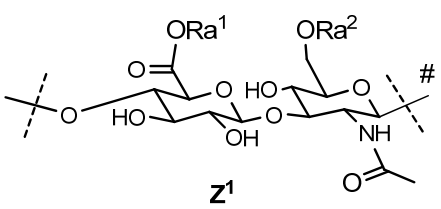
WHAT IS CLAIMED IS:

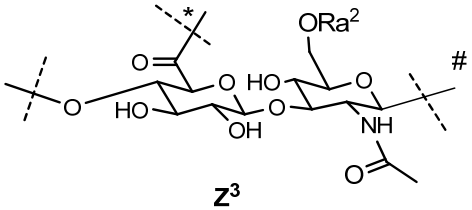
1. A cross-linked hyaluronic acid drug conjugate comprising a plurality of hyaluronic acid polymers 2A and a plurality of hyaluronic acid polymers 2B, wherein:

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



Z1

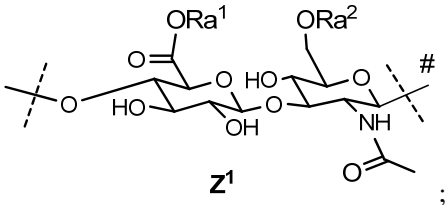
and



Z3

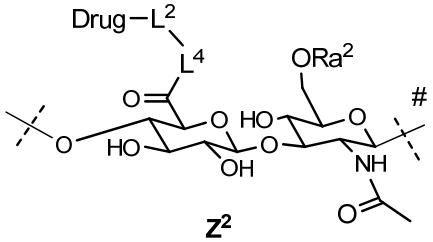
;

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



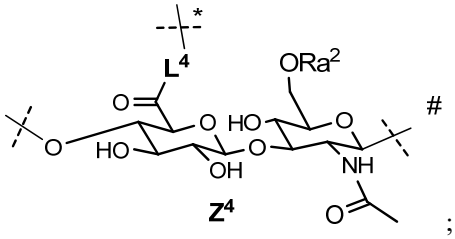
Z1

;



Z2

and



Z4

;

wherein

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

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

a dashed line 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 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 a biodegradable or non-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; and

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

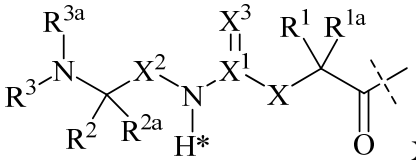
the number of Z^1 units in 2B is from about 0.75t to about 0.94t;

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 cross-linked hyaluronic acid drug 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;

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

$-R^3$ and $-R^{3a}$ are independently selected from the group consisting of -H and C_{1-6} alkyl, provided that in case one of $-R^3$ and $-R^{3a}$ 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 $-NR^{10}-(C=O)-R^{11}$;

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

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

optionally, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, $-R^4/-R^{4a}$, $-R^5/-R^{5a}$, $-R^8/-R^{8a}$ and $-R^9/-R^{9a}$ 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 and -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 cross-linked hyaluronic acid drug conjugate of claim 2, wherein:

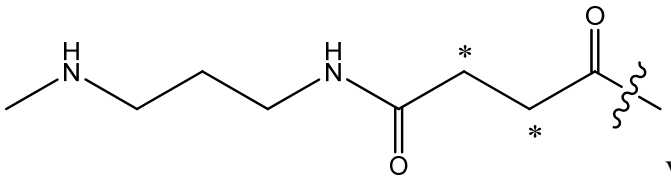
X^3 is =O;

-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 cross-linked hyaluronic acid drug conjugate of claims 1 or 2, wherein the reversible prodrug linker L^2 is of the formula VIIa(i):

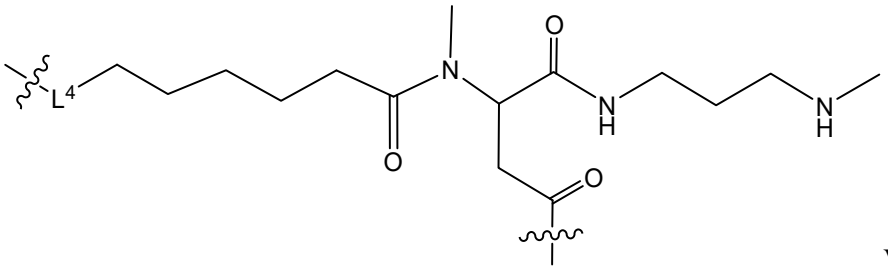


VIIa(i)

wherein

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

5. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 3 wherein the reversible prodrug linker L^2 together with spacer L^4 is of the formula VIIc:



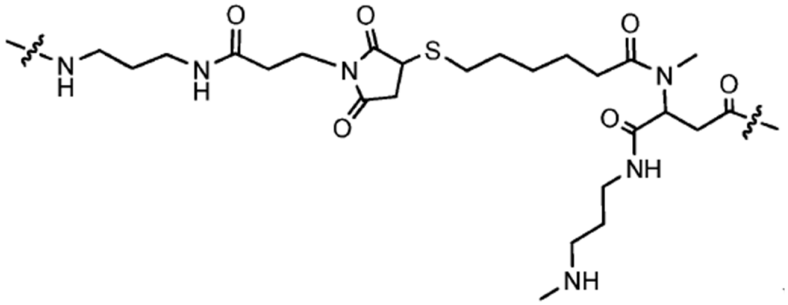
VIIc

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 cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 5, wherein the combined reversible prodrug linker L^2 together with spacer L^4 is of formula VIId



VIId,

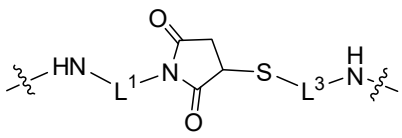
wherein

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 polymer 2B.

7. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 6 wherein

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

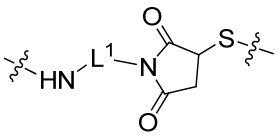


wherein

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;

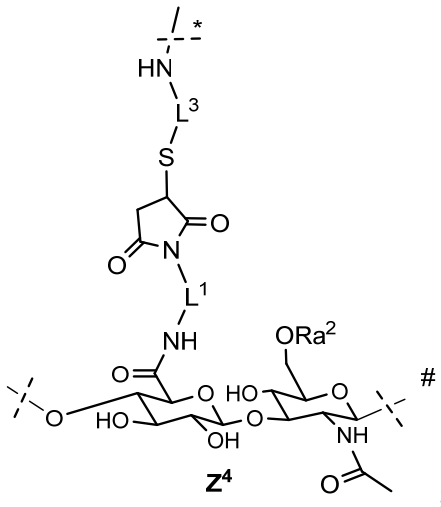
wherein

L^1 is a spacer; and

L^3 is a biodegradable spacer.

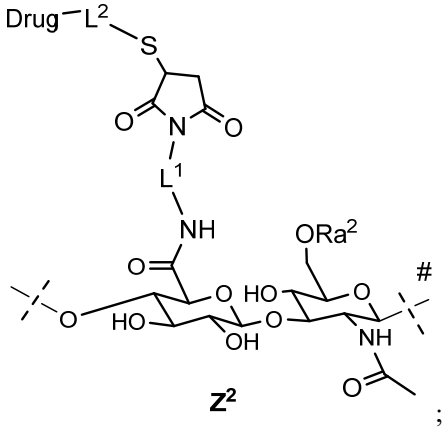
8. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 7, wherein

unit Z^4 is



; and

unit Z^2 is



;

wherein

L^1 is a spacer;

L^3 is a biodegradable spacer; and

Drug, Ra^2 and L^2 are as recited in claim 1.

9. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 8, wherein spacer L^1 and biodegradable spacer L^3 are independently selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y1})-$, $-S(O)_2N(R^{y1})-$, $-S(O)N(R^{y1})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y1})S(O)_2N(R^{y1a})-$, -S- $-N(R^{y1})-$, $-OC(OR^{y1})(R^{y1a})-$, $-N(R^{y1})C(O)N(R^{y1a})-$, $-OC(O)N(R^{y1})-$, C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl; wherein -T-, C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl are optionally substituted with one or more $-R^{y2}$, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y3})-$, $-S(O)_2N(R^{y3})-$, $-S(O)N(R^{y3})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y3})S(O)_2N(R^{y3a})-$, -S-, $-N(R^{y3})-$, $-OC(OR^{y3})(R^{y3a})-$, $-N(R^{y3})C(O)N(R^{y3a})-$ and $-OC(O)N(R^{y3})-$; wherein

