

CLAIMS

What is claimed is:

1. An isolated antibody that specifically binds vascular endothelial growth factor (VEGF), wherein the antibody comprises the following six hypervariable regions (HVRs):
 - (a) an HVR-H1 comprising the amino acid sequence of DYWIH (SEQ ID NO: 1);
 - (b) an HVR-H2 comprising the amino acid sequence of GITPAGGYTRYADSVKG (SEQ ID NO: 7);
 - (c) an HVR-H3 comprising the amino acid sequence of FVFFLPYAMDY (SEQ ID NO: 3);
 - (d) an HVR-L1 comprising the amino acid sequence of RASQDVSTAVA (SEQ ID NO: 8);
 - (e) an HVR-L2 comprising the amino acid sequence of SASFLYS (SEQ ID NO: 9); and
 - (f) an HVR-L3 comprising the amino acid sequence of QQGYGAPFT (SEQ ID NO: 10).
2. The antibody of claim 1, wherein the antibody further comprises the following heavy chain variable (VH) domain framework regions (FRs):
 - (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTIS (SEQ ID NO: 13);
 - (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGGLEWVA (SEQ ID NO: 14);
 - (c) an FR-H3 comprising the amino acid sequence of RFTISADTSKNTAYLQMRSLRAEDTAVYYCAR (SEQ ID NO: 15); and
 - (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 16).
3. The antibody of claim 1 or 2, wherein the antibody further comprises the following light chain variable (VL) domain FRs:
 - (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17);
 - (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 18);
 - (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISLQPEDAATYYC (SEQ ID NO: 19); and
 - (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20).
4. An isolated antibody that specifically binds VEGF, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 11 and (b) a VL domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 12.
5. The antibody of claim 4, wherein the VH domain further comprises the following FRs:
 - (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTIS (SEQ ID NO: 13);

- (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 14);
 - (c) an FR-H3 comprising the amino acid sequence of RFTISADTSKNTAYLQMRSLRAEDTAVYYCAR (SEQ ID NO: 15); and
 - (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 16); wherein optionally
- the VH domain comprises the amino acid sequence of SEQ ID NO: 11; and wherein optionally the VL domain further comprises the following FRs:
- (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17);
 - (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 18);
 - (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISLQPEDAATYYC (SEQ ID NO: 19); and
 - (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20), wherein optionally
- the VL domain comprises the amino acid sequence of SEQ ID NO: 12.

6. An isolated antibody that specifically binds VEGF, wherein the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 11 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12.

7. An isolated antibody that specifically binds VEGF, wherein the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 50.

8. An isolated antibody that specifically binds VEGF, wherein the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 49 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 50.

9. The antibody of any one of claims 1-8, wherein the antibody is capable of inhibiting the binding of VEGF to a VEGF receptor; wherein optionally the VEGF receptor is VEGF receptor 1 (Flt-1), or VEGF receptor 2 (KDR); wherein optionally the antibody binds human VEGF (hVEGF) with a K_d of about 2 nM or lower, wherein optionally the antibody binds hVEGF with a K_d between about 75 pM and about 2 nM, wherein optionally the antibody binds hVEGF with a K_d between about 75 pM and about 600 pM, wherein optionally the antibody binds hVEGF with a K_d between about 75 pM and about 500 pM, and wherein optionally the antibody binds hVEGF with a K_d of about 60 pM.

10. The antibody of any one of claims 1-9, wherein the antibody has a melting temperature (T_m) of greater than about 83.5°C; wherein optionally
the antibody has a T_m of about 85°C to about 91°C, and wherein optionally
the antibody has a T_m of about 89°C.

11. The antibody of any one of claims 1-10, wherein the antibody is monoclonal, human, humanized, or chimeric.

12. The antibody of any one of claims 1-6 and 9-11, wherein the antibody is an antibody fragment that binds VEGF.

13. The antibody of claim 12, wherein the antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

14. The antibody of claim 13, wherein the antibody fragment is an Fab.

15. The antibody of any one of claims 1-14, wherein the antibody is a monospecific antibody.

16. The antibody of any one of claims 1-14, wherein the antibody is a multispecific antibody, wherein optionally

the multispecific antibody is a bispecific antibody, wherein optionally

the bispecific antibody binds VEGF and a second biological molecule selected from the group consisting of IL-1 β ; interleukin-6 (IL-6); interleukin-6 receptor (IL-6R); interleukin-13 (IL-13); IL-13 receptor (IL-13R); PDGF; angiopoietin; angiopoietin 2; Tie2; S1P; integrins $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha 5\beta 1$; betacellulin; apelin/APJ; erythropoietin; complement factor D; TNF α ; HtrA1; a VEGF receptor; ST-2 receptor; and a protein genetically linked to age-related macular degeneration (AMD) risk, wherein optionally

