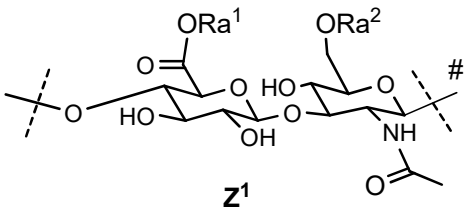
WHAT IS CLAIMED IS:

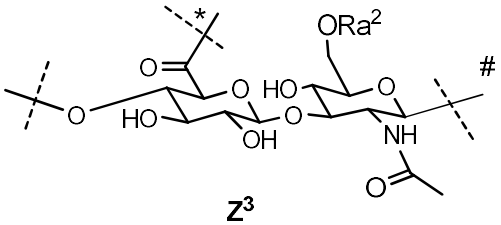
1. A cross-linked HA drug conjugate comprising a plurality of hyaluronic acid polymers 2A and a plurality of hyaluronic acid polymers 2B, wherein:

each 2A comprises a plurality of linearly connected units, the units consisting essentially of:



Z1

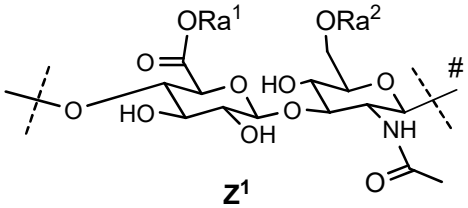
; and



Z3

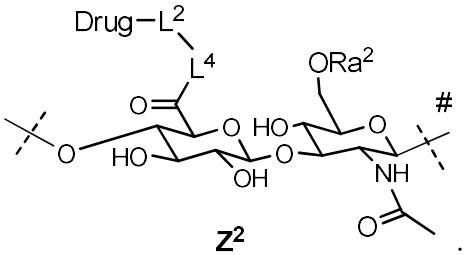
;

each 2B comprises a plurality of linearly connected units, the units consisting essentially of:



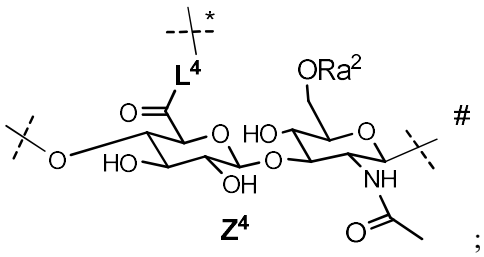
Z1

;



Z2

; and



Z4

;

wherein

an unmarked dashed line indicate a point of attachment to an adjacent unit at a dashed line marked with #, or to a hydrogen,

a dashed line marked with # indicate a point of attachment to an adjacent unit at an unmarked dashed line, or to a hydroxyl; and

a dashed line marked marked with * indicates a point of cross-linking attachment between a unit Z^3 of 2A and a unit Z^4 of 2B, such that at least one 2A is cross-linked to at least one 2B;

Drug is a therapeutic agent;

Ra^1 and Ra^2 are each independently is hydrogen; C_{1-4} alkyl; an alkali metal ion, an ammonium ion, or an alkaline earth metal ion;

L^2 is a reversible prodrug linker;

L^4 is an optionally biodegradable spacer and may be the same or different in Z^2 and Z^4;

2A comprises a total of s units wherein s is from 25 to 2500, wherein;

the number of Z^1 units in 2A is from about 0.8s to about 0.99s, and

the number of Z^3 units is from about 0.1s to about 0.01s;

2B comprising a total of t units wherein t is from 25 to 2500, wherein;

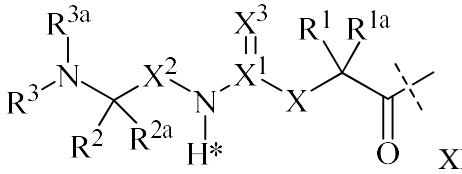
the number of Z^1 units in 2B is from about 0.75t to about 0.94t;

the combined number of Z^2 and Z^4 units is from about 0.14t to about 0.06t;

the number of Z^2 units is at least 0.01t; and

the number of Z^4 units is at least 0.01t.

