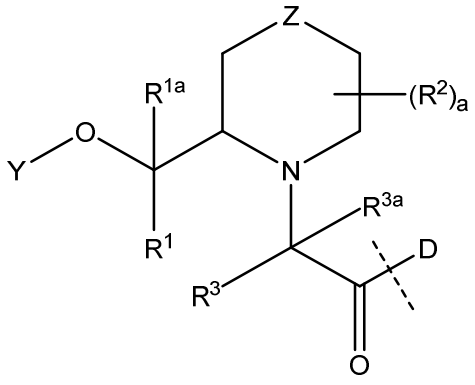
CLAIMS

~~What is claimed is:~~

1. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (I), where D ~~comprises~~is an ANGPTL3 polypeptide comprising at least one primary amine; and

~~R is a linker suitable for release of D:~~

R has the formula:



(I),

where the dashed line indicates attachment to the primary amine of D;

R^1 is hydrogen or C_1-C_4alkyl;

R^{1a} is hydrogen or C_1-C_4alkyl, or CR^1R^{1a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^2 is independently selected at each occurrence from C_1-C_4alkyl or oxo, or two R^2 groups taken in combination with the carbon atom(s) to which they are attached form a fused C_3-C_6 cycloalkyl or spiro C_3-C_6cycloalk-1,1-diyl group;

a is 0, 1, 2, 3 or 4;

R^3 is hydrogen or C_1-C_4alkyl;

R^{3a} is hydrogen, C_1-C_4alkyl, or CR^3R^{3a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

Y is $C(O)R^4$, $C(O)OR^4$, $C(O)NHR^4$, $C(O)NR^5R^6$, $SiR^5R^6R^7$, or $CR^{12}R^{12a}OR^{13}$;

R^{12} is hydrogen or C_1-C_4alkyl;

R^{12a} is hydrogen or C_1-C_4alkyl, or $CR^{12}R^{12a}$, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^{13} is C_1-C_4alkyl; or

R^{12} and R^{13}, taken in combination with $C(R^{12a})$ and O form a 5, 6, or 7-member cyclic ether;

R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by C_1-C_4alkoxy;

R^5 and R^6 are each independently selected from C_1-C_4alkyl and C_3-C_6cycloalkyl;

R^7 is C_1-C_8alkyl, C_3-C_7cycloalkyl, C_1-C_8alkoxy, C_3-C_7cycloalkyloxy, heterocycloalkyloxy, or -$(OCHR^3CH_2)_bO$-C_1-C_4alkyl, wherein the heterocycloalkyloxy is a 4 to 7 member saturated heterocyclic ring having one ring heteroatom selected from N, O, and S and optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups;

b is an integer of from 1 to 10;

Z is ~~CH-L-A, CH-A~~, N-L-A, [[or]] N-A, or NR^9;

L is an optionally substituted bivalent linker Q-[Sp-Q]h-Q;

Q is independently selected at each occurrence from a bond, O, C(O), N(H), N(C_1-C_4alkyl), C(O)NH, C(O)N(C_1-C_4alkyl), N(H)C(O), N(C_1-C_4alkyl)C(O), N(H)C(O)O, N(C_1-C_4alkyl)C(O)O, OC(O)N(H), OC(O)N(C1-C_4alkyl), N(H)C(O)N(H), N(C_1-C_4alkyl)C(O)N(H), N(H)C(O)N(C_1-C_4alkyl), N(C_1-C4alkyl)C(O)N(C_1-C_4alkyl), C(O)O, OC(O), OC(O)O, S, $S(O)_2$, N(H)$S(O)_2$, N(C_1-C_4alkyl)$S(O)_2$, $S(O)_2$N(H), $S(O)_2$N(C_1-C_4alkyl), C_1-C_2alkyl-C(O)N(H), N(H)C(O)C_1-C_2alkyl, C_1-C_2alkyl-C(O)O, OC(O)C_1-C_2alkyl, 1,2,3-triazole, $OP(O)_2$, $P(O)_2O$, C_1-C_4alkyl-$P(O)_2$-O, or O-$P(O)_2$-C_1-$_4$alkyl;

Sp is independently selected at each occurrence from an optionally substituted C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $[W\text{-}O]_g$, C_1-C_8alkyl-$[O\text{-}W]_g$, $[O\text{-}W]_g$-O-C_1-C_8alkyl, C_1-C_8Calkyl-$[O\text{-}W]_g$-O-C_1-C_8alkyl, or oligopeptide;

h is an integer of between 1 and 20;

g is a weighted average number of between about 2 and about 50;

~~L~~R^9 is ~~an~~selected from hydrogen, C_1-C_8 alkyl, C(O)-$(CH_2)_n$-Q-A, C(O)C_1-C_8 alkyl, or –C(O)$(CH_2)_g[O–W]_g(NHC(O))_m(CH_2)_g[O–W]_p$-Q-A, wherein the alkyl group is optionally substituted ~~bivalent linker~~with 0 or 1 Q-A;

W is C_2-C_4alkyl-1,2-diyl in which a hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

A is hydrogen, C_1-C_8alkyl, C(O)C_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, C(O)OC_1-C_8alkyl, [[R^{10};]], or R^{11}~~, wherein the alkyl group is optionally substituted with 0 or 1 R^{10}~~;

~~R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier;~~,; and

R^{11} is a carrier.

2. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein D comprises an ANGPTL3 polypeptide having at least 95% identity to any one of SEQ ID ~~NO~~NOS: 1 or 3–45.

3. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein D comprises ~~any one of SEQ ID NO:1 or 3–45.~~

~~4. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein D comprises an ANGPTL3 polypeptide having a K423Q substitution or a K423 deletion.~~

~~5. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein D comprises~~ an ANGPTL3 polypeptide comprising amino acid residues 201–460; 207–460; 225–455; 225–455; 225–460; 225–460; 226–455; 226–455; 226–460; 226–460; 228–455; 228–455; 228–460; 228–460; 233–455; 233–455; 233–460; 233–460; 241–455; 241–455; 241–460; 241–460; 242–455; 242–455; 242–460; or 242–460, each in reference to SEQ ID NO:1.

~~6~~4. The drug delivery system or pharmaceutically acceptable salt of ~~claim 1~~claim1, wherein D comprises an ANGPTL3 polypeptide comprising at least 95% identity to amino acid residues 242–460 in reference to SEQ ID NO:1 and a K423Q substitution.

~~7~~5. The drug delivery system or pharmaceutically acceptable salt of claim 1~~, wherein D comprises an ANGPTL3 polypeptide comprising amino acid residues 242–460 in reference to SEQ ID NO:1 and a K423Q substitution (SEQ ID NO:19).~~

~~8. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 7~~ wherein R^1 is hydrogen or methyl, R^{1a} is hydrogen or methyl, or CR^1R^{1a}, taken in combination form a cyclopropan-1,1-diyl group.

~~9~~6. The drug delivery system or pharmaceutically acceptable salt of ~~any one of claims~~claim 1 ~~to 8~~, wherein the variable a is 0.

~~10~~7. The drug delivery system or pharmaceutically acceptable salt of ~~any one of claims~~claim 1 ~~to 9~~, wherein R^3 and R^{3a} are each hydrogen.

~~11~~8. The drug delivery system or pharmaceutically acceptable salt of ~~any one of claims~~claim 1 ~~to 10~~, wherein

Y is $C(O)R^4$ and R^4 is C_1-C_6alkyl, C_3-C_6cycloalkyl or C_1-C_2alkoxyC_1-C_2alkyl~~.~~, or

~~12. The drug delivery system or pharmaceutically acceptable salt of claim 11, wherein R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl.~~

~~13. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 10, wherein Y is $SiR^5R^6R^7$;~~

Y is $SiR^5R^6R^7$;

wherein

R^5 and R^6 are each methyl, ethyl, propyl or isopropyl; and

R^7 is C_1-C_4 alkyl, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, 2-ethoxyethoxy, 2-isopropoxy-ethoxy, tetrahydropyranyloxy, or -$(OCHR^3CH_2)_bO$-C_1-C_4alkyl -where b is 2, 3, or 4.

~~14~~9. The drug delivery system or pharmaceutically acceptable salt of ~~any one of claims~~claim 8, wherein Y is $C(O)R^4$ and R^4 is methyl, ethyl, propyl, isopropyl, ~~1 to 13, wherein Z is CH-L-A, CH-A, N-L-A~~-methyl-cyclopropyl, or ~~N-A;~~methoxymethyl.

~~L is an optionally substituted bivalent linker Q-[Sp-Q]h-Q;~~

~~Q is independently selected at each occurrence from a bond, O, C(O), N(H), N(C_1-C_4alkyl), C(O)NH, C(O)N(C_1-C_4alkyl), N(H)C(O), N(C_1-C_4alkyl)C(O), N(H)C(O)O, N(C_1-C_4alkyl)C(O)O, OC(O)N(H), OC(O)N(C1-C_4alkyl), N(H)C(O)N(H), N(C_1-C_4alkyl)C(O)N(H), N(H)C(O)N(C_1-C_4alkyl), N(C_1-C4alkyl)C(O)N(C_1-C_4alkyl), C(O)O, OC(O), OC(O)O, S, $S(O)_2$, N(H)$S(O)_2$, N(C_1-C_4alkyl)$S(O)_2$, $S(O)_2$N(H), $S(O)_2$N(C_1-C_4alkyl), C_1-C_2alkyl-C(O)N(H), N(H)C(O)C_1-C_2alkyl, C_1-C_2alkyl-C(O)O, OC(O)C_1-C_2alkyl, 1,2,3-triazole, $OP(O)_2$, $P(O)_2O$, C_1-C_4alkyl-$P(O)_2$-O, or O-$P(O)_2$-C_1-$_4$alkyl;~~

~~Sp is independently selected at each occurrence from an optionally substituted C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $[W\text{-}O]_g$, C_1-C_8alkyl-$[O\text{-}W]_g$, $[O\text{-}W]_g$-O-C_1-C_8alkyl, C_1-C_8Calkyl-$[O\text{-}W]_g$-O-C_1-C_8alkyl, or oligopeptide;~~

~~h is an integer of between 1 and 20;~~

~~g is a weighted average number of between about 2 and about 50;~~

~~W is C_2-C_4alkyl-1,2-diyl in which a hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;~~

~~A is hydrogen, C_1-C_8alkyl, C(O)C_1-C_8alkyl, C(O)OC_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, R^{10}, or R^{11} wherein the alkyl group is optionally substituted with 0 or 1 R^{10};~~

~~R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and~~

~~R^{11} is a carrier.~~

~~15~~

10. The drug delivery system or pharmaceutically acceptable salt of ~~any one of claims~~claim 1 ~~to 13~~, wherein Z is ~~CHR^8 or~~ NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, C(O)-$(CH_2)_n$-Q-A, C(O)C_1-C_8 alkyl, or $-C(O)(CH_2)_q[O-W]_g(NHC(O))_m(CH_2)_q[O-W]_p$-Q-A, wherein the alkyl group is optionally substituted with 0 or 1 Q-A;

q is independently at each occurrence 1, 2, or 3;

g and p each independently have a weighted average length of between about 2 and about 50;

m is 1 or 0;

W is C_2-C_4alkyl-1,2-diyl in which a hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

Q is a bond, O, N(H) or N(C_1-C_4alkyl);

A is hydrogen, C_1-C_8alkyl, C(O)C_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, C(O)OC_1-C_8alkyl, R^{10}~~,~~ ~~or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};~~; and

~~R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and~~

R^{11} is a carrier.