the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, membrane-bound VEGF-receptor (mbVEGFR), or soluble VEGF receptor (sVEGFR), or

the protein genetically linked to AMD risk is selected from the group consisting of complement pathway components C2, factor B, factor H, CFHR3, C3b, C5, C5a, and C3a; HtrA1; ARMS2; TIMP3; HLA; interleukin-8 (IL-8); CX3CR1; TLR3; TLR4; CETP; LIPC, COL10A1; and TNFRSF10A.

17. A polynucleotide encoding the antibody of any one of claims 1-16.

18. A vector comprising the polynucleotide of claim 17.

19. A host cell comprising the vector of claim 18.

20. A method of producing the antibody of any one of claims 1-16, the method comprising culturing a host cell that comprises the vector of claim 18 and recovering the antibody.

21. The method of claim 20, wherein the host cell is prokaryotic, wherein optionally the host cell is *Escherichia coli*; or
the host cell is eukaryotic, wherein optionally
the host cell is a 293 cell, a CHO cell, a yeast cell, or a plant cell.

22. Use of the antibody of any one of claims 1-16 in the manufacture of a medicament for reducing or inhibiting angiogenesis in a subject having a disorder associated with pathological angiogenesis.

23. Use of the antibody of any one of claims 1-16 in the manufacture of a medicament for treating a disorder associated with pathological angiogenesis.

24. The use of claim 22 or 23, wherein the disorder associated with pathological angiogenesis is an ocular disorder or a cell proliferative disorder.

25. The use of claim 24, wherein the disorder associated with pathological angiogenesis is an ocular disorder.

26. The use of claim 24 or 25, wherein the ocular disorder is selected from the group consisting of age-related macular degeneration (AMD), macular degeneration, macular edema, diabetic macular edema (DME) (including focal, non-center DME and diffuse, center-involved DME), retinopathy, diabetic (DR) (including proliferative DR (PDR), non-proliferative DR (NPDR), and high-altitude DR), other ischemia-related retinopathies, retinopathy of prematurity (ROP), retinal vein occlusion (RVO) (including central RVO (CRVO) and branched RVO (BRVO) forms), CNV (including myopic CNV), corneal neovascularization, a disease associated with corneal neovascularization, retinal neovascularization, a disease associated with retinal/choroidal neovascularization, pathologic myopia, von Hippel-Lindau disease, histoplasmosis of the eye, familial exudative vitreoretinopathy (FEVR), Coats' disease, Norrie Disease, Osteoporosis-Pseudoglioma Syndrome (OPPG), subconjunctival hemorrhage, rubeosis, ocular neovascular disease, neovascular glaucoma, retinitis pigmentosa (RP), hypertensive retinopathy, retinal angiomatous proliferation, macular telangiectasia, iris neovascularization, intraocular neovascularization, retinal degeneration, cystoid macular edema (CME), vasculitis, papilloedema, retinitis, conjunctivitis (including infectious conjunctivitis and non-infectious (e.g., allergic) conjunctivitis), Leber congenital amaurosis, uveitis (including infectious and non-infectious uveitis), choroiditis, ocular histoplasmosis, blepharitis, dry eye, traumatic eye injury, and Sjögren's disease.

