effectively nonfunctional. Thus, disruption of both VEGF and DLL4 provides for different methods of action for potential anti-cancer treatment.

[012] While antibodies and various binding constructs are known in the art, there remains a need for better targeting and efficiency of binding to VEGF and DLL4, e.g., to treat cancer and tumorogenesis. There is thus a need in the art for improved multivalent binding proteins capable of binding DLL4 and VEGF. Accordingly, novel binding proteins are provided, wherein the binding proteins are capable of binding DLL4 and VEGF. In some embodiments, the binding proteins are capable of, e.g., binding to DLL4 and VEGF with improved binding affinity and/or neutralization potency.

SUMMARY

[012a] In one aspect, there is provided 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.

[012b] In one aspect, there is provided a binding protein conjugate comprising a binding protein as disclosed herein, 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.

[012c] In one aspect, there is provided an isolated nucleic acid encoding the binding protein as disclosed herein.

[012d] In one aspect, there is provided a vector comprising the isolated nucleic acid as disclosed herein.

[012e] In one aspect, there is provided a host cell comprising the vector as disclosed herein.

[012f] In one aspect, there is provided a method of producing a binding protein comprising culturing the host cell as disclosed herein in culture medium under conditions sufficient to produce the binding protein.

[012g] In one aspect, there is provided a protein produced by the method as disclosed herein.

[012h] In one aspect, there is provided a composition comprising the binding protein as disclosed herein and at least one additional agent.

[012i] In one aspect, there is provided a use of the binding protein as disclosed herein, or the pharmaceutical composition as disclosed herein, 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.

[012j] In one aspect, there is provided 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 as disclosed herein.

[012k] In one aspect, there is provided 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 as disclosed herein.

[013] Binding proteins capable of targeting two epitopes are provided, wherein the binding proteins are capable of binding DLL4 and VEGF. In an embodiment, binding proteins capable of binding epitopes of DLL4 and VEGF with high affinity are provided. In an embodiment, the binding proteins comprise a dual variable domain binding protein framework that contains the CDR and variable domain sequences listed in Table 2. In an embodiment, the dual variable domain binding protein framework comprises the framework disclosed in US Patent No. 7,612,181 (incorporated herein by reference in its entirety).

[014] In one embodiment, binding proteins comprising a polypeptide chain that can bind two epitopes of two different proteins (VEGF and DLL4) are provided, wherein the polypeptide chain comprises 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

represents an amino acid or polypeptide, X2 represents an Fc region and n is 0 or 1, are provided. In some embodiments, the VD1 and VD2 in the binding protein are heavy chain variable domains. In certain embodiments, VD1 and VD2 are capable of binding an epitope of DLL4 and an epitope of VEGF. In some embodiments, C is a heavy chain constant domain, such as CH1. In certain embodiments, X1 is a linker with the proviso that X1 is not CH1.

[015] In various embodiments, the binding protein disclosed herein comprises a polypeptide chain that binds an epitope of DLL4 and an epitope of VEGF, wherein the polypeptide chain comprises VD1-(X1)n-VD2-C-(X2)n, wherein VD1 comprises a first heavy chain variable domain, VD2 comprises a second heavy chain variable domain, C comprises a heavy chain constant domain, X1 comprises a linker, and X2 comprises an Fc region. In an embodiment, X1 is a linker with the proviso that it is not CH1. In an embodiment, the VD1 and VD2 heavy chain variable domains each comprise three CDRs chosen from the CDRs in SEQ ID NO: 39, 41, 43, 45, 47, 49, 51,

We claim:

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

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

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

X2 is an Fc region;

n is 0 or 1; and

wherein the binding protein binds DLL4 and VEGF, wherein VD1 and VD2 independently comprise three CDRs from SEQ ID NO: 39, 41, 43, 45, 47, 49, 51, or 53, and wherein at least one of VD1 and/or VD2 comprises three CDRs from SEQ ID NO: 39.

2. The binding protein according to claim 1, wherein VD1 and VD2 independently comprise SEQ ID NO: 39, 41, 43, 45, 47, 49, 51, or 53, and wherein at least one of VD1 and/or VD2 comprises SEQ ID NO: 39.

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

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

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

X2 does not comprise an Fc region;

n is 0 or 1; and

wherein the binding protein binds DLL4 and VEGF, wherein VD1 and VD2 independently comprise three CDRs from SEQ ID NO: 40, 42, 44, 46, 48, 50, 52, or 54, and wherein at least one of VD1 and/or VD2 comprises three CDRs from SEQ ID NO: 40.

4. The binding protein according to claim 3, wherein the VD1 and VD2 independently comprise SEQ ID NO: 40, 42, 44, 46, 48, 50, 52, or 54, and wherein at least one of VD1 and/or VD2 comprises SEQ ID NO: 40.

5. The binding protein according to claim 1 or 3, wherein (X1)n on the heavy and/or light chain is (X1)0 and/or (X2)n on the heavy and/or light chain is (X2)0.

6. A binding protein comprising first and second polypeptide chains, wherein the first polypeptide chain comprises a first VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first heavy chain variable domain;
VD2 is a second heavy chain variable domain;
C is a heavy chain constant domain;
X1 is a linker with the proviso that it is not CH2;
X2 is an Fc region;
n is 0 or 1; and

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

VD1 is a first light chain variable domain;
VD2 is a second light chain variable domain;
C is a light chain constant domain;
X1 is a linker with the proviso that it is not CH1 or CL;
X2 does not comprise an Fc region;
n is 0 or 1; and

wherein the binding protein binds DLL4 and VEGF, wherein the VD1 and VD2 heavy chain variable domains independently comprise three CDRs from SEQ ID NO: 39, 41, 43, 45, 47, 49, 51, or 53, wherein at least one of the VD1 and/or VD2 heavy chain variable domains comprises three CDRs from SEQ ID NO: 39; and wherein the VD1 and VD2 light chain variable domains independently comprise three CDRs from SEQ ID NO: 40, 42, 44, 46, 48, 50, 52, or 54, wherein at least one of the VD1 and/or VD2 light chain variable domains comprises three CDRs from SEQ ID NO: 40.

7. The binding protein according to claim 6, wherein wherein the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NO: 39, 41, 43, 45, 47, 49, 51, or 53, wherein at least one of the VD1 and/or VD2 heavy chain variable domains comprises SEQ ID NO: 39; and wherein the VD1 and VD2 light chain variable domains independently comprise SEQ ID NO: 40, 42, 44, 46, 48, 50, 52, or 54, wherein at least one of the VD1 and/or VD2 light chain variable domains comprises SEQ ID NO: 40.

8. The binding protein according to claim 1, 3, or 6, wherein X1 comprises any one of SEQ ID NO: 1-38 or a G/S based sequence.

9. The binding protein according to claim 6, wherein the binding protein comprises two first polypeptide chains and two second polypeptide chains.

10. The binding protein according to claim 1, 3, or 6, wherein the Fc region is a variant sequence Fc region.

11. The binding protein according to claim 1, 3, or 6, wherein the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD.

12. The binding protein according to claim 6, wherein the VD1 of the first polypeptide chain and the VD1 of the second polypeptide chain are from different first and second parent antibodies, respectively, or binding portions thereof.

13. The binding protein according to claim 6, wherein the VD2 of the first polypeptide chain and the VD2 of the second polypeptide chain are from different first and second parent antibodies, respectively, or binding portions thereof.

14. The binding protein according to claim 12 or 13, wherein the first and the second parent antibodies bind different epitopes on the same target or different targets.

15. The binding protein according to any one of claims 12-14, wherein the first parent antibody or binding portion thereof binds the first target with a potency different from the potency with which the second parent antibody or binding portion thereof binds the second target.

16. The binding protein according to any one of claims 12-14, wherein the first parent antibody or binding portion thereof binds the first target with an affinity different from the affinity with which the second parent antibody or binding portion thereof binds the second target.

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

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;
C is a heavy chain constant domain;
X1 is a linker with the proviso that it is not CH1;
X2 is an Fc region;
n is 0 or 1; and

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

VD1 is a first light chain variable domain;
VD2 is a second light chain variable domain;
C is a light chain constant domain;
X1 is a linker with the proviso that it is not CH1 or CL;
X2 does not comprise an Fc region;
n is 0 or 1; and

wherein the binding protein binds DLL4 and VEGF, wherein the VD1 and VD2 heavy chain variable domains independently comprise three CDRs from SEQ ID NO: 39, 41, 43, 45, 47, 49, 51, or 53, wherein at least one of the VD1 and/or VD2 heavy chain variable domains comprises three CDRs from SEQ ID NO: 39; and wherein the VD1 and VD2 light chain variable domains independently comprise three CDRs from SEQ ID NO: 40, 42, 44, 46, 48, 50, 52, or 54, wherein at least one of the VD1 and/or VD2 light chain variable domains comprises three CDRs from SEQ ID NO: 40.

