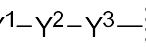
$(X\text{-}Y)_n\text{-}Z$ Formula (I)

wherein each X is independently a peptide having a molecular weight of from about 5 kDa to about 200 kDa; each Y is independently a hydrophilic linker; Z is a biocompatible polymer having a molecular weight of from about 0.1 MDa to about 3 MDa; and subscript n is an integer from 10 to 1000. . In another aspect, the present disclosure A conjugate of Formula I: $(X\text{-}Y)_n\text{-}Z$ Formula (I) wherein each X is independently a peptide having a molecular weight of from 5 kDa to 200 kDa; each Y is independently a hydrophilic linker, wherein each hydrophilic linker independently has the formula: ; wherein Y^1 is a thiol reactive group; Y^2 is a $C_{3\text{-}20}$ heteroalkylene having from 1 to 6 heteroatoms each independently N, O or S, or $-(CH_2CH_2O)_m-$, wherein subscript m is an integer of from 1 to 100; and Y^3 is a carboxy reactive group; Z is a biocompatible polymer having a molecular weight of from 0.1 MDa to 3 MDa; and subscript n is an integer from 10 to 1000.

[0008a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the conjugate as disclosed herein, and a pharmaceutically acceptable carrier.

[0008b] In another aspect, the present disclosure refers to the use of a conjugate as disclosed herein in the manufacture of a medicament for treating an ocular disease or disorder, wherein the medicament is to be intravitreal administered to a subject in need thereof.

[0008c] In another aspect, the present disclosure refers to the use of a conjugate as disclosed herein in the manufacture of a medicament for treating a disease or disorder in an articular joint, wherein the medicament is to be injected into the articular joint.

[0009] In another example, the present disclosure provides a pharmaceutical composition including a conjugate of the present invention and a pharmaceutically acceptable excipient.

[0010] In another example, the present disclosure provides a method of treating an ocular disease or disorder, the method comprising intravitreal administration to a subject in need thereof, a therapeutically effective amount of a conjugate of the present invention, thereby treating the ocular disease or disorder.

[0011] In another example, the present disclosure provides a method of treating a disease or disorder in an articular joint, the method comprising injecting into the articular joint an effective amount of a conjugate of the present invention, thereby treating the disease or disorder in the articular joint.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1 shows UV spectra of purified 830 kDa hyaluronic acid intermediates synthesized using different thiol reactive linkers. See Table 2 for conjugates.

WHAT IS CLAIMED IS:

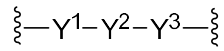
1. A conjugate of Formula I:

$$(X\text{-}Y)_n\text{-}Z \qquad \text{Formula (I)}$$

wherein

each X is independently a peptide having a molecular weight of from 5 kDa to 200 kDa;

each Y is independently a hydrophilic linker, wherein each hydrophilic linker independently has the formula:



wherein

Y^1 is a thiol reactive group;

Y^2 is a $C_{3\text{-}20}$ heteroalkylene having from 1 to 6 heteroatoms each independently N, O or S, or $-(CH_2CH_2O)_m-$, wherein subscript m is an integer of from 1 to 100; and

Y^3 is a carboxy reactive group;

Z is a biocompatible polymer having a molecular weight of from 0.1 MDa to 3 MDa; and

subscript n is an integer from 10 to 1000.

2. The conjugate of claim 1, wherein the peptide is an inhibitor of angiogenesis.

3. The conjugate of claim 2, wherein the peptide is a soluble vascular endothelial growth factor (VEGF) receptor, angiostatin, endostatin, vasostatin, an antibody specific for VEGF, or a DARPin specific for VEGF.

4. The conjugate of claim 2 or 3, wherein the peptide inhibits VEGF-A, VEGF-B, VEGF-C, VEGF-D, Ang-1, Ang-2, PDGF, or PlGF.

5. The conjugate of any one of claims 2 to 4, wherein the peptide is a monoclonal IgG antibody, an IgG antibody fragment, a single-chain variable region antibody, a single-domain heavy chain antibody, an adnectin, an affibody, an anticalin, a DARPin, a Kunitz-type inhibitor, or a receptor decoy.

6. The conjugate of claim 1, wherein the peptide modulates the activity of immune cell function.

7. The conjugate of claim 6, wherein the peptide inhibits tumor necrosis factor-α, interleukin-1β, interleukin-6, or interferon-γ.

8. The conjugate of claims 6 or 7, wherein the peptide inhibits tumor necrosis factor-α.

9. The conjugate of any one of claims 6 to 8, wherein the peptide is a monoclonal IgG antibody, an IgG antibody fragment, a single-chain variable region antibody, a single-domain heavy chain antibody, an adnectin, an affibody, an anticalin, a DARPin, a Kunitz-type inhibitor, or a receptor decoy.

