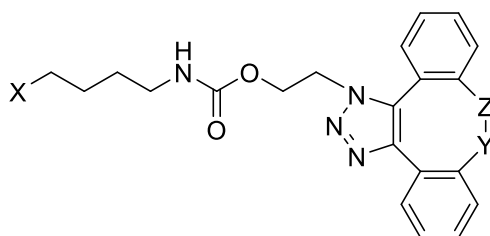


CLAIMS

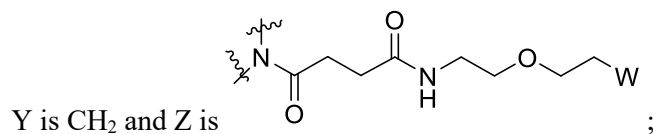
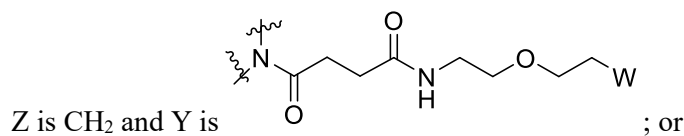
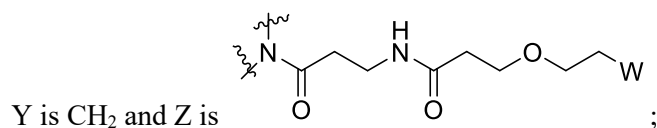
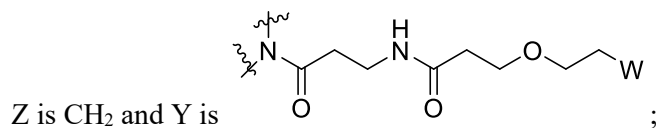
WHAT IS CLAIMED IS:

1. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (I):



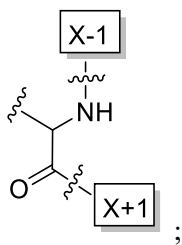
(I)

wherein:



W is a PEG group having a molecular weight of about 50 kDa;

X has the structure:

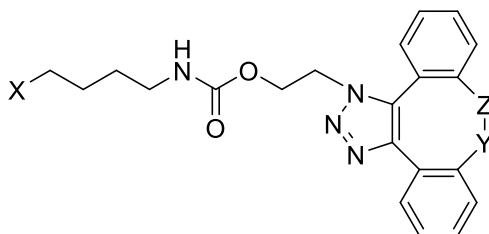


X-1 indicates the point of attachment to the preceding amino acid residue;

X+1 indicates the point of attachment to the following amino acid residue;

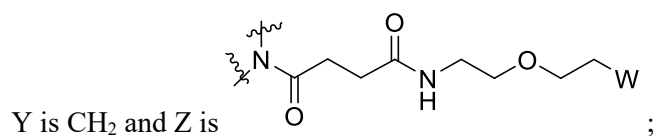
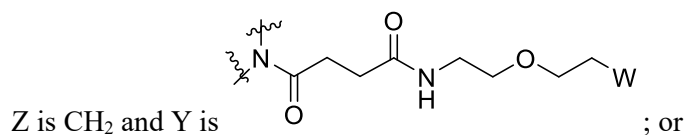
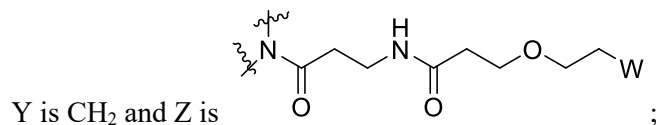
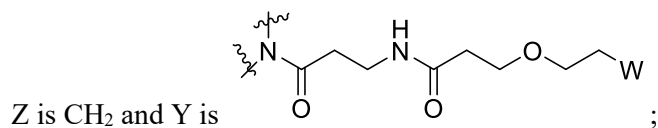
wherein the at least one amino acid residue replaced by the structure of Formula (I) is located in the IL-2 polypeptide at a position selected from K8, H15, L18, D19, N25, N87, E99, and N118, wherein the residue positions correspond to positions 8, 15, 18, 19, 25, 87, 99, and 118 as set forth in SEQ ID NO: 3.

2. The IL-2 conjugate of claim 1, wherein the IL-2 polypeptide comprises an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 3 in which the at least one amino acid residue replaced by the structure of Formula (I) is located in the IL-2 polypeptide at a position selected from K8, H15, L18, D19, N25, N87, E99, and N118.
3. The IL-2 conjugate of claim 1, wherein the IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 3 in which the at least one amino acid residue replaced by the structure of Formula (I) is located in the IL-2 polypeptide at a position selected from K8, H15, L18, D19, N25, N87, E99, and N118.
4. The IL-2 conjugate of claim 1, wherein the IL-2 polypeptide consists of the amino acid sequence of SEQ ID NO: 3 in which the at least one amino acid residue replaced by the structure of Formula (I) is located in the IL-2 polypeptide at a position selected from K8, H15, L18, D19, N25, N87, E99, and N118.
5. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (I):



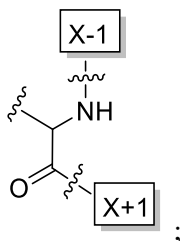
(I)

wherein:



W is a PEG group having a molecular weight of about 50 kDa;

X has the structure:

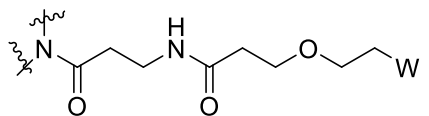


X-1 indicates the point of attachment to the preceding amino acid residue;

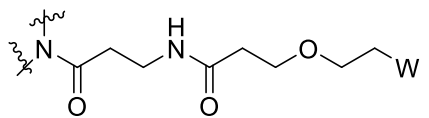
X+1 indicates the point of attachment to the following amino acid residue;

wherein the at least one amino acid residue replaced by the structure of Formula (I) is located in the IL-2 polypeptide at a position selected from K9, H16, L19, D20, N26, N88, E100, and N119, wherein the residue positions correspond to positions 9, 16, 19, 20, 26, 88, 100, and 119 as set forth in SEQ ID NO: 4.