~~16~~11. The drug delivery system or pharmaceutically acceptable salt of claim ~~15, wherein Z is NR^9;~~

~~R^9 is C(O)-$(CH_2)_n$-Q-A or -C(O)$(CH_2)_q[O-W]_g(NHC(O))_m(CH_2)_q[O-W]_p$-Q-A;~~

~~n is an integer of 1 to 8; and~~

~~A is R^{10} or R^{11}.~~

~~17. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16, wherein R^{10} is azidyl, alkynyl, substituted or unsubstituted C_7-C_{12} cycloalkynyl, substituted or unsubstituted C_7-C_{12} heterocycloalkynyl, substituted or unsubstituted C_7-C_{12} cycloalkenyl, norbornyl, substituted or unsubstituted vinyl carboxyl, substituted or unsubstituted vinyl sulfonyl, substituted or unsubstituted C_2-C_8 alkenyl, amino, thiol, substituted or unsubstituted C_1-C_8 carboxyl, substituted or unsubstituted C_1-C_8 carbonyl, -O-NH_2, hydrazidyl, maleimide, alpha-halo-carbonyl, furan, substituted or unsubstituted tetrazinyl, lysine, glutamine, cyclodextrin, or adamantanyl.~~

~~18. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 17, wherein R^{10} comprises a reactive functional group suitable for coupling the drug delivery system or pharmaceutically acceptable salt of Formula (I) to a carrier.~~

~~19. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16, wherein R^{11} is biodegradable.~~

~~20. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 or 19, wherein R^{11} comprises a polymer or cross-linked polymer.~~

~~21. The drug delivery system or pharmaceutically acceptable salt of claim 19 or 20~~1, wherein R^{11} comprises a hydrogel comprising one or more cross-linked polymers.

~~22~~12. The drug delivery system or pharmaceutically acceptable salt of ~~any one of claims~~claim 1 ~~to 16 and 19 to 21~~, wherein R^{11} comprises a polymer, cross-linked polymer, or hydrogel comprising one or more of hyaluronic acid, polyethylene glycol, polypropylene glycol, polyethylene oxide, polypropylene oxide, polyglutamate, polylysine, polysialic acid, polyvinyl alcohol, polyacrylate, polymethacrylate, polyacrylamide, polymethacrylamide, polyvinyl pyrrolidone, polyoxazoline, polyiminocarbonate, polyamino acid, hydrophilic polyester, polyamide, polyurethane, polyurea, dextran, agarose, xylan, mannan,

carrageenan, alginate, gelatin, collagen, albumin, cellulose, methylcellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxyethyl starch, chitosan, nucleic acids, derivatives thereof, co-polymers thereof, or combinations thereof.

~~23. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 22, wherein R^{11} comprises hyaluronic acid, polyethylene glycol, a cross-linked hydrogel of hyaluronic acid, a cross-linked hydrogel of polyethylene glycol, or combinations thereof.~~

~~24. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 23, wherein R^{11} comprises hyaluronic acid or polyethylene glycol.~~

~~25. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 23, wherein R^{11} comprises a hydrogel comprising cross-linked hyaluronic acid or cross-linked polyethylene glycol.~~

~~26. The drug delivery system or pharmaceutically acceptable salt of claim 24 or 25, wherein the hyaluronic acid or polyethylene glycol are functionalized with at least one functional group comprising azidyl, alkynyl, substituted or unsubstituted C_7-C_{12} cycloalkynyl, substituted or unsubstituted C_7-C_{12} heterocycloalkynyl, C_7-C_{12} cycloalkenyl, norbornyl, vinyl carboxyl, vinyl sulfonyl, C_2-C_8 alkenyl, amino, thiol, C_1-C_8 carboxyl, C_1-C_8 carbonyl, -O-NH2, carbohydrazide, maleimide, alpha-halo carbonyl, furan, substituted or unsubstituted tetrazinyl, lysine, glutamine, cyclodextrin, adamantanyl, or combinations thereof.~~

~~27. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 26~~13. The drug delivery system or pharmaceutically acceptable salt of claim 12, wherein R^{11} comprises a hydrogel comprising cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one side chain selected from -NH(W1)$(O(W1))_d$-V, wherein W1 is C_2-C_4alkyl-1,2-diyl in which a hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;
d is a number average of 0 to 500; and

V is a suitable functional group comprising azidyl, alkynyl, substituted or unsubstituted C_7-C_{12} cycloalkynyl, substituted or unsubstituted C_7-C_{12} heterocycloalkynyl, C_7-C_{12} cycloalkenyl, norbornyl, vinyl carboxyl, vinyl sulfonyl, C_2-C_8 alkenyl, amino, thiol, C_1-C_8 carboxyl, C_1-C_8 carbonyl, -O-NH2, carbohydrazide, maleimide, alpha-halo carbonyl, furan, substituted or unsubstituted tetrazinyl, lysine, glutamine, cyclodextrin, or adamantanyl.

~~28. The drug delivery system or pharmaceutically acceptable salt of claim 27, wherein V is azide.~~

~~29. A process for making a cross-linked carrier formulation, the process comprising:~~

~~(a) functionalizing a carrier molecule, R^{11};~~

~~(b) preparing a reactive cross-linker; and~~

~~(c) reacting the functionalized carrier molecule with the reactive cross-linker to form a cross-linked carrier by incubation for about 0.5 hours to about 48 hours at a temperature of about 4 °C to about 60 °C.~~

~~30. The process of claim 29, wherein the carrier molecule comprises hyaluronic acid or polyethylene glycol.~~

~~31. The process of claim 30, wherein the carrier molecule is functionalized with azide, sulfhydryl, amine, aminoxy (O-NH_2) or aldehyde moieties to provide reactive functional groups for cross-linking.~~

~~32. The process of any one of claims 29 to 31, wherein the preparation of the reactive crosslinker comprises reacting a polyethylene glycol with 1-((tert-butoxycarbonyl)amino)cyclopropane-1-carboxylic acid, 3-((tert-butoxycarbonyl)amino)propanoic acid, 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid, 2-(1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)acetic acid, 2-methyl-3-((tert-butoxycarbonyl)amino)propanoic acid, or 7-((tert-butoxycarbonyl)amino)heptanoic acid and deprotecting the functionalized polyethylene glycol ester.~~

33. The process of claim 32, wherein the preparation of the reactive crosslinker further comprises introduction at least two bicyclo[6.1.0]non-4-yn-9-yl)methyl groups after deprotection of the functionalzed polyethylene glycol ester.

34. A cross-linked hydrogel obtainable using the methods of any one of claims 29 to 33.

35. The cross-linked hydrogel of claim 34, wherein the carrier molecule is functionalized with azide.

36. A process for preparing a drug-adduct, comprising a traceless linker, R, coupled to an ANGPTL3 polypeptide comprising at least one primary amine, D, the process comprising:
(a) providing an ANGPTL3 polypeptide comprising at least one primary amine, D;
(b) reacting the biologically active agent with a traceless linker, R, that has an activated carbonyl functional group; and
(c) purifying the drug adduct from the reagents.

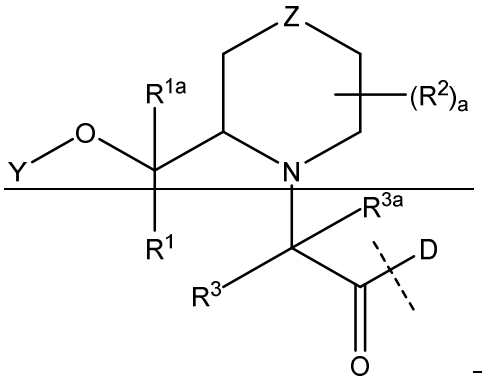
37. A drug adduct obtainable using the process of claim 36.

38. A process for making a drug delivery system, the process comprising:
(a) preparing a carrier molecule, R^{11}, wherein R^{11} is a cross-linked hydrogel; optionally, step (a) may further comprise purifying the cross-linked hydrogel carrier molecule R^{11};
(b) separately conjugating the traceless linker, R, to an ANGPTL3 polypeptide comprising at least one primary amine, D, thereby forming the traceless linker-D adduct; step (b) may optionally further comprise purification of the traceless linker-D adduct,
(c) conjugating the carrier molecule, R^{11}, with the traceless linker-D adduct; and
(d) purifying the drug delivery system from the reagents.

39. A drug delivery system made using the method of claim 38.

40. A method for treating macular degeneration comprising administering to a subject in need thereof a drug delivery system or pharmaceutically acceptable salt thereof comprising a conjugate D-R, that is represented by Formula (I), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine;

R is a linker suitable for release of D:



(I),

where the dashed line indicates attachment to the primary amine;

R^1 is hydrogen or C_1-C_4alkyl;

R^{1a} is hydrogen or C_1-C_4alkyl, or CR^1R^{1a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^2 is independently selected at each occurrence from C_1-C_4alkyl or oxo, or two R^2 groups taken in combination form a fused C_3-C_6 cycloalkyl or spiro C_3-C_6cycloalk-1,1-diyl group;

a is 0, 1, 2, 3 or 4;

R^3 is hydrogen or C_1-C_4alkyl;

R^{3a} is hydrogen, C_1-C_4alkyl, or CR^3R^{3a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

Y is $C(O)R^4$, $C(O)OR^4$, $C(O)NHR^4$, $C(O)NR^5R^6$, $SiR^5R^6R^7$, or $CR^{12}R^{12a}OR^{13}$;

R^{12} is hydrogen or C_1-C_4alkyl;

R^{12a} is hydrogen or C_1-C_4alkyl, or $CR^{12}R^{12a}$, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^{13} is C_1-C_4alkyl; or

$CHR^{12}OR^{13}$, taken in combination form a 5, 6, or 7-member cyclic ether;

R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by hydroxy, amino, C_1-C_4alkoxy or mono- and di-C_1-C_4alkylamino;

R^5 and R^6 are each independently selected from C_1-C_4alkyl and C_3-C_6cycloalkyl;

R^7 is C_1-C_8alkyl, C_3-C_7cycloalkyl, C_1-C_8alkoxy, C_3-C_7cycloalkyloxy, heterocycloalkyloxy, or $(OCHR^3CH_2)_bO$-C_1-C_4alkyl, wherein the heterocycloalkyloxy is a 4 to 7 member saturated heterocyclic ring having one ring heteroatom selected from N, O, and S and optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups;

b is an integer of from 1 to 10;

Z is CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-C_8 alkyl, or $C(O)(CH_2)_q[O-W]_g(NHC(O))_m(CH_2)_q[O-W]_p$-Q-A, wherein the alkyl group is optionally substituted with 0 or 1 Q-A;

q is independently at each occurrence 1, 2, or 3;

g and p each independently have a weighted average length of between about 2 and about 50;

m is 1 or 0;

W is C_2-C_4alkyl-1,2-diyl in which the hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

Q is a bond, O, N(H) or N(C_1-C_4alkyl);

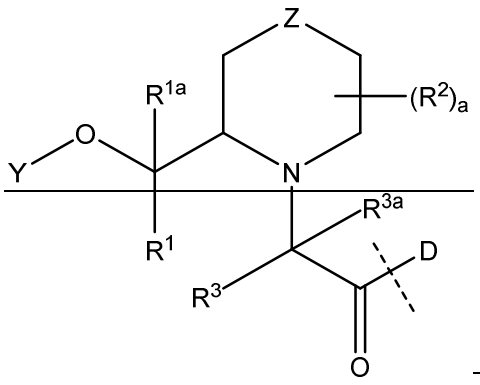
A is hydrogen, C_1-C_8alkyl, $C(O)C_1$-C_8alkyl, $C(O)N(H)C_1$-C_8alkyl, $C(O)OC_1$-C_8alkyl, R^{10}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

41. A method for treating musculoskeletal disorders comprising administering to a subject in need thereof a drug delivery system or pharmaceutically acceptable salt thereof comprising a conjugate D-R, that is represented by Formula (I), where D an ANGPTL3 polypeptide comprising at least one primary amine;