27. The use of any one of claims 24-26, wherein the ocular disorder is AMD, DME, DR, or RVO.

28. The use of claim 26 or 27, wherein the ocular disorder is AMD.
29. The use of any one of claims 26-28, wherein the AMD is wet AMD.
30. The use of claim 24, wherein the disorder associated with pathological angiogenesis is a cell proliferative disorder.
31. The use of claim 30, wherein the cell proliferative disorder is a cancer.
32. The use of claim 31, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, non-small cell lung cancer, non-Hodgkins lymphoma (NHL), renal cancer, prostate cancer, liver cancer, head and neck cancer, melanoma, ovarian cancer, mesothelioma, and multiple myeloma.
33. Use of the antibody of any one of claims 1-16 in the manufacture of a medicament for inhibiting vascular permeability in a subject suffering from a disorder associated with undesirable vascular permeability.
34. Use of the antibody of any one of claims 1-16 in the manufacture of a medicament for treating a disorder associated with undesirable vascular permeability in a subject in need thereof.
35. The use of claim 33 or 34, wherein the disorder associated with undesirable vascular permeability is selected from the group consisting of edema associated with brain tumors, ascites associated with malignancies, Meigs' syndrome, lung inflammation, nephrotic syndrome, pericardial effusion, pleural effusion, and permeability associated with cardiovascular diseases.
36. The use of any one of claims 22-35, wherein the medicament is to be administered with a second agent, wherein the second agent is selected from the group consisting of another antibody, a chemotherapeutic agent, a cytotoxic agent, an anti-angiogenic agent, an immunosuppressive agent, a prodrug, a cytokine, a cytokine antagonist, cytotoxic radiotherapy, a corticosteroid, an anti-emetic, a cancer vaccine, an analgesic, a growth-inhibitory agent, and a compound that binds to a second biological molecule.
37. The use of claim 36, wherein the anti-angiogenic agent is a VEGF antagonist.
38. The use of claim 37, wherein the VEGF antagonist is an anti-VEGF antibody, an anti-VEGF receptor antibody, a soluble VEGF receptor fusion protein, an aptamer, an anti-VEGF DARPIn®, or a VEGFR tyrosine kinase inhibitor.

39. The use of claim 38, wherein the anti-VEGF antibody is ranibizumab (LUCENTIS®), RTH-258, or a bispecific anti-VEGF antibody, wherein optionally the bispecific anti-VEGF antibody is an anti-VEGF/anti-Ang2 antibody, and wherein optionally the anti-VEGF/anti-Ang2 antibody is RG-7716, or wherein the soluble VEGF receptor fusion protein is aflibercept (EYLEA®), or wherein the aptamer is pegaptanib (MACUGEN®), or wherein the anti-VEGF DARPIn® is abicipar pegol, or wherein the VEGFR tyrosine kinase inhibitor is selected from the group consisting of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171), vatalanib (PTK787), semaxaminib (SU5416), and SUTENT® (sunitinib).

40. The use of claim 36, wherein the second biological molecule is selected from the group consisting of IL-1 β ; IL-6; IL-6R; IL-13; IL-13R; PDGF; angiopoietin; angiopoietin 2; Tie2; S1P; integrins α v β 3, α v β 5, and α 5 β 1; betacellulin; apelin/APJ; erythropoietin; complement factor D; TNF α ; HtrA1; a VEGF receptor; ST-2 receptor; and a protein genetically linked to AMD risk; wherein optionally

the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR; or

the protein genetically linked to AMD risk is selected from the group consisting of complement pathway components C2, factor B, factor H, CFHR3, C3b, C5, C5a, and C3a; HtrA1; ARMS2; TIMP3; HLA; IL-8; CX3CR1; TLR3; TLR4; CETP; LPC; COL10A1; and TNFRSF10A.

41. The use of claim 36 or 40, wherein the compound that binds a second biological molecule is an antibody or antigen-binding fragment thereof; wherein optionally

the antigen-binding antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

42. The use of any one of claims 22-41, wherein the antibody is to be administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonly, superchoroidally, topically, intravenously, intramuscularly, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intrathecally, intranasally, intravaginally, intrarectally, topically, intratumorally, intraperitoneally, peritoneally, intraventricularly, subcutaneously, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraorbitally, orally, transdermally, by inhalation, by injection, by eye drop, by implantation, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in cremes, or in lipid compositions.

43. The use of claim 42, wherein the antibody is to be administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonly, superchoroidally, or topically.

44. The use of claim 42 or 43, wherein the antibody is to be administered intravitreally by injection.

45. The use of claim 42 or 43, wherein the antibody is to be administered topically by eye drop or ointment.

46. The use of claim 42 or 43, wherein the antibody is to be administered by a port delivery device.

47. The use of any one of claims 22-46, wherein the subject is a human.

48. A pharmaceutical composition comprising the antibody of any one of claims 1-16.

49. The pharmaceutical composition of claim 48, further comprising a polymer; wherein optionally the polymer is a biodegradable polymer; or
wherein the pharmaceutical composition is formulated as a polymer solvent depot, a polymer implant, or a polymer micelle.

