In one ~~aspect~~example, 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 one aspect, the present disclosure refers to an antibody conjugate comprising (i) an antibody that specifically binds to vascular endothelial growth factor (VEGF) and (ii) a hyaluronic acid (HA) polymer covalently attached to the antibody, wherein the HA polymer has a polydispersity index (PDI) between 1.0 and 1.1, wherein the HA polymer has a molecular weight of 1 megadalton (MDa) or lower, and wherein 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 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

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 ~~example~~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 one ~~aspect~~example, the present disclosure refers to a pharmaceutical composition comprising any of the antibody conjugates described herein 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, 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~~example, the present disclosure refers to use of a pharmaceutical composition comprising any of the antibody conjugates described herein 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~~example, 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.

CLAIMS

What is claimed is:

1. An antibody conjugate comprising (i) an antibody that specifically binds to vascular endothelial growth factor (VEGF) and (ii) a hyaluronic acid (HA) polymer covalently attached to the antibody, wherein the HA polymer has a polydispersity index (PDI) ~~of~~ between 1.0 and 1.1 ~~or lower~~, wherein the HA polymer has a molecular weight of 1 megadalton (MDa) or lower, and wherein 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).

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~~ and 1.07~~, further optionally wherein the HA polymer has a PDI between 1.0001 to 1.06, further optionally wherein the HA polymer has a PDI of 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 1 megadalton (MDa) or lower, optionally~~ wherein the HA polymer has a molecular weight between 25 kDa and 500 kDa, ~~further~~ optionally wherein the HA polymer has a molecular weight between 100 kDa and 250 kDa, further optionally wherein the HA polymer has a molecular weight between 150 kDa and 200 kDa~~;~~.

5. The antibody conjugate of any one of claims 1-4, wherein ~~(ii)~~ the HA polymer is a linear HA polymer.~~;~~

6. The antibody conjugate of any one of claims 1-5, wherein ~~(iii)~~ the antibody conjugate has a hydrodynamic radius between 10 nm and 60 nm, optionally wherein the antibody conjugate has a hydrodynamic radius between 25 nm and 35 nm, further optionally wherein the hydrodynamic radius is 20 nm to 30 nm~~;~~.

7. The antibody conjugate of any one of claims 1-6, wherein ~~(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 2-fold or at least 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 (l) 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)1-7, 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).;

9. The antibody conjugate of any one of claims 1-8, 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).

1210. The antibody conjugate of claim 5 any one of claims 1-9, wherein 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 and (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.

13. The antibody conjugate of claim 12, 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).

1411. The antibody conjugate of claim 12 10or 13, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 11.

15. The antibody conjugate of any one of claims 12-14, 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).

1612. The antibody conjugate of claim 10 or 11any one of claims 12-15, wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 12.

17. The antibody conjugate of any one of claims 12-16, 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.

18. The antibody conjugate of claim 12, wherein 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 and (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.

1913. The antibody conjugate of claim 1811 or 12, 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: 48 or SEQ ID NO: 49 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 50.

~~20~~14. The antibody conjugate of any one of claims ~~5-19~~1-13, 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 2 nM or lower, optionally wherein the antibody binds hVEGF with a Kd between 75 pM and 2 nM, further optionally wherein the antibody binds hVEGF with a Kd between 75 pM and 600 pM, further optionally wherein the antibody binds hVEGF with a Kd between 75 pM and 500 pM, further optionally wherein the antibody binds hVEGF with a Kd of 60 pM;

(iii) the antibody has a melting temperature (Tm) of greater than 83.5°C, optionally wherein the antibody has a Tm of 85°C to 91°C, further optionally wherein the antibody has a Tm of 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 5 to 7, further optionally wherein the antibody has a pI of from 5 to 6.

~~21~~15. The antibody conjugate of any one of claims 1-~~20~~14, wherein~~:~~

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

16. The antibody conjugate of any one of claims 1-14, wherein~~(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.

17. The antibody conjugate of claim 16, ~~further optionally~~ wherein the antibody fragment is an Fab or Fab-C.~~;~~

18. The antibody conjugate of any one of claims 1-14, wherein ~~(iii)~~ the antibody is a monospecific antibody~~;~~.

19. The antibody conjugate of any one of claims 1-14, wherein ~~(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~~.

20. The antibody conjugate of any one of claims 1-14, wherein ~~(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.

~~22~~21. 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.

~~23~~22. 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.

~~24~~23. The antibody conjugate of any one of claims ~~5-20, 22, and 23~~1-22 for use in (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.

~~25~~24. The antibody conjugate for use of claim ~~24~~23, 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.

25. The antibody conjugate for use of claim 24, ~~optionally~~ wherein the ocular disorder is AMD, DME, DR, or RVO~~, further optionally wherein the AMD is wet AMD~~.

26. A pharmaceutical composition comprising the antibody conjugate of any one of claims 1-~~23~~ 22 and a pharmaceutically acceptable carrier, excipient, or diluent.

27. The pharmaceutical composition of claim 26, 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.

~~28. A pharmaceutical composition comprising the antibody conjugate of any one of claims 5-20, 22, and 23 for use in (i) treating an ocular disorder in a subject or (ii) reducing or inhibiting angiogenesis in a subject having an ocular disorder.~~

~~29. The pharmaceutical composition for use of claim 28, 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.~~

~~30~~28. Use of the antibody conjugate of any one of claims ~~5-20, 22, and 23~~1-22 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.

~~31~~29. The use of claim ~~30~~28, 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.

30. The use of claim 29, ~~optionally~~ wherein the ocular disorder is AMD, DME, DR, or RVO~~, further optionally wherein the AMD is wet AMD~~.

~~32. Use of a pharmaceutical composition comprising the antibody conjugate of any one of claims 5-20, 22, and 23 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.~~

~~33. The use of claim 32, 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.~~