18. The binding protein according to claim 17, wherein the VD1 and VD2 heavy chain variable domains independently comprise SEQ ID NO: 39, 41, 43, 45, 47, 49, 51, or 53, wherein at least one of the VD1 and/or VD2 heavy chain variable domains comprises SEQ ID NO: 39; and wherein the VD1 and VD2 light chain variable domains independently comprise SEQ ID NO: 40, 42, 44, 46, 48, 50, 52, or 54, wherein at least one of the VD1 and/or VD2 light chain variable domains comprises SEQ ID NO: 40.

19. The binding protein according to claim 1, 3, 6, or 17, wherein the binding protein has an on rate constant (K_{on}) to VEGF and/or DLL4 of at least about $10^2M^{-1}s^{-1}$; at least about $10^3M^{-1}s^{-1}$; at least about $10^4M^{-1}s^{-1}$; at least about $10^5M^{-1}s^{-1}$; or at least about $10^6M^{-1}s^{-1}$, as measured by surface plasmon resonance.

20. The binding protein according to claim 1, 3, 6, or 17, wherein the binding protein has an off rate constant (K_{off}) to VEGF and/or DLL4 of at most about $10^{-2}s^{-1}$; 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.

21. The binding protein according to claim 1, 3, 6, or 17, wherein the binding protein has an equilibrium dissociation constant (K_D) to VEGF and/or DLL4 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; or at most about 10^{-12} M, as measured by surface plasmon resonance.

22. A binding protein conjugate comprising a binding protein of claim 1, 3, 6, or 17, 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.

23. The binding protein conjugate according to claim 22, wherein the imaging agent is a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin.

24. The binding protein according to claim 1, 3, 6, or 17, wherein the binding protein is a crystallized binding protein.

25. An isolated nucleic acid encoding a binding protein amino acid sequence of claim 1, 3, 6, 17, or 22.

26. A vector comprising the isolated nucleic acid of claim 25.

27. The vector according to claim 26, wherein the vector is pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, pHybE, pBOS or pBJ.

28. A host cell comprising the vector of claim 26.

29. The host cell according to claim 28, wherein the host cell is a prokaryotic cell.

30. The host cell according to claim 28, wherein the host cell is a eukaryotic cell.

31. The host cell according to claim 30, wherein the eukaryotic cell is a protist cell, animal cell, plant cell, yeast cell, mammalian cell, avian cell, insect cell, or fungal cell.

32. A method of producing a binding protein comprising culturing a host cell according to any one of claims 28-31 in culture medium under conditions sufficient to produce the binding protein.

33. A protein produced by the method of claim 32.

34. A pharmaceutical composition comprising the binding protein according to any one of claims 1, 3, 6, 17, 22, or 33 and a pharmaceutically acceptable carrier.

35. The pharmaceutical composition according to claim 34, further comprising at least one additional agent.

36. The pharmaceutical composition according to claim 35, 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, a small molecule inhibitor), an anti-VEGF mAb; an anti-DLL4 mAb; 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.

37. The pharmaceutical composition according to claim 35 or 36, wherein the additional agent comprises at least one of 13-cis-Retinoic Acid; 2-CdA; 2-Chlorodeoxyadenosine; 5-Azacitidine; 5-Fluorouracil; 5-FU; 6-Mercaptopurine; 6-MP; 6-TG; 6-Thioguanine; Abraxane; an anti-VEGF mAb; an anti-DLL4 mAb; Accutane®; Actinomycin-D; Adriamycin®; Adrucil®; Afinitor®; Agrylin®; Ala-Cort®; Aldesleukin; Alemtuzumab; ALIMTA; Alitretinoin; Alkaban-AQ®; Alkeran®; All-transretinoic Acid; Alpha Interferon; Altretamine; Amethopterin; Amifostine; Aminoglutethimide; Anagrelide; Anandron®; Anastrozole; Arabinosylcytosine; Ara-C Aranesp®; Aredia®; Arimidex®; Aromasin®; Arranon®; Arsenic Trioxide; Arzerra™; Asparaginase; ATRA; Avastin®; Azacitidine; BCG; BCNU; Bendamustine; Bevacizumab; Bexarotene; BEXXAR®; Bicalutamide; BiCNU; Blenoxane®; Bleomycin; Bortezomib; Busulfan; Busulfex®; C225; Calcium Leucovorin; Campath®; Camptosar®; Camptothecin-11; Capecitabine; Carac™; Carboplatin; Carmustine; Carmustine Wafer; Casodex®; CC-5013; CCI-779; CCNU; CDDP; CeeNU; Cerubidine®; Cetuximab; Chlorambucil; Cisplatin; Citrovorum Factor; Cladribine; Cortisone; Cosmegen®; CPT-11; Cyclophosphamide; Cytadren®; Cytarabine; Cytarabine Liposomal; Cytosar-U®; Cytoxan®; Dacarbazine; Dacogen; Dactinomycin; Darbepoetin Alfa; Dasatinib; Daunomycin; Daunorubicin; Daunorubicin Hydrochloride; Daunorubicin Liposomal; DaunoXome®; Decadron; Decitabine; Delta-Cortef®; Deltasone®; Denileukin; Diftitox; DepoCyt™; Dexamethasone; Dexamethasone Acetate; Dexamethasone Sodium Phosphate; Dexasone; Dexrazoxane; DHAD; DIC; Diodex; Docetaxel; Doxil®; Doxorubicin; Doxorubicin Liposomal; Droxia™; DTIC; DTIC-Dome®; Duralone®; Efudex®; Eligard™; Ellence™; Eloxatin™; Elspar®; Emcyt®; Enalapril; Epirubicin; Epoetin Alfa; Erbitux; Erlotinib; Erwinia L-asparaginase; Estramustine; Ethyol Etopophos®; Etoposide; Etoposide Phosphate; Eulexin®; Everolimus; Evista®; Exemestane; Fareston®; Faslodex®; Femara®; Filgrastim; Floxuridine; Fludara®; Fludarabine; Fluoroplex®; Fluorouracil; Fluorouracil (cream); Fluoxymesterone; Flutamide; Folinic Acid; FUDR®; Fulvestrant; Gefitinib; Gemcitabine; Gemtuzumab ozogamicin; Gemzar; Gleevec™; Gliadel® Wafer; GM-CSF; Goserelin; Granulocyte-Colony Stimulating Factor (G-CSF); Granulocyte Macrophage Colony Stimulating Factor (G-MCSF); Halotestin®; Herceptin®; Hexadrol; Hexalen®; Hexamethylmelamine; HMM; Hycamtin®; Hydrea®; Hydrocort Acetate®;