50. The pharmaceutical composition of claim 49, wherein the polymer is a polylactic acid polyglycolic acid (PLGA) copolymer; wherein optionally
the pharmaceutical composition is formulated as a PLGA rod.

51. The pharmaceutical composition of any one of claims 48-50, for use in the treatment of a disorder associated with pathological angiogenesis or a disorder associated with undesirable vascular permeability in a mammal.

52. The pharmaceutical composition for use of claim 51, wherein the disorder associated with pathological angiogenesis is an ocular disorder or a cell proliferative disorder.

53. The pharmaceutical composition for use of claim 52, the disorder associated with pathological angiogenesis is an ocular disorder.

54. The pharmaceutical composition for use of claim 52 or 53, wherein the ocular disorder is selected from the group consisting of AMD, macular degeneration, macular edema, DME (including focal, non-center DME and diffuse, center-involved DME), retinopathy, DR (including PDR, NPDR, and high-altitude DR), other ischemia-related retinopathies, ROP, RVO (including CRVO and BRVO forms), CNV (including myopic CNV), corneal neovascularization, a disease associated with corneal neovascularization, retinal neovascularization, a disease associated with retinal/choroidal neovascularization, pathologic myopia, von Hippel-Lindau disease, histoplasmosis of the eye, FEVR, Coats' disease, Norrie Disease, OPPG, subconjunctival hemorrhage, rubeosis, ocular neovascular disease, neovascular glaucoma, RP, hypertensive retinopathy, retinal angiomatous proliferation, macular telangiectasia, iris neovascularization, intraocular neovascularization, retinal degeneration, CME, vasculitis, papilloedema, retinitis, conjunctivitis (including

infectious conjunctivitis and non-infectious (e.g., allergic) conjunctivitis), Leber congenital amaurosis, uveitis (including infectious and non-infectious uveitis), choroiditis, ocular histoplasmosis, blepharitis, dry eye, traumatic eye injury, and Sjögren's disease.

55. The pharmaceutical composition for use of any one of claims 52-54, wherein the ocular disorder is AMD, DME, DR, or RVO.

56. The pharmaceutical composition for use of any one of claims 52-55, wherein the ocular disorder is AMD.

57. The pharmaceutical composition for use of any one of claims 54-56, wherein the AMD is wet AMD.

58. The pharmaceutical composition for use of claim 52, wherein the disorder associated with pathological angiogenesis is a cell proliferative disorder.

59. The pharmaceutical composition for use of claim 58, wherein the cell proliferative disorder is a cancer.

60. The pharmaceutical composition for use of claim 59, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, non-small cell lung cancer, non-Hodgkins lymphoma (NHL), renal cancer, prostate cancer, liver cancer, head and neck cancer, melanoma, ovarian cancer, mesothelioma, and multiple myeloma.

61. The pharmaceutical composition for use of claim 51, wherein the disorder associated with undesirable vascular permeability is selected from the group consisting of edema associated with brain tumors, ascites associated with malignancies, Meigs' syndrome, lung inflammation, nephrotic syndrome, pericardial effusion, pleural effusion, and permeability associated with cardiovascular diseases.

62. The pharmaceutical composition for use of any one of claims 48-61, (i) further comprising a second agent, wherein the second agent is selected from the group consisting of another antibody, a chemotherapeutic agent, a cytotoxic agent, an anti-angiogenic agent, an immunosuppressive agent, a prodrug, a cytokine, a cytokine antagonist, cytotoxic radiotherapy, a corticosteroid, an anti-emetic, a cancer vaccine, an analgesic, a growth-inhibitory agent, and a compound that binds to a second biological molecule; wherein optionally (ii)

the anti-angiogenic agent is a VEGF antagonist; wherein optionally (iii)

the VEGF antagonist is an anti-VEGF antibody, an anti-VEGF receptor antibody, a soluble VEGF receptor fusion protein, an aptamer, an anti-VEGF DARPIn®, or a VEGFR tyrosine kinase inhibitor, wherein optionally the anti-VEGF antibody is ranibizumab (LUCENTIS®), RTH-258, or a bispecific anti-VEGF

antibody, wherein optionally the bispecific anti-VEGF antibody is an anti-VEGF/anti-Ang2 antibody and wherein optionally the anti-VEGF/anti-Ang2 antibody is RG-7716, or wherein the soluble VEGF receptor fusion protein is aflibercept (EYLEA®), or wherein the aptamer is pegaptanib (MACUGEN®), or wherein the anti-VEGF DARPIn® is abicipar pegol, or wherein the VEGFR tyrosine kinase inhibitor is selected from the group consisting of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171), vatalanib (PTK787), semaxaminib (SU5416), and SUTENT® (sunitinib).