R is a linker suitable for release of D:



~~(I),~~

~~where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;~~

~~R^1 is hydrogen or C_1-C_4alkyl;~~

~~R^{1a} is hydrogen or C_1-C_4alkyl, or CR^1R^{1a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;~~

~~R^2 is independently selected at each occurrence from C_1-C_4alkyl or oxo, or two R^2 groups taken in combination form a fused C_3-C_6 cycloalkyl or spiro C_3-C_6cycloalk-1,1-diyl group;~~

~~a is 0, 1, 2, 3 or 4;~~

~~R^3 is hydrogen or C_1-C_4alkyl;~~

~~R^{3a} is hydrogen, C_1-C_4alkyl, or CR^3R^{3a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;~~

~~Y is $C(O)R^4$, $C(O)OR^4$, $C(O)NHR^4$, $C(O)NR^5R^6$, $SiR^5R^6R^7$, or $CR^{12}R^{12a}OR^{13}$;~~

~~R^{12} is hydrogen or C_1-C_4alkyl;~~

~~R^{12a} is hydrogen or C_1-C_4alkyl, or $CR^{12}R^{12a}$, taken in combination form a C_3-C_6cycloalk-1,1-diyl;~~

~~R^{13} is C_1-C_4alkyl; or~~

~~$CHR^{12}OR^{13}$, taken in combination form a 5, 6, or 7-member cyclic ether;~~

~~R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by hydroxy, amino, C_1-C_4alkoxy or mono- and di-C_1-C_4alkylamino;~~

~~R^5 and R^6 are each independently selected from C_1-C_4alkyl and C_3-C_6cycloalkyl;~~

~~R^7 is C_1-C_8alkyl, C_3-C_7cycloalkyl, C_1-C_8alkoxy, C_3-C_7cycloalkyloxy, heterocycloalkyloxy, or $(OCHR^3CH_2)_bO$-C_1-C_4alkyl, wherein the~~

heterocycloalkyloxy is a 4 to 7 member saturated heterocyclic ring having one ring heteroatom selected from N, O, and S and optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups;

b is an integer of from 1 to 10;

Z is CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-C_8 alkyl, or $C(O)(CH_2)_q[O\text{-}W]_g(NHC(O))_m(CH_2)_q[O\text{-}W]_p$-Q-A, wherein the alkyl group is optionally substituted with 0 or 1 Q-A;

q is independently at each occurrence 1, 2, or 3;

g and p each independently have a weighted average length of between about 2 and about 50;

m is 1 or 0;

W is C_2-C_4alkyl-1,2-diyl in which the hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

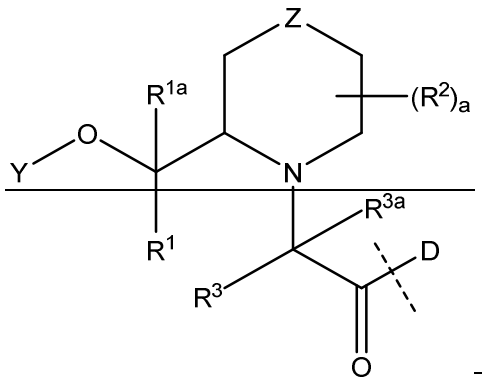
Q is a bond, O, N(H) or N(C_1-C_4alkyl);

A is hydrogen, C_1-C_8alkyl, $C(O)C_1$-C_8alkyl, $C(O)N(H)C_1$-C_8alkyl, $C(O)OC_1$-C_8alkyl, R^{10}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

42. A method for treating a disease or disorder comprising administering to a subject in need thereof a drug delivery system or pharmaceutically acceptable salt thereof comprising a conjugate D-R, that is represented by Formula (I), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; R is a linker suitable for release of D:



(I),

where the dashed line indicates attachment to the primary amine;

R^1 is hydrogen or C_1-C_4alkyl;

R^{1a} is hydrogen or C_1-C_4alkyl, or CR^1R^{1a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^2 is independently selected at each occurrence from C_1-C_4alkyl or oxo, or two R^2 groups taken in combination form a fused C_3-C_6 cycloalkyl or spiro C_3-C_6cycloalk-1,1-diyl group;

a is 0, 1, 2, 3 or 4;

R^3 is hydrogen or C_1-C_4alkyl;

R^{3a} is hydrogen, C_1-C_4alkyl, or CR^3R^{3a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

Y is $C(O)R^4$, $C(O)OR^4$, $C(O)NHR^4$, $C(O)NR^5R^6$, $SiR^5R^6R^7$, or $CR^{12}R^{12a}OR^{13}$;

R^{12} is hydrogen or C_1-C_4alkyl;

R^{12a} is hydrogen or C_1-C_4alkyl, or $CR^{12}R^{12a}$, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^{13} is C_1-C_4alkyl; or

$CHR^{12}OR^{13}$, taken in combination form a 5, 6, or 7-member cyclic ether;

R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

R^5 and R^6 are each independently selected from C_1-C_4alkyl and C_3-C_6cycloalkyl;

R^7 is C_1-C_8alkyl, C_3-C_7cycloalkyl, C_1-C_8alkoxy, C_3-C_7cycloalkyloxy, heterocycloalkyloxy, or $-(OCHR^3CH_2)_bO$-C_1-C_4alkyl, wherein the heterocycloalkyloxy is a 4 to 7 member saturated heterocyclic ring having one ring heteroatom selected from N, O, and S and optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups;

b is an integer of from 1 to 10;

Z is CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-C_8 alkyl, or $C(O)(CH_2)_q[O-W]_g(NHC(O))_m(CH_2)_q[O-W]_p$-Q-A, wherein the alkyl group is optionally substituted with 0 or 1 Q-A;

q is independently at each occurrence 1, 2, or 3;

g and p each independently have a weighted average length of between about 2 and about 50;

m is 1 or 0;

W is C_2-C_4alkyl-1,2-diyl in which the hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

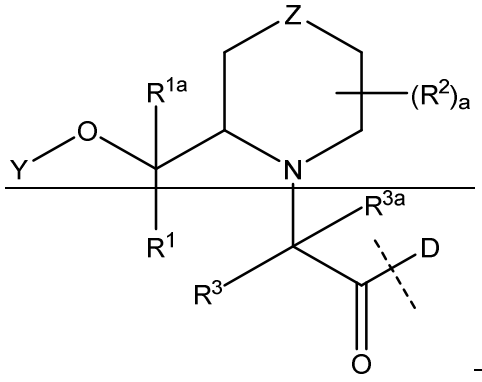
Q is a bond, O, N(H) or N(C_1-C_4alkyl);

A is hydrogen, C_1-C_8alkyl, C(O)C_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, C(O)OC_1-C_8alkyl, R^{10}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

43. A means for extending half-life of an ANGPTL3 polypeptide comprising at least one primary amine, D, the means comprising attaching D to R, that is represented by Formula (I), where R is a linker suitable for release of D:



(I),

where the dashed line indicates attachment to the primary amine;

R^1 is hydrogen or C_1-C_4alkyl;

R^{1a} is hydrogen or C_1-C_4alkyl, or CR^1R^{1a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^2 is independently selected at each occurrence from C_1-C_4alkyl or oxo, or two R^2 groups taken in combination form a fused C_3-C_6-cycloalkyl or spiro C_3-C_6cycloalk-1,1-diyl group;

a is 0, 1, 2, 3 or 4;

R^3 is hydrogen or C_1-C_4alkyl;

R^{3a} is hydrogen, C_1-C_4alkyl, or CR^3R^{3a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

Y is $C(O)R^4$, $C(O)OR^4$, $C(O)NHR^4$, $C(O)NR^5R^6$, $SiR^5R^6R^7$, or $CR^{12}R^{12a}OR^{13}$;

R^{12} is hydrogen or C_1-C_4alkyl;

R^{12a} is hydrogen or C_1-C_4alkyl, or $CR^{12}R^{12a}$, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^{13} is C_1-C_4alkyl; or

$CHR^{12}OR^{13}$, taken in combination form a 5, 6, or 7-member cyclic ether;

R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by hydroxy, amino, C_1-C_4alkoxy or mono- and di-C_1-C_4alkylamino;

R^5 and R^6 are each independently selected from C_1-C_4alkyl and C_3-C_6cycloalkyl;

R^7 is C_1-C_8alkyl, C_3-C_7cycloalkyl, C_1-C_8alkoxy, C_3-C_7cycloalkyloxy, heterocycloalkyloxy, or $-(OCHR^3CH_2)_bO$-C_1-C_4alkyl, wherein the heterocycloalkyloxy is a 4 to 7 member saturated heterocyclic ring having one ring heteroatom selected from N, O, and S and optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups;

b is an integer of from 1 to 10;

Z is CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-C_8 alkyl, or $C(O)(CH_2)_q[O-W]_g(NHC(O))_m(CH_2)_q[O-W]_p$-Q-A, wherein the alkyl group is optionally substituted with 0 or 1 Q-A;

q is independently at each occurrence 1, 2, or 3;

g and p each independently have a weighted average length of between about 2 and about 50;

m is 1 or 0;

W is C_2-C_4alkyl-1,2-diyl in which the hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

Q is a bond, O, N(H) or $N(C_1$-C_4alkyl);

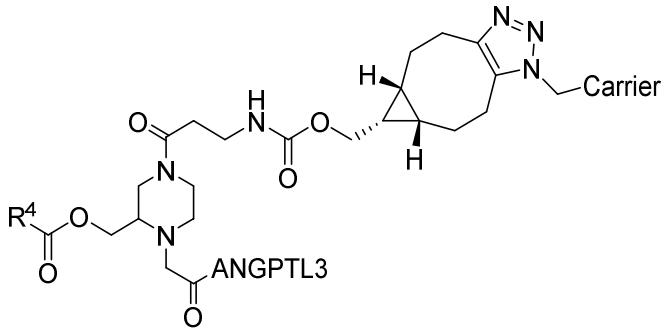
A is hydrogen, C_1-C_8alkyl, $C(O)C_1$-C_8alkyl, $C(O)N(H)C_1$-C_8alkyl, $C(O)OC_1$-C_8alkyl, R^{10}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

~~R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and~~

~~R^{11} is a carrier.~~

~~44. The means of claim 43, wherein D comprises an ANGPTL3 polypeptide having at least 95% identity to any one of SEQ ID NO: 1 or 3–45.~~

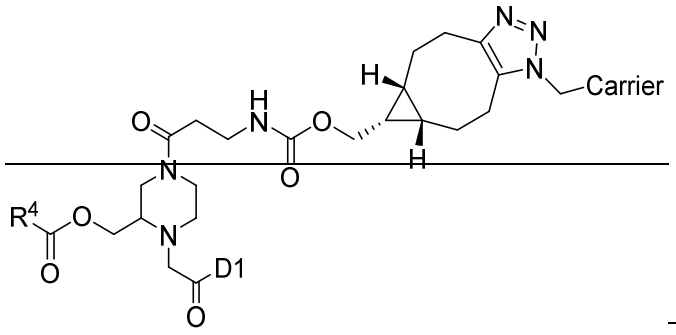
~~45~~14. A drug delivery system comprising Formula (III):



(III),

wherein ANGPTL3 comprises an ANGPTL3 polypeptide having at least 95% identity to any one of SEQ ID NO: 1 or 3–45, or combinations thereof.