Hydrocortisone; Hydrocortisone Sodium Phosphate; Hydrocortisone Sodium Succinate; Hydrocortone Phosphate; Hydroxyurea; Ibritumomab; Ibritumomab Tiuxetan; Idamycin®; Idarubicin Ifex®; Interferon-alpha; Interferon-alpha-2b (PEG Conjugate); Ifosfamide; Interleukin-11 (IL-11); Interleukin-2 (IL-2); Imatinib mesylate; Imidazole Carboxamide; Intron A®; Iressa®; Irinotecan; Isotretinoin; Ixabepilone; Ixempra™; KADCYCLA®; Kidrolase (t) Lanacort®; Lapatinib; L-asparaginase; LCR; Lenalidomide; Letrozole; Leucovorin; Leukeran; Leukine™; Leuprolide; Leurocristine; Leustatin™; Liposomal Ara-C; Liquid Pred®; Lomustine; L-PAM; L-Sarcolysin; Lupron®; Lupron Depot®; Matulane®; Maxidex; Mechlorethamine; Mechlorethamine Hydrochloride; Medralone®; Medrol®; Megace®; Megestrol; Megestrol Acetate; Melphalan; Mercaptopurine; Mesna; Mesnex™; Methotrexate; Methotrexate Sodium; Methylprednisolone; Meticorten®; Mitomycin; Mitomycin-C; Mitoxantrone M-Prednisol®; MTC; MTX; Mustargen®; Mustine; Mutamycin®; Myleran®; Mylocel™; Mylotarg®; Navelbine®; Nelarabine; Neosar®; Neulasta™; Neumega®; Neupogen®; Nexavar®; Nifedipine; Nilandron®; Nilotinib; Nilutamide; Nipent®; Nitrogen Mustard Novaldex®; Novantrone®; Nplate; Octreotide; Octreotide acetate; Ofatumumab; Oncospar®; Oncovin®; Ontak®; Onxal™; Oprelvekin; Orapred®; Orasone®; Oxaliplatin; Paclitaxel; Paclitaxel Protein-bound; Pamidronate; Panitumumab; Panretin®; Paraplatin®; Pazopanib; Pediapred®; PEG Interferon; Pegaspargase; Pegfilgrastim; PEG-INTRON™; PEG-L-asparaginase; PEMETREXED; Pentostatin; Phenylalanine Mustard; Platinol®; Platinol-AQ®; Prednisolone; Prednisone; Prelone®; Procarbazine; PROCRIT®; Proleukin®; Prolifeprospan 20 with Carmustine Implant; Purinethol®; Raloxifene; Revlimid®; Rheumatrex®; Rituxan®; Rituximab; Roferon-A®; Romiplostim; Rubex®; Rubidomycin hydrochloride; Sandostatin®; Sandostatin LAR®; Sargramostim; Solu-Cortef®; Solu-Medrol®; Sorafenib; SPRYCEL™; STI-571; Streptozocin; SU11248; Sunitinib; Sutent®; Tamoxifen Tarceva®; Targretin®; Tasigna®; Taxol®; Taxotere®; Temodar®; Temozolomide Temsirolimus; Teniposide; TESPA; Thalidomide; Thalomid®; TheraCys®; Thioguanine; Thioguanine Tabloid®; Thiophosphoamide; Thioplex®; Thiotepa; TICE®; Toposar®; Topotecan; Toremifene; Torisel®; Tositumomab; Trastuzumab; Treanda®; Tretinoin; Trexall™; Trisenox®; TSPA; TYKERB®; VCR; Vectibix™; Velban®; Velcade®; VePesid®; Vesanoid®; Viadur™; Vidaza®; Vinblastine; Vinblastine Sulfate; Vincasar Pfs®; Vincristine; Vinorelbine; Vinorelbine tartrate; VLB; VM-26; Vorinostat; Votrient; VP-16; Vumon®; Xeloda®; Zanosar®; Zevalin™; Zinecard®; Zoladex®; Zoledronic acid; Zolinza; Zometa®; Leucovorin; 5-FU; Temozolomide; Gemcitabine; Paclitaxel; Regorafenib; and Pertuzumab.

38. Use of the binding protein according to claim 1, 3, 6, 17, 22, or 33 in the preparation of a medicament for the treatment of a disease or a disorder in a subject.

39. The use according to claim 38, wherein the disease or disorder 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, atherosclerosis, or any other angiogenesis dependent or independent disease characterized by vasculuar overgrowth, edema, or aberrant DLL4 or VEGF activity.

40. The use according to claim 38, wherein administration to the subject is parenteral, subcutaneous, intramuscular, intravenous, intraocular, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal,

intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

41. A method for generating a binding protein capable of binding VEGF and DLL4, or fragments thereof, the method comprising the steps of:

a) obtaining a nucleic acid encoding a first parent antibody or binding portion thereof, capable of binding a first target selected from VEGF and DLL4;

b) obtaining a nucleic acid encoding a second parent antibody or binding portion thereof, capable of binding a second target selected from VEGF and DLL4;

c) using the nucleic acids of steps (a) and (b) to prepare nucleic acid construct(s) encoding the polypeptide chain(s) of any one of claims 1, 3, 6, 17, 22, or 33;

d) expressing the polypeptide chain(s) in an isolated host cell,

such that a binding protein capable of binding VEGF and DLL4 is generated.

42. The method according to claim 41, wherein the method generates the binding protein of any one of claims 1, 3, 6, 17, 22, or 33.

43. The method according to claim 41, wherein the Fc region is a variant sequence Fc region.

44. The method according to claim 41, wherein the Fc region is an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, or IgD.

45. The method according to claim 41, wherein the first parent antibody or binding portion thereof binds the first target with a different affinity and/or potency than the affinity and/or potency with which the second parent antibody or binding portion thereof binds the second target.

46. 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, 3, 6, 17, 22, or 33.

47. The method according to claim 46, 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.

48. The method according to claim 46, wheren the at least one detectable label is on the at least one binding protein.

49. The method according to claim 46, 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.

50. The method according to claim 46, 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 competes with VEGF or DLL4 or fragment thereof in the test sample for binding to 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 a fragment thereof is indirectly correlated with the signal generated by the detectable label.

51. The method according to any one of claims 46-50, 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 46-51, 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 46-52, wherein the method detects the presence of both DLL4 and VEGF in a sample.

54. A method for determining the amount or concentration of VEGF or DLL4, or a fragment thereof, in a test sample by an immunoassay, wherein the immunoassay comprises:

(a) contacting the test sample with at least one binding protein and at least one detectable label; and

(b) comparing a signal generated by the detectable label with the signal generated by a control or calibrator comprising a known amount or concentration of VEGF or DLL4 or fragment thereof that has been contacted with the at least one binding protein and the at least one detectable label,

wherein the calibrator is optionally part of a series of calibrators in which each calibrator differs from the other calibrators in the series by having a different amount or concentration of VEGF or DLL4 or a fragment thereof, and

wherein the at least one binding protein comprises the binding protein of any one of claims 1, 3, 6, 17, 22, or 33.

55. The method according to claim 54, 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.

56. The method according to claim 54, wheren the at least one detectable label is on the at least one binding protein.

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

(i) contacting the test sample with at least one binding protein, wherein the binding protein binds to an epitope on VEGF or DLL4 or a 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 an epitope on VEGF or DLL4 or a fragment thereof in the test sample that is not bound by the binding protein; and

(iii) determining the amount or concentration of VEGF or DLL4 or a fragment thereof in the test sample based on the signal generated by the detectable label in the second complex,

wherein the amount or concentration of VEGF or DLL4 or a fragment thereof in the test sample is directly proportional to the signal generated by the detectable label.

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

(i) contacting the test sample with at least one binding protein, wherein the binding protein binds to an epitope on VEGF or DLL4 or a 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 competes with VEGF or DLL4 or a fragment thereof in the test sample for binding to the binding protein; and

(iii) determining the amount or concentration of VEGF or DLL4 or a 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 a fragment thereof in the test sample is indirectly proportional to the signal generated by the detectable label.

59. The method according to any one of claims 54-58, 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.

60. The method according to any one of claims 54-59, wherein the method is adapted for use in an automated system or a semi-automated system.

61. The method according to any one of claims 54-60, wherein the method determines the amount or concentration of DLL4 and VEGF in the sample.

62. 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, 3, 6, 17, 22, or 33.

63. A binding protein comprising a VH sequence selected from SEQ ID NO: 55-63 and 74.

64. A binding protein comprising a VL sequence selected from SEQ ID NO: 64-73.

65. A binding protein comprising a VH sequence selected from SEQ ID NO: 55-63 and 74 and a VL sequence selected from SEQ ID NO: 64-73.

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

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

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

X2 is an Fc region;

n is 0 or 1; and

wherein the binding protein binds VEGF and DLL4, and further wherein the binding protein binds:

(a) VEGF with an off rate constant (K_{off}) of at most about 5.42 x 10^{-5} s^{-1} and/or a dissociation constant (K_D) of at most about 7.40 x 10^{-9} M, as determined by surface plasmon resonance; or

(b) DLL4 with an off rate constant (K_{off}) of at most about 2.63 x 10^{-3} s^{-1} and/or a dissociation constant (K_D) of at most about 3.40 x 10^{-8} M or 5.00 x 10^{-8} M, as determined by surface plasmon resonance.

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

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

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

X2 does not comprise an Fc region;

n is 0 or 1; and

wherein the binding protein binds VEGF and DLL4, and further wherein the binding protein binds:

(a) VEGF with an off rate constant (K_{off}) of at most about 5.42 x 10^{-5} s^{-1} and/or a dissociation constant (K_D) of at most about 7.40 x 10^{-9} M, as determined by surface plasmon resonance; or

(b) DLL4 with an off rate constant (K_{off}) of at most about 2.63 x 10^{-3} s^{-1} and/or a dissociation constant (K_D) of at most about 3.40 x 10^{-8} M or 5.00 x 10^{-8} M, as determined by surface plasmon resonance.