2. The hydrogel conjugate of claim 1, wherein the reversible prodrug linker L^2 coupling the drug to spacer L^4 is of formula XIIa



XIIa

wherein:

the dashed line indicates the attachment to a nitrogen of a drug compound (not shown) by forming an amide bond;

-X- is $-C(R^4R^{4a})-$; $-N(R^4)-$; -O-; $-C(R^4R^{4a})-C(R^5R^{5a})-$; $-C(R^5R^{5a})-C(R^4R^{4a})-$; $-C(R^4R^{4a})-N(R^6)-$; $-N(R^6)-C(R^4R^{4a})-$; $-C(R^4R^{4a})-O-$; $-O-C(R^4R^{4a})-$; or $-C(R^7R^{7a})-$;

X^1 is C; or S(O);

$-X^2-$ is $-C(R^8R^{8a})-$; or $-C(R^8R^{8a})-C(R^9R^{9a})-$;

$=X^3$ is =O; =S; or =N-CN;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^8$, $-R^{8a}$, $-R^9$, $-R^{9a}$ are independently selected from the group consisting of -H; and C_{1-6} alkyl;

$-R^3$, $-R^{3a}$ are independently selected from the group consisting of -H; and C_{1-6} alkyl, provided that in case one of $-R^3$, $-R^{3a}$ or both are other than -H they are connected to N to which they are attached through an SP^3-hybridized carbon atom;

$-R^7$ is $-N(R^{10}R^{10a})$; or $-NR^{10}-(C=O)-R^{11}$;

$-R^{7a}$, $-R^{10}$, $-R^{10a}$, $-R^{11}$ are independently of each other -H; or C_{1-10} alkyl;

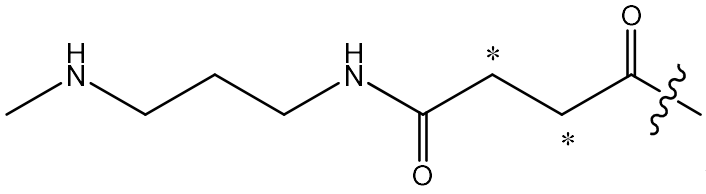
optionally, one or more of the pairs $-R^{1a}/-R^{4a}$, $-R^{1a}/-R^{5a}$, $-R^{1a}/-R^{7a}$, $-R^{4a}/-R^{5a}$, $-R^{8a}/-R^{9a}$ form a chemical bond;

optionally, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, $-R^4/-R^{4a}$, $-R^5/-R^{5a}$, $-R^8/-R^{8a}$,

-R^9/-R^{9a} are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl; or 3- to 10-membered heterocyclyl;
optionally, one or more of the pairs -R^1/-R^4, -R^1/-R^5, -R^1/-R^6, -R^1/-R^{7a}, -R^4/-R^5, -R^4/-R^6, -R^8/-R^9, -R^2/-R^3 are joined together with the atoms to which they are attached to form a ring A;
optionally, R^3/R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;
Ring A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and
wherein the group of formula XIIa is substituted with -L^4 provided that the hydrogen marked with the asterisk in formula (XIIa) is not replaced by -L^4 or other substituent;
wherein -L^4- is a single chemical bond or a spacer moiety as defined herein..

3. The hydrogel conjugate of claim 2, wherein:
X^3 is =O;
-R^1 and -R^{1a} are hydrogen;
-R^3 is methyl and R^{3a} is hydrogen; and
X is -C(R^7R^{7a})-; with R^7 being NR^{10}-(C=O)-R^{11}.