~~46. A~~15. The drug delivery system ~~comprising Formula (IV):~~



~~(IV),~~

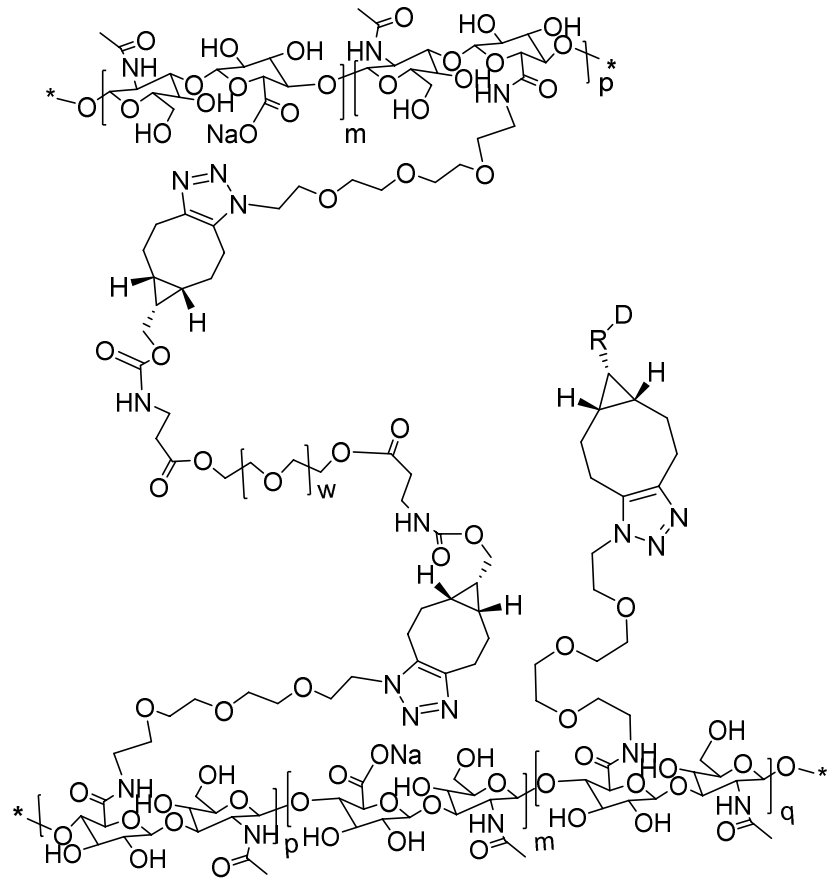
according to claim 14, wherein ~~SEQ ID NO:19 comprises an~~ ANGPTL3 is a polypeptide comprising amino acid residues 242–460 in reference to SEQ ID NO:1 and a K423Q substitution.

~~47. A drug delivery system comprising D-R-R^{11}, wherein R comprises a traceless linker, coupled to a biologically-active agent, D; D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R^{11} comprises a plurality of hyaluronic acid~~

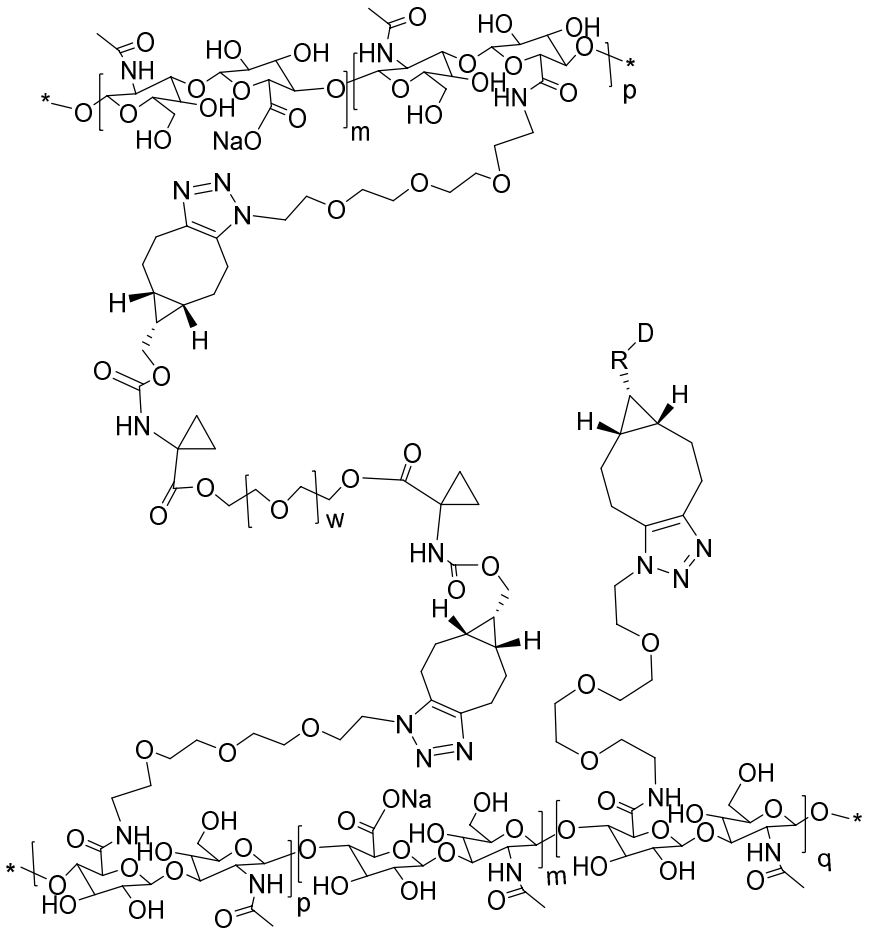
~~polymers each of which comprises a random series of unfunctionalized D-glucuronic acid monomers, one or more D-glucuronic acid monomers functionalized with a cross-linker, or one or more D-glucuronic acid monomers functionalized with a drug adduct, D–R.~~

~~48. The drug delivery system of claim 47, wherein D comprises an ANGPTL3 polypeptide having at least 95% identity to any one of SEQ ID NO: 1 or 3–45.~~

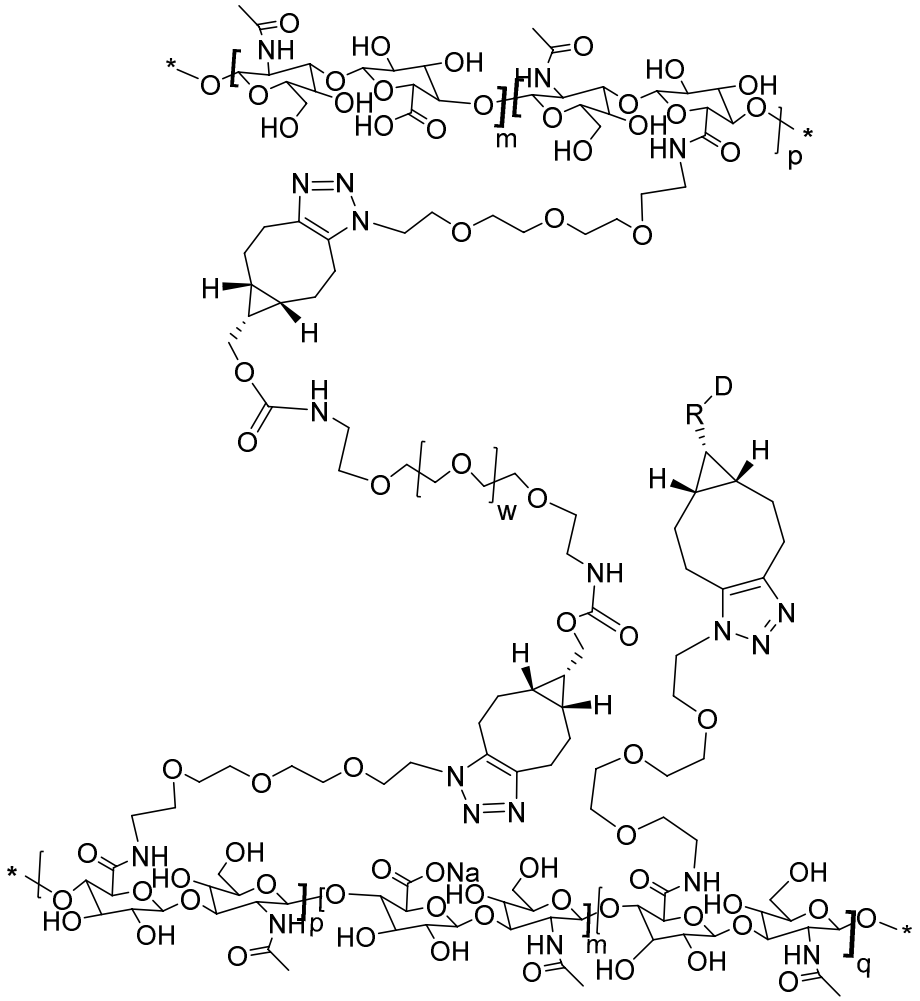
~~49. A~~16. The drug delivery system or pharmaceutically acceptable salt thereof ~~comprising D–R, that is represented by Formula~~ according to claim 1, having one of the following formulae:



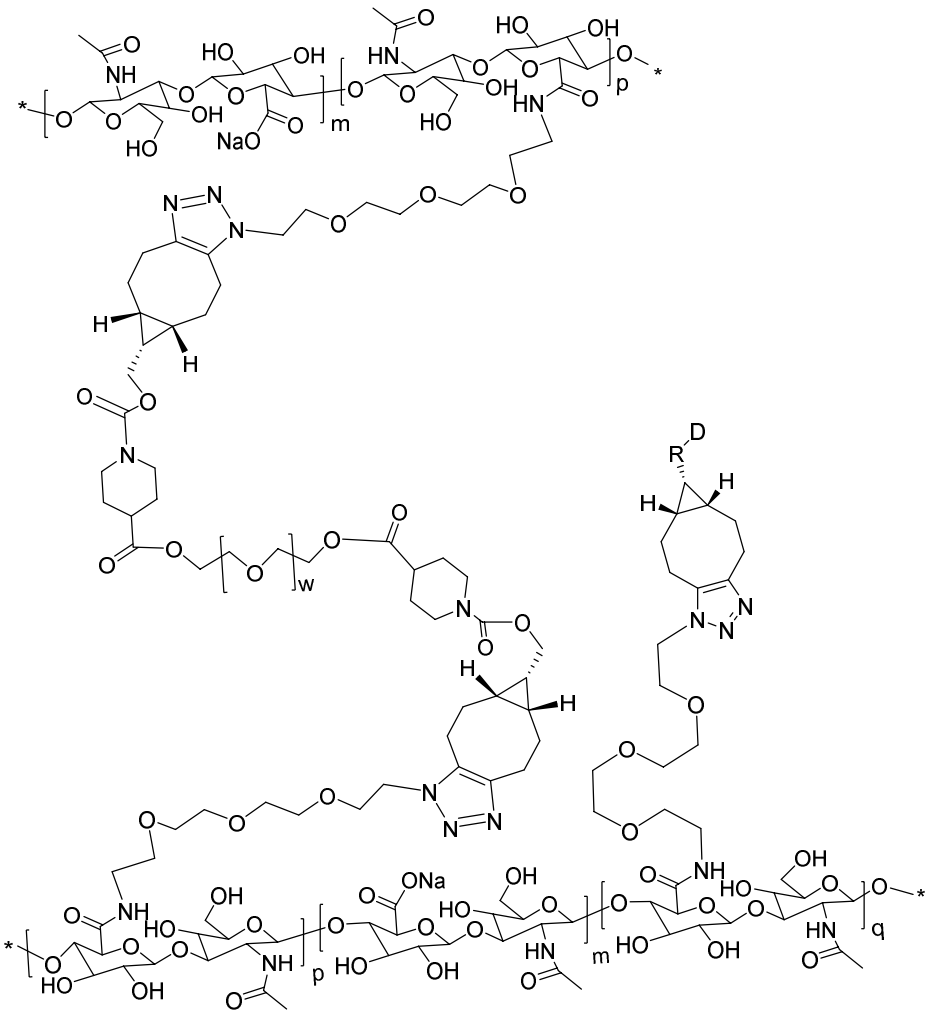
(XXIV), ~~where D is an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release D:~~