68. A binding protein comprising first and second polypeptide chains, wherein said first polypeptide chain comprises VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

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

X2 is an Fc region;

n is 0 or 1; and

wherein said second polypeptide chain comprises VD1-(X1)n-VD2-C-(X2)n, wherein

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

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

X2 does not comprise an Fc region;

and n is 0 or 1; and

wherein the binding protein binds VEGF and DLL4, and further wherein the binding protein binds:

(a) VEGF with an off rate constant (K_{off}) of at most about 5.42 x 10^{-5} s^{-1} and/or a dissociation constant (K_D) of at most about 7.40 x 10^{-9} M, as determined by surface plasmon resonance; or

(b) DLL4 with an off rate constant (K_{off}) of at most about 2.63 x 10^{-3} s^{-1} and/or a dissociation constant (K_D) of at most about 3.40 x 10^{-8} M or 5.00 x 10^{-8} M, as determined by surface plasmon resonance.

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

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

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

X2 is an Fc region;

n is 0 or 1; and

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

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

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

X2 does not comprise an Fc region;

n is 0 or 1; and

wherein the binding protein binds VEGF and DLL4, and further wherein the binding protein binds:

(a) VEGF with an off rate constant (K_{off}) of at most about 5.42 x 10^{-5} s^{-1} and/or a dissociation constant (K_D) of at most about 7.40 x 10^{-9} M, as determined by surface plasmon resonance; or

(b) DLL4 with an off rate constant (K_{off}) of at most about 2.63 x 10^{-3} s^{-1} and/or a dissociation constant (K_D) of at most about 3.40 x 10^{-8} M or 5.00 x 10^{-8} M, as determined by surface plasmon resonance.

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

VD1 is a first heavy chain variable domain;

VD2 is a second heavy chain variable domain;

C is a heavy chain constant domain;

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

X2 is an Fc region;

n is 0 or 1; and

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

VD1 is a first light chain variable domain;

VD2 is a second light chain variable domain;

C is a light chain constant domain;

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

X2 does not comprise an Fc region;

and n is 0 or 1; and

wherein

(i) the binding protein binds VEGF and DLL4;

(ii) the VD1 and VD2 heavy chain variable domains independently comprise three CDRs from SEQ ID NO: 39, 41, 43, 45, 47, 49, 51, or 53, wherein at least one of the VD1 and/or VD2 heavy chain variable domains comprises three CDRs from SEQ ID NO: 39; and/or wherein the VD1 and VD2 light chain variable domains independently comprise three CDRs from SEQ ID NO: 40, 42, 44, 46, 48, 50, 52, or 54, wherein at least one of the VD1 and/or VD2 light chain variable domains comprises three CDRs from SEQ ID NO: 40; and

(iii)the binding protein binds:

(a) VEGF with an off rate constant (K_{off}) of at most about 5.42 x 10^{-5} s^{-1} and/or a dissociation constant (K_D) of at most about 7.40 x 10^{-9} M, as determined by surface plasmon resonance; or

(b) DLL4 with an off rate constant (K_{off}) of at most about 2.63 x 10^{-3} s^{-1} and/or a dissociation constant (K_D) of at most about 3.40 x 10^{-8} M or 5.00 x 10^{-8} M, as determined by surface plasmon resonance.

71. The binding protein according to claims 66-70, wherein the binding protein binds VEGF and DLL4, and wherein the heavy chain variable domain comprises SEQ ID NO: 55-63 and 74.

72. The binding protein according to claims 66-70, , wherein the binding protein binds VEGF and DLL4, and wherein the the light chain variable domain comprises SEQ ID NO: 64-73.

73. The binding protein according to claims 66-70, wherein the binding protein binds VEGF and DLL4, wherein the heavy chain variable domain comprises SEQ ID

NO: 55-63 and 74, and wherein the the light chain variable domain comprises SEQ ID NO: 64-73.

74. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, or 66-70, wherein (X1)n is selected from SEQ ID NO: 1-38.

75. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, or 66-70, wherein the VD1 heavy chain and VD1 light chain variable domains, if present, and/or VD2 heavy chain and VD2 light chain variable domains, if present, comprise three CDRs from SEQ ID NOs: 39 and 40, respectively.

76. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, or 66-70, wherein the binding protein is: h1A11.1-L-AV (comprising SEQ ID NOS: 55 and 64); h1A11.1-S-AV (comprising SEQ ID NOS: 56 and 65); h1A11.1-GS10-AV (comprising SEQ ID NOS: 57 and 66); h1A11.1-GS14-AV (comprising SEQ ID NOS: 58 and 67); AV-L- h1A11.1 (comprising SEQ ID NOS: 59 and 68); AV-S- h1A11.1 (comprising SEQ ID NOS: 60 and 69); AV-GS6- h1A11.1 (comprising SEQ ID NOS: 61 and 70); AV-GS10- h1A11.1 (comprising SEQ ID NOS: 62 and 71); AV-GS14- h1A11.1 (comprising SEQ ID NOS: 63 and 72); or h1A11.1-SL-Av (comprising SEQ ID NOS: 73 and 74).

77. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein binds to DLL4-expressing cells with an EC_{50} of at most about 5.04 nM in a flow cytometry (FACS) assay.

78. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein interferes with DLL4 binding to Notch1 with an IC50 of at most about 3503 nM in a Notch competition ELISA assay or comeption FACS assat.

79. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein prevents Notch1 activation with an IC50 of at most about 7.47 nM in a Notch reporter assay.

80. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein binds to VEGF with an EC50 of at most about 2.50 nM in a capture ELISA assay.

81. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein interferes with cell survival / proliferation with an IC50 of at most about 37.2 nM in a VEGF competition ELISA assay.

82. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein interferes with VEGF binding to VEGFR with an IC50 of at most about 4.2 nM in an endothelial cell proliferation assay.

83. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein produces a reduction in the size of an HT-29 human colorectal adenocarcinoma tumor xenograft in female mice of at least about 47%, and a delay in tumor growth of at least about 42%, as compared to mice not treated with the binding protein.

84. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein produces a reduction in the size of a U87-MG glioblastoma tumor xenograft in female mice of at least about 64%, and a delay in tumor growth of at least about 48%, as compared to mice not treated with the binding protein.

85. The binding protein according to any one of claims 1, 3, 6, 17, 22, 33, 66-70, or 76, wherein the binding protein, in combination with Temozolomide, produces a reduction in the size of a U87-MG glioblastoma tumor xenograft in female mice of at least about 65%, and a delay in tumor growth of at least about 45%, as compared to mice not treated with the binding protein.

86. A binding protein comprising SEQ ID NO: 73 and 74.

87. The binding protein according to claim 1, 3, 6, or 10, wherein the Fc region is an Fc region from a human IgG1 LALA mutant.

88. A pharmaceutical composition comprising:
one or more amino acid,
one or more polysaccharide and/or polysorbate, and
a binding protein at a concentration of about 0.1-100 mg/ml,

wherein the pharmaceutical composition is at a pH of about 5.0-7.0, and

wherein the binding protein comprises 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.

89. The pharmaceutical composition of claim 88, wherein at least one amino acid is histidine and is present at a concentration of about 10-20 mM, or about 15mM.

90. The pharmaceutical composition of claim 88 or 89, wherein the pH of the composition is about 5.5-6.0, or about 5.5, or about 6.0.

91. The pharmaceutical composition of any one of claims 88-90, wherein at least one polysaccharide is sucrose and is present at a concentration of about 0-8.0% weight/volume (w/v).

92. The pharmaceutical composition of any one of claims 88-91, wherein the polysorbate is polysorbate 80 and is at a concentration of about 0-0.06% w/v.

93. The pharmaceutical composition of any one of claims 88-92, wherein at least one amino acid is arginine and is present at a concentration of about 0-1.5% w/v.

94. The pharmaceutical composition of any one of claims 88-93, wherein the binding protein is present at a concentration of about 1-100 mg/ml, or about 1-15 mg/ml, or about 1-7.5 mg/ml, or about 2.5-7.5 mg/ml, or about 5-7.5 mg/ml, or about 25-100 mg/ml, or about 20-60 mg/ml, or about 25-50 mg/ml, or about 25 mg/ml, or about 50 mg/ml.

95. The pharmaceutical composition of any one of claims 88-93, wherein the binding protein is at a concentration of about 0.1-60 mg/ml, , or about about 0.1-25 mg/ml, or about 1.0-60 mg/ml, or about 0.5-60 mg/ml, or about 0.1-2.0 mg/ml, or about 0.5-2.0 mg/ml, or about 1-5 mg/ml, or about 1-7.5 mg/ml, or about 1-15 mg/ml, or about 0.5 mg/ml, or about 1.0 mg/ml.