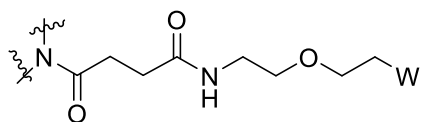
6. The IL-2 conjugate of claim 5, wherein the IL-2 polypeptide comprises an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 4 in which the at least one amino acid residue replaced by the structure of Formula (I) is located in the IL-2 polypeptide at a position selected from K9, H16, L19, D20, N26, N88, E100, and N119.
7. The IL-2 conjugate of claim 5, wherein the IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 4 in which the at least one amino acid residue replaced by the structure of Formula (I) is located in the IL-2 polypeptide at a position selected from K9, H16, L19, D20, N26, N88, E100, and N119.
8. The IL-2 conjugate of claim 5, wherein the IL-2 polypeptide consists of the amino acid sequence of SEQ ID NO: 4 in which the at least one amino acid residue replaced by the structure of Formula (I) is located in the IL-2 polypeptide at a position selected from K9, H16, L19, D20, N26, N88, E100, and N119.
9. The IL-2 conjugate of any one of claims 1-8, wherein Z is CH₂ and Y is



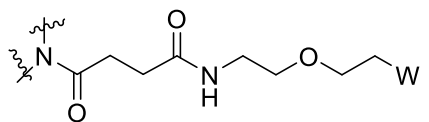
10. The IL-2 conjugate of any one of claims 1-8, wherein Y is CH₂ and Z is



11. The IL-2 conjugate of any one of claims 1-8, wherein Z is CH₂ and Y is

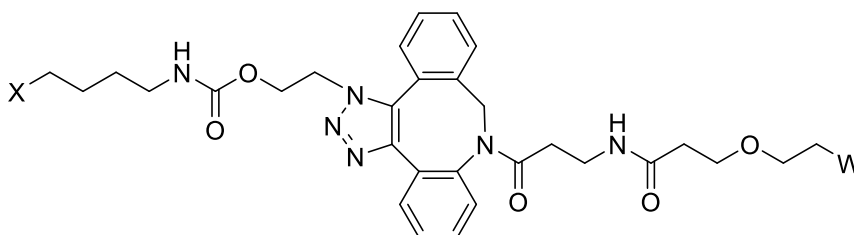


12. The IL-2 conjugate of any one of claims 1-8, wherein Y is CH₂ and Z is

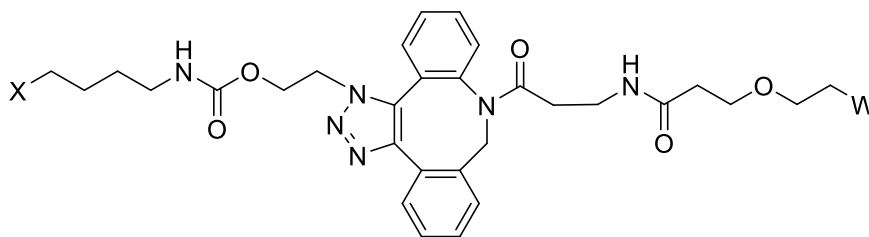


13. The IL-2 conjugate of any one of claims 5-12, wherein the position is K9.

14. The IL-2 conjugate of any one of claims 5-12, wherein the position is H16.
15. The IL-2 conjugate of any one of claims 5-12, wherein the position is L19.
16. The IL-2 conjugate of any one of claims 5-12, wherein the position is D20.
17. The IL-2 conjugate of any one of claims 5-12, wherein the position is N26.
18. The IL-2 conjugate of any one of claims 5-12, wherein the position is N88.
19. The IL-2 conjugate of any one of claims 5-12, wherein the position is E100.
20. The IL-2 conjugate of any one of claims 5-12, wherein the position is N119.
21. The IL-2 conjugate of any one of claims 1-4 and 9-12, wherein the position is K8.
22. The IL-2 conjugate of any one of claims 1-4 and 9-12, wherein the position is H15.
23. The IL-2 conjugate of any one of claims 1-4 and 9-12, wherein the position is L18.
24. The IL-2 conjugate of any one of claims 1-4 and 9-12, wherein the position is D19.
25. The IL-2 conjugate of any one of claims 1-4 and 9-12, wherein the position is N25.
26. The IL-2 conjugate of any one of claims 1-4 and 9-12, wherein the position is N87.
27. The IL-2 conjugate of any one of claims 1-4 and 9-12, wherein the position is E99.
28. The IL-2 conjugate of any one of claims 1-4 and 9-12, wherein the position is N118.
29. An IL-2 conjugate comprising the amino acid sequence of any one of SEQ ID NOS: 49-52, 54-57, 214-217, and 219-222, wherein [AzK_PEG50kDa] has the structure of Formula (II) or Formula (III):



(II)

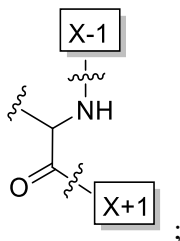


(III)

wherein:

W is a PEG group having a molecular weight of about 50 kDa;

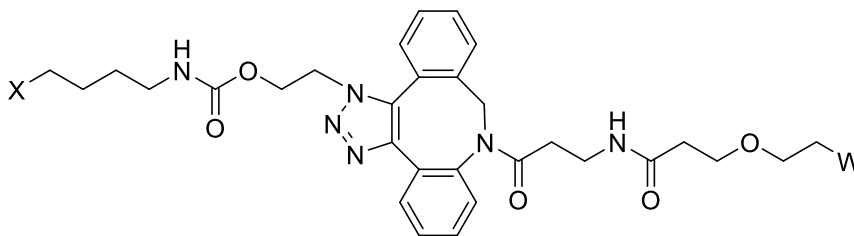
X has the structure:



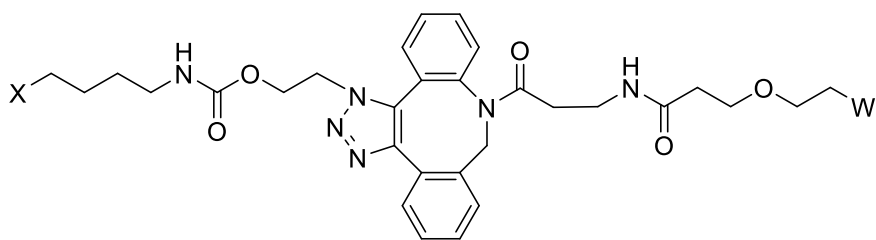
X-1 indicates the point of attachment to the preceding amino acid residue; and

X+1 indicates the point of attachment to the following amino acid residue.

30. A pharmaceutical composition comprising a mixture of IL-2 conjugates, wherein the mixture comprises (i) an IL-2 conjugate comprising the amino acid sequence of any one of SEQ ID NOS: 49-52, 54-57, 214-217, and 219-222, in which [AzK_PEG50kDa] has the structure of Formula (II), and (ii) an IL-2 conjugate comprising the amino acid sequence of any one of SEQ ID NOS: 49-52, 54-57, 214-217, and 219-222, in which [AzK_PEG50kDa] has the structure of Formula (III):



(II)

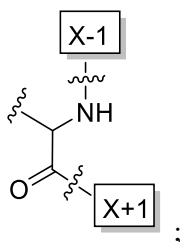


(III)

wherein:

W is a PEG group having a molecular weight of about 50 kDa;

