

WHAT IS CLAIMED IS:

- 1 1. A conjugate of Formula I:

2 (X-Y)_n-Z Formula (I)

3 wherein

4 each X is independently a peptide having a molecular weight of from about 5 kDa to

5 about 200 kDa;

6 each Y is independently a hydrophilic linker;

7 Z is a biocompatible polymer having a molecular weight of from about 0.1 MDa to

8 about 3 MDa; and

9 subscript n is an integer from 10 to 1000.
- 1 2. The conjugate of claim 1, wherein the peptide is an inhibitor of

2 angiogenesis.
- 1 3. The conjugate of claim 2, wherein the peptide is a soluble vascular

2 endothelial growth factor (VEGF) receptor, angiostatin, endostatin, vasostatin, an antibody

3 specific for VEGF, or a DARPIn specific for VEGF.
- 1 4. The conjugate of claim 2 or 3, wherein the peptide inhibits VEGF-A,

2 VEGF-B, VEGF-C, VEGF-D, Ang-1, Ang-2, PDGF, or PlGF.
- 1 5. The conjugate of any one of claims 2 to 4, wherein the peptide is a

2 monoclonal IgG antibody, an IgG antibody fragment, a single-chain variable region antibody,

3 a single-domain heavy chain antibody, an adnectin, an affibody, an anticalin, a DARPIn, a

4 Kunitz-type inhibitor, or a receptor decoy.
- 1 6. The conjugate of claim 1, wherein the peptide modulates the activity of

2 immune cell function.
- 1 7. The conjugate of claim 6, wherein the peptide inhibits tumor necrosis

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

2 necrosis factor-α.

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

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

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

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

1 13. The conjugate of any one of claims 6 to 12, wherein the peptide has a
2 sequence:
3 QVQLQESGGGLVQPGGSLRLSCAASGRTFSDHSGYTYTIGWFRQAPGKEREF
4 VARIYWSSGNTYYADSVKGRFAISRDIKNTVDLTMNNLEPEDTAVYYCAAR
5 DGIPTSRSVESYNYWGQGTQVTVSS (SEQ ID NO:1).

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



4 wherein

5 Y¹ is a thiol reactive group;

6 Y² is a C₃₋₂₀ heteroalkylene having from 1 to 6 heteroatoms each independently N, O
7 or S, or -(CH₂CH₂O)_m-, wherein subscript m is an integer of from 1 to 100;

8 and

9 Y³ is a carboxy reactive group.

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



4 wherein

5 Y^1 is a thiol reactive group;

6 Y^3 is a carboxy reactive group; and

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

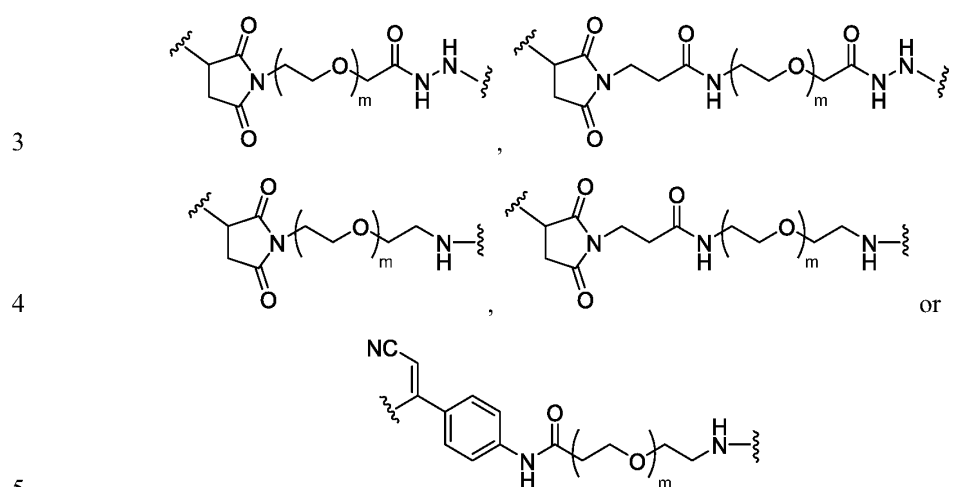
1 16. The conjugate of claim 15, wherein

2 Y^1 is a thiol, arylpropionitrile or maleimide; and

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

1 17. The conjugate of any one of claims 14 to 16, wherein the hydrophilic

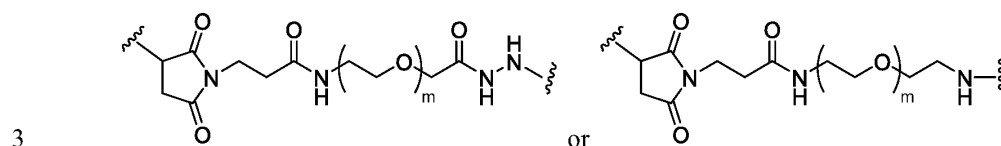
2 linker has the formula:



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

1 18. The conjugate of any one of claims 14 to 17, wherein the hydrophilic

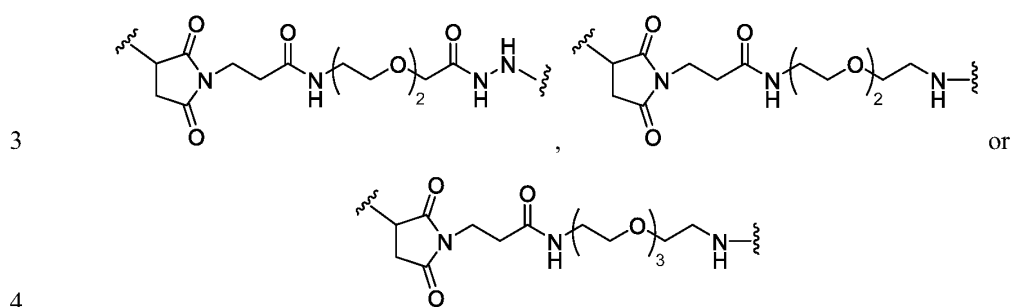
2 linker has the formula:



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

1 19. The conjugate of any one of claims 14 to 18, wherein the hydrophilic

2 linker has the formula:



1 20. The conjugate of any one of claims 1 to 19, wherein the biocompatible
2 polymer is a polysaccharide.

1 21. The conjugate of any one of claims 1 to 20, wherein the biocompatible
2 polymer is a glycosaminoglycan.

1 22. The conjugate of any one of claims 1 to 21, wherein the biocompatible
2 polymer is hyaluronic acid.

1 23. The conjugate of any one of claims 1 to 22, wherein the biocompatible
2 polymer has a molecular weight of from about 0.2 MDa to about 1.5 MDa.

1 24. The conjugate of any one of claims 1 to 23, wherein the biocompatible
2 polymer has a molecular weight of about 0.9 MDa.

1 25. The conjugate of any one of claims 1 to 22, wherein the biocompatible
2 polymer has a molecular weight of from about 0.8 MDa to about 3 MDa.

1 26. The conjugate of any one of claims 1 to 22, wherein the biocompatible
2 polymer has a molecular weight of about 2 MDa.

1 27. The conjugate of any one of claims 1 to 26, wherein subscript n is an
2 integer of from 10 to 400.

1 28. The conjugate of any one of claims 1 to 27, wherein subscript n is an
2 integer of from 10 to 100.

1 29. The conjugate of any one of claims 1 to 28, wherein subscript n is an
2 integer of from 50 to 100.

1 30. A pharmaceutical composition comprising the conjugate of any one of
2 claims 1 to 29, and a pharmaceutically acceptable carrier.

1 31. A method of treating an ocular disease or disorder, the method
2 comprising intravitreal administration to a subject in need thereof, a therapeutically effective
3 amount of a conjugate of any one of claims 1 to 29, thereby treating the ocular disease or
4 disorder.

1 32. The method of claim 31, wherein the ocular disorder is macular
2 degeneration, choroidal neovascularization, retinal neovascularization, proliferative
3 vitreoretinopathy, diabetic retinopathy, glaucoma, or ocular inflammation.

1 33. The method of claim 31 or 32, wherein the vitreous half-life of the
2 conjugate is at least 2 weeks.

1 34. The method of any one of claims 31 to 33, wherein the subject is a
2 human.

1 35. The method of any one of claims 31 to 34, wherein the conjugate is
2 administered once every two months, once every three months, once every 6 months, or once
3 a year.

1 36. The method of any one of claims 31 to 35, wherein the vitreous half-
2 life of the conjugate is at least 2-fold greater than the half-life of the biologically active
3 polypeptide not conjugated to the biocompatible polymer.

1 37. A method of treating a disease or disorder in an articular joint, the
2 method comprising injecting into the articular joint an effective amount of a conjugate of any
3 one of claims 1 to 29, thereby treating the disease or disorder in the articular joint.

1 38. The method of claim 37, wherein the diffusion half-life of the
2 conjugate is at least about 2 times longer than the peptide.

1 39. The method of claims 37 or 38, wherein the diffusion half-life of the
2 conjugate is from about 2 to about 100 times longer than the peptide.

1 40. The method of any one of claims 37 to 39, wherein the intra-articular
2 half-life of the conjugate is at least about 20% longer than the peptide.

1 41. The method of any one of claims 37 to 40, wherein the intra-articular
2 half-life of the conjugate is from about 20% to about 1000% longer than the peptide.

1 42. The method of any one of claims 37 to 41, wherein the disease or
2 disorder is rheumatoid arthritis, wear-related osteoarthritis, age-related osteoarthritis, post-
3 traumatic osteoarthritis, psoriatic arthritis, and aseptic implant loosening, joint effusion,
4 ankylosing spondylitis, bursitis, gout, reactive arthritis, synovitis, or avascular necrosis.

1 43. The method of any one of claims 37 to 42, wherein the conjugate is
2 injected into the articular joint no more than about once a month.

1 44. The method of any one of claims 37 to 43, wherein the conjugate is
2 injected into the articular joint from about once a month to once every 6 months.

1 45. The method of any one of claims 37 to 44, wherein the conjugate is
2 injected into the articular joint once every 2 months or once every 3 months.