4. The hydrogel conjugate of any of claim1 or 2 wherein the reversible prodrug linker L^2 is of the formula VIIa(i):

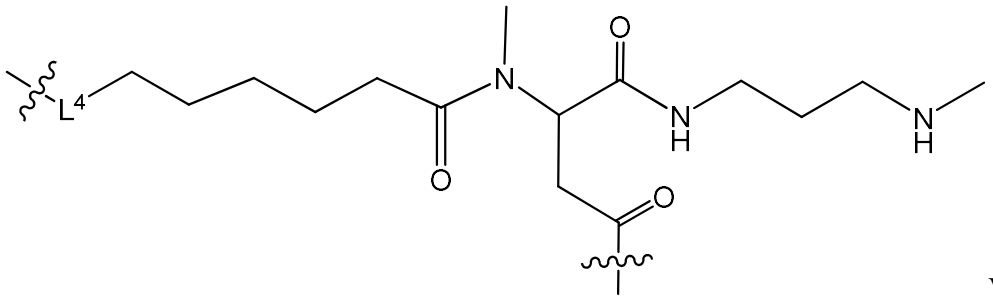


VIIa(i)

wherein:

each asterisk represents an independent site of attachment to the spacer L^4.

5. The hydrogel conjugate of any of claims 1 through 4 wherein the reversible prodrug linker L^2 together with spacer L^4 is of the formula VIIc:



VIIc

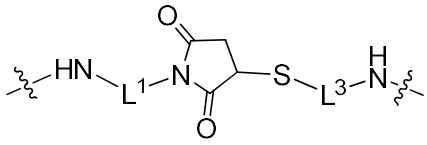
wherein:

the right-most wavy line represents the point of attachment to the nitrogen atom of Drug; and

the left-most wavy line represents the point of attachment to a unit Z^2 of hyaluronic acid 2B.

6. The hydrogel conjugate of any of claims 1 through 5 wherein:

the spacer L^4 connecting hyaluronic acid polymer 2A to hylauronic acid polymer 2B is of the formula:

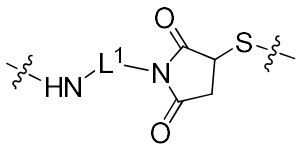


wherein:

the right-most wavy line represents the point of attachement to a unit Z^3 on hyaluronic acid polymer 2A; and

the left-most wavy line represents the point of attachment to a unit Z^4 on hyaluronic acid polymer 2B;

the spacer L_4 joining reversible prodrug linker L^2 to hyaluronic acid polymer 2B is of the formula



wherein:

the right-most wavy line represents the point of attachement to L^2; and

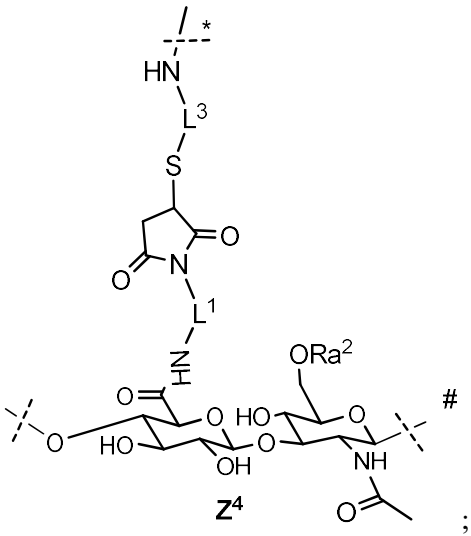
the left-most wavy line represents the point of attachment to a unit Z^2 on hyaluronic acid polymer 2B;

wherein:

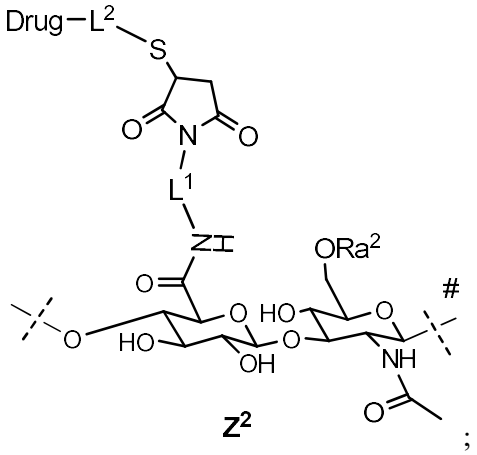
L^1 is a spacer; and

L^3 is abiodegradable spacer.