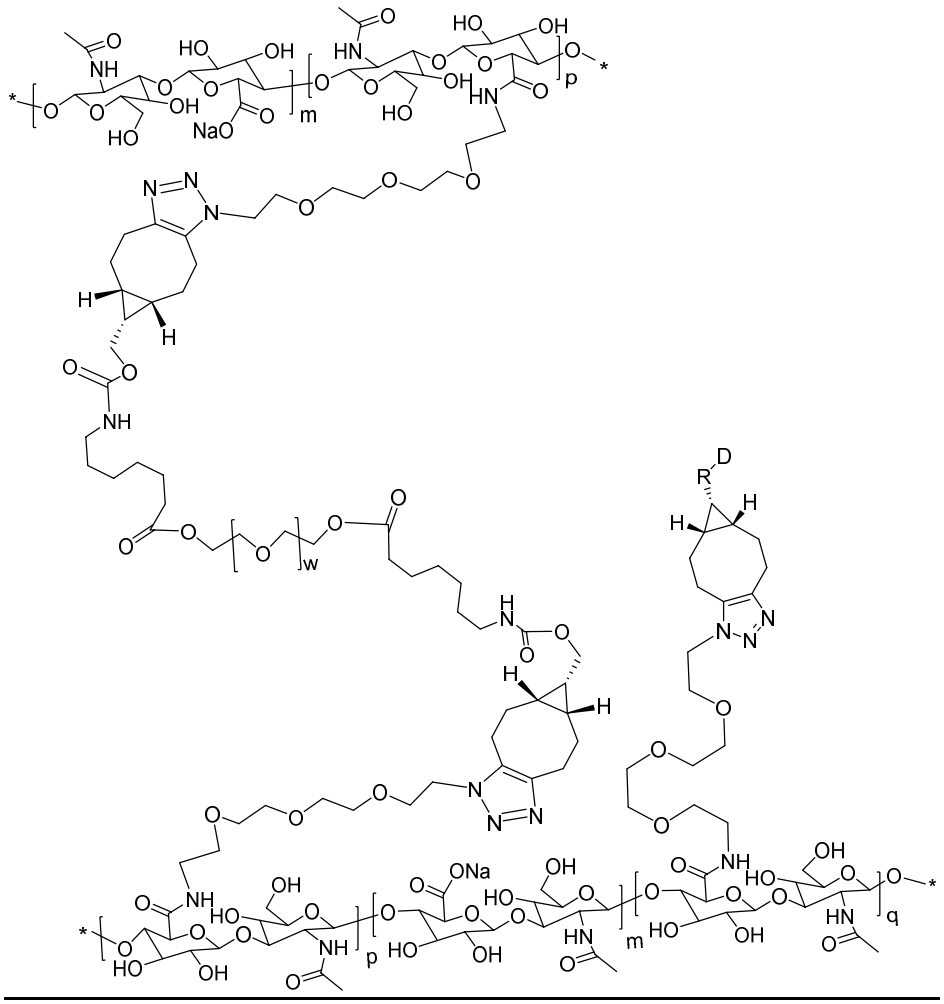
(XXV).

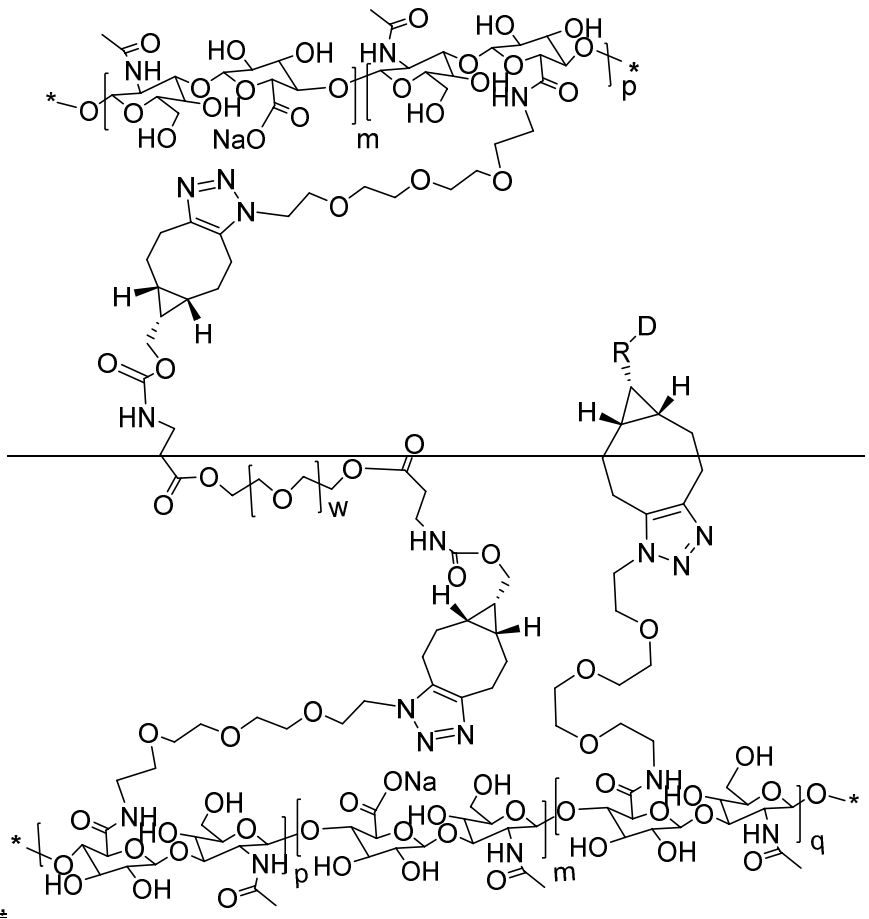


(XXVI).



(XXVII).



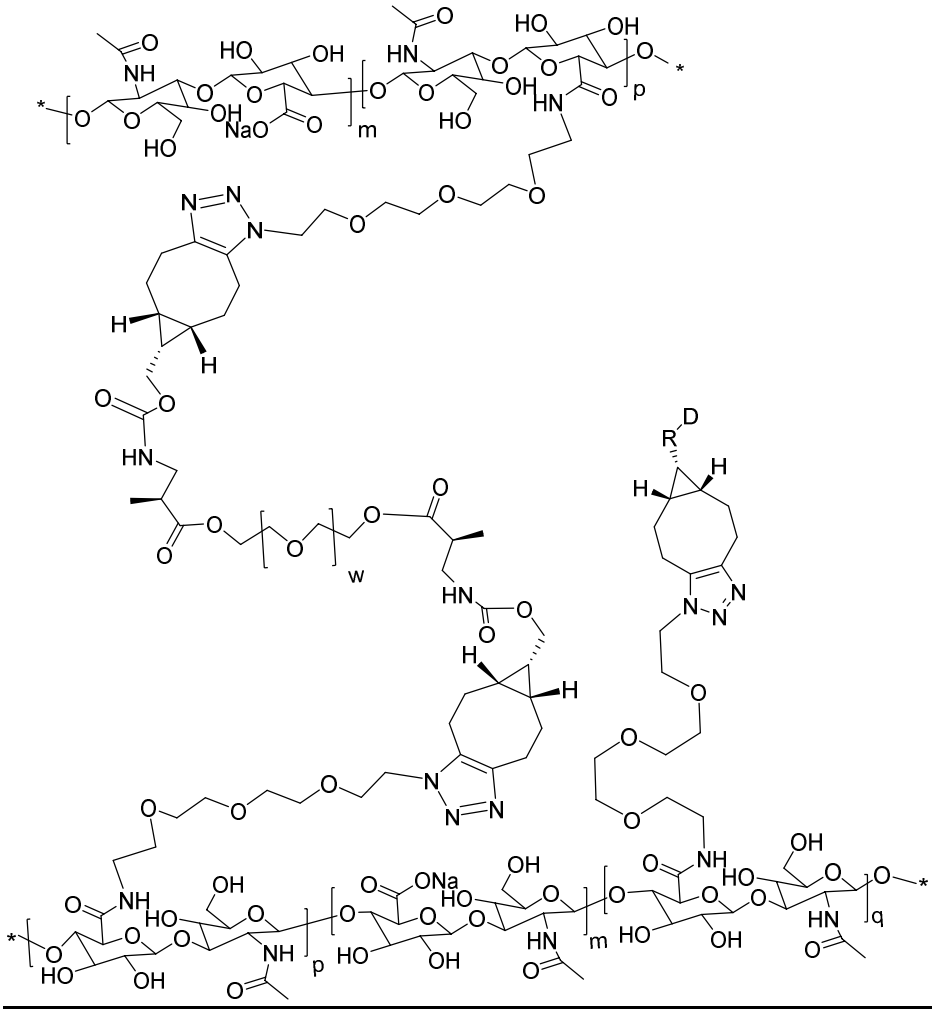


(XXVIII).

~~(XXIV).~~

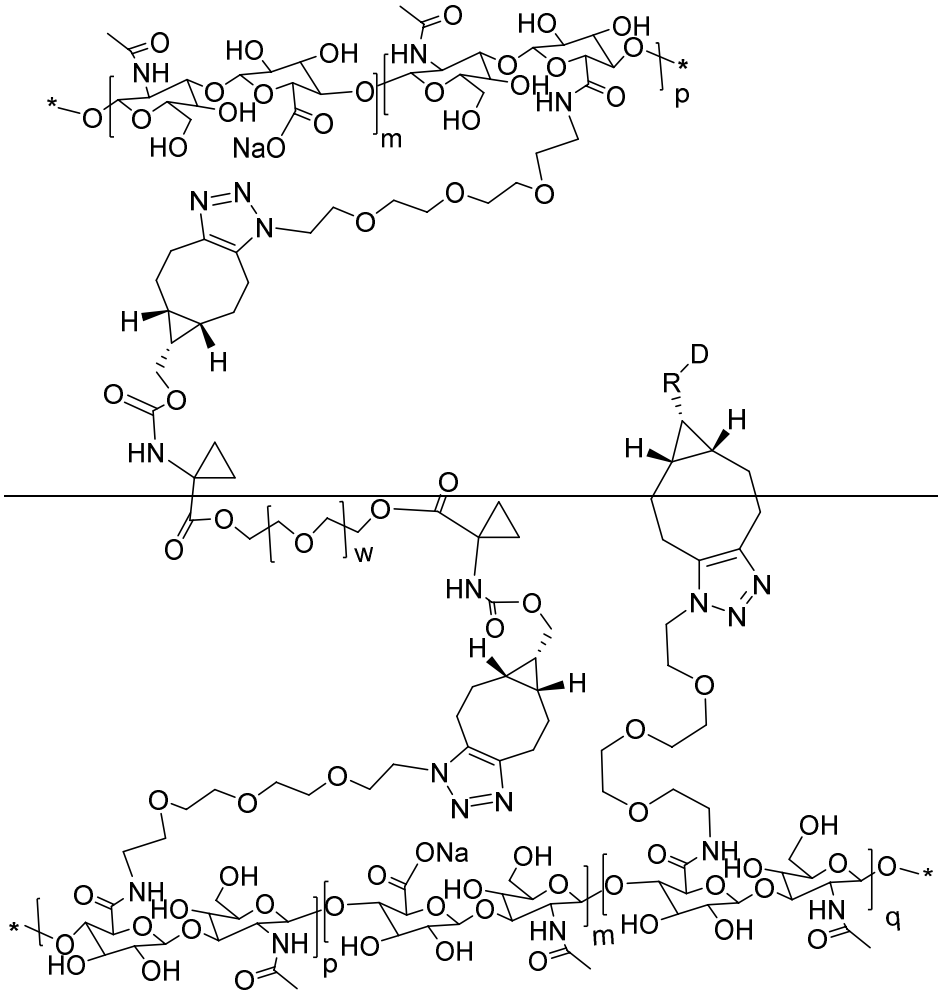
~~50. A~~

or



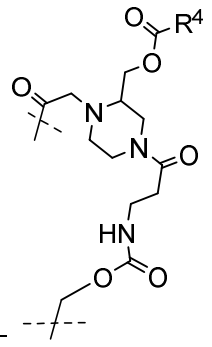
(XXIX).

