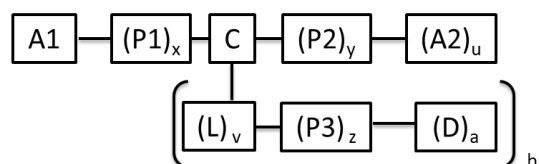


CLAIMS

What is claimed is:

1. A targeting conjugate, wherein the targeting conjugate comprises the following structure:



wherein:

A1 is a first targeting moiety specifically recognizes a first target molecule;

A2 is a second targeting moiety specifically recognizes a second target molecule;

P1 is a first cleavage site;

P2 is a second cleavage site;

P3 is a third cleavage site;

C is a conjugation site;

L is a linker;

D is an effector molecule;

x = 1;

y = 0 or 1;

z = 0 or 1;

v = 0 or 1;

u = 1;

a=1-20; and

b=1-20.

2. The targeting conjugate of claim 1, wherein the first and/or second targeting moiety independently comprises a targeting peptide, or an antibody or antigen-binding fragment thereof.
3. The targeting conjugate of claim 1 or 2, wherein the cleavage is triggered by a condition at a target site.
4. The targeting conjugate of claim 3, wherein

i) the condition at the target site is selected from the group consisting of: protease, pH change, redox change, hypoxia, oxidative stress, hyperthermia, and extracellular ATP concentration; and/or

ii) the target site is a site of a disease.

5. The targeting conjugate of any one of claims 1-4, wherein the cleavage is by a protease.

6. The targeting conjugate of claim 5, wherein the protease is urinary-type plasminogen activator (uPA), and wherein the cleavage site comprises the amino acid sequence of any of SEQ ID NOs: 50-55.

7. The targeting conjugate of any one of claims 1-6, wherein the effector molecule is selected from the group consisting of a therapeutic agent, an oligonucleotide, and a detectable label.

8. The targeting conjugate of any one of claims 1-7, wherein the targeting conjugate comprises

i) a moiety having the structure of 5'Amino Modifier-Spacer-P_h-Cytosine-phosphodiester-Guanine Oligodeoxynucleotides (CpG ODN), or

ii) a moiety having the structure of 3'Amino Modifier-Spacer-P_h-CpG ODN;

wherein Spacer is (CH₂)_n-(polyethylene glycol (PEG))_m, P is a cleavage site, and wherein h, n and m are integers, h=0 or 1, n≥1, and m≥0.

9. The targeting conjugate of any one of claims 1-8, wherein the first and/or second target molecule is independently an immune checkpoint molecule or a tumor antigen.

10. The targeting conjugate of any one of claims 1-9, wherein A1 is a first targeting peptide, or a first antibody or antigen-binding fragment thereof recognizing the first target molecule, and wherein A2 is a second targeting peptide, or a second antibody or antigen-binding fragment thereof recognizing the second target molecule.

11. The targeting conjugate of claim 9 or 10, wherein

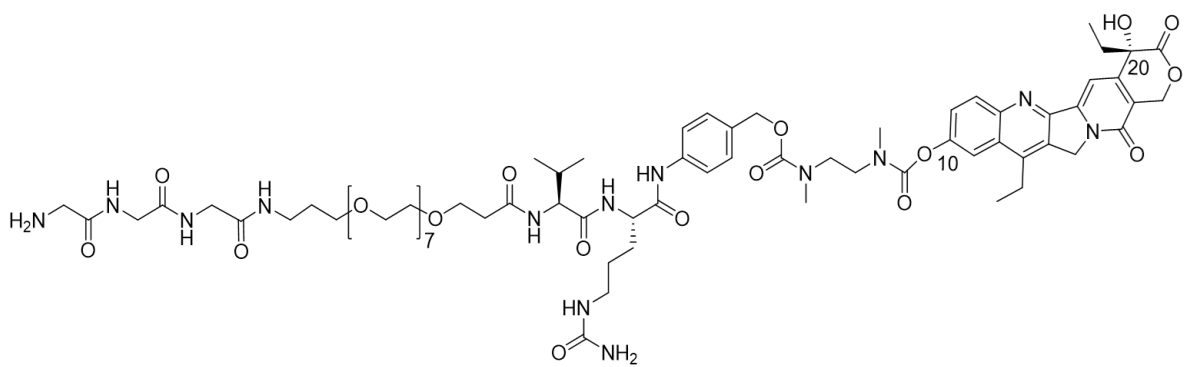
i) the first target molecule is a first immune checkpoint molecule, and the second target molecule is a second immune checkpoint molecule; or

ii) the first target molecule is a first tumor antigen, and the second target molecule is a second tumor antigen.