96. The pharmaceutical composition of any one of claims 88-95, wherein the pharmaceutical composition is lyophilized.

97. The pharmaceutical composition of any one of claims 88-96, wherein the pharmaceutical composition is hydrated or has been lyophilized and rehydrated.

98. The pharmaceutical composition of claim 97, wherein the pharmaceutical composition is in a hydrating solution comprising dextrose and/or saline.

99. The pharmaceutical composition of claim 98, wherein the dextrose is at a concentration of about 5% w/v and/or the saline is at a concentration of about 0.9% w/v

100. The pharmaceutical composition of any one of claims 88-99, wherein the pharmaceutical composition comprises about 15 mM histidine, about 0.03% (w/v) polysorbate 80, about 4.0% (w/v) sucrose, and about 25 mg/ml of the binding protein, or about 1-15 mg/ml of the binding protein, and is at a pH of about 6.0, wherein the binding protein comprises SEQ ID NO: 73 and SEQ ID NO: 74.

101. The pharmaceutical composition of any one of claims 88-100, wherein the binding protein comprises:

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

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

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

three CDRs from SEQ ID NO: 41 and three CDRs from SEQ ID NO: 42,
three CDRs from SEQ ID NO: 43 and three CDRs from SEQ ID NO: 44,
three CDRs from SEQ ID NO: 45 and three CDRs from SEQ ID NO: 46,
three CDRs from SEQ ID NO: 47 and three CDRs from SEQ ID NO: 48,

three CDRs from SEQ ID NO: 49 and three CDRs from SEQ ID NO: 50,
three CDRs from SEQ ID NO: 51 and three CDRs from SEQ ID NO: 52,
or
three CDRs from SEQ ID NO: 53 and three CDRs from SEQ ID NO: 54.

102. The pharmaceutical composition of any one of claims 88-101, wherein the binding protein comprises:

(i) variable domains that form a functional target binding site for DLL4 comprising:
SEQ ID NO: 39 and/or SEQ ID NO: 40, and
(ii) variable domains that form a functional target binding site for VEGF comprising:
a sequence selected from the group consisting of SEQ ID NO: 41-54.

103. The pharmaceutical composition of any one of claims 88-102, 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.

104. The pharmaceutical composition of any one of claims 88-103, 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,

SEQ ID NO: 43 and SEQ ID NO: 44,

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

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

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

SEQ ID NO: 51 and SEQ ID NO: 52, or

SEQ ID NO: 53 and SEQ ID NO: 54.

105. The pharmaceutical composition of any one of claims 88-104, wherein the binding protein comprises two first and two second polypeptide chains, forming four functional target binding sites.

106. The pharmaceutical composition of any one of claims 88-105, wherein the binding protein is capable of binding:

(a) VEGF with a dissociation constant (K_D) of at most about 7.40 x 10^{-9} M, as measured by surface plasmon resonance; and/or

(b) DLL4 with a dissociation constant (K_D) of at most about 3.40 x 10^{-8} M or 5.00 x 10^{-8} M, as measured by surface plasmon resonance.

107. The pharmaceutical composition of any one of claims 88-106, wherein

(a) linker X1 in the binding protein comprises any one of SEQ ID NOs 1-38 or a G/S based sequence,

(b) linker X1 in the binding protein is not CL.

(c) the Fc region of the binding protein is a variant sequence Fc region,

(d) the Fc region is an Fc region from a human IgG1 LALA mutant,

(e) 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, and/or

(f) the binding protein is a crystallized binding protein.

108. The pharmaceutical composition of any one of claims 88-107, wherein the binding protein comprises:

SEQ ID NO: 55 and SEQ ID NO: 56,
SEQ ID NO: 57 and SEQ ID NO: 58,
SEQ ID NO: 59 and SEQ ID NO: 60,
SEQ ID NO: 61 and SEQ ID NO: 62,
SEQ ID NO: 63 and SEQ ID NO: 64,
SEQ ID NO: 65 and SEQ ID NO: 66,
SEQ ID NO: 67 and SEQ ID NO: 68,
SEQ ID NO: 69 and SEQ ID NO: 70,
SEQ ID NO: 71 and SEQ ID NO: 72, or
SEQ ID NO: 73 and SEQ ID NO: 74.

109.The pharmaceutical composition of any one of claims 88-108, wherein the binding protein comprises

(i) variable domains that form a functional target binding site for DLL4 comprising:
three CDRs from SEQ ID NO: 39 and three CDRs from SEQ ID NO: 40, and
(ii) variable domains that form a functional target binding site for VEGF comprising:
three CDRs from SEQ ID NO: 41 and three CDRs from SEQ ID NO: 42.

110.The pharmaceutical composition of any one of claims 88-109, 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.

111.The pharmaceutical composition of any one of claims 88-110, wherein the binding protein comprises h1A11.1-SL-Av (comprising SEQ ID NOS: 73 and 74).

112.The pharmaceutical composition according to claim 88-111, wherein the Fc region is an Fc region from a human IgG1 LALA mutant.

113. The pharmaceutical composition of any one of claims 88-112, further comprising at least one additional agent.

114. The pharmaceutical composition of claim 113, wherein the at least one 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.

115. The pharmaceutical composition of claim 113 or 114, wherein the at least one additional agent comprises at least one of 13-cis-Retinoic Acid; 2-CdA; 2-Chlorodeoxyadenosine; 5-Azacitidine; 5-Fluorouracil; an anti-VEGF mAb; an anti-DLL4 mAb; 5-FU; 6-Mercaptopurine; 6-MP; 6-TG; 6-Thioguanine; Abraxane; Accutane®;

Actinomycin-D; Adriamycin®; Adrucil®; Afinitor®; Agrylin®; Ala-Cort®; Aldesleukin; Alemtuzumab; ALIMTA; Alitretinoin; Alkaban-AQ®; Alkeran®; All-transretinoic Acid; Alpha Interferon; Altretamine; Amethopterin; Amifostine; Aminoglutethimide; Anagrelide; Anandron®; Anastrozole; Arabinosylcytosine; Ara-C Aranesp®; Aredia®; Arimidex®; Aromasin®; Arranon®; Arsenic Trioxide; Arzerra™; Asparaginase; ATRA; Avastin®; Azacitidine; BCG; BCNU; Bendamustine; Bevacizumab; Bexarotene; BEXXAR®; Bicalutamide; BiCNU; Blenoxane®; Bleomycin; Bortezomib; Busulfan; Busulfex®; C225; Calcium Leucovorin; Campath®; Camptosar®; Camptothecin-11; Capecitabine; Carac™; Carboplatin; Carmustine; Carmustine Wafer; Casodex®; CC-5013; CCI-779; CCNU; CDDP; CeeNU; Cerubidine®; Cetuximab; Chlorambucil; Cisplatin; Citrovorum Factor; Cladribine; Cortisone; Cosmegen®; CPT-11; Cyclophosphamide; Cytadren®; Cytarabine; Cytarabine Liposomal; Cytosar-U®; Cytoxan®; Dacarbazine; Dacogen; Dactinomycin; Darbepoetin Alfa; Dasatinib; Daunomycin; Daunorubicin; Daunorubicin Hydrochloride; Daunorubicin Liposomal; DaunoXome®; Decadron; Decitabine; Delta-Cortef®; Deltasone®; Denileukin; Diftitox; DepoCyt™; Dexamethasone; Dexamethasone Acetate; Dexamethasone Sodium Phosphate; Dexasone; Dexrazoxane; DHAD; DIC; Diodex; Docetaxel; Doxil®; Doxorubicin; Doxorubicin Liposomal; Droxia™; DTIC; DTIC-Dome®; Duralone®; Efudex®; Eligard™; Ellence™; Eloxatin™; Elspar®; Emcyt®; Enalapril; Epirubicin; Epoetin Alfa; Erbitux; Erlotinib; Erwinia L-asparaginase; Estramustine; Ethyo;l Etopophos®; Etoposide; Etoposide Phosphate; Eulexin®; Everolimus; Evista®; Exemestane; Fareston®; Faslodex®; Femara®; Filgrastim; Floxuridine; Fludara®; Fludarabine; Fluoroplex®; Fluorouracil; Fluorouracil (cream); Fluoxymesterone; Flutamide; Folinic Acid; FUDR®; Fulvestrant; Gefitinib; Gemcitabine; Gemtuzumab ozogamicin; Gemzar; Gleevec™; Gliadel® Wafer; GM-CSF; Goserelin; Granulocyte-Colony Stimulating Factor (G-CSF); Granulocyte Macrophage Colony Stimulating Factor (G-MCSF); Halotestin®; Herceptin®; Hexadrol; Hexalen®; Hexamethylmelamine; HMM; Hycamtin®; Hydrea®; Hydrocort Acetate®; Hydrocortisone; Hydrocortisone Sodium Phosphate; Hydrocortisone Sodium Succinate; Hydrocortone Phosphate; Hydroxyurea; Ibritumomab; Ibritumomab Tiuxetan; Idamycin®; Idarubicin Ifex®; Interferon-alpha; Interferon-alpha-2b (PEG Conjugate); Ifosfamide; Interleukin-11 (IL-11); Interleukin-2 (IL-2); Imatinib mesylate; Imidazole Carboxamide; Intron A®; Iressa®; Irinotecan; Isotretinoin; Ixabepilone; Ixempra™; KADCYCLA®; Kidrolase (t) Lanacort®; Lapatinib; L-asparaginase; LCR; Lenalidomide; Letrozole; Leucovorin; Leukeran; Leukine™; Leuprolide; Leurocristine; Leustatin™; Liposomal Ara-C; Liquid Pred®; Lomustine; L-PAM; L-Sarcolysin; Lupron®; Lupron

