OPTIMIZED ANTIBODY COMPOSITIONS FOR TREATMENT OF OCULAR DISORDERS

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 22, 2018, is named 50474-160WO3_Sequence_Listing_3.22.18_ST25 and is 57,671 bytes in size.

FIELD OF THE INVENTION

The invention relates generally to antibody conjugates, cysteine engineered antibodies, compositions (e.g., pharmaceutical compositions) thereof, and methods of use thereof.

BACKGROUND OF THE INVENTION

Angiogenesis is a tightly-regulated process through which new blood vessels form from pre-existing blood vessels. Although angiogenesis is important during development to ensure adequate blood circulation, many disorders are associated with pathological angiogenesis, such as ocular disorders (e.g., age-related macular degeneration, AMD) and cell proliferative disorders (e.g., cancer). Vascular endothelial growth factor (VEGF) is a clinically-validated driver of angiogenesis, and neutralization of VEGF (e.g., using an anti-VEGF blocking antibody), can be used to treat disorders associated with pathological angiogenesis.

Current approaches for treatment of ocular disorders associated with pathological angiogenesis (e.g., AMD (e.g., wet AMD), diabetic macular edema (DME), diabetic retinopathy (DR), and retinal vein occlusion (RVO)) typically involve intravitreal injection of VEGF antagonists (e.g., the anti-VEGF Fab ranibizumab). Because the site of action of anti-VEGF Fabs is in the back of the eye at the retina, and also because Fabs can have relatively short residence time in the eye, maximum patient benefit from anti-VEGF Fabs is typically obtained by relatively frequent dosings (e.g., every four weeks, Q4W) by intravitreal injection. Long-acting delivery of anti-VEGF antibodies or antibody fragments (e.g., Fabs) for ocular disorders may be desired, at least in part, to decrease dosing frequency, which can improve patient convenience and compliance.

There remains a need for antibody compositions for long-acting delivery for treatment of ocular disorders (e.g., AMD (e.g., wet AMD), diabetic macular edema (DME), diabetic retinopathy (DR), and retinal vein occlusion (RVO)).

SUMMARY

The disclosure provides antibody conjugates that include monodisperse polymers (e.g., monodisperse hyaluronic acid (HA) polymers) covalently linked to antibodies (e.g., anti-VEGF antibodies), cysteine engineered antibodies that can be used, e.g., in preparing antibody conjugates, compositions that include antibody conjugates (e.g., pharmaceutical compositions), as well as methods of making and using the same, for example, for therapeutic uses.

In one aspect, the present disclosure refers to an antibody conjugate comprising (i) an antibody and (ii) a hyaluronic acid (HA) polymer covalently attached to the antibody, wherein the HA polymer has a polydispersity index (PDI) of 1.1 or lower. In some examples, the HA polymer has a PDI between 1.0 to 1.1. In some examples, the HA polymer has a PDI between 1.0 to about 1.05. In some examples, the HA polymer has a PDI between about 1.0001 to about 1.05. In some examples, the HA polymer has a PDI of about 1.001. In some examples, the HA polymer has a molecular weight of about 1 megadalton (MDa) or lower. In some examples, the HA polymer has a molecular weight between about 25 kDa and about 500 kDa. In some examples, the HA polymer has a molecular weight between about 100 kDa and about 250 kDa. In some examples, the HA polymer has a molecular weight between about 150 kDa and about 200 kDa. In some examples, the HA polymer is a linear HA polymer. In some examples, the antibody conjugate has a hydrodynamic radius between about 10 nm and about 60 nm. In some examples, the antibody conjugate has a hydrodynamic radius between about 25 nm and about 35 nm. In some examples, the hydrodynamic radius is about 20 nm to about 30 nm.

In some examples of the preceding aspect, the antibody conjugate has an ocular half-life that is increased relative to a reference antibody that is not covalently attached to the HA polymer. In some examples, the ocular half-life is increased at least about 2-fold relative to the reference antibody. In some examples, the ocular half-life is increased at least about 4-fold relative to the reference antibody. In some examples, the ocular half-life is a vitreal half-life. In some examples, the reference antibody is identical to the antibody of the antibody conjugate.

