cell lung cancer, adenocarcinoma, oropharynx cancer, hypopharynx cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, gallbladder cancer, bile duct cancer, small intestine cancer, urinary tract cancer, kidney cancer, bladder cancer, urothelium cancer, female genital tract cancer, cervical cancer, uterus cancer, ovarian cancer, choriocarcinoma, gestational trophoblastic disease, male genital tract cancer, prostate cancer, seminal vesicles cancer, testical cancer, germ cell tumors, endocrine gland cancer, thyroid cancer, adrenal gland cancer, pituitary gland cancer, skin cancer, hemangiomas, melanomas, sarcomas, bone sarcoma, soft tissue sarcoma, Kaposi's sarcoma, tumors of the brain, tumors of the nerves, tumors of the eyes, tumors of the meninges, astrocytomas, glioma, glioblastomas, retinoblastomas, neuromas, neuroblastomas, Schwannomas, and meningiomas, solid tumors arising from hematopoietic malignancies, leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, stomach cancer, bladder cancer, prostate cancer, rectal cancer, hematopoietic malignancies, Abetalipoprotemia, acrocyanosis, acute leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), B cell lymphoma, Burkitt's lymphoma, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), colorectal carcinoma, hairy cell leukemia, malignant lymphoma, malignant histiocytosis, malignant melanoma, multiple myeloma, pancreatic carcinoma, paraneoplastic syndrome, hypercalcemia of malignancy, sarcomas, solid tumors, macular degeneration, diabetes mellitus type 1, diabetic retinopathy, or atherosclerosis.

40. The use of any one of claims 34-37, wherein the disease is colon cancer and/or the medicament further comprises one or more of irinotecan, leucovorin, temozolomide, gemcitabine, paclitaxel, capecitabine, and 5-FU.

41. The use of any one of claims 34-37, wherein the disease is glioblastoma and/or the medicament further comprises temozolomide.

42. The use of any one of claims 34-37, wherein the disease is pancreatic cancer and/or the medicament further comprises gemcitabine.

43. The use of any one of claims 34-37, wherein the disease is breast cancer and/or the medicament further comprises paclitaxel.

44. The use of any one of claims 34-43, wherein the medicament further comprises:

one or more amino acid,

one or more polysaccharide and/or polysorbate, and

the binding protein at a concentration of 0.1-100 mg/ml,

wherein the pharmaceutical composition is at a pH of 5.0-7.0.

45. The use of claim 44, wherein the one or more amino acid comprises histidine and is present at a concentration of 10-20 mM.

46. The use of claim 44 or 45, wherein the one or more polysaccharide comprises sucrose and is present at a concentration of 0-8.0% weight/volume (w/v).

47. The use of any one of claims 44-46, wherein the polysorbate is polysorbate 80 and is at a concentration of 0-0.06% w/v.

48. The use of any one of claims 44-47, wherein the one or more amino acid comprises arginine and is present at a concentration of 0-1.5% w/v.

49. The use of any one of claims 44-48, wherein the binding protein is present at a concentration of 0.1- 25 mg/ml.

50. The use of claim 44, wherein the composition comprises 15 mM histidine, 0.03% (w/v) polysorbate 80, 4% (w/v) sucrose, and 1-25 mg/ml of the binding protein, and is at a pH of 6.

51. A method of detecting the presence of at least one of VEGF or DLL4, or a fragment thereof, in a test sample by an immunoassay,

wherein the immunoassay comprises contacting the test sample with at least one binding protein and at least one detectable label, wherein the at least one binding protein comprises the binding protein of any one of claims 1-12.

52. The method according to claim 51, wherein the at least one detectable label comprises a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

53. The method according to claim 51, wherein the at least one detectable label is on the at least one binding protein.

54. The method according to claim 51, further comprising:

(i) contacting the test sample with the at least one binding protein, wherein the binding protein binds to an epitope on VEGF or DLL4 or fragment thereof in the test sample so as to form a first complex;
(ii) contacting the first complex with at least one detectable label to form a second complex, wherein the detectable label binds to the binding protein or to an epitope on VEGF or DLL4 or fragment thereof in the test sample that is not bound by the binding protein; and
(iii) detecting the presence of VEGF or DLL4 or fragment thereof in the test sample based on the signal generated by the detectable label in the second complex, wherein the presence of VEGF or DLL4 or fragment thereof is directly correlated with the signal generated by the detectable label.

55. The method according to any one of claims 51-54, wherein the test sample is from a patient and the method further comprises diagnosing, prognosticating, or assessing the efficacy of therapeutic or prophylactic treatment of the patient, and wherein if the method further comprises assessing the efficacy of therapeutic or prophylactic treatment of the patient, the method optionally further comprises modifying the therapeutic or prophylactic treatment of the patient as needed to improve efficacy.

56. The method according to any one of claims 51-55, wherein the method is adapted for use in an automated system or a semi-automated system.

57. The method according to any one of claims 51-56, wherein the method determines the amount or concentration of DLL4 and VEGF in the sample.

58. A kit for use in assaying a test sample for the presence, amount, or concentration of DLL4, VEGF, or both, the kit comprising

(a) instructions for assaying the test sample for VEGF and/or DLL4 or fragment(s) thereof; and

(b) at least one binding protein comprising the binding protein of any one of claims 1-12.

59. The binding protein of any one of claims 1-12, further comprising:

one or more amino acid,

one or more polysaccharide and/or polysorbate, and

the binding protein at a concentration of 0.1-100 mg/ml,

wherein the pharmaceutical composition is at a pH of 5.0-7.0.

60. The binding protein of claim 59, wherein the one or more amino acid comprises histidine and is present at a concentration of 10-20 mM.

61. The binding protein of claim 59 or 60, wherein the one or more polysaccharide comprises sucrose and is present at a concentration of 0-8.0% weight/volume (w/v).

62. The binding protein of any one of claims 59-61, wherein the polysorbate is polysorbate 80 and is at a concentration of 0-0.06% w/v.

63. The binding protein of any one of claims 59-62, wherein the one or more amino acid comprises arginine and is present at a concentration of 0-1.5% w/v.

64. The binding protein of any one of claims 59-63, wherein the binding protein is present at a concentration of 0.1- 25 mg/ml.

65. The binding protein of claim 59, wherein the composition comprises 15 mM histidine, 0.03% (w/v) polysorbate 80, 4% (w/v) sucrose, and 1-25 mg/ml of the binding protein, and is at a pH of 6.