Depot®; Matulane®; Maxidex; Mechlorethamine; Mechlorethamine Hydrochloride; Medralone®; Medrol®; Megace®; Megestrol; Megestrol Acetate; Melphalan; Mercaptopurine; Mesna; Mesnex™; Methotrexate; Methotrexate Sodium; Methylprednisolone; Meticorten®; Mitomycin; Mitomycin-C; Mitoxantrone M-Prednisol®; MTC; MTX; Mustargen®; Mustine; Mutamycin®; Myleran®; Mylocel™; Mylotarg®; Navelbine®; Nelarabine; Neosar®; Neulasta™; Neumega®; Neupogen®; Nexavar®; Nifedipine; Nilandron®; Nilotinib; Nilutamide; Nipent®; Nitrogen Mustard Novaldex®; Novantrone®; Nplate; Octreotide; Octreotide acetate; Ofatumumab; Oncospar®; Oncovin®; Ontak®; Onxal™; Oprelvekin; Orapred®; Orasone®; Oxaliplatin; Paclitaxel; Paclitaxel Protein-bound; Pamidronate; Panitumumab; Panretin®; Paraplatin®; Pazopanib; Pediapred®; PEG Interferon; Pegaspargase; Pegfilgrastim; PEG-INTRON™; PEG-L-asparaginase; PEMETREXED; Pentostatin; Phenylalanine Mustard; Platinol®; Platinol-AQ®; Prednisolone; Prednisone; Prelone®; Procarbazine; PROCRIT®; Proleukin®; Prolifeprospan 20 with Carmustine Implant; Purinethol®; Raloxifene; Revlimid®; Rheumatrex®; Rituxan®; Rituximab; Roferon-A®; Romiplostim; Rubex®; Rubidomycin hydrochloride; Sandostatin®; Sandostatin LAR®; Sargramostim; Solu-Cortef®; Solu-Medrol®; Sorafenib; SPRYCEL™; STI-571; Streptozocin; SU11248; Sunitinib; Sutent®; Tamoxifen Tarceva®; Targretin®; Tasigna®; Taxol®; Taxotere®; Temodar®; Temozolomide Temsirolimus; Teniposide; TESPA; Thalidomide; Thalomid®; TheraCys®; Thioguanine; Thioguanine Tabloid®; Thiophosphoamide; Thioplex®; Thiotepa; TICE®; Toposar®; Topotecan; Toremifene; Torisel®; Tositumomab; Trastuzumab; Treanda®; Tretinoin; Trexall™; Trisenox®; TSPA; TYKERB®; VCR; Vectibix™; Velban®; Velcade®; VePesid®; Vesanoid®; Viadur™; Vidaza®; Vinblastine; Vinblastine Sulfate; Vincasar Pfs®; Vincristine; Vinorelbine; Vinorelbine tartrate; VLB; VM-26; Vorinostat; Votrient; VP-16; Vumon®; Xeloda®; Zanosar®; Zevalin™; Zinecard®; Zoladex®; Zoledronic acid; Zolinza; Zometa®; Leucovorin; 5-FU; Temozolomide; Gemcitabine; Paclitaxel; Regorafenib; and Pertuzumab.

116. The pharmaceutical composition of any one of claims 113-115, wherein the at least one additional agent comprises at least one of Irinotecan; Leucovorin; 5-FU; Folfiri; Enalapril; Nifedipine; Clonidine; Temozolomide; Gemcitabine; Paclitaxel; Regorafenib; capecitabine; and Pertuzumab.

117. The pharmaceutical composition of any one of claims 88-116 for use in treating a disease or a disorder in a subject.

118. The pharmaceutical composition of claim 117, wherein the disease or disorder 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, atherosclerosis, or any other angiogenesis dependent or independent disease characterized by vasculuar overgrowth, edema, or aberrant DLL4 or VEGF activity.

119. The pharmaceutical composition of claim 117 or 118, wherein the pharmaceutical composition is formulated for subcutaneous, intramuscular, intravenous, intraocular, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal administration.

120. A method of treatment, comprising administering the pharmaceutical composition of any one of claims 88-119 to a subject in need thereof.

121. The method of claim 120, wherein the pharmaceutical composition is administered to treat 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, atherosclerosis, or any other angiogenesis dependent or independent disease characterized by vasculuar overgrowth, edema, or aberrant DLL4 or VEGF activity.

122. The method of claim 120 or 121, wherein the pharmaceutical composition is administered to treat colon cancer, optionally in combination with one or more of irinotecan, leucovorin, temozolomide, gemcitabine, paclitaxel, capecitabine, and 5-FU.

123. The method of claim 120 or 121, wherein the pharmaceutical composition is administered to treat glioblastoma, optionally in combination with temozolomide.

124. The method of claim 120 or 121, wherein the pharmaceutical composition is administered to treat pancreatic cancer, optionally in combination with gemcitabine.

125. The method of claim 120 or 121, wherein the pharmaceutical composition is administered to treat breast cancer, optionally in combination with paclitaxel.

126.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) variable domains that form a functional target binding site for DLL4 comprising:
CDRs 1-3 from SEQ ID NO: 39 and CDRs 1-3 from SEQ ID NO: 40, and
(ii) variable domains that form a functional target binding site for VEGF comprising:
CDRs 1-3 from SEQ ID NO: 41 and CDRs 1-3 from SEQ ID NO: 42,
CDRs 1-3 from SEQ ID NO: 43 and CDRs 1-3 from SEQ ID NO: 44,
CDRs 1-3 from SEQ ID NO: 45 and CDRs 1-3 from SEQ ID NO: 46,
CDRs 1-3 from SEQ ID NO: 47 and CDRs 1-3 from SEQ ID NO: 48,
CDRs 1-3 from SEQ ID NO: 49 and CDRs 1-3 from SEQ ID NO: 50,
CDRs 1-3 from SEQ ID NO: 51 and CDRs 1-3 from SEQ ID NO: 52, or
CDRs 1-3 from SEQ ID NO: 53 and CDRs 1-3 from SEQ ID NO: 54.

127. The binding protein of claim 126, wherein the binding protein comprises:

(i) variable domains that form a functional target binding site for DLL4 comprising:
SEQ ID NO: 39 and/or SEQ ID NO: 40, and

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

a sequence selected from the group consisting of SEQ ID NO: 41-54.

128. The binding protein of claim 126 or 127, 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.

129. The binding protein of any one of claims 126-128, 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,

SEQ ID NO: 43 and SEQ ID NO: 44,

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

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

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

SEQ ID NO: 51 and SEQ ID NO: 52, or
SEQ ID NO: 53 and SEQ ID NO: 54.

130. The binding protein of any one of claims 126-129, wherein the binding protein comprises two first and two second polypeptide chains, forming four functional target binding sites.

131. The binding protein of any one of claims 126-130, wherein the binding protein is capable of binding:

(a) VEGF with a dissociation constant (K_D) of at most about 7.40 x 10^{-9} M, as measured by surface plasmon resonance; and/or

(b) DLL4 with a dissociation constant (K_D) of at most about 3.40 x 10^{-8} M or 5.00 x 10^{-8} M, as measured by surface plasmon resonance.

132. The binding protein of any one of claims 126-131, wherein

(a) linker X1 in the binding protein comprises any one of SEQ ID NOs 1-38 or a G/S based sequence,

(b) linker X1 in the binding protein is not CH1 or CL.