In some examples of the preceding aspect, the antibody specifically binds to a biological molecule selected from the group consisting of vascular endothelial growth factor (VEGF); 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. In some examples, the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR. In some examples, 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.

In some examples of the preceding aspect, the antibody specifically binds to VEGF. In some examples, 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 $GX_1TPX_2GGX_3X_4X_5YX_6DSVX_7X_8$ (SEQ ID NO: 2), wherein X_1 is Ile or His, X_2 is Ala or Arg, X_3 is Tyr or Lys, X_4 is Thr or Glu, X_5 is Arg, Tyr, Gln, or Glu, X_6 is Ala or Glu, X_7 is Lys or Glu, and X_8 is Gly or Glu; (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 $RASQX_1VSTAVA$ (SEQ ID NO: 4), wherein X_1 is Asp or Arg; (e) an HVR-L2 comprising the amino acid sequence of $X_1ASFLYS$ (SEQ ID NO: 5), wherein X_1 is Ser or Met; and (f) an HVR-L3 comprising the amino acid sequence of X_1QGYGX_2PFT (SEQ ID NO: 6), wherein X_1 is Gln, Asn, or Thr and X_2 is Ala, Asn, Gln, or Arg. In some examples, the antibody comprises the following six 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), GITPAGGYEYYADSVKG (SEQ ID NO: 21), or GITPAGGYEYYADSVEG (SEQ ID NO: 22); (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) or QQGYGNPFT (SEQ ID NO: 23).

In some examples of the above aspect, the antibody comprises the following six 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). In some examples, 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 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). In some examples, 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 GVPSRFSGSGSGTDFTLTISSLQPEDAATYYC (SEQ ID NO: 19); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20).

In some examples of the above aspect, the antibody comprises the following six 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 GITPAGGYEYYADSVEG (SEQ ID NO: 22); (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 QQGYGNPFT (SEQ ID NO: 23). In some examples, the antibody further comprises the following 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 GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 24); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20).

In some examples of the above aspect, the antibody comprises the following six 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 GITPAGGYEYYADSVEG (SEQ ID NO: 22); (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). In some examples, the antibody further comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17), DIQMTQSPESLSASVGDEVTITC (SEQ ID NO: 25), or DIQMTQSPSSLSASVGDEVTITC (SEQ ID NO: 26); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 18) or WYQQKPGEAPKLLIY (SEQ ID NO: 27); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISSLQPEDAATYYC (SEQ ID NO: 19) or GVPSRFSGSGSGTDFTLTIESLQPEDAATYYC (SEQ ID NO: 28); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1 comprising the amino acid sequence of EEQLVEEGGGLVQPGESLELSCAASGFEIS (SEQ ID NO: 29) or EEQLVEEGGGLVQPGESLRLSCAASGFEIS (SEQ ID NO: 52); (b) an FR-H2 comprising the amino acid sequence of WVRQEPGEGLEWVA (SEQ ID NO: 30); (c) an FR-H3 comprising the amino acid sequence of RFTISADTSENTAYLQMNELRAEDTAVYYCAR (SEQ ID NO: 31); and (d) an FR-H4 comprising the amino acid sequence of WGQGELVTVSS (SEQ ID NO: 32).

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 11, 40, or 42; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 12, 41, or 46; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, 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) or WVRQEPGKGLEWVA (SEQ ID NO: 39); (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). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 11. In some examples, the VL domain further comprises the following FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17) or DIQMTQSPSSLSASVGDRVTIDC (SEQ ID NO: 45); (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 GVPSRFSGSGSGTDFTLTISSLQPEDAATYYC (SEQ ID NO: 19), GVPSRFSGSGSGTDFTLTISSLQPEDSATYYC (SEQ ID NO: 44), or GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC (SEQ ID NO: 54); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20) or FGQGTKVEVK (SEQ ID NO: 55). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 12.