17. The drug delivery system or pharmaceutically acceptable salt thereof ~~comprising D-R, that is represented by Formula~~ according to claim 16, wherein each R has the following formula~~(XXV), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D~~:



~~(XXV).~~

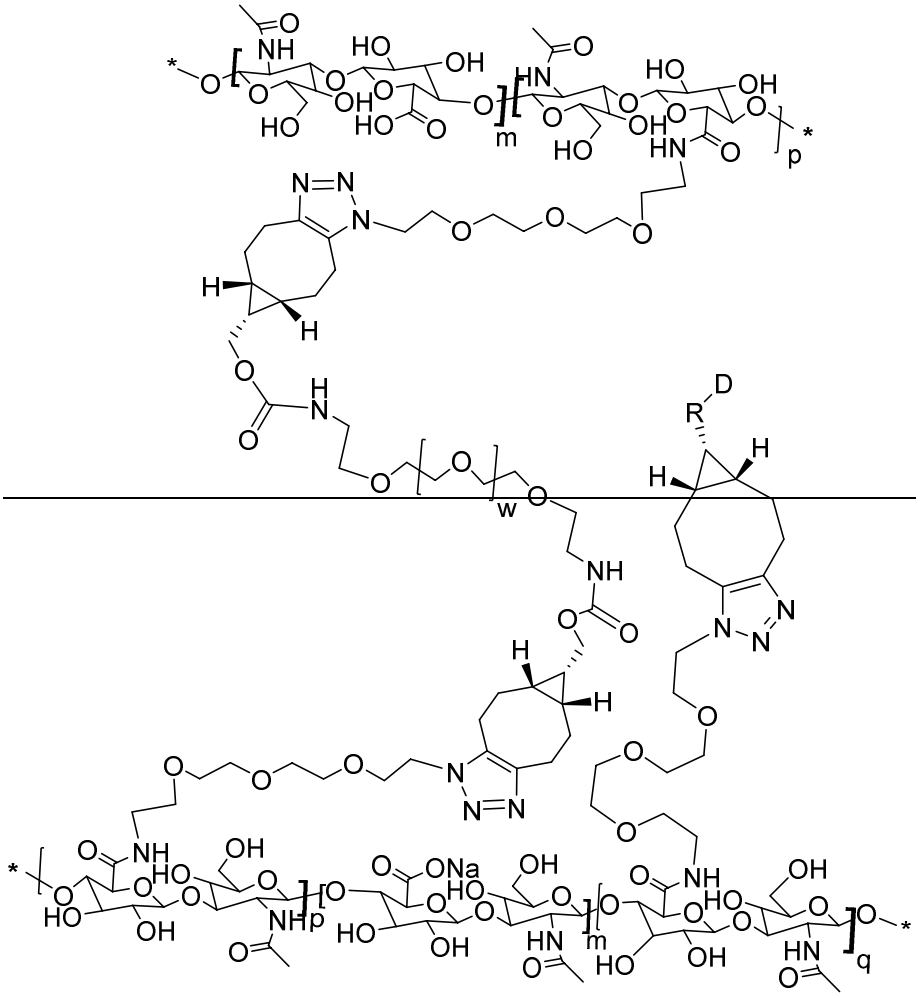
~~51. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that~~



~~is represented by Formula~~

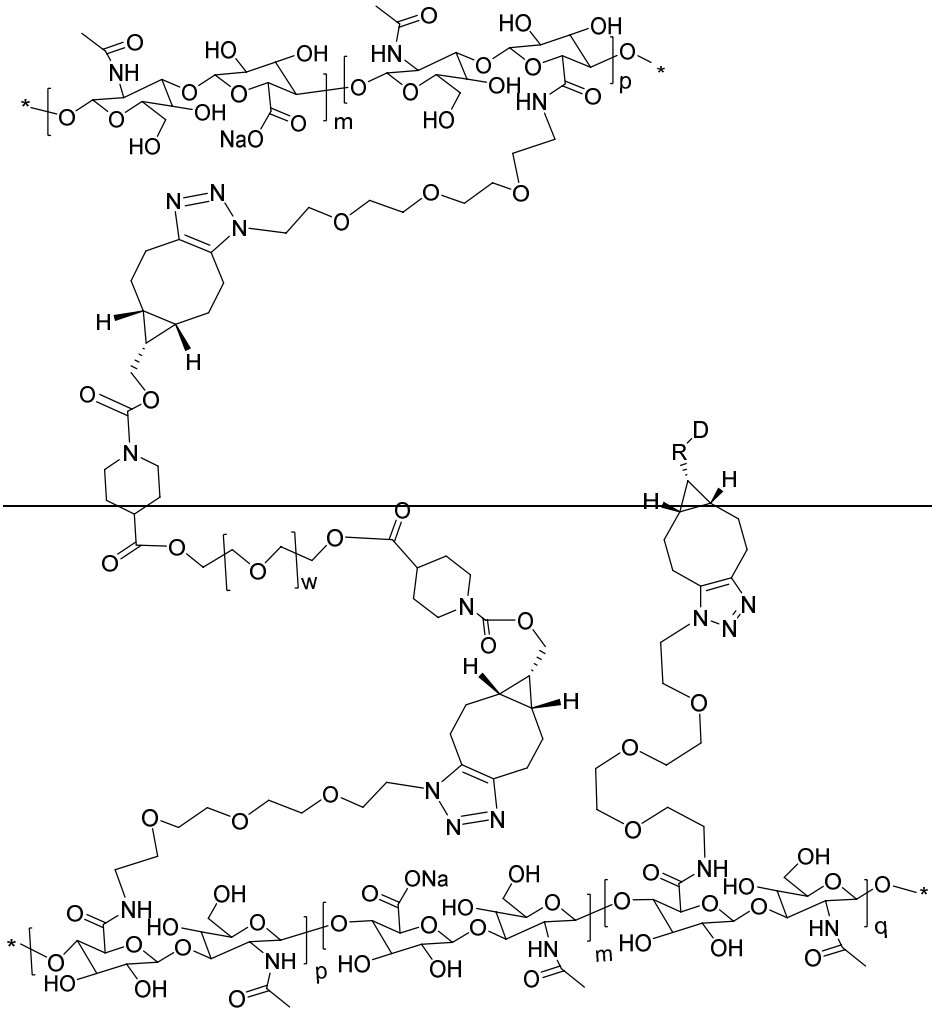
wherein the dashed lines indicate attachment to D and the bicyclo[6.1.0]non-4-yn-9-yl moiety, and

~~(XXVI), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D:~~



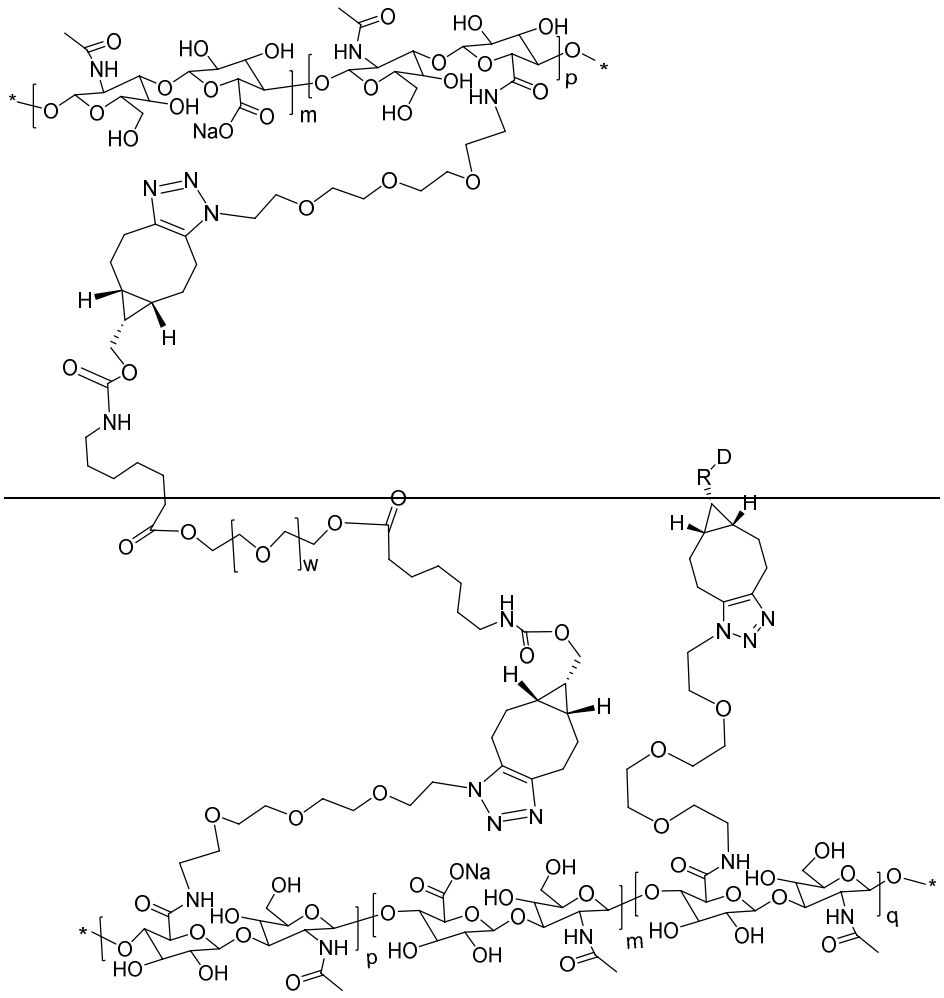
~~(XXVI).~~

~~52. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXVII), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D:~~