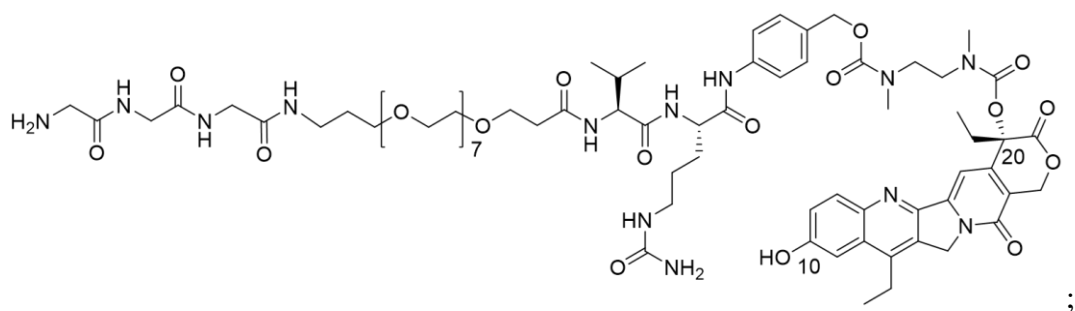
12. The targeting conjugate of claim 9 or 10, wherein
 - i) the first target molecule is an immune checkpoint molecule, and the second target molecule is a tumor antigen; or
 - ii) the first target molecule is a tumor antigen, and the second target molecule is an immune checkpoint molecule.
13. The targeting conjugate of any one of claims 9-12, wherein the immune checkpoint molecule is PD-L1, and/or the tumor antigen is Trop-2.
14. The targeting conjugate of any one of claims 1-13, wherein the conjugation site is a transglutaminase conjugation site.
15. The targeting conjugate of claim 14, wherein
 - i) the conjugation site comprises a plurality of glutamine-containing tags that are fused to each other in tandem; and/or
 - ii) the transglutaminase conjugation site comprises the amino acid sequence of any of SEQ ID NOs: 1-49, and 153-155.
16. The targeting conjugate of any one of claims 1-15, wherein L is represented by the formula $(\text{Gly})_n\text{-(PEG)}_m\text{-P-p-aminobenzyl alcohol (PAB)-(dimethylethylenediamine (DMAE))}_k$, $(\text{Gly})_n\text{-(PEG)}_m\text{-VC-PAB-(DMAE)}_k$ or $(\text{Gly})_n\text{-(PEG)}_m\text{-Val-Ala-PAB-(DMAE)}_k$, and wherein n, m, and k are integers, $n \geq 1$, $m \geq 2$, k is 0 or 1, and P is a cleavage site.
17. The targeting conjugate of any one of claims 1-16, wherein

A1 is a full-length anti-PD-L1 antibody, A2 is an anti-Trop-2 scFv, sdAb, or scFab; wherein:

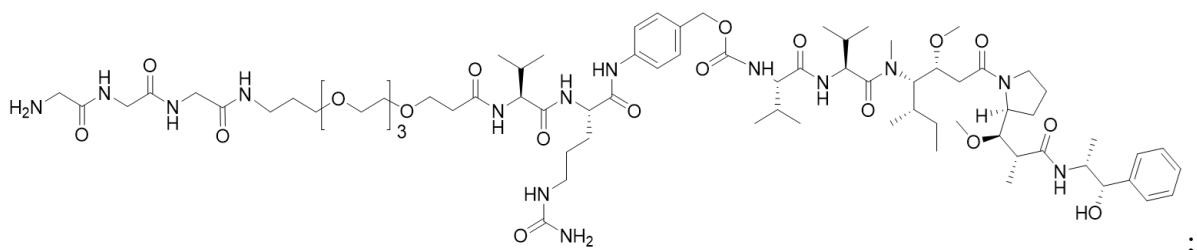
 - i) $y=0$, and P1 and C are fused to the C-terminus of one or both heavy chains of the full-length anti-PD-L1 antibody, and wherein A2 is fused to the C-terminus of C at the C-terminus the one or both heavy chains of the full-length anti-PD-L1 antibody; or
 - ii) $y=1$, and P1, C, and P2 are fused to the C-terminus of one or both heavy chains of the full-length anti-PD-L1 antibody, and wherein A2 is fused to the C-terminus of P2 at the C-terminus the one or both heavy chains of the full-length anti-PD-L1 antibody.
18. The targeting conjugate of any one of claims 1-7 and 9-17, wherein the targeting conjugate comprises a structure selected from the group consisting of Formulae (1)-(7)