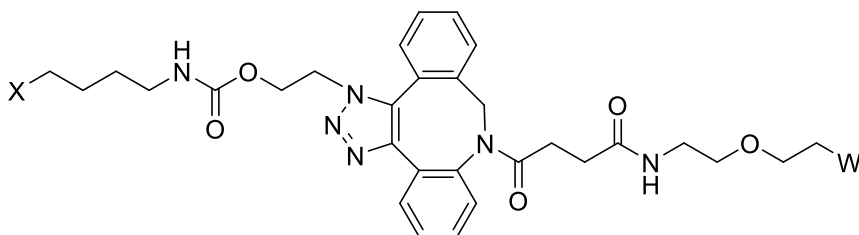
X has the structure:



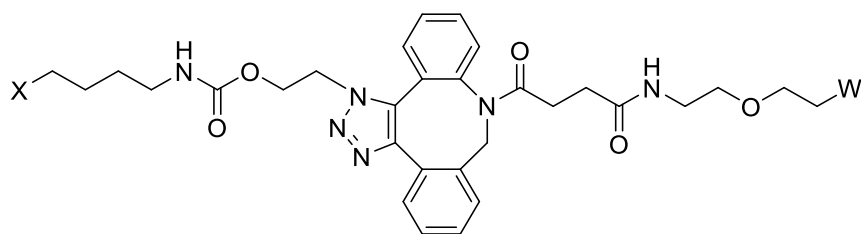
X-1 indicates the point of attachment to the preceding amino acid residue; and

X+1 indicates the point of attachment to the following amino acid residue.

31. An IL-2 conjugate comprising the amino acid sequence of any one of SEQ ID NOS: 124-127, 129-132, 169-172 and 174-177, wherein [AzK_L1_PEG50kDa] has the structure of Formula (IV) or Formula (V):



(IV)

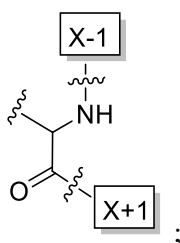


(V)

wherein:

W is a PEG group having a molecular weight of about 50 kDa;

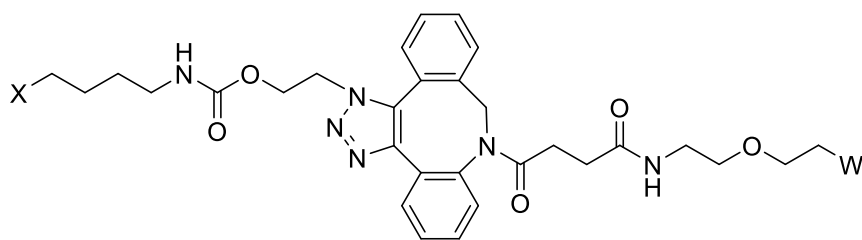
X has the structure:



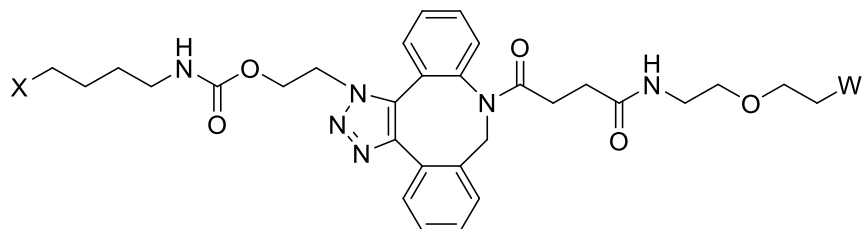
X-1 indicates the point of attachment to the preceding amino acid residue; and

X+1 indicates the point of attachment to the following amino acid residue.

32. The IL-2 conjugate of claim 31, wherein the IL-2 conjugate has the amino acid sequence of SEQ ID NO: 170.
33. The IL-2 conjugate of claim 31, wherein the IL-2 conjugate comprises the amino acid sequence of SEQ ID NO: 125.
34. A pharmaceutical composition comprising a mixture of IL-2 conjugates, wherein the mixture comprises (i) an IL-2 conjugate comprising the amino acid sequence of any one of SEQ ID NOS: 124-127, 129-132, 169-172 and 174-177, in which [AzK_L1_PEG50kDa] has the structure of Formula (IV), and (ii) an IL-2 conjugate comprising the amino acid sequence of any one of SEQ ID NOS: 124-127, 129-132, 169-172, and 174-177, in which [AzK_L1_PEG50kDa] has the structure of Formula (V):



(IV)

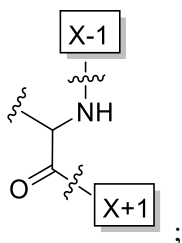


(V)

wherein:

W is a PEG group having a molecular weight of about 50 kDa; and

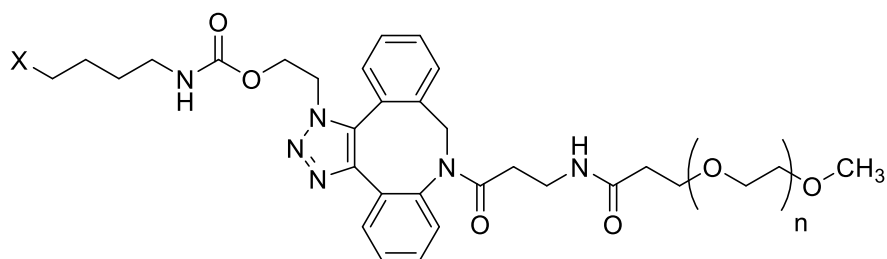
X has the structure:



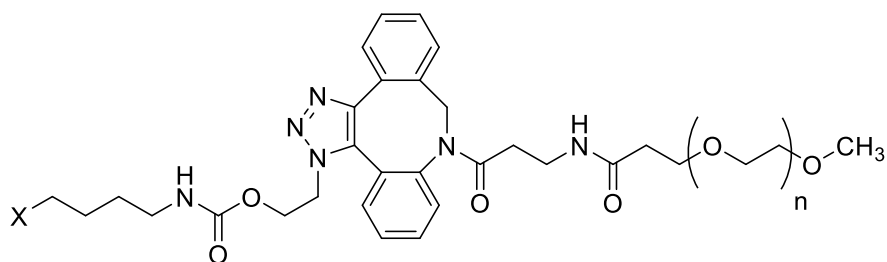
X-1 indicates the point of attachment to the preceding amino acid residue; and

X+1 indicates the point of attachment to the following amino acid residue.