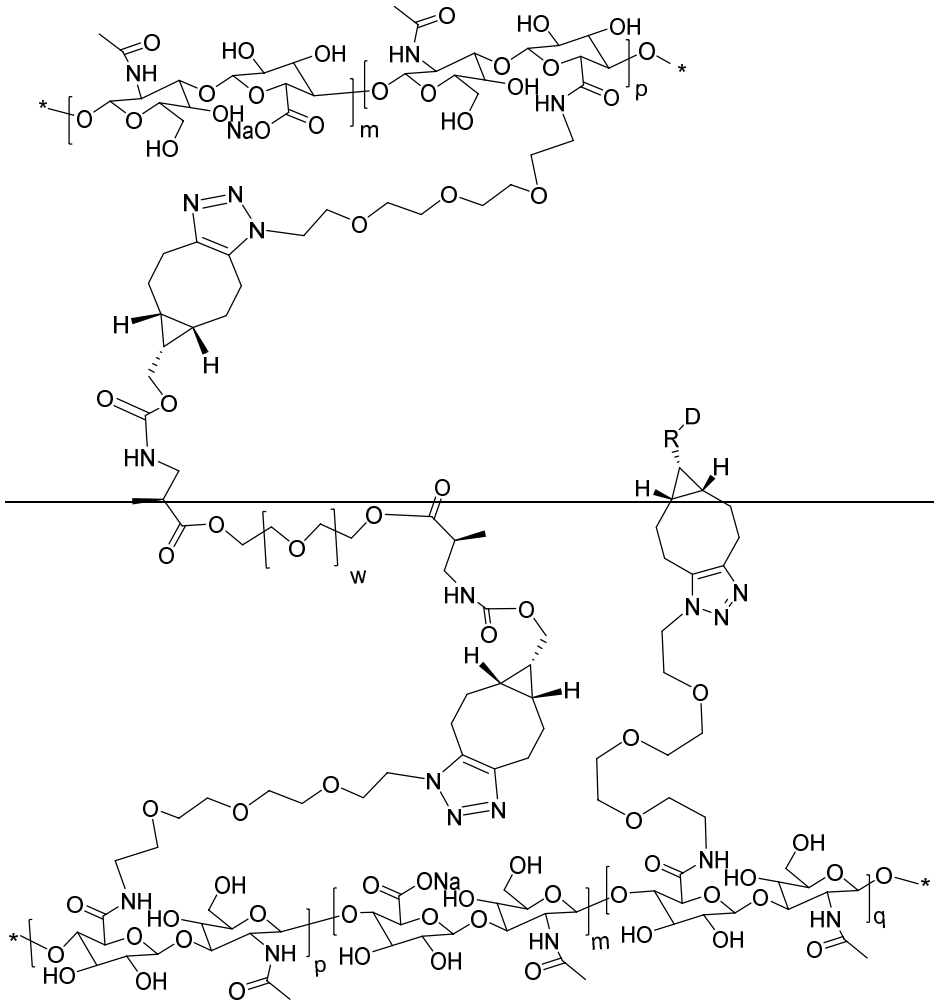
~~(XXVII).~~

~~53. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXVIII), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D:~~



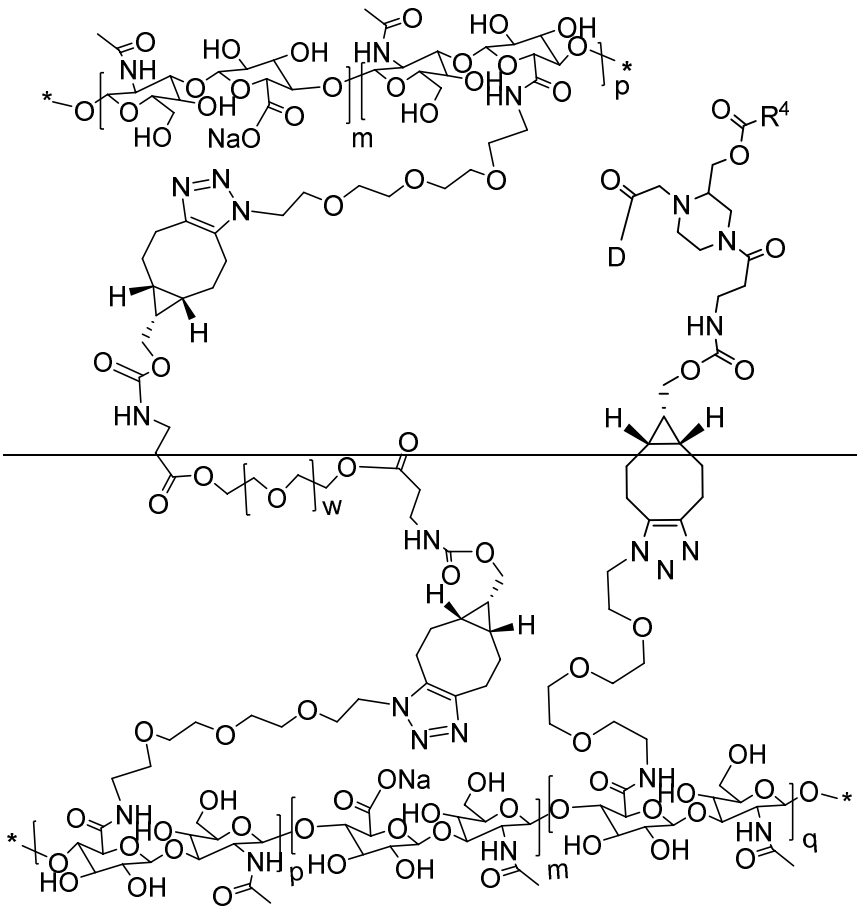
~~(XXVIII).~~

~~54. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXIX), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D:~~



~~(XXIX).~~

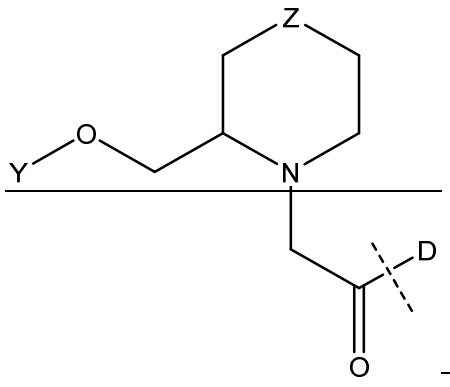
~~55. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXX), where Drug, D, comprises an ANGPTL3 polypeptide comprising at least one primary amine; and~~ R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl~~:~~.



~~(XXX).~~

~~56. A~~

18. The drug delivery system or pharmaceutically acceptable salt thereof ~~comprising D–R, that is represented by Formula (XXXI), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D:~~of claim 1, wherein



~~(XXXI),~~

~~where the dashed line indicates attachment to the primary amine;~~

Y is $C(O)R^4$;

R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by C_1-C_4alkoxy;

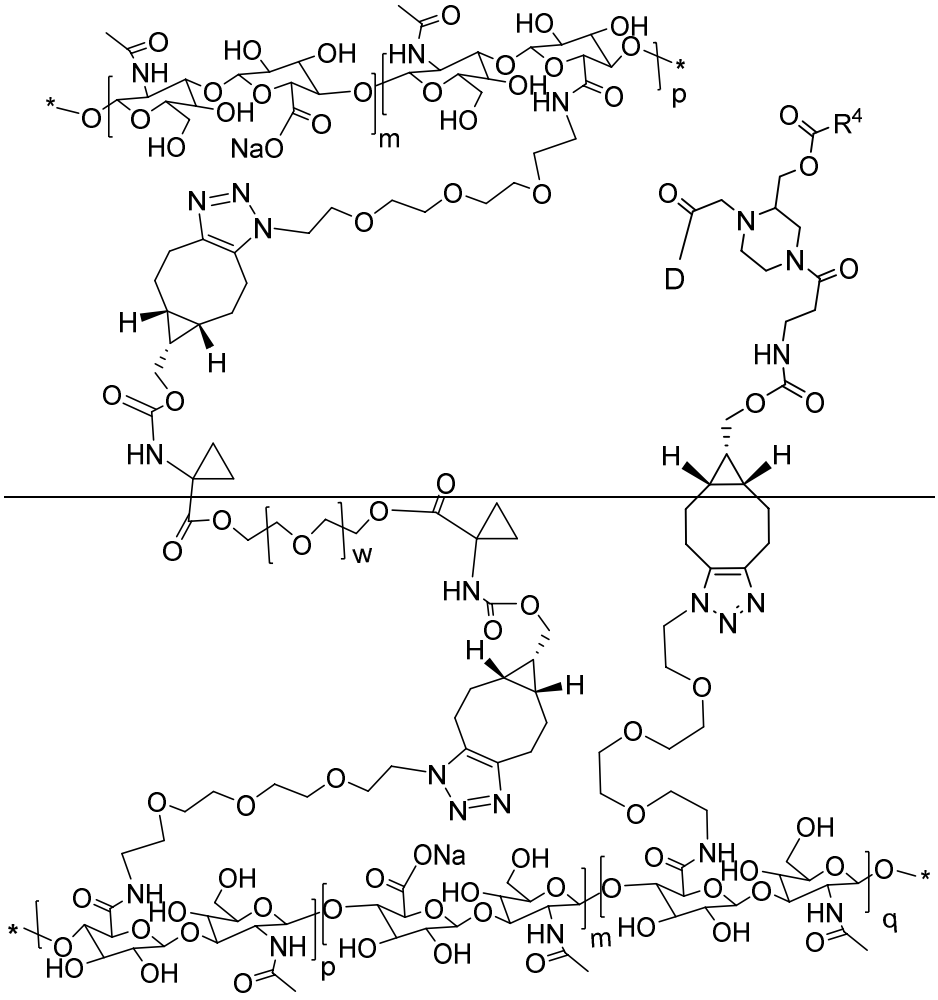
Z is N-L-A;

L is $C(O)CH_2CH_2NH$;

A is R^{11}; and

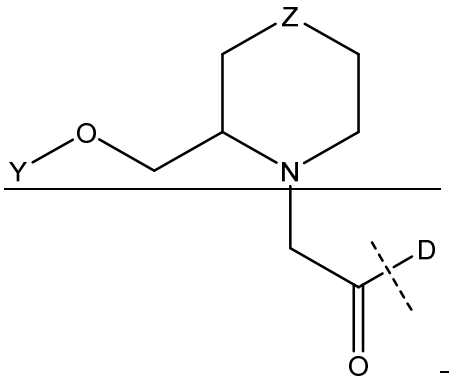
R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[3-(((((1*R*,8*S*,9s)-bicyclo[6.1.0]non-4-yn-9-yl)methoxy)carbonyl)amino)propanoate~~]~~.], or

~~57. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXXII), where Drug, D, comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:~~



~~(XXXII).~~

~~58. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula XXXIII, where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D:~~