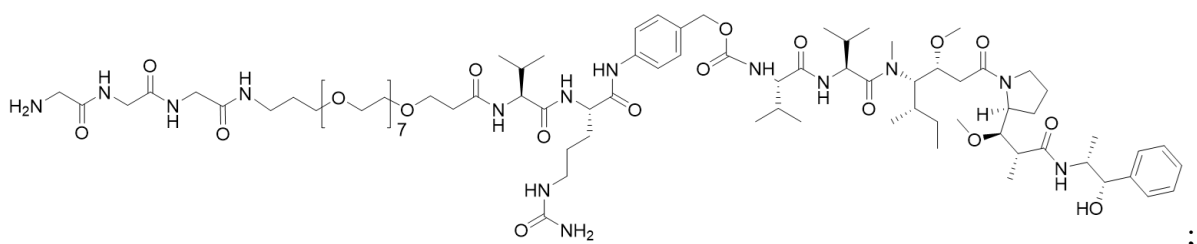
Formula (1)



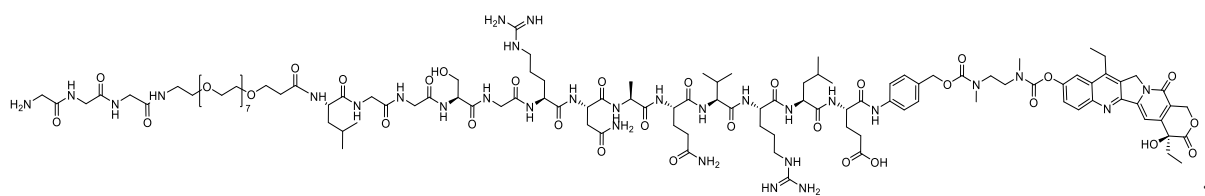
Formula (2)



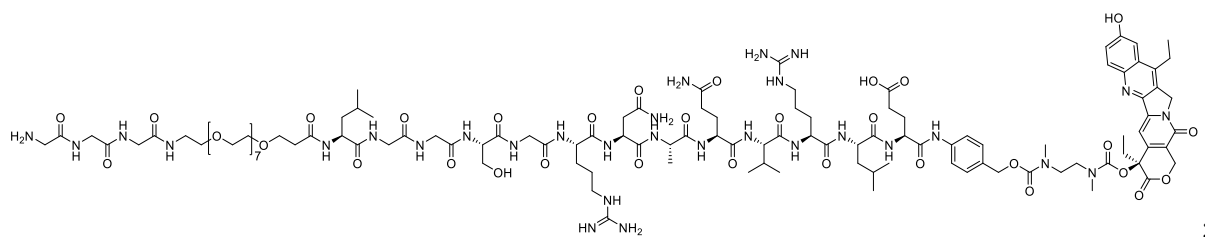
Formula (3)



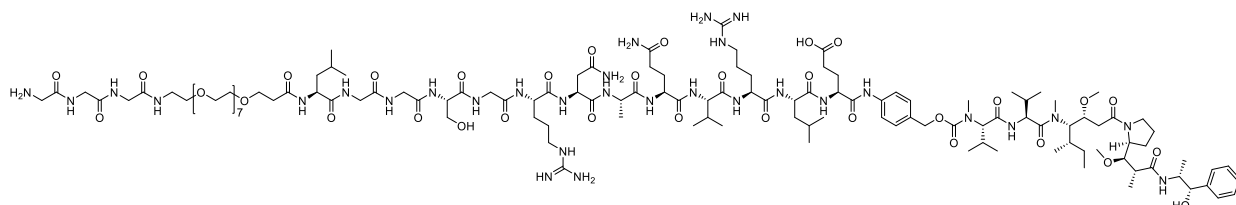
Formula (4)



Formula (5)