(c) the Fc region of the binding protein is a variant sequence Fc region,

(d) the Fc region is an Fc region from a human IgG1 LALA mutant,

(e) 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, and/or

(f) the binding protein is a crystallized binding protein.

133. The binding protein of any one of claims 126-132, wherein the binding protein comprises:

SEQ ID NO: 55 and SEQ ID NO: 56,
SEQ ID NO: 57 and SEQ ID NO: 58,
SEQ ID NO: 59 and SEQ ID NO: 60,
SEQ ID NO: 61 and SEQ ID NO: 62,
SEQ ID NO: 63 and SEQ ID NO: 64,
SEQ ID NO: 65 and SEQ ID NO: 66,
SEQ ID NO: 67 and SEQ ID NO: 68,
SEQ ID NO: 69 and SEQ ID NO: 70,
SEQ ID NO: 71 and SEQ ID NO: 72, or
SEQ ID NO: 73 and SEQ ID NO: 74.

134.The binding protein of any one of claims 126-133, wherein the binding protein comprises

(i) variable domains that form a functional target binding site for DLL4 comprising:
CDRs 1-3 from SEQ ID NO: 39 and CDRs 1-3 from SEQ ID NO: 40, and

(ii) variable domains that form a functional target binding site for VEGF comprising:
CDRs 1-3 from SEQ ID NO: 41 and CDRs 1-3 from SEQ ID NO: 42.

135.The binding protein of any one of claims 126-134, 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.

136.The binding protein of any one of claims 126-135, wherein the binding protein comprises h1A11.1-SL-Av (comprising SEQ ID NOS: 73 and 74).

137. The binding protein according to claim 126-136, wherein the Fc region is an Fc region from a human IgG1 LALA mutant.

138. A pharmaceutical formulation comprising:
one or more amino acid,
one or more polysaccharide and/or polysorbate, and
a binding protein at a concentration of about 0.1-100 mg/ml,
wherein the pharmaceutical formulation is at a pH of about 5.0-7.0, and
wherein the binding protein comprises 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.

139. The pharmaceutical formulation of claim 138, wherein at least one amino acid is histidine and is present at a concentration of about 10-20 mM, or about 15mM.

140. The pharmaceutical formulation of claim 138 or 139, wherein the pH of the formulation is about 5.5-6.0, or about 5.5, or about 6.0.

141. The pharmaceutical formulation of any one of claims 138-140, wherein at least one polysaccharide is sucrose and is present at a concentration of about 0-8.0% weight/volume (w/v).

142. The pharmaceutical formulation of any one of claims 138-141, wherein the polysorbate is polysorbate 80 and is at a concentration of about 0-0.06% w/v.

143. The pharmaceutical formulation of any one of claims 138-142, wherein at least one amino acid is arginine and is present at a concentration of about 0-1.5% w/v.

144. The pharmaceutical formulation of any one of claims 138-143, wherein the binding protein is present at a concentration of about 1-100 mg/ml, or about 1-15 mg/ml, or about 1-7.5 mg/ml, or about 2.5-7.5 mg/ml, or about 5-7.5 mg/ml, or about 25-100 mg/ml, or about 20-60 mg/ml, or about 25-50 mg/ml, or about 25 mg/ml, or about 50 mg/ml, or about 0.1-60 mg/ml, , or about about 0.1-25 mg/ml, or about 1.0-60 mg/ml, or about 0.5-60 mg/ml, or about 0.1-2.0 mg/ml, or about 0.5-2.0 mg/ml, or about 1-5 mg/ml, or about 1-7.5 mg/ml, or about 1-15 mg/ml, or about 0.5 mg/ml, or about 1.0 mg/ml.

145. The pharmaceutical formulation of any one of claims 138-144, wherein the pharmaceutical formulation is lyophilized.

146. The pharmaceutical formulation of any one of claims 138-144, wherein the pharmaceutical formulation is hydrated or has been lyophilized and rehydrated.

147. The pharmaceutical formulation of claim 146, wherein the pharmaceutical formulation is in a hydrating solution comprising dextrose and/or saline.

148. The pharmaceutical formulation of claim 147, wherein the dextrose is at a concentration of about 5% w/v and/or the saline is at a concentration of about 0.9% w/v.

149. The pharmaceutical formulation of any one of claims 138-148, wherein the pharmaceutical formulation comprises about 15 mM histidine, about 0.03% (w/v) polysorbate 80, about 4% (w/v) sucrose, and about 0.1-25 mg/ml of the binding protein, or about 1-15 mg/ml of the binding protein, and is at a pH of about 6, 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.

150. The pharmaceutical formulation of any one of claims 138-149, wherein the binding protein comprises:

(i) variable domains that form a functional target binding site for DLL4 and comprise:
CDRs 1-3 from SEQ ID NO: 39 and CDRs 1-3 from SEQ ID NO: 40, and

(ii) variable domains that form a functional target binding site for VEGF and comprise:
CDRs 1-3 from SEQ ID NO: 41 and CDRs 1-3 from SEQ ID NO: 42,
CDRs 1-3 from SEQ ID NO: 43 and CDRs 1-3 from SEQ ID NO: 44,
CDRs 1-3 from SEQ ID NO: 45 and CDRs 1-3 from SEQ ID NO: 46,
CDRs 1-3 from SEQ ID NO: 47 and CDRs 1-3 from SEQ ID NO: 48,
CDRs 1-3 from SEQ ID NO: 49 and CDRs 1-3 from SEQ ID NO: 50,
CDRs 1-3 from SEQ ID NO: 51 and CDRs 1-3 from SEQ ID NO: 52, or

CDRs 1-3 from SEQ ID NO: 53 and CDRs 1-3 from SEQ ID NO: 54.

151. The pharmaceutical formulation of any one of claims 138-150, wherein the binding protein comprises:

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

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

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

a sequence selected from the group consisting of SEQ ID NO: 41-54.

152. The pharmaceutical formulation of any one of claims 138-151, 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.

153. The pharmaceutical formulation of any one of claims 138-152, 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,

SEQ ID NO: 43 and SEQ ID NO: 44,

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

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

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

SEQ ID NO: 51 and SEQ ID NO: 52, or

SEQ ID NO: 53 and SEQ ID NO: 54.

154. The pharmaceutical formulation of any one of claims 138-153, wherein the binding protein comprises two first and two second polypeptide chains, forming four functional target binding sites.

155. The pharmaceutical formulation of any one of claims 138-154, wherein the binding protein is capable of binding:

(a) VEGF with a dissociation constant (K_D) of at most about 7.40 x 10^{-9} M, as measured by surface plasmon resonance; and/or

(b) DLL4 with a dissociation constant (K_D) of at most about 3.40 x 10^{-8} M or 5.00 x 10^{-8} M, as measured by surface plasmon resonance.

156. The pharmaceutical formulation of any one of claims 138-155, wherein

(a) linker X1 in the binding protein comprises any one of SEQ ID NOs 1-38 or a G/S based sequence,

(b) linker X1 in the binding protein is not CH1 or CL.

(c) the Fc region of the binding protein is a variant sequence Fc region,

(d) the Fc region is an Fc region from a human IgG1 LALA mutant,

(e) 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, and/or

(f) the binding protein is a crystallized binding protein.

157. The pharmaceutical formulation of any one of claims 138-156, wherein the binding protein comprises:

SEQ ID NO: 55 and SEQ ID NO: 56,

SEQ ID NO: 57 and SEQ ID NO: 58,

SEQ ID NO: 59 and SEQ ID NO: 60,
SEQ ID NO: 61 and SEQ ID NO: 62,
SEQ ID NO: 63 and SEQ ID NO: 64,
SEQ ID NO: 65 and SEQ ID NO: 66,
SEQ ID NO: 67 and SEQ ID NO: 68,
SEQ ID NO: 69 and SEQ ID NO: 70,
SEQ ID NO: 71 and SEQ ID NO: 72, or
SEQ ID NO: 73 and SEQ ID NO: 74.

158.The pharmaceutical formulation of any one of claims 138-157, wherein the binding protein comprises

(i) variable domains that form a functional target binding site for DLL4 comprising:
CDRs 1-3 from SEQ ID NO: 39 and CDRs 1-3 from SEQ ID NO: 40, and
(ii) variable domains that form a functional target binding site for VEGF comprising:
CDRs 1-3 from SEQ ID NO: 41 and CDRs 1-3 from SEQ ID NO: 42.

159.The pharmaceutical formulation of any one of claims 138-158, 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.