In some examples of the above aspect, 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.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 40 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 42 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 42 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 41.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 33 or 51; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 12, 34, 35, 36, 37, or 38; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the antibody further comprises the following FRs: (a) an FR-H1 comprising the amino acid sequence of EEQLVEEGGGLVQPGESLELSCAASGFEIS (SEQ ID NO: 29) or EEQLVEEGGGLVQPGESLRLSCAASGFEIS (SEQ ID NO: 52); (b) an FR-H2 comprising the amino acid sequence of WVRQEPGEGLEWVA (SEQ ID NO: 30); (c) an FR-H3 comprising the amino acid sequence of RFTISADTSENTAYLQMNELRAEDTAVYYCAR (SEQ ID NO: 31); and (d) an FR-H4 comprising the amino acid sequence of WGQGELVTVSS (SEQ ID NO: 32). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 33. In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 51. In some examples, the antibody further comprises the following FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17), DIQMTQSPESLSASVGDEVTITC (SEQ ID NO: 25), or DIQMTQSPSSLSASVGDEVTITC (SEQ ID NO: 26); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 18) or WYQQKPGEAPKLLIY (SEQ ID NO: 27); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISSLQPEDAATYYC (SEQ ID NO: 19), GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 24), or GVPSRFSGSGSGTDFTLTIESLQPEDAATYYC (SEQ ID NO: 28); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 34. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 35. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 36. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 37. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 12. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 38.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 38.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 34.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 35.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 36.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 37.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 51 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 38.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 51 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 35.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 51 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 37.

In some examples of the above aspect, the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 51 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12.

In some examples of the above aspect, 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.

In some examples of the above aspect, 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.

In some examples of any of the preceding aspects, the antibody is capable of inhibiting the binding of VEGF to a VEGF receptor. In some examples, the VEGF receptor is VEGF receptor 1 (Flt-1). In some examples, the VEGF receptor is VEGF receptor 2 (KDR).

In some examples of any of the preceding aspects, the antibody binds human VEGF (hVEGF) with a Kd of about 2 nM or lower. In some examples, the antibody binds hVEGF with a Kd between about 75 pM and about 2 nM. In some examples, the antibody binds hVEGF with a Kd between about 75 pM and about 600 pM. In some examples, the antibody binds hVEGF with a Kd between about 75 pM and about 500 pM. In some examples, the antibody binds hVEGF with a Kd of about 80 pM. In some examples, the antibody binds hVEGF with a Kd of about 60 pM.

In some examples of any of the preceding aspects, the antibody has a melting temperature (Tm) of greater than about 83.5°C. In some examples, the antibody has a Tm of about 85°C to about 91°C. In some examples, the antibody has a Tm of about 89°C.

In some examples of any of the preceding aspects, the antibody has an isoelectric point (pI) of lower than 8. In some examples, the antibody has a pI from about 5 to about 7. In some examples, the antibody has a pI of from about 5 to about 6.

In some examples of any of the preceding aspects, the antibody is monoclonal, human, humanized, or chimeric.

In some examples of any of the preceding aspects, the antibody is an antibody fragment that binds VEGF. In some examples, the antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments. In some examples, the antibody fragment is an Fab.

In some examples of any of the preceding aspects, the antibody is a monospecific antibody. In other examples of any of the preceding aspects, the antibody is a multispecific antibody. In some examples, the multispecific antibody is a bispecific antibody. In some examples, the bispecific antibody binds VEGF and a second biological molecule selected from the group consisting of interleukin 1β (IL-1β); 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 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 age-related macular degeneration (AMD) risk. In some examples, the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, membrane-bound VEGF-receptor (mbVEGFR), or soluble VEGF receptor (sVEGFR). In some examples, 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.

In some examples of any of the preceding aspects, the antibody is a cysteine engineered antibody. In some examples, the cysteine engineered antibody comprises a cysteine mutation in the heavy chain selected from the group consisting of HC-A118C, HC-A140C, and HC-L174C (EU numbering), or a cysteine mutation in the light chain selected from the group consisting of LC-K149C and LC-V205C (Kabat numbering). In some examples, the cysteine mutation in the heavy chain is HC-A118C (EU numbering). In some examples, the cysteine mutation in the heavy chain is HC-A140C (EU numbering). In some examples, the cysteine mutation in the heavy chain is HC-L174C (EU numbering). In some examples, the cysteine mutation in the light chain is LC-K149C (Kabat numbering). In some examples, the cysteine mutation in the light chain is LC-V205C (Kabat numbering). In some examples, the HA polymer is covalently attached to the antibody at the cysteine mutation.