7. The hydrogel conjugate of any of claims 1 through 6, wherein:

unit Z^4 is 

Z^4 ; and

unit Z^2 is 

Z^2 ;

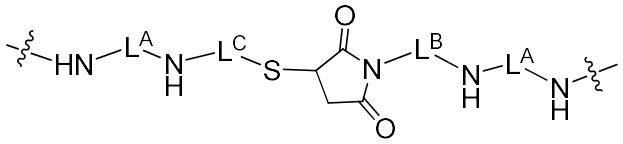
wherein:

L^1 is a spacer;

L^3 is abiodegradable spacer; and

2A, 2B, Drug, R^{a1}, R^{a2}, R^{a3}, R^{a4}, L_2, Z^1, Z^2, Z^3 and Z^4 are as recited in claim 1.

8. The hydrogel conjugate of any of claims 1 through 5 wherein the spacer L^4 connecting hyaluronic acid polymer 2A to Hylauronic acid polymer 2B is of the formula:

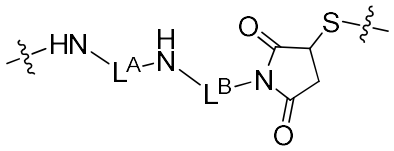


wherein:

the right-most wavy line represents the point of attachement to a unit Z^3 on hyaluronic acid polymer 2B; and

the left-most wavy line represents the point of attachment to a unit Z^4 on hyaluronic acid polymer 2A;

and the spacer L_4 joining reversible prodrug linker L^2 to hyaluronic acid polymer 2A is of the formula



wherein:

the right-most wavy line represents the point of attachement to L^2; and

the left-most wavy line represents the point of attachment to a unit Z^2 on hyaluronic acid polymer 2B;

wherein:

L^A is a spacer;

L^B is a spacer; and

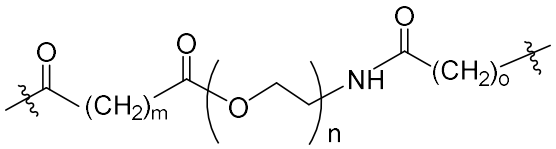
L^C is a biodegradable spacer.

9. The hydrogel conjugate of claim 8, wherein L^A is optionally substituted and/or optionally interrupted C_{1-10} alkylene.

10. The hydrogel conjugate of claim 8 or 9, wherein L^A is linear C_{2-4} alkylene.

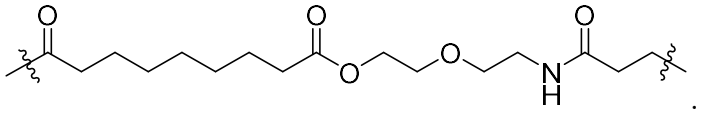
11. The hydrogel conjugate of any of claims 8-10, wherein L^B is linear -(O)-C_{1-5} alkylene.

12. The hydrogel conjugate of any of claims 8-11, wherein L^C is:



wherein m is from 0 to 10, n is from 1 to 4, and o is from 1 to 4.

13. The hydrogel conjugate of any of claims 8-11, wherein L^C is:



14. The hydrogel conjugate ofany of claims 8-13, wherein the drug is an antibody.

15. The hydrogel conjugate of claim 14, wherein the antibody is a VEGF antagonist.

16. The hydrogel conjugate of claim 15, wherein the antibody is an anti-VEGF antibody fragment.

17. The hydrogel conjugate of claim 16, the antibody fragment is a Fab antibody fragment.

18. The hydrogel conjugate of claim 17, wherein the Fab antibody fragment is ranibizumab.

19. The hydrogel conjugate of any one of claims 1-18, wherein the antibody-hydrogel conjugate has an ocular effective half-life that is increased relative to a reference antibody that is not covalently attached to the hydrogel.

20. The hydrogel conjugate of claim 19, wherein the ocular effective half-life is increased at least about 2-fold relative to the reference antibody.

21. The hydrogel conjugate of claim 20, wherein the ocular effective half-life is increased at least about 2.5-fold relative to the reference antibody.

22. The hydrogel conjugate of claim 21, wherein the ocular effective half-life is increased at least about 3-fold relative to the reference antibody.