35. The pharmaceutical composition of claim 34, wherein the IL-2 conjugates each comprise the amino acid sequence of SEQ ID NO: 170.
36. The pharmaceutical composition of claim 34, wherein the IL-2 conjugates each comprise the amino acid sequence of SEQ ID NO: 125.
37. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (VI) or Formula (VII):



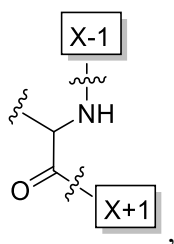
(VI)



(VII)

wherein:

n is an integer such that a PEG group having the structure of $-(\text{OCH}_2\text{CH}_2)_n\text{-OCH}_3$ has a molecular weight of about 50 kDa;



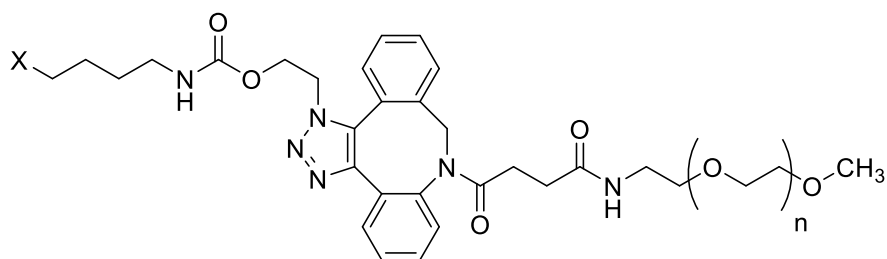
X has the structure:

X-1 indicates the point of attachment to the preceding amino acid residue;

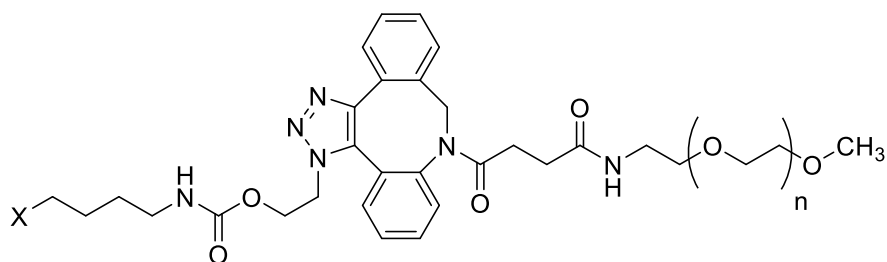
X+1 indicates the point of attachment to the following amino acid residue; and

the at least one amino acid residue replaced by the structure of Formula (VI) or Formula (VII) is located in the IL-2 polypeptide at a position selected from K8, H15, L18, D19, N25, N87, E99, and N118, wherein the residue positions correspond to positions 8, 15, 18, 19, 25, 87, 99, and 118 as set forth in SEQ ID NO: 3.

38. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (VIII) or Formula (IX):



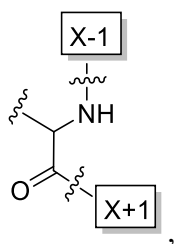
(VIII)



(IX)

wherein:

n is an integer such that a PEG group having the structure of $-(OCH_2CH_2)_n-OCH_3$ has a molecular weight of about 50 kDa;



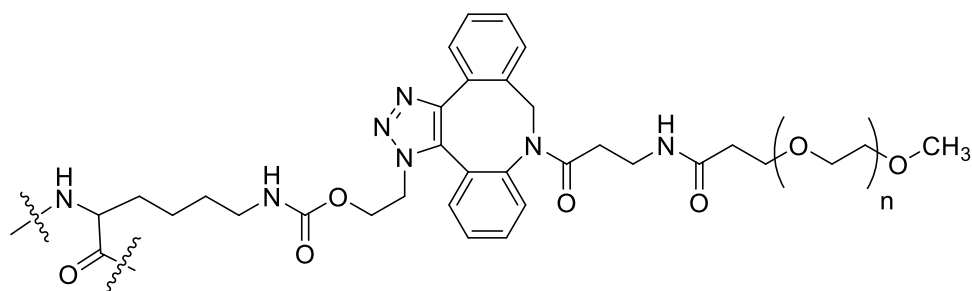
X has the structure:

X-1 indicates the point of attachment to the preceding amino acid residue;

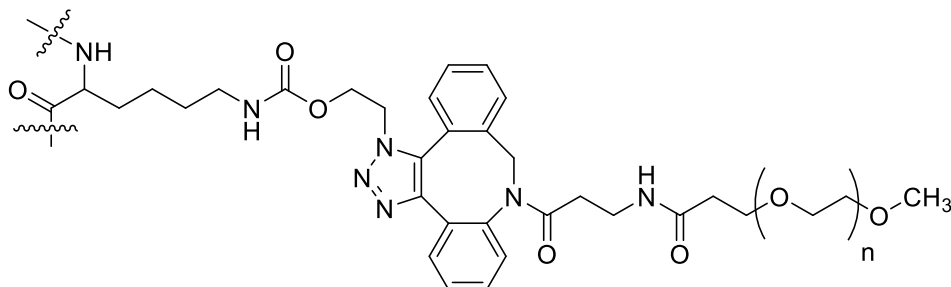
X+1 indicates the point of attachment to the following amino acid residue; and

the at least one amino acid residue replaced by the structure of Formula (VIII) or Formula (IX) is located in the IL-2 polypeptide at a position selected from K8, H15, L18, D19, N25, N87, E99, and N118, wherein the residue positions correspond to positions 8, 15, 18, 19, 25, 87, 99, and 118 as set forth in SEQ ID NO: 3.

39. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (X) or Formula (XI):



(X)



(XI)

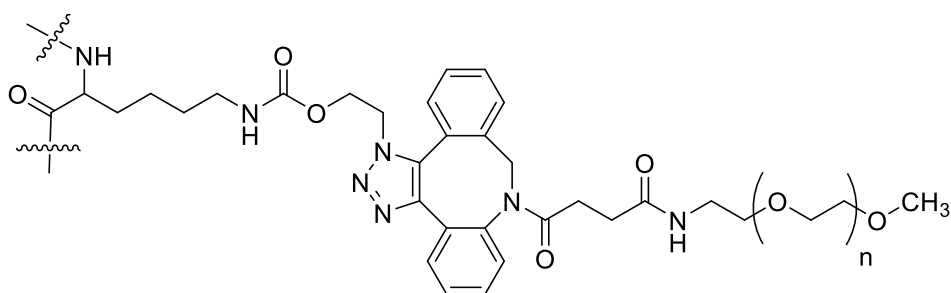
wherein:

n is an integer such that a PEG group having the structure of $-(OCH_2CH_2)_n-OCH_3$ has a molecular weight of about 50 kDa; and

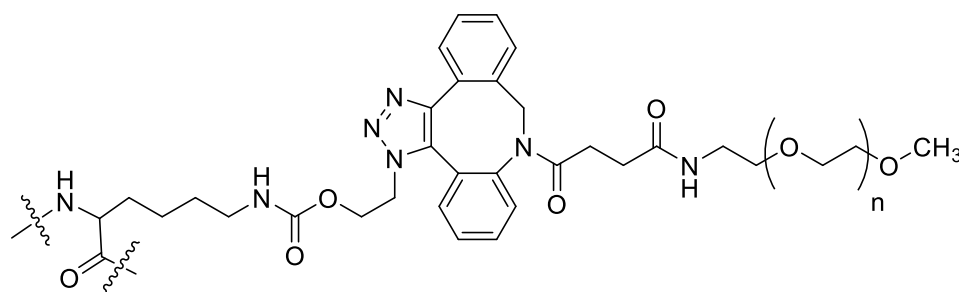
the wavy lines indicate covalent bonds to the first amino acid residues preceding the at least one amino acid residue and the first amino acid residue following the at least one amino acid residue, respectively, within SEQ ID NO: 3; and

the at least one amino acid residue replaced by the structure of Formula (X) or Formula (XI) is located in the IL-2 polypeptide at a position selected from K8, H15, L18, D19, N25, N87, E99, and N118, wherein the residue positions correspond to positions 8, 15, 18, 19, 25, 87, 99, and 118 as set forth in SEQ ID NO: 3.

40. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (XII) or Formula (XIII):



(XII)



(XIII)

wherein:

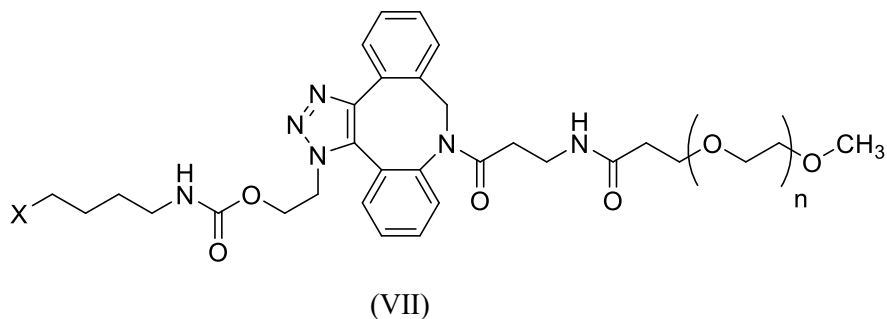
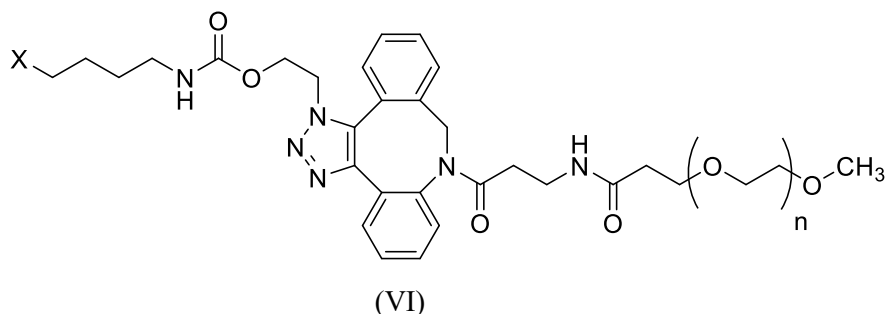
n is an integer such that a PEG group having the structure of $-(\text{OCH}_2\text{CH}_2)_n\text{-OCH}_3$ has a molecular weight of about 50 kDa;

the wavy lines indicate covalent bonds to the first amino acid residues preceding the at least one amino acid residue and the first amino acid residue following the at least one amino acid residue, respectively, within SEQ ID NO: 3; and

the at least one amino acid residue replaced by the structure of Formula (XII) or Formula (XIII) is located in the IL-2 polypeptide at a position selected from K8, H15, L18, D19, N25, N87, E99, and N118, wherein the residue positions correspond to positions 8, 15, 18, 19, 25, 87, 99, and 118 as set forth in SEQ ID NO: 3.

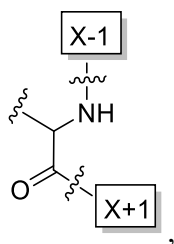
41. The IL-2 conjugate of any one of claims 37-40, wherein the IL-2 polypeptide comprises an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 3 in which the position is selected from K8, H15, L18, D19, N25, N87, E99, and N118.
42. The IL-2 conjugate of any one of claims 37-40, wherein the IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 3 in which the position is selected from K8, H15, L18, D19, N25, N87, E99, and N118.

43. The IL-2 conjugate of any one of claims 37-40, wherein the IL-2 polypeptide consists of the amino acid sequence of SEQ ID NO: 3 in which the position is selected from K8, H15, L18, D19, N25, N87, E99, and N118.
44. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (VI) or Formula (VII):



wherein:

n is an integer such that a PEG group having the structure of $-(\text{OCH}_2\text{CH}_2)_n\text{-OCH}_3$ has a molecular weight of about 50 kDa; and



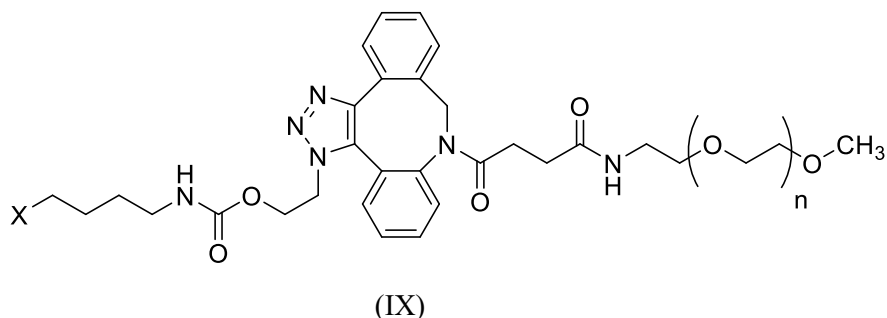
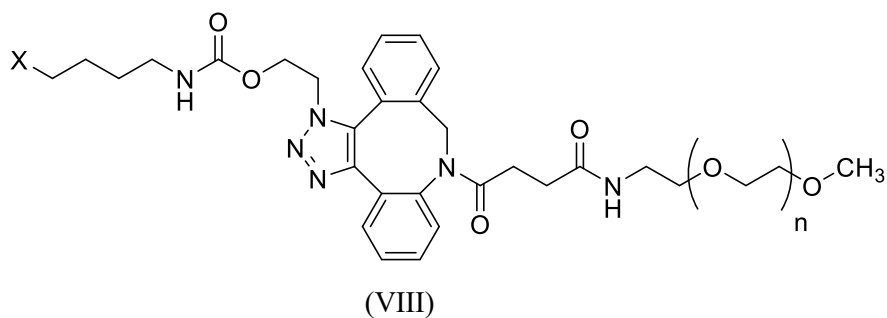
X-1 indicates the point of attachment to the preceding amino acid residue;

X+1 indicates the point of attachment to the following amino acid residue; and

the at least one amino acid residue replaced by the structure of Formula (VI) or Formula (VII) is located in the IL-2 polypeptide at a position selected from K9, H16, L19, D20, N26, N88, E100, and

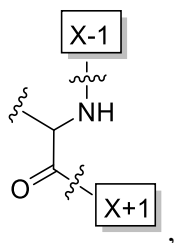
N119, wherein the residue positions correspond to positions 9, 16, 19, 20, 26, 88, 100, and 119 as set forth in SEQ ID NO: 4.

45. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (VIII) or Formula (IX):



wherein:

n is an integer such that a PEG group having the structure of $-(\text{OCH}_2\text{CH}_2)_n\text{-OCH}_3$ has a molecular weight of about 50 kDa;



X has the structure:

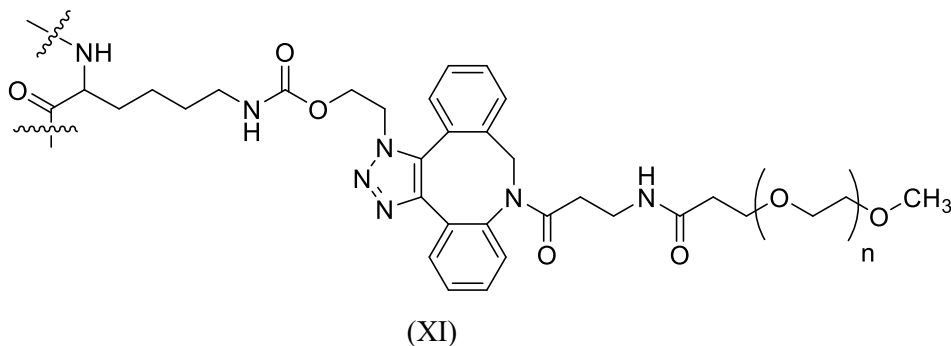
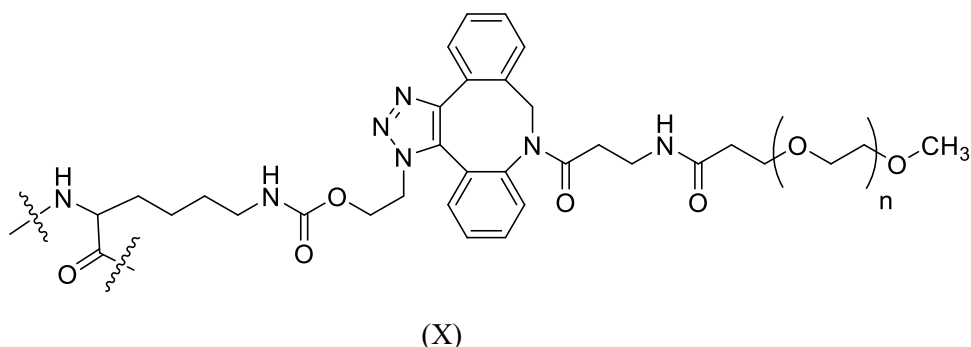
X-1 indicates the point of attachment to the preceding amino acid residue;

X+1 indicates the point of attachment to the following amino acid residue; and

the at least one amino acid residue replaced by the structure of Formula (VIII) or Formula (IX) is located in the IL-2 polypeptide at a position selected from K9, H16, L19, D20, N26, N88, E100, and

N119, wherein the residue positions correspond to positions 9, 16, 19, 20, 26, 88, 100, and 119 as set forth in SEQ ID NO: 4.

46. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (X) or Formula (XI):



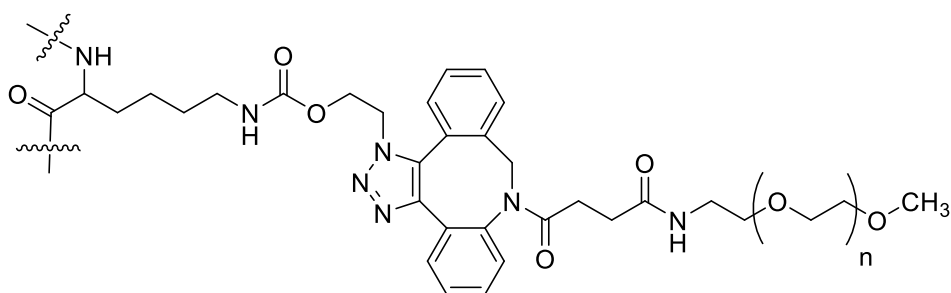
wherein:

n is an integer such that a PEG group having the structure of $-(\text{OCH}_2\text{CH}_2)_n-\text{OCH}_3$ has a molecular weight of about 50 kDa; and

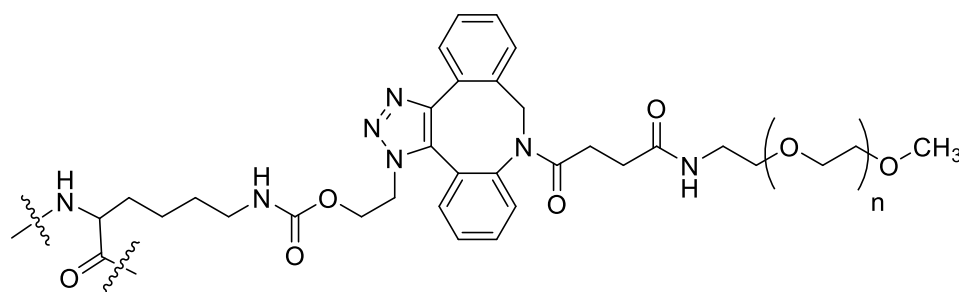
the wavy lines indicate covalent bonds to the first amino acid residues preceding the at least one amino acid residue and the first amino acid residue following the at least one amino acid residue, respectively, within SEQ ID NO: 4; and

the at least one amino acid residue replaced by the structure of Formula (X) or Formula (XI) is located in the IL-2 polypeptide at a position selected from K9, H16, L19, D20, N26, N88, E100, and N119, wherein the residue positions correspond to positions 9, 16, 19, 20, 26, 88, 100, and 119 as set forth in SEQ ID NO: 4.

47. An IL-2 conjugate comprising an IL-2 polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 4 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the structure of Formula (XII) or Formula (XIII):



(XII)



(XIII)

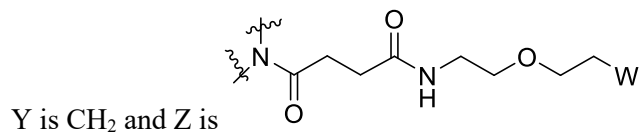
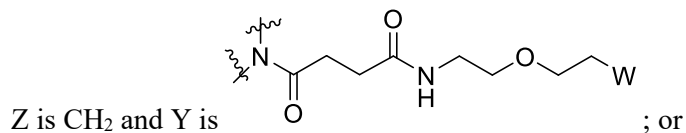
wherein:

n is an integer such that a PEG group having the structure of $-(OCH_2CH_2)_n-OCH_3$ has a molecular weight of about 50 kDa; and

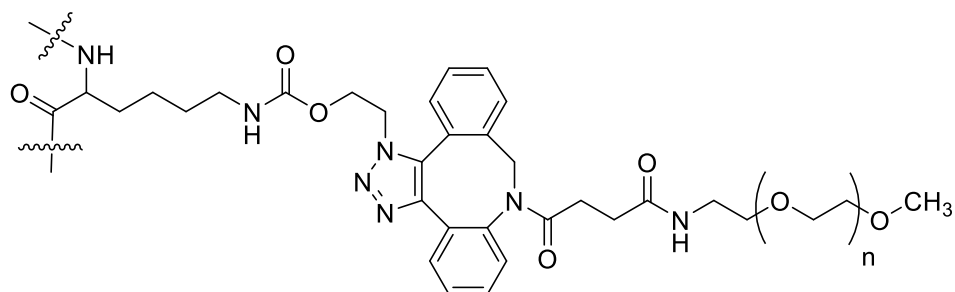
the wavy lines indicate covalent bonds to the first amino acid residues preceding the at least one amino acid residue and the first amino acid residue following the at least one amino acid residue, respectively, within SEQ ID NO: 4.