In another aspect, the present disclosure refers to an antibody conjugate comprising (i) an antibody that specifically binds VEGF and (ii) an HA polymer covalently attached to the antibody, wherein the HA polymer has a PDI of 1.05, and 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.

In yet another aspect, the present disclosure refers to an antibody conjugate comprising (i) an antibody that specifically binds VEGF and (ii) an HA polymer covalently attached to the antibody, wherein the HA polymer has a PDI of 1.05, and wherein the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 or SEQ ID NO: 49 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 50.

In one example, any of the preceding antibody conjugates can be used as a medicament.

In another example, any of the preceding antibody conjugates can be used in the manufacture of a medicament for treating an ocular disorder in a subject. In one aspect, the present disclosure refers to use of any of the preceding antibody conjugates in the manufacture of a medicament for (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

In another example, any of the preceding antibody conjugates can be used in reducing or inhibiting angiogenesis in a subject having an ocular disorder.

In another example any of the preceding antibody conjugates can be used in treating an ocular disorder in a subject.

In one aspect, the present disclosure refers to any of the preceding antibody conjugates for use in (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

In some examples of any of the preceding aspects, 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 retinopathy (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 (CRVO) and branched (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. In some examples, the ocular disorder is AMD, DME, DR, or RVO. In some examples, the ocular disorder is AMD. In some examples, the AMD is wet AMD. In some examples, the ocular disorder is DME.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising any of the antibody conjugates described herein and a pharmaceutically acceptable carrier, excipient, or diluent. In some examples, the pharmaceutical composition further comprises a second agent, wherein the second agent is selected from the group consisting of an antibody, an anti-angiogenic agent, a cytokine, a cytokine antagonist, a corticosteroid, an analgesic, and a compound that binds to a second biological molecule. In some examples, the anti-angiogenic agent is a VEGF antagonist. In some examples, 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. In some examples, the anti-VEGF antibody is ranibizumab (LUCENTIS®), RTH-258, or a bispecific anti-VEGF antibody. In some examples, the bispecific anti-VEGF antibody is an anti-VEGF/anti-Ang2 antibody. In some examples, the anti-VEGF/anti-Ang2 antibody is RG-7716. In some examples, the soluble VEGF receptor fusion protein is aflibercept (EYLEA®). In some examples, the aptamer is pegaptanib (MACUGEN®). In some examples, the anti-VEGF DARPin® is abicipar pegol. In some examples, 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). In some examples, 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. In some examples, the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR. In some examples, 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. In some examples, the compound that binds a second biological molecule is an antibody or antigen-binding fragment thereof. In some examples, the antigen-binding antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments. In some examples, the antigen-binding antibody fragment is an Fab.

In one example, any of the preceding pharmaceutical compositions can be used as a medicament.

In another example, any of the preceding pharmaceutical compositions can be used in the manufacture of a medicament for treating an ocular disorder in a subject. In one aspect, the present disclosure refers to use of any of the preceding pharmaceutical compositions in the manufacture of a medicament for (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

In another example, any of the preceding pharmaceutical compositions can be used in reducing or inhibiting angiogenesis in a subject having an ocular disorder.

In another example, any of the preceding pharmaceutical compositions can be used in treating an ocular disorder in a subject.

In one aspect, the present disclosure refers to any of the preceding pharmaceutical compositions for use in (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

In some examples of any of the preceding aspects, 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 retinopathy (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 (CRVO) and branched (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. In some examples, the ocular disorder is AMD, DME, DR, or RVO. In some examples, the ocular disorder is AMD. In some examples, the AMD is wet AMD. In some examples, the ocular disorder is DME.

In another example, the disclosure features a method of reducing or inhibiting angiogenesis in a subject having an ocular disorder, comprising administering to the subject an effective amount of any of the antibody conjugates described herein or any of the pharmaceutical compositions described herein, thereby reducing or inhibiting angiogenesis in the subject.

In another example, the disclosure features a method of treating an ocular disorder, the method comprising administering an effective amount of any of the antibody conjugates described herein or any of the pharmaceutical compositions described herein to a subject in need of such treatment.

In some examples of any of the preceding aspects, 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 retinopathy (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 (CRVO) and branched (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. In some examples, the ocular disorder is AMD, DME, DR, or RVO. In some examples, the ocular disorder is AMD. In some examples, the AMD is wet AMD. In some examples, the ocular disorder is DME.