23. The hydrogel conjugate of claim 22, wherein the ocular effective half-life is increased at least about 3.5-fold relative to the reference antibody.

24. The hydrogel conjugate of claim 23, wherein the ocular effective half-life is increased at least about 4-fold relative to the reference antibody.

25. The hydrogel conjugate of claim 24, wherein the ocular effective half-life is increased at least about 5-fold relative to the reference antibody.

26. The hydrogel conjugate of claim 25, wherein the ocular effective half-life is increased at least about 6-fold relative to the reference antibody.

27. The hydrogel conjugate of any one of claims 19-26, wherein the ocular effective half-life is a vitreal effective half-life.

28. The hydrogel conjugate of any one of claims 19-27, wherein the reference antibody is identical to the antibody of the hydrogel conjugate.

29. A pharmaceutical composition comprising the hydrogel conjugate of any one of claims 1-28 and a pharmaceutically acceptable carrier, excipient, or diluent.

30. The pharmaceutical composition of claim 29, 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.

31. The pharmaceutical composition of claim 30, wherein the anti-angiogenic agent is a VEGF antagonist.

32. The pharmaceutical composition of claim 31, 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.

33. The pharmaceutical composition of claim 32, wherein the anti-VEGF antibody is ranibizumab (LUCENTIS®), RTH-258, or a bispecific anti-VEGF antibody.

34. The pharmaceutical composition of claim 33, wherein the bispecific anti-VEGF antibody is an anti-VEGF/anti-Ang2 antibody.

35. The pharmaceutical composition of claim 34, wherein the anti-VEGF/anti-Ang2 antibody is RG-7716.

36. The pharmaceutical composition of claim 32, wherein the soluble VEGF receptor fusion protein is aflibercept (EYLEA®).

37. The pharmaceutical composition of claim 32, wherein the aptamer is pegaptanib (MACUGEN®).

38. The pharmaceutical composition of claim 32, wherein the anti-VEGF DARPin® is abicipar pegol.

39. The pharmaceutical composition of claim 32, wherein the VEGFR tyrosine kinase inhibitor is selected from the group consisting of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171), vatalanib (PTK787), semaxaminib (SU5416), and SUTENT® (sunitinib).

40. The pharmaceutical composition of claim 30, wherein the second biological molecule is selected from the group consisting of IL-1β; IL-6; IL-6R; IL-13; IL-13R; PDGF; angiopoietin; angiopoietin 2; Tie2; S1P; integrins αvβ3, αvβ5, and α5β1; betacellulin; apelin/APJ; erythropoietin; complement factor D; TNFα; HtrA1; a VEGF receptor; ST-2 receptor; and a protein genetically linked to AMD risk.

41. The pharmaceutical composition of claim 40, wherein the VEGF receptor is VEGFR1, VEGFR2, VEGFR3, mbVEGFR, or sVEGFR.

42. The pharmaceutical composition of claim 40, 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.

43. The pharmaceutical composition of any one of claims 30 and 40-42, wherein the compound that binds a second biological molecule is an antibody or antigen-binding fragment thereof.

44. The pharmaceutical composition of claim 43, wherein the antigen-binding antibody fragment is selected from the group consisting of Fab, Fab-C, Fab'-SH, Fv, scFv, and (Fab')2 fragments.

45. The pharmaceutical composition of any one of claims 29-44 for use as a medicament.

46. The pharmaceutical composition of any one of claims 29-44 for use in the manufacture of a medicament for treating a disorder associated with pathological angiogenesis in a subject.

47. The pharmaceutical composition of any one of claims 29-44 for use in reducing or inhibiting angiogenesis in a subject having a disorder associated with pathological angiogenesis.

48. The pharmaceutical composition of any one of claims 29-44 for use in treating a disorder associated with pathological angiogenesis in a subject.

49. The pharmaceutical composition for use of any one of claims 29-44, wherein the disorder associated with pathological angiogenesis is an ocular disorder.