$-R^{y1}$ and $-R^{y1a}$ are each independently selected from the group consisting of -H, -T, C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl and 8- to 30-membered heteropolycyclyl;

each $-R^{y2}$ is selected from the group consisting of halogen and C_{1-6} alkyl;

each $-R^{y3}$ and $-R^{y3a}$ are each independently of each other selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

biodegradable spacer L^3 comprises at least one biodegradable linkage.

10. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 9, wherein spacer L^1 and biodegradable spacer L^3 are independently selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y1})-, -S(O)$_2$N(R^{y1})-, -S(O)$_2$-, C_{1-50} alkyl and C_{2-50} alkenyl; wherein -T-, C_{1-50} alkyl and C_{2-50} alkenyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C_{1-50} alkyl and C_{2-50} alkenyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y3})-, -S(O)$_2$N(R^{y3})-, -S(O)$_2$-, -S- and -N(R^{y3})-; wherein

-R^{y1} and -R^{y1a} are each independently selected from the group consisting of -H and C_{1-10} alkyl;

each T is independently 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;

each -R^{y2} is selected from the group consisting of halogen and C_{1-6} alkyl;

each -R^{y3} and -R^{y3a} are each independently of each other selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

biodegradable spacer L^3 comprises at least one biodegradable linkage.

11. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 10, wherein spacer L^1 and biodegradable spacer L^3 are independently a C_{1-20} alkyl chain, wherein the C_{1-20} alkyl chain is optionally interrupted by one or more groups independently selected from -O-, -T- and -C(O)N(R^{y1})-; and wherein the C_{1-20} alkyl chain is optionally substituted with one or more groups independently selected from -OH, -T and -C(O)N(R^{y6})R^{y6a}); wherein

-R^{y1}, -R^{y6} and -R^{y6a} are independently selected from the group consisting of H and C_{1-4} alkyl;

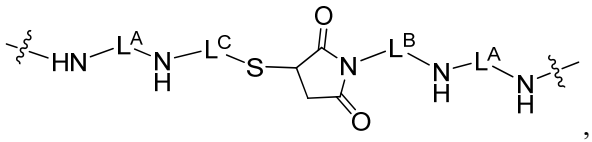
T is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl and 8- to 30-membered heteropolycyclyl; and

biodegradable spacer L^3 comprising at least one biodegradable linkage.

12. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 11, wherein the spacer L^1 is selected from the group consisting of is C_{1-12} alkyl, C_{2-10} alkyl or C_{3-8} alkyl, wherein C_{1-12} alkyl, C_{2-10} alkyl or C_{3-8} alkyl are optionally interrupted by one or more groups selected from the group consisting of -C(O)N(R^{y3})- and -N(R^{y3})-.

13. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 6 wherein

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



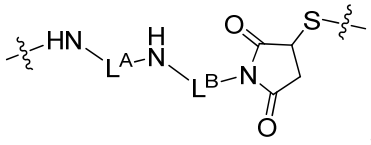
,

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

he 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

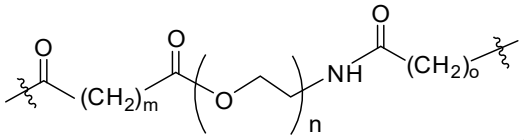
L^C is a biodegradable spacer.

14. The cross-linked hyaluronic acid drug conjugate of claim 13, wherein L^A is optionally substituted and/or optionally interrupted C_{1-10} alkylene.

15. The cross-linked hyaluronic acid drug conjugate of claims 13 or 14, wherein L^A is linear C_{2-4} alkylene.

16. The cross-linked hyaluronic acid drug conjugate of any one of claims 13 to 15, wherein L^B is linear -(O)-C_{1-5} alkylene.