48. The IL-2 conjugate of any one of claims 44-47, wherein the IL-2 polypeptide comprises an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 4 in which the position is selected from K9, H16, L19, D20, N26, N88, E100, and N119.
49. The IL-2 conjugate of any one of claims 44-47, wherein the IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 4 in which the position is selected from K9, H16, L19, D20, N26, N88, E100, and N119.
50. The IL-2 conjugate of any one of claims 44-47, wherein the IL-2 polypeptide consists of the amino acid sequence of SEQ ID NO: 4 in which the position is selected from K9, H16, L19, D20, N26, N88, E100, and N119.

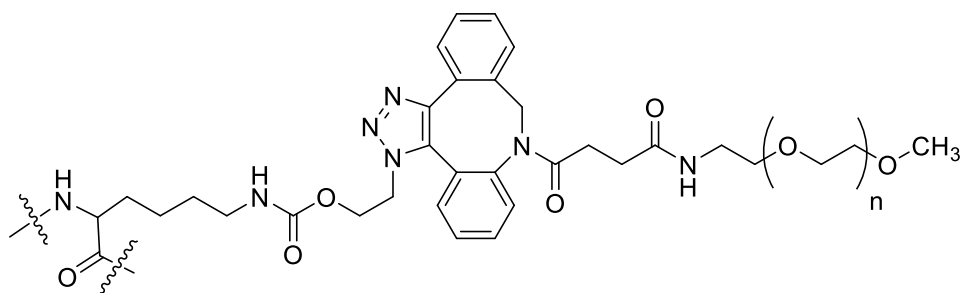
51. The IL-2 conjugate of claim 14, wherein:



52. An IL-2 conjugate consisting of the amino acid sequence of SEQ ID NO: 3 in which a modified amino acid of the structure of Formula (XII) or Formula (XIII) is present at position 15 of SEQ ID NO: 3 instead of histidine:



(XII)



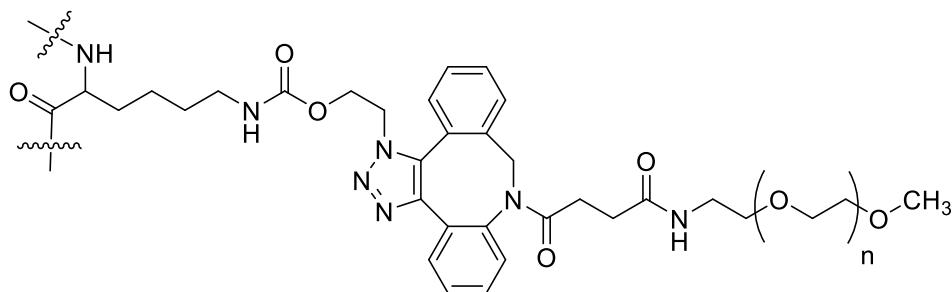
(XIII)

wherein:

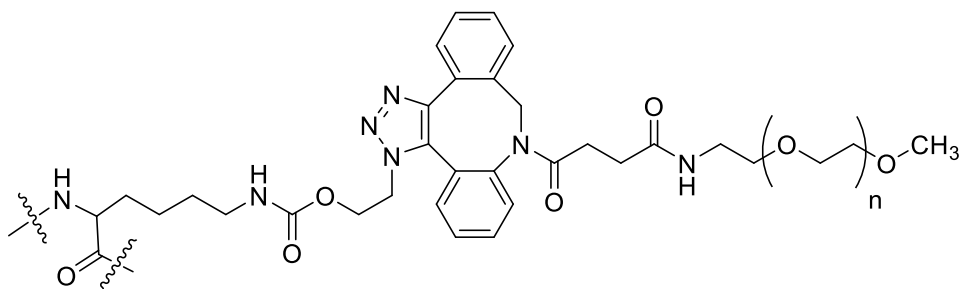
n is an integer such that a PEG group having the structure of $-(\text{OCH}_2\text{CH}_2)_n\text{-OCH}_3$ has a molecular weight of about 50 kDa; and

the wavy lines indicate covalent bonds to an amino acid residue at position 14 and an amino acid residue at position 16, respectively, within SEQ ID NO: 3.

53. An IL-2 conjugate comprising the amino acid sequence of SEQ ID NO: 80, wherein X in SEQ ID NO: 80 is N6-(2-azidoethoxy)-carbonyl-L-lysine (AzK) covalently attached via a conjugating moiety comprising a dibenzocyclooctyne group to a PEG group having a molecular weight of about 50 kDa.
54. The IL-2 conjugate of claim 53, wherein the AzK covalently attached via the conjugating moiety to the PEG group is collectively represented by the structure of Formula (XII) or Formula (XIII):



(XII)



(XIII)

wherein:

n is an integer such that the PEG group having the structure of $-(\text{OCH}_2\text{CH}_2)_n\text{-OCH}_3$ has a molecular weight of about 50 kDa; and

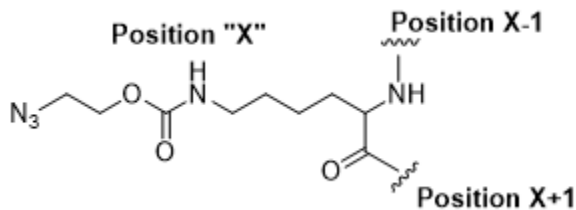
the wavy lines indicate covalent bonds to the first amino acid residue preceding the X and the first amino acid residue following the X, respectively, within SEQ ID NO: 80.

55. A pharmaceutical composition comprising a mixture of IL-2 conjugates of claim 54, wherein the mixture comprises (i) an IL-2 conjugate comprising the structure of Formula (XII) and (ii) an IL-2 conjugate comprising the structure of Formula (XIII).
56. The pharmaceutical composition of claim 55, further comprising a diluent, a buffering agent, a stabilizer, a surfactant, or any combination thereof.
57. The pharmaceutical composition of claim 55, further comprising sorbitol.
58. The pharmaceutical composition of claim 55, further comprising polysorbate-20.