50. The pharmaceutical composition for use of claim 49, 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.

51. The pharmaceutical composition for use of claim 50, wherein the ocular disorder is AMD, DME, DR, or RVO.

52. The pharmaceutical composition for use of claim 50 or 51, wherein the ocular disorder is AMD.

53. The pharmaceutical composition for use of any one of claims 50-52, wherein the AMD is wet AMD.

54. A method for treating an ocular indication, the method comprising administering a therapeutic amount of a solution of the composition of any one of claims 29-53 to a subject in need of such treatment.

55. The method of claim 54 wherein the administration is intraocular.

56. The method of claim 54 wherein the composition is injected into the vitreum of the subject.

57. The method of claim 56 wherein the composition is injected using a needle having a gauge of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32.

58. The method of claim 54, wherein the ocular indication is selected from 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.

59. The method of claim 58, wherein the ocular indication is AMD, DME, DR, or RVO.

60. The method of claim 59, wherein the ocular indication is AMD.

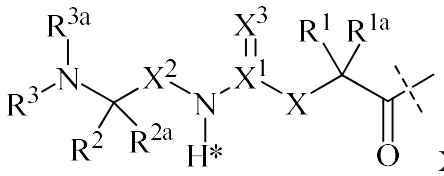
61. The method of claim 60, wherein the AMD is wet AMD.

62. A method for producing a hydrogel drug conjugate, the method comprising:
(a) providing a first hyaluronic acidor a derivative thereof, having at least three first reactive groups thereon;
(b) providing a second hyaluronic acid or a derivative thereof, having at least two second reactive group thereon, wherein the first and second reactive groups are capable reacting with each other to form a covalent bond;
(c) coupling at least one drug to one of the first reactive groups; and
(d) cross-linking the first and second hyaluronic acids by reaction of a first reactive group and a second reactive group to form a cross-linker and form the hydrogel conjugate;
wherein events (b) and (c) may optionally be interchanged.

63. The method of claim 62, wherein the drug is coupled to the first hyaluronic acid via a reversible prodrug linker.

64. The method of claim 63 wherein the drug is coupled to the reversible prodrug linker and purified to form a purified drug-reversible prodrug linker conjugate prior to coupling with the first hyaluronic acid, wherein the drug-reversible prodrug linker conjugate is purified by:
(a) tagging the drug-reversible prodrug linker conjugate with a purification tag to form a tagged drug-reversible prodrug linker conjugate mixture;
(b) purifying a tagged drug-reversible prodrug linker monoconjugate from the mixture by chromatographic separation; and
(c) removing the purification tag from the tagged drug-reversible prodrug linker monoconjugate to form the purified drug-reversible prodrug linker conjugate.

65. The method of claim 63 wherein the reversible prodrug linker coupling the drug to the first hyaluronic acid is of formula XIIa



XIIa

wherein:

the dashed line indicates the attachment to a nitrogen of a drug compound (not shown) by forming an amide bond;

-X- is -C(R^4R^{4a})-; -N(R^4)-; -O-; -C(R^4R^{4a})-C(R^5R^{5a})-; -C(R^5R^{5a})-C(R^4R^{4a})-; -C(R^4R^{4a})-N(R^6)-; -N(R^6)-C(R^4R^{4a})-; -C(R^4R^{4a})-O-; -O-C(R^4R^{4a})-; or -C(R^7R^{7a})-;

X^1 is C; or S(O);

-X^2- is -C(R^8R^{8a})-; or -C(R^8R^{8a})-C(R^9R^{9a})-;

=X^3 is =O; =S; or =N-CN;

-R^1, -R^{1a}, -R^2, -R^{2a}, -R^4, -R^{4a}, -R^5, -R^{5a}, -R^6, -R^8, -R^{8a}, -R^9, -R^{9a} are independently selected from the group consisting of -H; and C_{1-6} alkyl;

-R^3, -R^{3a} are independently selected from the group consisting of -H; and C_{1-6} alkyl, provided that in case one of -R^3, -R^{3a} or both are other than -H they are connected to N to which they are attached through an SP^3-hybridized carbon atom;

-R^7 is -N($R^{10}R^{10a}$); or -NR^{10}-(C=O)-R^{11};