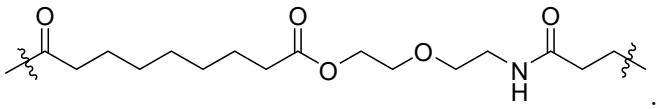
17. The cross-linked hyaluronic acid drug conjugate of any one of claims 13 to 16, wherein L^C is



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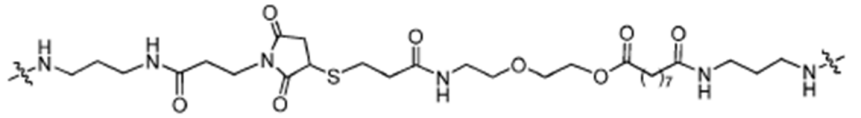
wherein m is from 0 to 10, n is from 1 to 4, and o is from 1 to 4.

18. The cross-linked hyaluronic acid drug conjugate of any one of claims 13 to 17, wherein L^C is



.

19. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 12 wherein the spacer L^4 connecting hyaluronic acid polymer 2A to hylauronic acid polymer 2B is of the formula



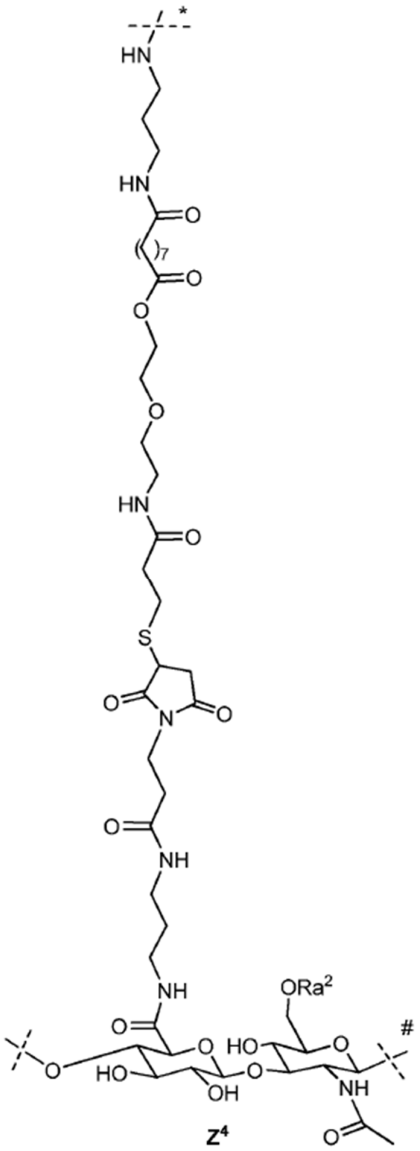
,

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.

20. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 12 and 19, wherein the unit Z^4 of hyaluronic acid polymer 2B is of formula



wherein

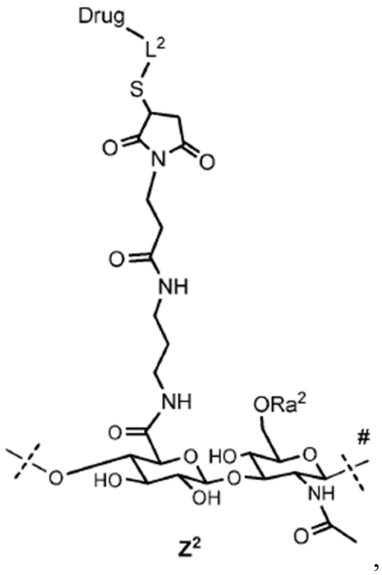
an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen;

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

a dashed line 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; and

Ra^2 is as defined in any one of claims 1 to 12 and 19.

21. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 20, wherein the unit Z^2 of hyaluronic acid polymer 2B is of formula



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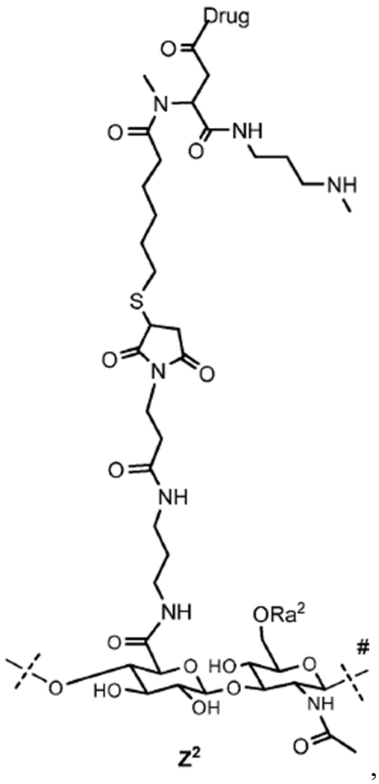
wherein

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

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

Drug, L^2 and Ra^2 are as defined in any one of claims 1 to 20.

22. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 21, wherein the unit Z^2 of hyaluronic acid polymer 2B is of formula



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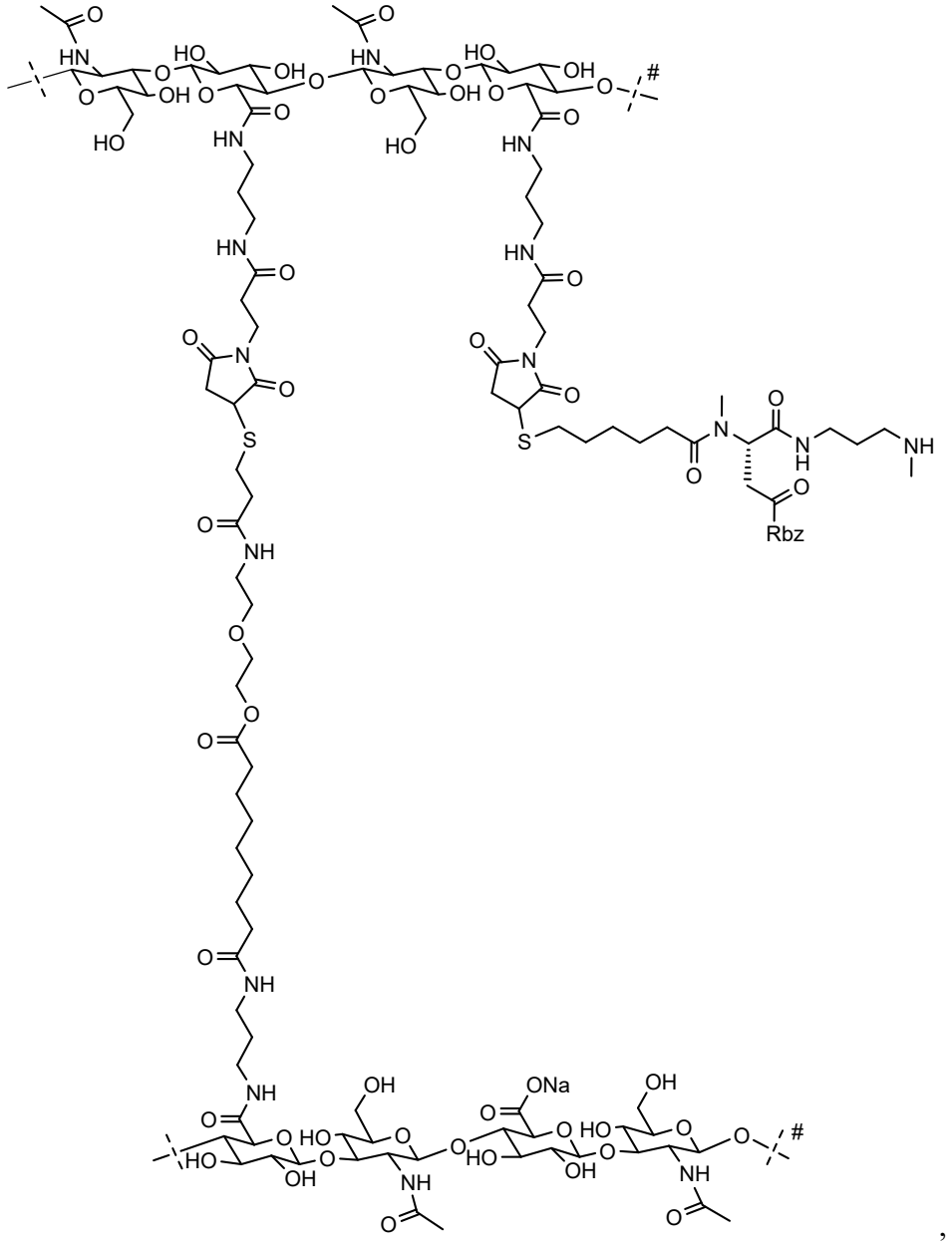
wherein

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

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

Drug and Ra^2 are as defined in any one of claims 1 to 21.

23. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 22, wherein the hyaluronic acid drug conjugate comprises a moiety according to formula



,

wherein

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

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

Rbz is ranibizumab.

24. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 23, wherein the drug is an antibody.

25. The cross-linked hyaluronic acid drug conjugate of claim 24, wherein the antibody is a VEGF antagonist.

26. The cross-linked hyaluronic acid drug conjugate of claim 25, wherein the antibody is an anti-VEGF antibody fragment.

27. The cross-linked hyaluronic acid drug conjugate of claim 26, the antibody fragment is a Fab antibody fragment.

28. The cross-linked hyaluronic acid drug conjugate of claim 27, wherein the Fab antibody fragment is ranibizumab.

29. The cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 28, 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.

30. The cross-linked hyaluronic acid drug conjugate of claim 29, wherein the ocular effective half-life is increased at least about 2-fold relative to the reference antibody.

31. The cross-linked hyaluronic acid drug conjugate of claim 30, wherein the ocular effective half-life is increased at least about 2.5-fold relative to the reference antibody.

32. The cross-linked hyaluronic acid drug conjugate of claim 30, wherein the ocular effective half-life is increased at least about 3-fold relative to the reference antibody.

33. The cross-linked hyaluronic acid drug conjugate of claim 32, wherein the ocular effective half-life is increased at least about 3.5-fold relative to the reference antibody.

34. The cross-linked hyaluronic acid drug conjugate of claim 33, wherein the ocular effective half-life is increased at least about 4-fold relative to the reference antibody.

35. The cross-linked hyaluronic acid drug conjugate of claim 34, wherein the ocular effective half-life is increased at least about 5-fold relative to the reference antibody.

36. The cross-linked hyaluronic acid drug conjugate of claim 35, wherein the ocular effective half-life is increased at least about 6-fold relative to the reference antibody.

37. The cross-linked hyaluronic acid drug conjugate of any one of claims 29 to 36, wherein the ocular effective half-life is a vitreal effective half-life.

38. The cross-linked hyaluronic acid drug conjugate of any one of claims 29 to 37, wherein the reference antibody is identical to the antibody of the hydrogel conjugate.

39. A pharmaceutical composition comprising the cross-linked hyaluronic acid drug conjugate of any one of claims 1 to 38 and a pharmaceutically acceptable carrier, excipient, or diluent.

40. The cross-linked hyaluronic acid drug conjugate of any one of claims 29 to 38 or the pharmaceutical composition of claim 39 for use as a medicament.

41. Use of the pharmaceutical composition of claim 39 in the manufacture of a medicament for treating a disorder associated with pathological angiogenesis in a subject.

42. Use of the pharmaceutical composition of claim 39 in the manufacture of a medicament for use in reducing or inhibiting angiogenesis in a subject having a disorder associated with pathological angiogenesis.

43. The use of claims 41 or 42, wherein the disorder associated with pathological angiogenesis is an ocular disorder.

44. The use of claim 43, 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.

45. The use of claim 44, wherein the ocular disorder is AMD, DME, DR, or RVO.

46. The use of claims 44 or 45, wherein the ocular disorder is AMD.

47. The use of claim 46, wherein the AMD is wet AMD.

48. Use of a solution of the composition of claim 39 in the manufacture of a medicament for treating an ocular indication in a subject in need of such treatment.

49. The use of claim 48, wherein the treatment is intraocular.

50. The use of claim 48, wherein the composition is to be injected into the vitreum of the subject.

51. The use of claim 50, wherein the composition is to be injected using a needle having a gauge of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32.

52. The use of any one of claims 48 to 51, wherein the ocular indication 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.

53. The use of claim 52, wherein the ocular indication is AMD, DME, DR, or RVO.

54. The use of claim 53, wherein the ocular indication is AMD.

55. The use of claim 54, wherein the AMD is wet AMD.