160.The pharmaceutical formulation of any one of claims 138-159, wherein the binding protein comprises h1A11.1-SL-Av (comprising SEQ ID NOS: 73 and 74).

161.The pharmaceutical formulation according to claim 138-160, wherein the Fc region is an Fc region from a human IgG1 LALA mutant.

162. The pharmaceutical formulation of any one of claims 138-161, further comprising at least one additional agent.

163. The pharmaceutical formulation of claim 162, wherein the at least one 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.

164. The pharmaceutical formulation of claim 162 or 163, wherein the at least one additional agent comprises at least one of 13-cis-Retinoic Acid; 2-CdA; 2-Chlorodeoxyadenosine; 5-Azacitidine; 5-Fluorouracil; an anti-VEGF mAb; an anti-DLL4 mAb; 5-FU; 6-Mercaptopurine; 6-MP; 6-TG; 6-Thioguanine; Abraxane; Accutane®; Actinomycin-D; Adriamycin®; Adrucil®; Afinitor®; Agrylin®; Ala-Cort®; Aldesleukin; Alemtuzumab; ALIMTA; Alitretinoin; Alkaban-AQ®; Alkeran®; All-transretinoic Acid; Alpha Interferon; Altretamine; Amethopterin; Amifostine; Aminoglutethimide; Anagrelide; Anandron®; Anastrozole; Arabinosylcytosine; Ara-C Aranesp®; Aredia®;

Arimidex®; Aromasin®; Arranon®; Arsenic Trioxide; Arzerra™; Asparaginase; ATRA; Avastin®; Azacitidine; BCG; BCNU; Bendamustine; Bevacizumab; Bexarotene; BEXXAR®; Bicalutamide; BiCNU; Blenoxane®; Bleomycin; Bortezomib; Busulfan; Busulfex®; C225; Calcium Leucovorin; Campath®; Camptosar®; Camptothecin-11; Capecitabine; Carac™; Carboplatin; Carmustine; Carmustine Wafer; Casodex®; CC-5013; CCI-779; CCNU; CDDP; CeeNU; Cerubidine®; Cetuximab; Chlorambucil; Cisplatin; Citrovorum Factor; Cladribine; Cortisone; Cosmegen®; CPT-11; Cyclophosphamide; Cytadren®; Cytarabine; Cytarabine Liposomal; Cytosar-U®; Cytoxan®; Dacarbazine; Dacogen; Dactinomycin; Darbepoetin Alfa; Dasatinib; Daunomycin; Daunorubicin; Daunorubicin Hydrochloride; Daunorubicin Liposomal; DaunoXome®; Decadron; Decitabine; Delta-Cortef®; Deltasone®; Denileukin; Diftitox; DepoCyt™; Dexamethasone; Dexamethasone Acetate; Dexamethasone Sodium Phosphate; Dexasone; Dexrazoxane; DHAD; DIC; Diodex; Docetaxel; Doxil®; Doxorubicin; Doxorubicin Liposomal; Droxia™; DTIC; DTIC-Dome®; Duralone®; Efudex®; Eligard™; Ellence™; Eloxatin™; Elspar®; Emcyt®; Enalapril; Epirubicin; Epoetin Alfa; Erbitux; Erlotinib; Erwinia L-asparaginase; Estramustine; Ethyol Etopophos®; Etoposide; Etoposide Phosphate; Eulexin®; Everolimus; Evista®; Exemestane; Fareston®; Faslodex®; Femara®; Filgrastim; Floxuridine; Fludara®; Fludarabine; Fluoroplex®; Fluorouracil; Fluorouracil (cream); Fluoxymesterone; Flutamide; Folinic Acid; FUDR®; Fulvestrant; Gefitinib; Gemcitabine; Gemtuzumab ozogamicin; Gemzar; Gleevec™; Gliadel® Wafer; GM-CSF; Goserelin; Granulocyte-Colony Stimulating Factor (G-CSF); Granulocyte Macrophage Colony Stimulating Factor (G-MCSF); Halotestin®; Herceptin®; Hexadrol; Hexalen®; Hexamethylmelamine; HMM; Hycamtin®; Hydrea®; Hydrocort Acetate®; Hydrocortisone; Hydrocortisone Sodium Phosphate; Hydrocortisone Sodium Succinate; Hydrocortone Phosphate; Hydroxyurea; Ibritumomab; Ibritumomab Tiuxetan; Idamycin®; Idarubicin Ifex®; Interferon-alpha; Interferon-alpha-2b (PEG Conjugate); Ifosfamide; Interleukin-11 (IL-11); Interleukin-2 (IL-2); Imatinib mesylate; Imidazole Carboxamide; Intron A®; Iressa®; Irinotecan; Isotretinoin; Ixabepilone; Ixempra™; KADCYCLA®; Kidrolase (t) Lanacort®; Lapatinib; L-asparaginase; LCR; Lenalidomide; Letrozole; Leucovorin; Leukeran; Leukine™; Leuprolide; Leurocristine; Leustatin™; Liposomal Ara-C; Liquid Pred®; Lomustine; L-PAM; L-Sarcolysin; Lupron®; Lupron Depot®; Matulane®; Maxidex; Mechlorethamine; Mechlorethamine Hydrochloride; Medralone®; Medrol®; Megace®; Megestrol; Megestrol Acetate; Melphalan; Mercaptopurine; Mesna; Mesnex™; Methotrexate; Methotrexate Sodium; Methylprednisolone; Meticorten®; Mitomycin; Mitomycin-C; Mitoxantrone M-

Prednisol®; MTC; MTX; Mustargen®; Mustine; Mutamycin®; Myleran®; Mylocel™; Mylotarg®; Navelbine®; Nelarabine; Neosar®; Neulasta™; Neumega®; Neupogen®; Nexavar®; Nifedipine; Nilandron®; Nilotinib; Nilutamide; Nipent®; Nitrogen Mustard Novaldex®; Novantrone®; Nplate; Octreotide; Octreotide acetate; Ofatumumab; Oncospar®; Oncovin®; Ontak®; Onxal™; Oprelvekin; Orapred®; Orasone®; Oxaliplatin; Paclitaxel; Paclitaxel Protein-bound; Pamidronate; Panitumumab; Panretin®; Paraplatin®; Pazopanib; Pediapred®; PEG Interferon; Pegaspargase; Pegfilgrastim; PEG-INTRON™; PEG-L-asparaginase; PEMETREXED; Pentostatin; Phenylalanine Mustard; Platinol®; Platinol-AQ®; Prednisolone; Prednisone; Prelone®; Procarbazine; PROCRIT®; Proleukin®; Prolifeprospan 20 with Carmustine Implant; Purinethol®; Raloxifene; Revlimid®; Rheumatrex®; Rituxan®; Rituximab; Roferon-A®; Romiplostim; Rubex®; Rubidomycin hydrochloride; Sandostatin®; Sandostatin LAR®; Sargramostim; Solu-Cortef®; Solu-Medrol®; Sorafenib; SPRYCEL™; STI-571; Streptozocin; SU11248; Sunitinib; Sutent®; Tamoxifen Tarceva®; Targretin®; Tasigna®; Taxol®; Taxotere®; Temodar®; Temozolomide Temsirolimus; Teniposide; TESPA; Thalidomide; Thalomid®; TheraCys®; Thioguanine; Thioguanine Tabloid®; Thiophosphoamide; Thioplex®; Thiotepa; TICE®; Toposar®; Topotecan; Toremifene; Torisel®; Tositumomab; Trastuzumab; Treanda®; Tretinoin; Trexall™; Trisenox®; TSPA; TYKERB®; VCR; Vectibix™; Velban®; Velcade®; VePesid®; Vesanoid®; Viadur™; Vidaza®; Vinblastine; Vinblastine Sulfate; Vincasar Pfs®; Vincristine; Vinorelbine; Vinorelbine tartrate; VLB; VM-26; Vorinostat; Votrient; VP-16; Vumon®; Xeloda®; Zanosar®; Zevalin™; Zinecard®; Zoladex®; Zoledronic acid; Zolinza; Zometa®; Irinotecan; Leucovorin; 5-FU; Temozolomide; Gemcitabine; Paclitaxel; Regorafenib; and Pertuzumab.

165. The pharmaceutical formulation of any one of claims 162-164, wherein the at least one additional agent comprises at least one of Irinotecan; Leucovorin; Folfiri; 5-FU; Enalapril; Nifedipine; Clonidine; Temozolomide; Gemcitabine; Capecitabine; Paclitaxel; Regorafenib; and Pertuzumab.

166. The binding protein of claim 136 or the pharmaceutical formulation of claim 160, 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.

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.