Formula (6)



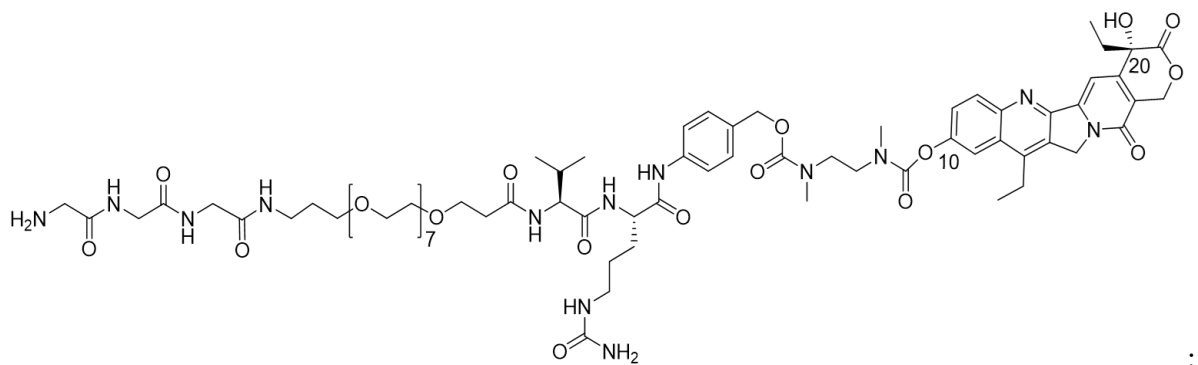
Formula (7).

19. The targeting conjugate of any one of claims 1-18, wherein:

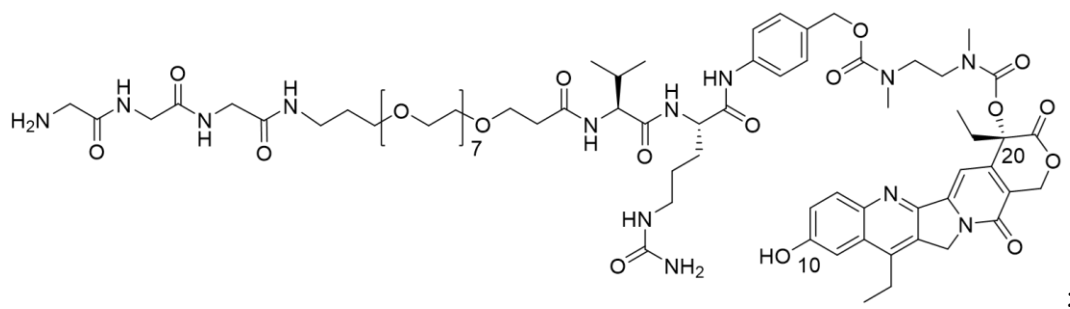
i) $y=0$, $z=0$, $v=1$, $a=1-10$, and $b=2-10$; or

ii) $y=0$, $z=1$, $v=1$, $a=1-10$, and $b=2-10$.

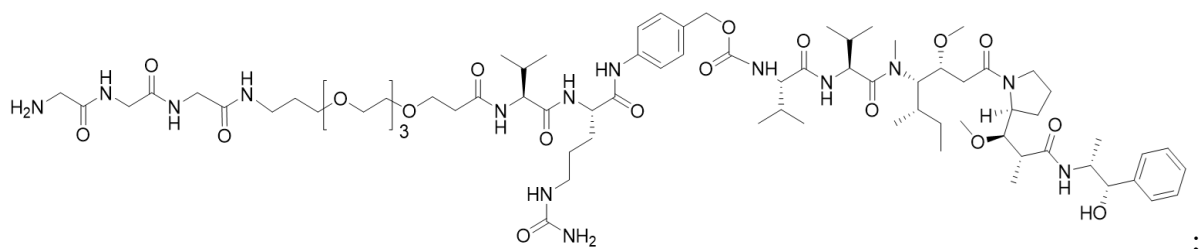
20. A targeting conjugate comprising a targeting moiety conjugated to a therapeutic agent, wherein the targeting conjugate comprises a structure selected from the group consisting of Formulae (1)-(7)