-R^{7a}, -R^{10}, -R^{10a}, -R^{11} are independently of each other -H; or C_{1-10} alkyl;

optionally, one or more of the pairs -R^{1a}/-R^{4a}, -R^{1a}/-R^{5a}, -R^{1a}/-R^{7a}, -R^{4a}/-R^{5a}, -R^{8a}/-R^{9a} form a chemical bond;

optionally, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, -R^4/-R^{4a}, -R^5/-R^{5a}, -R^8/-R^{8a}, -R^9/-R^{9a} are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl; or 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs -R^1/-R^4, -R^1/-R^5, -R^1/-R^6, -R^1/-R^{7a}, -R^4/-R^5, -R^4/-R^6, -R^8/-R^9, -R^2/-R^3 are joined together with the atoms to which they are attached to form a ring A;

optionally, R^3/R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

Ring A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

wherein the group of formula XIIa is substituted with -L^4 provided that the hydrogen marked with the asterisk in formula (XIIa) is not replaced by -L^4 or other substituent;

wherein -L^4- is a single chemical bond or a spacer moiety as defined herein.

66. The method of claim 65 wherein:

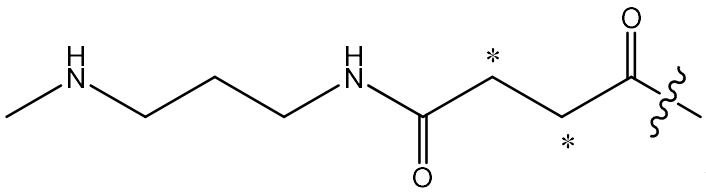
X^3 is =O;

-R^1 and -R^{1a} are hydrogen;

-R^3 is methyl and R^{3a} is hydrogen; and

X is -$C(R^7R^{7a})$-; with R^7 being NR^{10}-(C=O)-R^{11}.

67. The method of claim 63 wherein the reversible prodrug linker is of the formula VIIa(i):

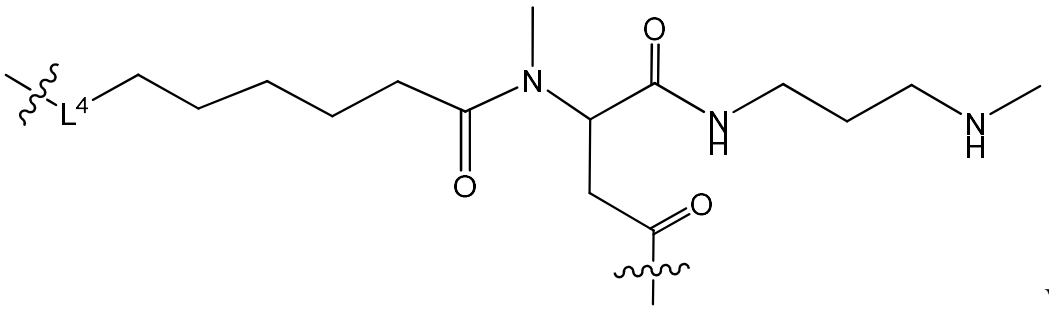


VIIa(i)

wherein:

each asterisk represents an independent site of attachment to the first hyaluronic acid by a spacer L^4.

68. The method of claim 63 wherein the reversible prodrug linker together with an optionally spacer L_4, is of the formula VIIc:



VIIc

wherein:

the right-most wavy line represents the point of attachment to the nitrogen atom of a drug;

the left-most wavy line represents the point of attachment to the first hyaluronic acid; and

L^4 is an optionally biodegradable spacer.

69. The method of claim 62 wherein the cross-linker comprises a biodegradable spacer moiety.

70. The method of claim 69 wherein the cross-linker comprises an azelaic acid ester moiety.

71. The method of claim 62, wherein the drug is an antibody.

72. The method of claim 71, wherein the antibody is a VEGF antagonist.

73. The method of claim 72, wherein the antibody is an anti-VEGFantibody fragment.

74. The method of claim 73, the antibody fragment is a Fab antibody fragment.

75. The method of claim 74, wherein the Fab antibody fragment is ranibizumab.