59. A dispenser device comprising the pharmaceutical composition of claim 55.
60. A syringe comprising the pharmaceutical composition of claim 55.
61. A vial comprising the pharmaceutical composition of claim 55.
62. Use of the IL-2 conjugate of any one of claims 1-29, 31-33, and 37-54, or the pharmaceutical composition of any one of claims 30, 34-36, and 55-58, in the manufacture of a medicament for treating an autoimmune disease in a subject in need thereof.
63. The use of claim 62, wherein the autoimmune disease is selected from graft versus host disease (GVHD), atopic dermatitis, Crohn's disease, alopecia areata, autoimmune hemolytic anemia, autoimmune hepatitis, dermatomyositis, type 1 diabetes, juvenile/pediatric type 1 diabetes, juvenile idiopathic arthritis, glomerulonephritis, Graves' disease, Guillain-Barré syndrome, idiopathic thrombocytopenic purpura, myasthenia gravis, multiple sclerosis, pemphigus/pemphigoid, pernicious anemia, polyarteritis nodosa, polymyositis, primary biliary cholangitis, primary biliary cirrhosis, nonalcoholic steatohepatitis (NASH), psoriasis, rheumatoid arthritis, scleroderma, CREST syndrome, Sjögren's syndrome, systemic lupus erythematosus, thyroiditis, uveitis, vitiligo, Wegener's granulomatosis, Addison's disease (adrenal insufficiency), Hashimoto thyroiditis, autoimmune hepatitis, infertility, ANCA-associated vasculitis, psoriatic arthritis, Celiac disease, ulcerative colitis, lichen sclerosus, and Behcet's disease.
64. The use of claim 62 or 63, wherein the subject exhibits an increased concentration of rheumatoid factor in a blood sample of the subject prior to administration to the subject of the IL-2 conjugate or the pharmaceutical composition.
65. Use of the IL-2 conjugate of any one of claims 1-29, 31-33, and 37-54, or the pharmaceutical composition of any one of claims 30, 34-36, and 55-58, in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof, wherein the subject, prior to administration of the IL-2 conjugate or the pharmaceutical composition, is determined that the concentration of rheumatoid factor in a blood sample of the subject is greater than about 14 IU/mL.
66. The use of claim 62 or 63, wherein the subject exhibits an abnormal erythrocyte sedimentation rate (ESR) in a blood sample of the subject, optionally determined using the Westergren rate method or the Wintrobe rate method, prior to administration to the subject of the IL-2 conjugate or the pharmaceutical composition.

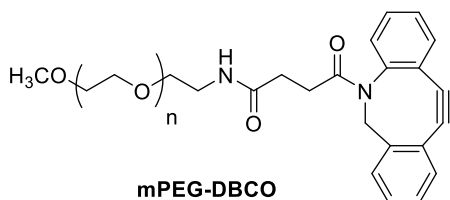
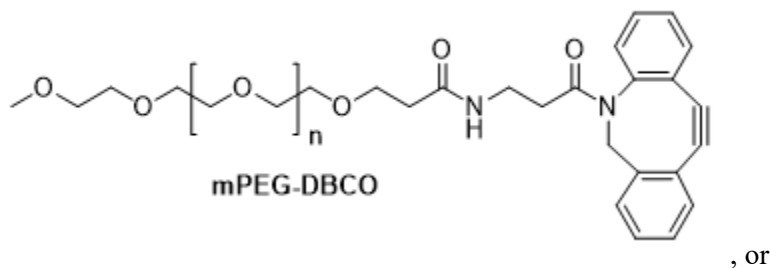
67. Use of the IL-2 conjugate of any one of claims 1-29, 31-33, and 37-54, or the pharmaceutical composition of any one of claims 30, 34-36, and 55-58, in the manufacture of a medicament for treating an autoimmune disease in a subject in need thereof, wherein the subject, prior to administration of the IL-2 conjugate or the pharmaceutical composition, is determined to have an abnormal ESR in a blood sample of the subject.
68. Use of the IL-2 conjugate of any one of claims 1-29, 31-33, and 37-54, or the pharmaceutical composition of any one of claims 30, 34-36, and 55-58, in the manufacture of a medicament for treating an autoimmune disease in a subject in need thereof, wherein the subject, prior to administration of the IL-2 conjugate or the pharmaceutical composition, is determined to have an abnormal concentration of C-reactive protein (CRP) in a blood sample of the subject.
69. The use of claim 68, wherein the subject exhibits a concentration of C-reactive protein (CRP) in the blood sample greater than 10 mg/L prior to administration to the subject of the IL-2 conjugate or pharmaceutical composition.
70. Use of the IL-2 conjugate of any one of claims 1-29, 31-33, and 37-54, or the pharmaceutical composition of any one of claims 30, 34-36, and 55-58, in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof, wherein the subject, prior to administration of the IL-2 conjugate or the pharmaceutical composition, is determined to have an abnormal concentration of anti-cyclic citrullinated peptide (anti-CCP) in the blood sample of the subject.
71. Use of the IL-2 conjugate of any one of claims 1-29, 31-33, and 37-54, or the pharmaceutical composition of any one of claims 30, 34-36, and 55-58, in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof, wherein the subject, prior to administration of the IL-2 conjugate or the pharmaceutical composition, is determined that the concentration of anti-cyclic citrullinated peptide (anti-CCP) in the blood sample of the subject is greater than about 20 IU/mL.
72. A method of making an IL-2 conjugate, comprising:

reacting an IL-2 polypeptide comprising an unnatural amino acid of formula



at Position X of the IL-2 polypeptide, wherein the IL-2 polypeptide comprises the amino acid sequence of SEQ ID NO: 3 or 4 in which at least one amino acid residue in the IL-2 polypeptide is replaced by the unnatural amino acid, Position X-1 indicates the point of attachment to the preceding amino acid residue, Position X+1 indicates the point of attachment to the following amino acid residue,

with an mPEG-DBCO of formula



wherein n is such that the mPEG-DBCO comprises an mPEG having a molecular weight of about 50 kDa,

thereby producing the IL-2 conjugate,

wherein position X is selected from K8, H15, L18, D19, N25, N87, E99, and N118, in reference to the amino acid positions within SEQ ID NO: 3, or position X is selected from K9, H16, L19, D20, N26, N88, E100, and N119, in reference to the amino acid positions within SEQ ID NO: 4.

73. The method of claim 72, wherein Position X is K8, H15, L18, D19, N25, N87, E99, or N118, in reference to the amino acid positions within SEQ ID NO: 3.

74. The method of claim 72, wherein Position X is K9, H16, L19, D20, N26, N88, E100, or N119, in reference to the amino acid positions within SEQ ID NO: 4.

75. The method of claim 72, wherein the IL-2 conjugate is the IL-2 conjugate of any one of claims 1-29, 31-33, and 37-54.