In some examples of any of the preceding aspects, the method further comprises administering to the subject an effective amount of a second agent, wherein the second agent is selected from the group consisting of an antibody, an anti-angiogenic agent, a cytokine, a cytokine antagonist, a corticosteroid, an analgesic, and a compound that binds to a second biological molecule. In some examples, the anti-angiogenic agent is a VEGF antagonist. In some examples, 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. In some examples, the anti-VEGF antibody is ranibizumab (LUCENTIS®), RTH-258, or a bispecific anti-VEGF antibody. In some examples, the bispecific anti-VEGF antibody is an anti-VEGF/anti-Ang2 antibody. In some examples, the anti-VEGF/anti-Ang2 antibody is RG-7716. In some examples, the soluble VEGF receptor fusion protein is aflibercept (EYLEA®). In some examples, the aptamer is pegaptanib (MACUGEN®). In some examples, the anti-VEGF DARPin® is abicipar pegol. In some examples, 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). In some examples, 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. In some examples, the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR. In some examples, 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. In some examples, the compound that binds a second biological molecule is an antibody or antigen-binding fragment thereof. In some examples, the antigen-binding antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

In some examples of any of the preceding aspects, the antibody conjugate or the pharmaceutical composition is 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. In some examples, the antibody conjugate or the pharmaceutical composition is administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonly, superchoroidally, or topically. In some examples, the antibody conjugate or the pharmaceutical composition is administered intravitreally by injection. In some examples, the antibody conjugate or the pharmaceutical composition is administered topically by eye drop or ointment. In some examples, the antibody conjugate or the pharmaceutical composition is administered by a port delivery device.

In some examples of any of the preceding aspects, the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A is a graph showing a population distribution of molecular weights (in terms of molar mass) in a representative sample of 200 kDa HA.

FIG. 1B is a graph showing a population distribution of the number of maleimides on a 200 kDa HA chain resulting from a Monte Carlo simulation of stochastic modification with each acid group having a 5% chance of modification.

FIG. 1C is a graph showing the polydispersity of 40 kDa, 200 kDa, and 600 kDa HA polymers. The table below the graph shows the number-average molecular weight (Mn), weight-average molecular weight (Mw), polydispersity index (PDI), and molecular weight (MW) range (in terms of Mw) for the indicated samples.

FIG. 2 is a series of graphs showing that HA-G6.31.AARR conjugates have differences in physical stability under physiologically relevant stress conditions as assessed by size exclusion chromatography (SEC) in-line with refractive index (RI) and multi-angle light scattering (MALS) detectors (SEC-RI-MALS). The series labels refer to the HA backbone molecular weight (40 kDa ("40K"); 200 kDa ("200K"); and 600 kDa ("600K") and Fab loading level.

CLAIMS

What is claimed is:

1. An antibody conjugate comprising (i) an antibody and (ii) a hyaluronic acid (HA) polymer covalently attached to the antibody, wherein the HA polymer has a polydispersity index (PDI) of 1.1 or lower.

2. The antibody conjugate of claim 1, wherein the HA polymer has a PDI between 1.0 to 1.1, optionally wherein the HA polymer has a PDI between 1.0 to about 1.07, further optionally wherein the HA polymer has a PDI between about 1.0001 to about 1.06, further optionally wherein the HA polymer has a PDI of about 1.05.

3. The antibody conjugate of claim 1 or 2, wherein the HA polymer has a PDI of 1.05.

4. The antibody conjugate of any one of claims 1-3, wherein:

(i) the HA polymer has a molecular weight of about 1 megadalton (MDa) or lower, optionally wherein the HA polymer has a molecular weight between about 25 kDa and about 500 kDa, further optionally wherein the HA polymer has a molecular weight between about 100 kDa and about 250 kDa, further optionally wherein the HA polymer has a molecular weight between about 150 kDa and about 200 kDa;

(ii) the HA polymer is a linear HA polymer;

(iii) the antibody conjugate has a hydrodynamic radius between about 10 nm and about 60 nm, optionally wherein the antibody conjugate has a hydrodynamic radius between about 25 nm and about 35 nm, further optionally wherein the hydrodynamic radius is about 20 nm to about 30 nm;

(iv) the antibody conjugate has an ocular half-life that is increased relative to a reference antibody that is not covalently attached to the HA polymer, optionally wherein the ocular half-life is increased at least about 2-fold or at least about 4-fold relative to the reference antibody, further optionally wherein the ocular half-life is a vitreal half-life, further optionally wherein the reference antibody is identical to the antibody of the antibody conjugate; and/or

(v) the antibody specifically binds to a biological molecule selected from the group consisting of vascular endothelial growth factor (VEGF); 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, optionally wherein the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR; ST-2 receptor; and a protein genetically linked to AMD risk, optionally wherein 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.