10. The conjugate of any one of claims 6 to 9, wherein the peptide has a molecular weight of from 5 kDa to 30 kDa.

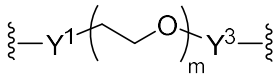
11. The conjugate of any one of claims 6 to 10, wherein the peptide has a molecular weight of from 10 kDa to 20 kDa.

12. The conjugate of any one of claims 6 to 11, wherein the peptide has an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10.

13. The conjugate of any one of claims 6 to 12, wherein the peptide has a sequence:

QVQLQESGGGLVQPGGSLRLSCAASGRTFSDHSGYTYTIGWFRQAPGKEREF VARIYWSSGNTYYADSVKGRFAISRDIAKNTVDLTMNNLEPEDTAVYYCAAR DGIPTSRSVESYNYWGQGTQVTVSS (SEQ ID NO:1).

14. The conjugate of any one of claims 1 to 13, wherein each hydrophilic linker independently has the formula:



wherein

Y^1 is a thiol reactive group;

Y^3 is a carboxy reactive group; and

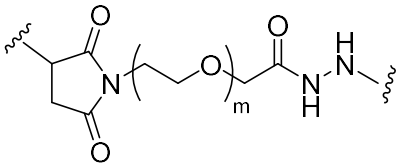
subscript m is an integer of from 1 to 100.

15. The conjugate of claim 14, wherein

Y^1 is a thiol, arylpropiolonitrile or maleimide; and

Y^3 is an amine or a N-acylhydrazide.

16. The conjugate of any one of claims 14 to 15, wherein the hydrophilic linker has the formula: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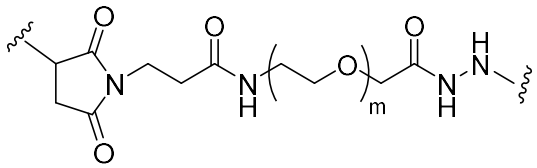
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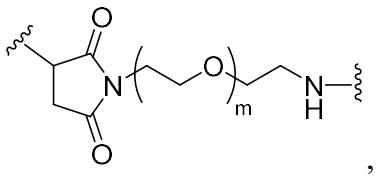
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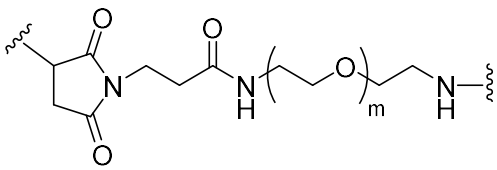
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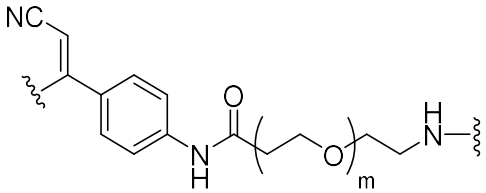
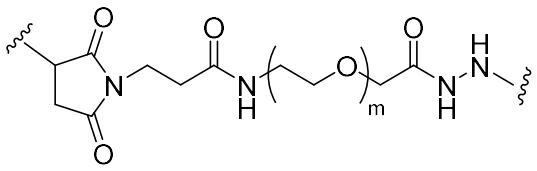


wherein subscript m is an integer of from 1 to 100.

17. The conjugate of any one of claims 14 to 16, wherein the hydrophilic linker has the formula: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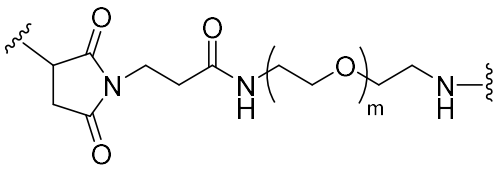
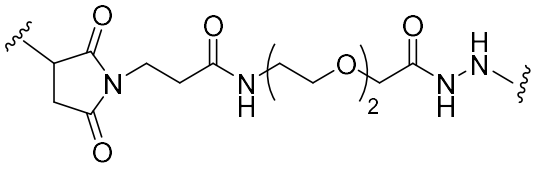


wherein subscript m is an integer of from 1 to 100.

18. The conjugate of any one of claims 14 to 17, wherein the hydrophilic linker has the formula: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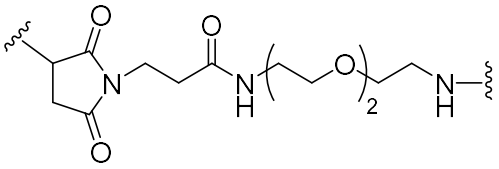
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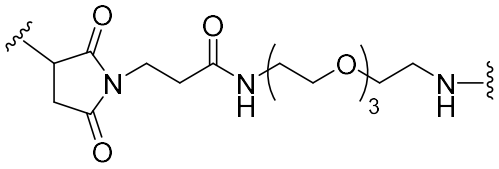
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19. The conjugate of any one of claims 1 to 18, wherein the hydrophilic linker corresponds to any one of the following:

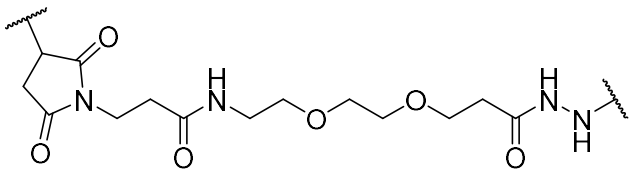
1-[3-({[2-(3-Hydrazino-3-oxopropoxy)ethoxy]methyl}amino)-3-oxopropyl]-1*H*-pyrrole-2,5-dione,

1-(3-{2-[2-(3-Hydrazino-3-oxopropoxy)ethoxy]ethylamino}-3-oxopropyl)-1*H*-pyrrole-2,5-dione, or

1-[3-(2-{2-[2-(2-Aminoethoxy)ethoxy]ethoxy}ethylamino)-3-oxopropyl]-1H-pyrrole-2,5-dione.

20. The conjugate of any one of claims 1 to 19, wherein the hydrophilic linker corresponds to 1-(3-{2-[2-(3-Hydrazino-3-oxopropoxy)ethoxy]ethylamino}-3-oxopropyl)-1*H*-pyrrole-2,5-dione.

21. The conjugate of any one of claims 1 to 20, wherein the hydrophilic linker is



22. The conjugate of any one of claims 1 to 21, wherein the biocompatible polymer is a polysaccharide.

23. The conjugate of any one of claims 1 to 22, wherein the biocompatible polymer is a glycosaminoglycan.

24. The conjugate of any one of claims 1 to 23, wherein the biocompatible polymer is hyaluronic acid.

25. The conjugate of any one of claims 1 to 24, wherein the biocompatible polymer has a molecular weight of from 0.2 MDa to 1.5 MDa.

26. The conjugate of any one of claims 1 to 25, wherein the biocompatible polymer has a molecular weight of about 0.9 MDa.

27. The conjugate of any one of claims 1 to 24, wherein the biocompatible polymer has a molecular weight of from 0.8 MDa to 3 MDa.

28. The conjugate of any one of claims 1 to 24, wherein the biocompatible polymer has a molecular weight of about 2 MDa.

29. The conjugate of any one of claims 1 to 28, wherein subscript n is an integer of from 10 to 400.

30. The conjugate of any one of claims 1 to 29, wherein subscript n is an integer of from 10 to 100.

31. The conjugate of any one of claims 1 to 30, wherein subscript n is an integer of from 50 to 100.

32. A pharmaceutical composition comprising the conjugate of any one of claims 1 to 31, and a pharmaceutically acceptable carrier.

33. Use of a conjugate of any one of claims 1 to 31 in the manufacture of a medicament for treating an ocular disease or disorder, wherein the medicament is to be intravitreal administered to a subject in need thereof.

34. The use of claim 33, wherein the ocular disorder is macular degeneration, choroidal neovascularization, retinal neovascularization, proliferative vitreoretinopathy, diabetic retinopathy, glaucoma, or ocular inflammation.

35. The use of claim 33 or 34, wherein the vitreous half-life of the conjugate is at least 2 weeks.

36. The use of any one of claims 33 to 35, wherein the subject is a human.

37. The use of any one of claims 33 to 36, wherein the conjugate is to be administered once every two months, once every three months, once every 6 months, or once a year.

38. The use of any one of claims 33 to 37, wherein the vitreous half-life of the conjugate is at least 2-fold greater than the half-life of the biologically active polypeptide not conjugated to the biocompatible polymer.

39. Use of a conjugate of any one of claims 1 to 31 in the manufacture of a medicament for treating a disease or disorder in an articular joint, wherein the medicament is to be injected into the articular joint.

40. The use of claim 39, wherein the diffusion half-life of the conjugate is at least about 2 times longer than the peptide.

41. The use of claims 39 or 40, wherein the diffusion half-life of the conjugate is from 2 to 100 times longer than the peptide.

42. The use of any one of claims 39 to 41, wherein the intra-articular half-life of the conjugate is at least about 20% longer than the peptide.

43. The use of any one of claims 39 to 42, wherein the intra-articular half-life of the conjugate is from 20% to 1000% longer than the peptide.

44. The use of any one of claims 39 to 43, wherein the disease or disorder is rheumatoid arthritis, wear-related osteoarthritis, age-related osteoarthritis, post-traumatic osteoarthritis, psoriatic arthritis, and aseptic implant loosening, joint effusion, ankylosing spondylitis, bursitis, gout, reactive arthritis, synovitis, or avascular necrosis.

45. The use of any one of claims 39 to 44, wherein the conjugate is to be injected into the articular joint no more than about once a month.

46. The use of any one of claims 39 to 45, wherein the conjugate is to be injected into the articular joint from about once a month to once every 6 months.

47. The use of any one of claims 39 to 46, wherein the conjugate is to be injected into the articular joint once every 2 months or once every 3 months.