63. The pharmaceutical composition for use of claim 62(i), wherein the second biological molecule is selected from the group consisting of IL-1 β ; IL-6; IL-6R; IL-13; IL-13R; PDGF; angiopoietin; angiopoietin 2; Tie2; S1P; integrins $\alpha\beta$ 3, $\alpha\beta$ 5, and α 5 β 1; betacellulin; apelin/APJ; erythropoietin; complement factor D; TNF α ; HtrA1; a VEGF receptor; ST-2 receptor; and a protein genetically linked to AMD risk; wherein optionally

the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR, or

the protein genetically linked to AMD risk is selected from the group consisting of complement pathway components C2, factor B, factor H, CFHR3, C3b, C5, C5a, and C3a; HtrA1; ARMS2; TIMP3; HLA; IL-8; CX3CR1; TLR3; TLR4; CETP; LPC, COL10A1; and TNFRSF10A.

64. The pharmaceutical composition for use of claim 62(i) or 63, wherein the compound that binds a second biological molecule is an antibody or antigen-binding fragment thereof; wherein optionally

the antigen-binding antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

65. A fusion protein comprising the antibody of any one of claims 1-16 covalently attached to an HA binding domain.

66. The fusion protein of claim 65, wherein

(i) the HA binding domain is covalently attached to the heavy chain or the light chain of the antibody; wherein optionally

(ii) the HA binding domain is covalently attached to the C-terminus of the heavy chain or to the C-terminus of the light chain, wherein optionally

(iii) the fusion protein further comprises a linker, the linker being positioned between the antibody and the HA binding domain, wherein optionally

(iv) the linker comprises the amino acid sequence of GGGGS (SEQ ID NO: 61), wherein optionally

(v) the linker consists of the amino acid sequence of GGGGS (SEQ ID NO: 61); wherein optionally

(vi) the antibody is an antibody fragment that binds VEGF, wherein optionally

(vii) the antibody fragment is selected from the group consisting of Fab, Fab-C, Fab', Fab'-SH, Fv, scFv, and (Fab')₂ fragments, wherein optionally

(viii) the antibody fragment is an Fab, wherein optionally

(ix) the HA binding domain is covalently attached to the C-terminus of the CH1 domain of the Fab, or the CL domain of the Fab; wherein optionally

(x) the HA binding domain is selected from the group consisting of a link module, a G1 domain, and a lysine-rich oligopeptide, wherein optionally

(xi) the HA binding domain is a link module, wherein optionally

(xii) the link module is selected from the group consisting of tumor necrosis factor-stimulated gene 6 (TSG6), CD44, lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), hyaluronan and proteoglycan link protein (HAPLN) 1, HAPLN2, HAPLN3, HAPLN4, aggrecan, brevican, neurocan, phosphacan, versican, CAB61358, KIA0527, stabilin-1, and stabilin-2 link modules, wherein optionally

(xiii) the link module is a TSG6 link module, wherein optionally

(xiv) the TSG6 link module is a human TSG6 link module or a rabbit TSG6 link module, wherein optionally

(xv) the TSG link module is a human TSG6 link module; wherein optionally

(xvi) the human TSG6 link module comprises amino acid residues 36-128 of human TSG6; and wherein optionally

(xvii) the fusion protein further comprises at least one additional HA binding domain, wherein optionally

(xviii) the at least one additional HA binding domain is covalently attached to the heavy chain or the light chain of the antibody.

67. The fusion protein of claim 66(xvii) or 66(xviii), wherein (i) the at least one additional HA binding protein is linked to the antibody by a linker; wherein optionally

(ii) the linker comprises the amino acid sequence of GGGGS (SEQ ID NO: 61), wherein optionally

(iii) the linker consists of the amino acid sequence of GGGGS (SEQ ID NO: 61); wherein optionally

(iv) a first HA binding domain is covalently attached to the heavy chain and a second HA binding domain is covalently attached to the light chain, wherein optionally

(v) the first HA binding domain is linked to the C-terminus of the heavy chain and the second HA binding domain is linked to the C-terminus of the light chain; wherein optionally

(vi) the at least one additional HA binding protein is selected from the group consisting of a link module, a G1 domain, and a lysine-rich oligopeptide, wherein optionally

(vii) the at least one additional HA binding protein is a link module, wherein optionally

(viii) the link module is a TSG6 link module, wherein optionally

(ix) the TSG6 link module is a human TSG6 link module or a rabbit TSG6 link module, wherein optionally

(x) the TSG6 link module is a human TSG6 link module.