5. The antibody conjugate of any one of claims 1-4, wherein the antibody specifically binds to VEGF.

6. The antibody conjugate of claim 5, 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 $GX_1TPX_2GGX_3X_4X_5YX_6DSVX_7X_8$ (SEQ ID NO: 2), wherein X_1 is Ile or His, X_2 is Ala or Arg, X_3 is Tyr or Lys, X_4 is Thr or Glu, X_5 is Arg, Tyr, Gln, or Glu, X_6 is Ala or Glu, X_7 is Lys or Glu, and X_8 is Gly or Glu;

(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 $RASQX_1VSTAVA$ (SEQ ID NO: 4), wherein X_1 is Asp or Arg;

(e) an HVR-L2 comprising the amino acid sequence of $X_1ASFLYS$ (SEQ ID NO: 5), wherein X_1 is Ser or Met; and

(f) an HVR-L3 comprising the amino acid sequence of X_1QGYGX_2PFT (SEQ ID NO: 6), wherein X_1 is Gln, Asn, or Thr and X_2 is Ala, Asn, Gln, or Arg.

7. The antibody conjugate of claim 6, wherein (I) the antibody comprises the following six 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), GITPAGGYEYYADSVKG (SEQ ID NO: 21), or GITPAGGYEYYADSVEG (SEQ ID NO: 22);

(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) or QQGYGNPFT (SEQ ID NO: 23); wherein optionally (II) the antibody is selected from a group consisting of

(i) an antibody comprising the following six 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);

(ii) an antibody comprising the following six 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 GITPAGGYEYYADSVEG (SEQ ID NO: 22);

(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 QQGYGNPFT (SEQ ID NO: 23); and
(iii) an antibody comprising the following six 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 GITPAGGYEYYADSVEG (SEQ ID NO: 22);
(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).

8. The antibody conjugate of any one of claims 5-7(I) and 7(II)(i), 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 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 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 GVPSRFSGSGSGTDFTLTISSLQPEDAATYYC (SEQ ID NO: 19); and
(d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20).

9. The antibody conjugate of claim 7(II)(ii), wherein the antibody further comprises the following 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 GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 24); and
(d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20).

10. The antibody conjugate of claim 7(II)(iii), wherein the antibody further comprises the following VL domain FRs:

(a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17), DIQMTQSPESLSASVGDEVTITC (SEQ ID NO: 25), or DIQMTQSPSSLSASVGDEVTITC (SEQ ID NO: 26);

(b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 18) or WYQQKPGEAPKLLIY (SEQ ID NO: 27);

(c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISSLQPEDAATYYC (SEQ ID NO: 19) or GVPSRFSGSGSGTDFTLTIESLQPEDAATYYC (SEQ ID NO: 28); and

(d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20).

11. The antibody conjugate of any one of claims 7(II)(ii)-7(II)(iii), 9, and 10, wherein the antibody further comprises the following VH domain FRs:

(a) an FR-H1 comprising the amino acid sequence of EEQLVEEGGGLVQPGESLELSCAASGFEIS (SEQ ID NO: 29) or EEQLVEEGGGLVQPGESLRLSCAASGFEIS (SEQ ID NO: 52);

(b) an FR-H2 comprising the amino acid sequence of WVRQEPGEGLEWVA (SEQ ID NO: 30);

(c) an FR-H3 comprising the amino acid sequence of RFTISADTSENTAYLQMNELRAEDTAVYYCAR (SEQ ID NO: 31); and

(d) an FR-H4 comprising the amino acid sequence of WGQGELVTVSS (SEQ ID NO: 32).