~~(XXXIII),~~

~~where the dashed line indicates attachment to the primary amine;~~

~~Y is $C(O)R^4$;~~

~~R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by C_1-C_4alkoxy;~~

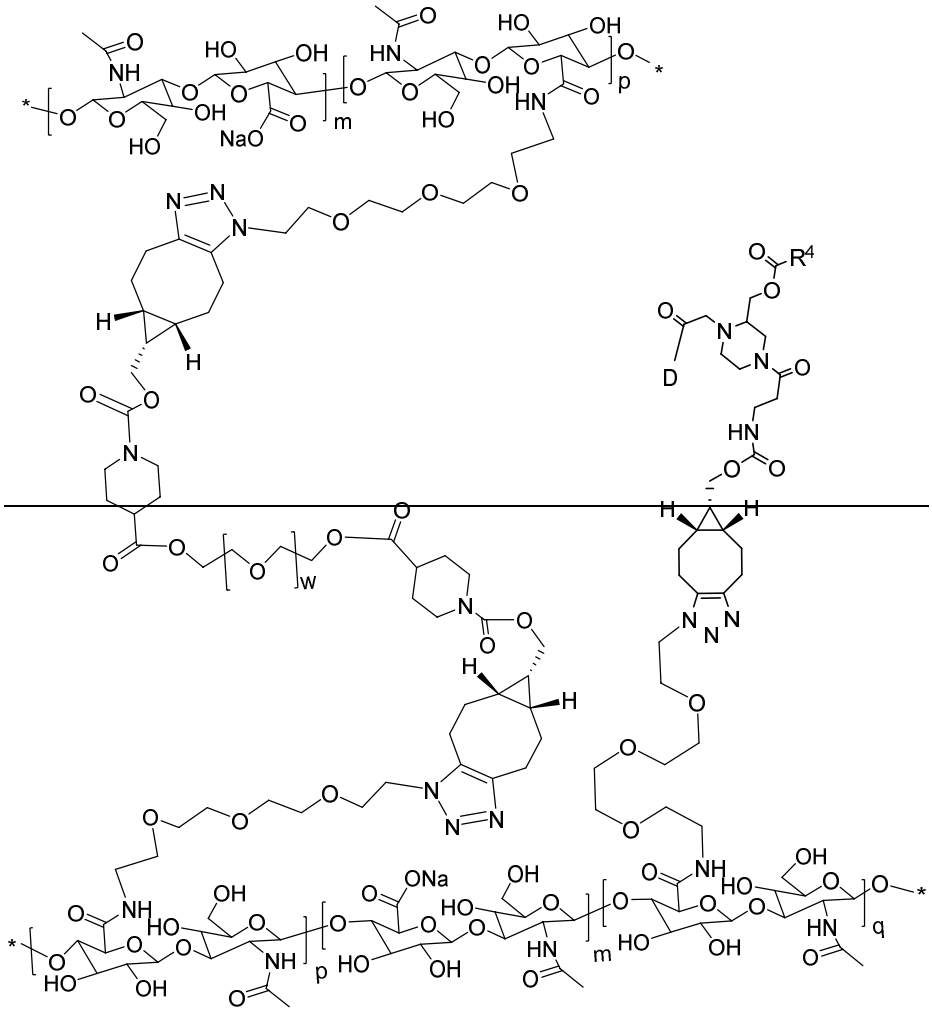
~~Z is N-L-A;~~

~~L is $C(O)CH_2CH_2NH$;~~

~~A is R^{11}; and~~

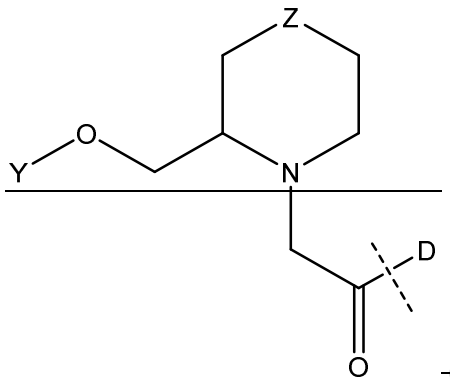
R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[1-((((1′*R*,8′*S*,9′s)-bicyclo[6.1.0]non-4′-yn-9′-yl)methoxy)carbonyl)amino-cyclopropane-1-carboxylic acid ester~~].~~], or

~~59. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXXIV), where Drug, D, comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:~~



~~(XXXIV).~~

~~60. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula XXXV, where Drug, D, comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D:~~



~~(XXXV),~~

~~where the dashed line indicates attachment to the primary amine;~~

~~Y is $C(O)R^4$;~~

~~R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by C_1-C_4alkoxy;~~

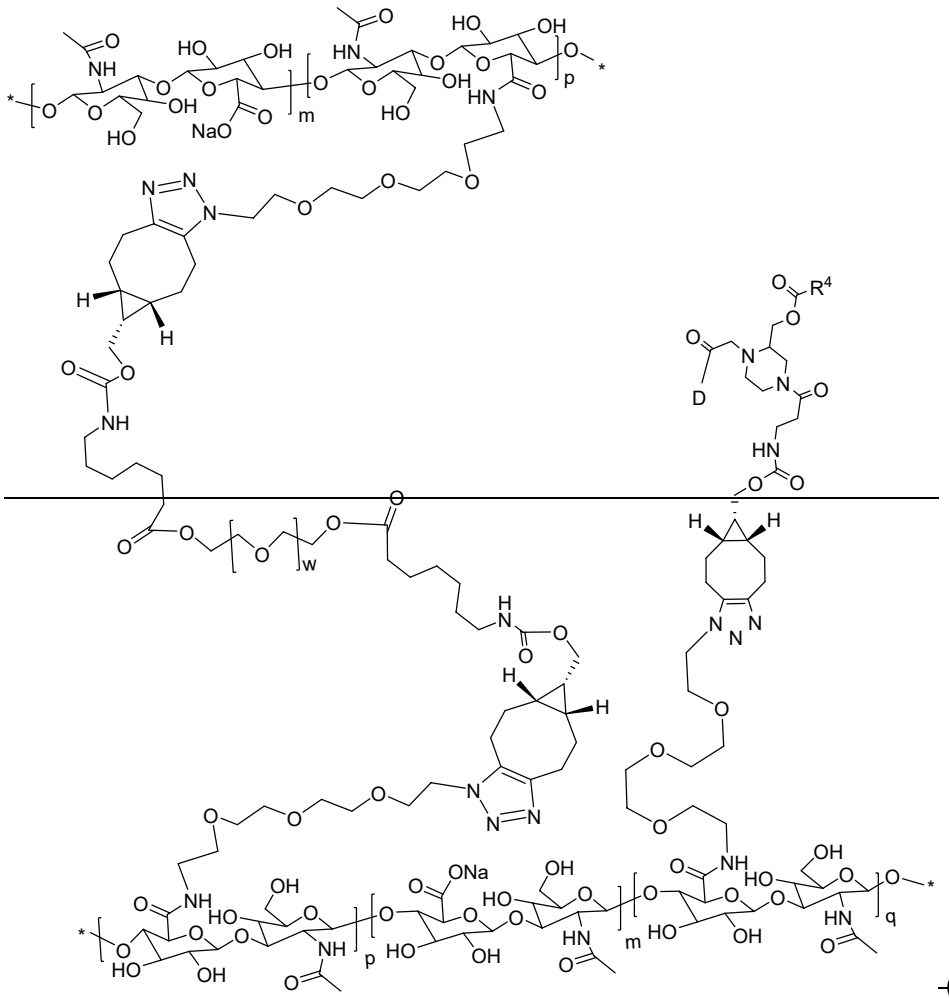
~~Z is N-L-A;~~

~~L is $C(O)CH_2CH_2NH$;~~

~~A is R^{11}; and~~

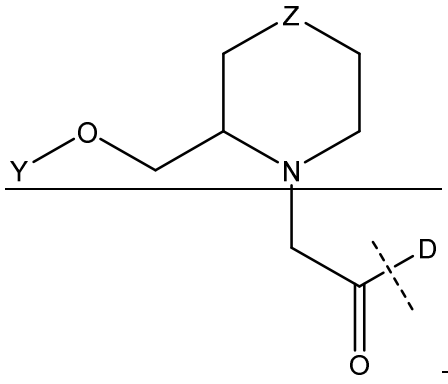
R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[1-((((1′*R*,8′*S*,9′s)-bicyclo[6.1.0]non-4′-yn-9′-yl)methoxy)carbonyl)piperidine-4-carboxylic acid ester~~].~~], or

~~61. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXXVI), where Drug, D, comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:~~



~~(XXXVI).~~

~~62. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula XXXVII, where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R is a linker suitable for release of D:~~



~~(XXXVII),~~

~~where the dashed line indicates attachment to the primary amine;~~

~~Y is C(O)R^4;~~

~~R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by C_1-C_4alkoxy;~~

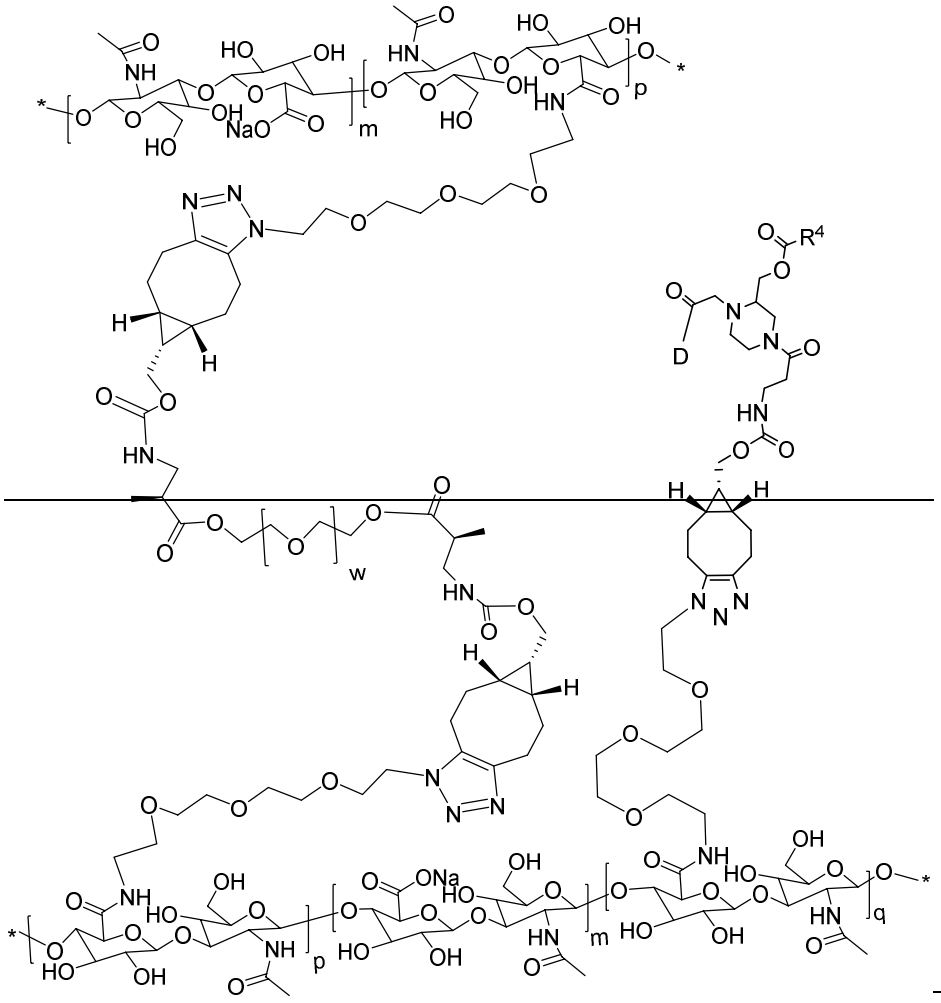
~~Z is N-L-A;~~

~~L is C(O)CH_2CH_2NH;~~

~~A is R^{11}; and~~

R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of N(H)$(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[7-(((((1′*R*,8′*S*,9′s)-bicyclo[6.1.0]non-4′-yn-9′-yl)methoxy)carbonyl)amino)heptanoate~~].~~], or

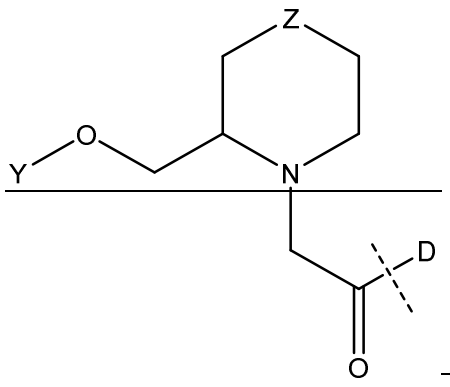
~~63. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXXVIII), where Drug, D, comprises an ANGPTL3 polypeptide comprising at least one primary amine; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:~~



~~(XXXVIII).~~

~~64. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXXIX), where D comprises an ANGPTL3 polypeptide comprising at least one primary amine; and~~

~~R is a linker suitable for release of D:~~



~~(XXXIX),~~

~~where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;~~

~~Y is $C(O)R^4$;~~

~~R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by C_1-C_4alkoxy;~~

~~Z is N-L-A;~~

~~L is $C(O)CH_2CH_2NH$;~~

~~A is R^{11}; and~~

R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[2-methyl-3-(((((1′*R*,8′*S*,9′s)-bicyclo[6.1.0]non-4′-yn-9′-yl)methoxy)carbonyl)amino)propanoate].

~~65. The drug delivery systems of any one of claims 55 to 64, wherein D is SEQ ID NO:19 and R^4 is -CH3, $-CH_2CH_3$, $-CH(CH_3)CH_3$, or methylcyclopropyl.~~

~~66. The drug delivery systems of any one of claims 55 to 65, wherein D is SEQ ID NO:19 and R^4 is $-CH_3$.~~

~~67. The drug delivery systems of any one of claims 55 to 66, wherein the D-R adduct comprises:~~