68. The fusion protein of claim 67(ix) or 67(x), wherein the human TSG6 link module comprises amino acid residues 36-128 of human TSG6.

69. The fusion protein of any one of claims 65-68, wherein

- (i) the fusion protein specifically binds to VEGF and HA; wherein optionally
- (ii) the fusion protein binds HA with a K_d of about 2 μ M or lower, wherein optionally
- (iii) the fusion protein binds HA with a K_d between about 1 nM and about 500 nM, wherein optionally
- (iv) the fusion protein binds HA with a K_d between about 1 nM and about 50 nM, wherein optionally
- (v) the fusion protein binds HA with a K_d of about 10 nM; and wherein optionally
- (vi) the fusion protein has an ocular half-life that is increased relative to a reference antibody that is not covalently attached to a HA binding domain, wherein optionally
- (vii) the ocular half-life is increased at least about 2-fold relative to the reference antibody, and wherein optionally
- (viii) the ocular half-life is increased at least about 4-fold relative to the reference antibody.

70. The fusion protein of any one of claims 69(vi)-69(viii), wherein the ocular half-life is a vitreal half-life; wherein optionally

the reference antibody is identical to the antibody of the fusion protein.

71. Use of the fusion protein of any one of claims 65-70 in the manufacture of a medicament for reducing or inhibiting angiogenesis in a subject having a disorder associated with pathological angiogenesis.

72. Use of the fusion protein of any one of claims 65-70 in the manufacture of a medicament for treating a disorder associated with pathological angiogenesis in a subject in need of such treatment.

73. The use of claim 71 or 72, wherein

- (i) the disorder associated with pathological angiogenesis is an ocular disorder; wherein optionally
- (ii) the ocular disorder is selected from the group consisting of AMD, macular degeneration, macular edema, DME (including focal, non-center DME and diffuse, center-involved DME), retinopathy, DR (including PDR, NPDR, and high-altitude DR), other ischemia-related retinopathies, ROP, RVO (including CRVO and BRVO forms), CNV (including myopic CNV), corneal neovascularization, a disease associated with corneal neovascularization, retinal neovascularization, a disease associated with retinal/choroidal neovascularization, pathologic myopia, von Hippel-Lindau disease, histoplasmosis of the eye, FEVR, Coats' disease, Norrie Disease, OPPG, subconjunctival hemorrhage, rubeosis, ocular neovascular disease, neovascular glaucoma, RP, hypertensive retinopathy, retinal angiomatous proliferation, macular telangiectasia, iris neovascularization, intraocular neovascularization, retinal degeneration, CME, vasculitis, papilloedema, retinitis, conjunctivitis (including infectious conjunctivitis and non-infectious (e.g., allergic) conjunctivitis), Leber congenital amaurosis, uveitis (including infectious and non-infectious uveitis), choroiditis, ocular histoplasmosis, blepharitis, dry eye, traumatic eye injury, and Sjögren's disease; wherein optionally
- (iii) the ocular disorder is AMD, DME, DR, or RVO; wherein optionally

(iv) the ocular disorder is AMD.

74. The use of any one of claims 73(ii)-73(iv), wherein the AMD is wet AMD.

75. The use of any one of claims 71-74, wherein

(i) the medicament is to be administered with a second agent, wherein the second agent is selected from the group consisting of another antibody, an anti-angiogenic agent, a cytokine, a cytokine antagonist, a corticosteroid, an analgesic, and a compound that binds to a second biological molecule; wherein optionally

(ii) the anti-angiogenic agent is a VEGF antagonist; wherein optionally

(iii) the VEGF antagonist is an anti-VEGF antibody, an anti-VEGF receptor antibody, a soluble VEGF receptor fusion protein, an aptamer, an anti-VEGF DARPIn®, or a VEGFR tyrosine kinase inhibitor; wherein optionally

(iv) the anti-VEGF antibody is ranibizumab (LUCENTIS®), RTH-258, or a bispecific anti-VEGF antibody; wherein optionally

(v) the bispecific anti-VEGF antibody is an anti-VEGF/anti-Ang2 antibody; and wherein optionally

(vi) the anti-VEGF/anti-Ang2 antibody is RG-7716.