12. The antibody conjugate of claim 5, wherein:

(I) the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 11, 40, or 42; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 12, 41, or 46; or (c) a VH domain as in (a) and a VL domain as in (b); optionally 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) or WVRQEPGKGLEWVA (SEQ ID NO: 39);

(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); further optionally wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 11; further optionally wherein the VL domain further comprises the following FRs:

(a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17) or DIQMTQSPSSLSASVGDRVTIDC (SEQ ID NO: 45);

(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 GVPSRFSGSGSGTDFTLTISSLQPEDAATYYC (SEQ ID NO: 19) GVPSRFSGSGSGTDFTLTISSLQPEDSATYYC (SEQ ID NO: 44), or GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC (SEQ ID NO: 54); and

(d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20) or FGQGTKVEVK (SEQ ID NO: 55); further optionally wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 12; further optionally wherein:

(i) 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;

(ii) the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 40 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12;

(iii) the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 42 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12; or

(iv) the antibody comprises (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 42 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 41; or

(II) the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 33 or 51; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 12, 34, 35, 36, 37, or 38; or (c) a VH domain as in (a) and a VL domain as in (b); optionally wherein the antibody further comprises the following FRs:

(a) an FR-H1 comprising the amino acid sequence of EEQLVEEGGGLVQPGESLELSCAASGFEIS (SEQ ID NO: 29) or EEQLVEEGGGLVQPGESLRLSCAASGFEIS (SEQ ID NO: 52);

(b) an FR-H2 comprising the amino acid sequence of WVRQEPGEGLEWVA (SEQ ID NO: 30);

(c) an FR-H3 comprising the amino acid sequence of RFTISADTSENTAYLQMNELRAEDTAVYYCAR (SEQ ID NO: 31); and

(d) an FR-H4 comprising the amino acid sequence of WGQGELVTVSS (SEQ ID NO: 32); further optionally wherein

the VH domain comprises the amino acid sequence of SEQ ID NO: 33 or SEQ ID NO: 51; further optionally wherein the antibody further comprises the following FRs:

(a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 17), DIQMTQSPESLSASVGDEVTITC (SEQ ID NO: 25), or DIQMTQSPSSLSASVGDEVTITC (SEQ ID NO: 26);

(b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 18) or WYQQKPGEAPKLLIY (SEQ ID NO: 27);

(c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISSLQPEDAATYYC (SEQ ID NO: 19),

GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 24), or
GVPSRFSGSGSGTDFTLTIESLQPEDAATYYC (SEQ ID NO: 28); and

(d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 20); further optionally wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 12, or SEQ ID NO: 38;

further optionally wherein the antibody comprises:

(i) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 38;

(ii) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 34;

(iii) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 35;

(iv) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 36;

(v) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 37;

(vi) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 33 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12;

(vii) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 51 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 38;

(viii) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 51 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 35;

(ix) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 51 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 37;

(x) (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 51 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 12;

(xi) (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; or

(xii) (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.

13. The antibody conjugate of any one of claims 5-12, wherein:

(i) the antibody is capable of inhibiting the binding of VEGF to a VEGF receptor, optionally wherein the VEGF receptor is VEGF receptor 1 (Flt-1) or VEGF receptor 2 (KDR);

(ii) the antibody binds human VEGF (hVEGF) with a Kd of about 2 nM or lower, optionally wherein the antibody binds hVEGF with a Kd between about 75 pM and about 2 nM, further optionally wherein the antibody binds hVEGF with a Kd between about 75 pM and about 600 pM, further optionally wherein the

antibody binds hVEGF with a Kd between about 75 pM and about 500 pM, further optionally wherein the antibody binds hVEGF with a Kd of about 60 pM;

(iii) the antibody has a melting temperature (Tm) of greater than about 83.5°C, optionally wherein the antibody has a Tm of about 85°C to about 91°C, further optionally wherein the antibody has a Tm of about 89°C; and/or

(iv) the antibody has an isoelectric point (pI) of lower than 8, optionally wherein the antibody has a pI of from about 5 to about 7, further optionally wherein the antibody has a pI of from about 5 to about 6.