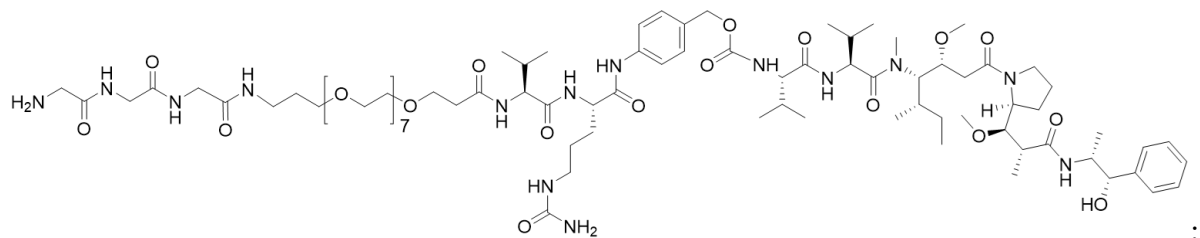
Formula (1)



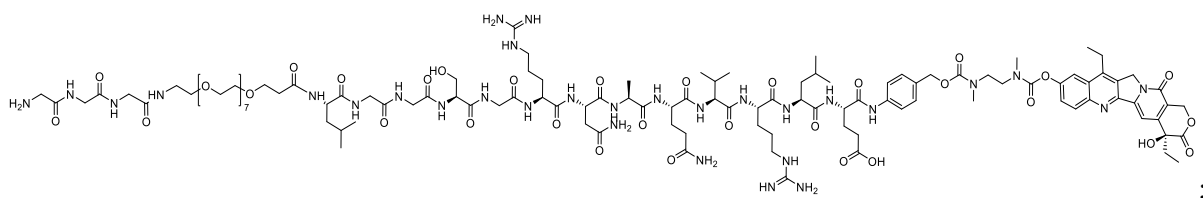
Formula (2)



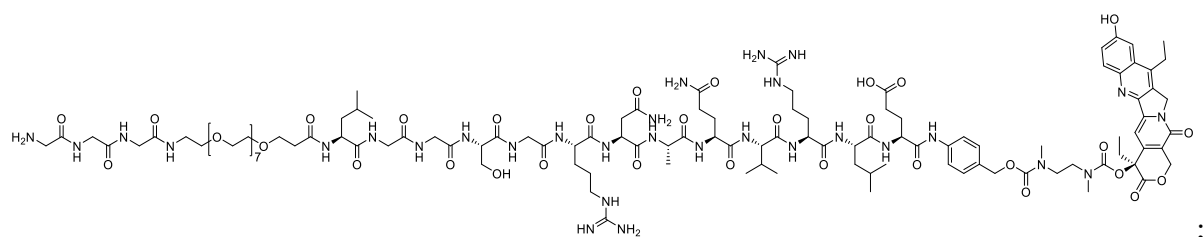
Formula (3)



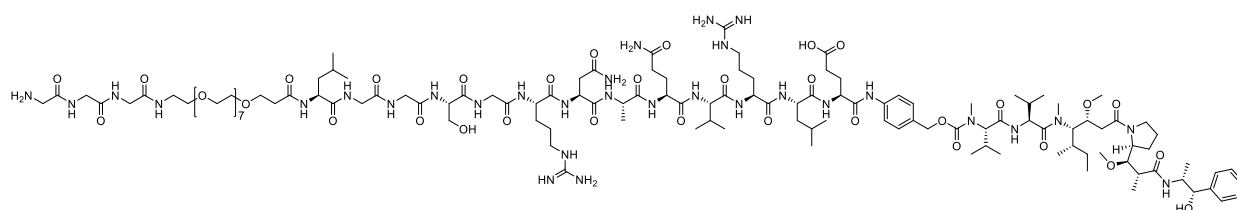
Formula (4)



Formula (5)



Formula (6)



Formula (7).

21. A composition comprising a plurality of targeting conjugates of any one of claims 1-20.
22. A composition of claim 21, wherein the composition is for use in treating a disease in an individual, and the first target molecule and/or the second target molecule are associated with the disease.

23. A composition of claim 21, wherein the composition is for use in diagnosing a disease in an individual, wherein the first target molecule and/or the second target molecule are associated with the disease, wherein the effector molecule is a detectable label, and wherein detection of the detectable label is indicative of the presence of the disease.
24. A method of making a targeting conjugate of any one of claims 1-20, wherein the method comprises conjugating the effector molecule to the targeting moiety.