76. The use of claim 75(iii), wherein the soluble VEGF receptor fusion protein is aflibercept (EYLEA®), or wherein the aptamer is pegaptanib (MACUGEN®), or

wherein the anti-VEGF DARPIn® is abicipar pegol, or

wherein the VEGFR tyrosine kinase inhibitor is selected from the group consisting of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474), 4-(4-fluoro-2-methylindol-5-ylloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171), vatalanib (PTK787), semaxaminib (SU5416), and SUTENT® (sunitinib).

77. The use of claim 75(i), wherein the second biological molecule is selected from the group consisting of IL-1β; IL-6; IL-6R; IL-13; IL-13R; PDGF; angiopoietin; angiopoietin 2; Tie2; S1P; integrins αvβ3, αvβ5, and α5β1; betacellulin; apelin/APJ; erythropoietin; complement factor D; TNFα; HtrA1; a VEGF receptor; ST-2 receptor; and a protein genetically linked to AMD risk; wherein optionally

the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR, or

the protein genetically linked to AMD risk is selected from the group consisting of complement pathway components C2, factor B, factor H, CFHR3, C3b, C5, C5a, and C3a; HtrA1; ARMS2; TIMP3; HLA; IL-8; CX3CR1; TLR3; TLR4; CETP; LPC; COL10A1; and TNFRSF10A.

78. The use of of claim 75(i) or 77, wherein the compound that binds a second biological molecule is an antibody or antigen-binding fragment thereof; wherein optionally

the antigen-binding antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

79. The use of any one of claims 71-78, wherein

(i) the medicament is to be administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonly, superchoroidally, topically, intravenously, intramuscularly, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intrathecally, intranasally, intravaginally, intrarectally, topically, intratumorally, intraperitoneally, peritoneally, intraventricularly, subcutaneously, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraorbitally, orally, transdermally, by inhalation, by injection, by eye drop, by implantation, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in cremes, or in lipid compositions; wherein optionally

(ii) the medicament is to be administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonly, superchoroidally, or topically; and wherein optionally

(iii) the medicament is to be administered intravitreally by injection, or topically by eye drop or ointment.

80. The use of claim 79(i) or 79(ii), wherein the medicament is to be administered by a port delivery device.

81. The use of any one of claims 71-80, wherein the subject is a human.

82. A pharmaceutical composition comprising the fusion protein of any one of claims 65-70.

83. The pharmaceutical composition of claim 82, for use in the treatment of a disorder associated with pathological angiogenesis in a mammal.

84. The pharmaceutical composition for use of claim 83, wherein

(i) the disorder associated with pathological angiogenesis is an ocular disorder; wherein optionally

(ii) the ocular disorder is selected from the group consisting of AMD, macular degeneration, macular edema, DME (including focal, non-center DME and diffuse, center-involved DME), retinopathy, DR (including PDR, NPDR, and high-altitude DR), other ischemia-related retinopathies, ROP, RVO (including CRVO and BRVO forms), CNV (including myopic CNV), corneal neovascularization, a disease associated with corneal neovascularization, retinal neovascularization, a disease associated with retinal/choroidal neovascularization, pathologic myopia, von Hippel-Lindau disease, histoplasmosis of the eye, FEVR, Coats' disease, Norrie Disease, OPPG, subconjunctival hemorrhage, rubeosis, ocular neovascular disease, neovascular glaucoma, RP, hypertensive retinopathy, retinal angiomatous proliferation, macular telangiectasia, iris neovascularization, intraocular neovascularization, retinal degeneration, CME, vasculitis, papilloedema, retinitis, conjunctivitis (including infectious conjunctivitis and non-infectious (e.g., allergic) conjunctivitis), Leber congenital amaurosis, uveitis (including infectious and non-infectious uveitis), choroiditis, ocular histoplasmosis, blepharitis, dry eye, traumatic eye injury, and Sjögren's disease; and wherein optionally

(iii) the ocular disorder is AMD, DME, DR, or RVO.