14. The antibody conjugate of any one of claims 1-13, wherein:

(i) the antibody is monoclonal, human, humanized, or chimeric;

(ii) the antibody is an antigen-binding antibody fragment, optionally wherein the antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments, further optionally wherein the antibody fragment is an Fab;

(iii) the antibody is a monospecific antibody;

(iv) the antibody is a multispecific antibody, optionally wherein the multispecific antibody is a bispecific antibody, further optionally wherein the bispecific antibody binds VEGF and a second biological molecule 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, optionally wherein the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR; ST-2 receptor; and a protein genetically linked to AMD risk, optionally wherein 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; or

(v) the antibody is a cysteine engineered antibody, optionally wherein the cysteine engineered antibody comprises a cysteine mutation in the heavy chain selected from the group consisting of HC-A118C, HC-A140C, and HC-L174C (EU numbering), or a cysteine mutation in the light chain selected from the group consisting of LC-K149C and LC-V205C (Kabat numbering), further optionally wherein the HA polymer is covalently attached to the antibody at the cysteine mutation.

15. An antibody conjugate comprising (i) an antibody that specifically binds VEGF and (ii) an HA polymer covalently attached to the antibody, wherein the HA polymer has a PDI of 1.05, and 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.

16. An antibody conjugate comprising (i) an antibody that specifically binds VEGF and (ii) an HA polymer covalently attached to the antibody, wherein the HA polymer has a PDI of 1.05, and wherein the

antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 or SEQ ID NO: 49 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 50.

17. The antibody conjugate of any one of claims 1-16 for use in (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

18. The antibody conjugate for use of claim 17, 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 retinopathy (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 (CRVO) and branched (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, optionally wherein the ocular disorder is AMD, DME, DR, or RVO, further optionally wherein the AMD is wet AMD.

19. A pharmaceutical composition comprising the antibody conjugate of any one of claims 1-16 and a pharmaceutically acceptable carrier, excipient, or diluent.

20. The pharmaceutical composition of claim 19, further comprising a second agent, wherein the second agent is selected from the group consisting of an antibody, an anti-angiogenic agent, a cytokine, a cytokine antagonist, a corticosteroid, an analgesic, and a compound that binds to a second biological molecule, optionally wherein:

(i) the anti-angiogenic agent is a VEGF antagonist, optionally 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, further optionally wherein the anti-VEGF antibody is ranibizumab (LUCENTIS®), RTH-258, or a bispecific anti-VEGF antibody, further optionally wherein the bispecific anti-VEGF antibody is an anti-VEGF/anti-Ang2 antibody, further optionally wherein the anti-VEGF/anti-Ang2 antibody is RG-7716, further optionally wherein the soluble VEGF receptor

fusion protein is aflibercept (EYLEA®), further optionally wherein the aptamer is pegaptanib (MACUGEN®), further optionally wherein the anti-VEGF DARPin® is abicipar pegol, further optionally 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); or

(ii) 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, optionally wherein the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR; ST-2 receptor; and a protein genetically linked to AMD risk, optionally wherein 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, further optionally the compound that binds a second biological molecule is an antibody or antigen-binding fragment thereof, further optionally wherein the antigen-binding antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

21. The pharmaceutical composition of claim 19 or 20 for use in (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

22. The pharmaceutical composition for use of claim 21, 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 proliferative DR (PDR), NPDR, and high-altitude DR), other ischemia-related retinopathies, ROP, RVO (including central (CRVO) and branched (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, optionally wherein the ocular disorder is AMD, DME, DR, or RVO, further optionally wherein the AMD is wet AMD.

23. Use of the antibody conjugate of any one of claims 1-16 in the manufacture of a medicament for (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

24. The use of claim 23, 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 proliferative DR (PDR), NPDR, and high-altitude DR), other ischemia-related retinopathies, ROP, RVO (including central (CRVO) and branched (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, optionally wherein the ocular disorder is AMD, DME, DR, or RVO, further optionally wherein the AMD is wet AMD.

25. Use of the pharmaceutical composition of claim 19 or 20 in the manufacture of a medicament for (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

26. The use of claim 25, 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 proliferative DR (PDR), NPDR, and high-altitude DR), other ischemia-related retinopathies, ROP, RVO (including central (CRVO) and branched (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, optionally wherein the ocular disorder is AMD, DME, DR, or RVO, further optionally wherein the AMD is wet AMD.