85. The pharmaceutical composition for use of claim 84(ii) or 84(iii), wherein the ocular disorder is AMD.

86. The pharmaceutical composition for use of any one of claims 84(ii), 84(iii) and 85, wherein the AMD is wet AMD.

87. The pharmaceutical composition for use of any one of claims 82-86, further comprising a second agent, wherein

(i) the second agent is selected from the group consisting of another antibody, an anti-angiogenic agent, a cytokine, a cytokine antagonist, a corticosteroid, an analgesic, and a compound that binds to a second biological molecule; wherein optionally

(ii) the anti-angiogenic agent is a VEGF antagonist; wherein optionally

(iii) the VEGF antagonist is an anti-VEGF antibody, an anti-VEGF receptor antibody, a soluble VEGF receptor fusion protein, an aptamer, an anti-VEGF DARPIn®, or a VEGFR tyrosine kinase inhibitor; wherein optionally

(iv) the anti-VEGF antibody is ranibizumab (LUCENTIS®), RTH-258, or a bispecific anti-VEGF antibody; wherein optionally

(v) the bispecific anti-VEGF antibody is an anti-VEGF/anti-Ang2 antibody; and wherein optionally

(vi) the anti-VEGF/anti-Ang2 antibody is RG-7716.

88. The pharmaceutical composition for use of claim 87(iii), wherein the soluble VEGF receptor fusion protein is aflibercept (EYLEA®), or

wherein the aptamer is pegaptanib (MACUGEN®), or

wherein the anti-VEGF DARPIn® is abicipar pegol, or

wherein the VEGFR tyrosine kinase inhibitor is selected from the group consisting of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474), 4-(4-fluoro-2-methylindol-5-ylloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171), vatalanib (PTK787), semaxaminib (SU5416), and SUTENT® (sunitinib).

89. The pharmaceutical composition for use of claim 87(i), wherein the second biological molecule is selected from the group consisting of IL-1 β ; IL-6; IL-6R; IL-13; IL-13R; PDGF; angiopoietin; angiopoietin 2; Tie2; S1P; integrins $\alpha\beta$ 3, $\alpha\beta$ 5, and α 5 β 1; betacellulin; apelin/APJ; erythropoietin; complement factor D; TNF α ; HtrA1; a VEGF receptor; ST-2 receptor; and a protein genetically linked to AMD risk; wherein optionally

(ii) the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR, or

(iii) the protein genetically linked to AMD risk is selected from the group consisting of complement pathway components C2, factor B, factor H, CFHR3, C3b, C5, C5a, and C3a; HtrA1; ARMS2; TIMP3; HLA; IL-8; CX3CR1; TLR3; TLR4; CETP; LIPC, COL10A1; and TNFRSF10A.

90. The pharmaceutical composition for use of any one of claims 87(i) and 89(ii)-89(iii), wherein the compound that binds a second biological molecule is an antibody or antigen-binding fragment thereof; wherein optionally

the antigen-binding antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

91. The antibody of any one of claims 1-16 for use in a method of reducing or inhibiting angiogenesis in a subject having a disorder associated with pathological angiogenesis.

92. The antibody of any one of claims 1-16 for use in a method of treating a disorder associated with pathological angiogenesis in a subject in need of such treatment.

93. The antibody of any one of claims 1-16 for use in a method of inhibiting vascular permeability in a subject suffering from a disorder associated with undesirable vascular permeability.

94. A composition comprising the antibody of any one of claims 1-16 for use in a method of reducing or inhibiting angiogenesis in a subject having a disorder associated with pathological angiogenesis.

95. A composition comprising the antibody of any one of claims 1-16 for use in a method of treating a disorder associated with pathological angiogenesis in a subject in need of such treatment.

96. A composition comprising the antibody of any one of claims 1-16 for use in a method of inhibiting vascular permeability in a subject suffering from a disorder associated with undesirable vascular permeability.

97. The fusion protein of any one of claims 65-70 for use in a method of reducing or inhibiting angiogenesis in a subject having a disorder associated with pathological angiogenesis.

98. The fusion protein of any one of claims 65-70 for use in a method of treating a disorder associated with pathological angiogenesis in a subject in need of such treatment.

99. A composition comprising the fusion protein of any one of claims 65-70 for use in a method of reducing or inhibiting angiogenesis in a subject having a disorder associated with pathological angiogenesis.

100. A composition comprising the fusion protein of any one of claims 65-70 for use in a method of treating a disorder associated with pathological angiogenesis in a subject in need of such treatment.