CLAIMS

1. A conjugate having a structure represented by General Formula I or a pharmaceutically acceptable salt thereof:

[General Formula I]

$$Ab\text{-}[L^{Ab}\text{-}(B)_l]_m$$

wherein,

Ab is an anti-Claudin 18 isoform 2 (CLDN18.2) antibody or antigen-binding fragment thereof comprising a heavy chain variable region and a light chain variable region, wherein

the heavy chain variable region comprises a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 2, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 4, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6; and

the light chain variable region comprises a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 9, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 11, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 13;

each L^{Ab} is, independently, a linker;

each B is, independently, a topoisomerase I inhibitor; and

l and m are each independently 1 to 20.

2. The conjugate of claim 1, wherein Ab comprises at least one of:

(i) a heavy chain variable region comprising:

the amino acid sequence of SEQ ID NO: 15;

an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 15 while maintaining the heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 2, the heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 4, and the heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6; or

an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 15 while maintaining the heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 2, the heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 4, and the heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6; or

(ii) a light chain variable region comprising:

the amino acid sequence of SEQ ID NO: 16;

an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 16 while maintaining the light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 9, the light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 11, and the light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 13; or

an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 16 while maintaining the light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 9, the light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 11, and the light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 13.

3. The conjugate of claim 1, wherein Ab comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 15 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 16.

4. The conjugate of any one of claims 1-3, wherein Ab is a humanized antibody or a human antibody.

5. The conjugate of any one of claims 1-4, wherein Ab is selected from a monoclonal antibody, a single chain antibody (scAb), a Fab fragment, a Fab' fragment, a F(ab')2 fragment, an scFab fragment, an Fv fragment, a dsFv fragment, a single chain variable fragment (scFv), an scFv-Fc fragment, a variant antibody, a multimeric antibody, a minibody, a diabody, a bispecific antibody, and a multispecific antibody.

6. The conjugate of any one of claims 1-5, wherein Ab comprises an IgA, IgG, IgM, IgE, or IgD constant domain, or is an IgA, IgG, IgM, IgE, or IgD antibody.

7. The conjugate of claim 6, wherein Ab comprises an IgG1, IgG2, IgG3, or IgG4 constant domain, or is an IgG1, IgG2, IgG3, or IgG4 antibody.

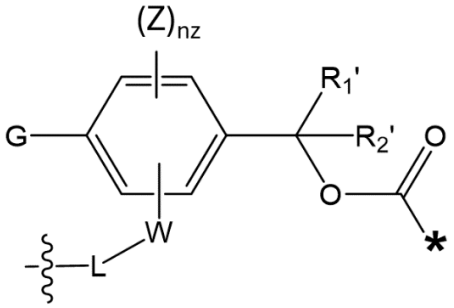
8. The conjugate of claim 6 or 7, wherein Ab comprises LALA mutations in a heavy chain constant region; optionally wherein

(i) the LALA mutations comprise L234A and L235A according to EU numbering convention; or

(ii) the LALA mutations are in a heavy chain constant region of Ab in place of amino acids corresponding to amino acids 237-238 in SEQ ID NO: 17.

9. The conjugate of any one of claims 1-8, wherein each linker comprises a moiety independently represented by General Formula II or a pharmaceutically acceptable salt thereof:

[General Formula II]



wherein

G is a sugar moiety or a glucuronic acid moiety;

each R_1' and R_2' are independently hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl, or R_1' and R_2', combine to complete a (C_3-C_8) cycloalkyl ring;

W is -C(O)-, -C(O)N(R')-, -N(R')C(O)-, -$(CH_2)_t$N(R')C(O)-, -C(O)O-, -$S(O_2)$N(R')-, -P(O)(R'')N(R')-, -S(O)N(R')-, or -$P(O_2)$N(R')-, wherein the indicated C(O), N, CH_2, S, or P is directly bonded to the phenyl ring of Formula II;

R' and R" are each independently hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, mono- or di-C_{1-8} alkylamino, C_{3-20} heteroaryl, or C_{6-20} aryl;

each Z is independently C_{1-8} alkyl, halogen, cyano, or nitro;

nz is an integer from 0 to 3;

t is an integer from 1 to 3;

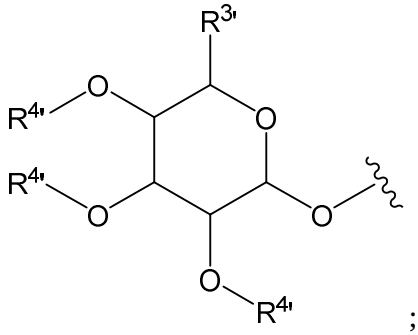
L is absent, C_1-C_{50} alkylene, C_1-C_{50} alkenylene, or 1-50 atom heteroalkylene;

* represents a connection point to B; and

〰 represents a connection point to Ab.

10. The conjugate of claim 9, wherein G is a sugar moiety represented by General Formula III:

[General Formula III]



;

wherein

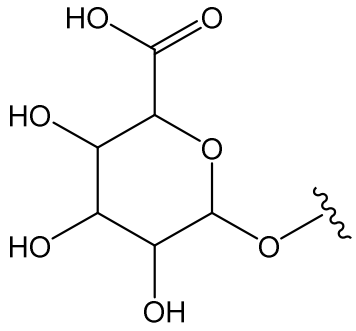
$R^{3'}$ is $-CH_2OR^{3A}$, or $-CO_2R^{3B}$;

R^{3A} is H or a hydroxyl protecting group;

R^{3B} is H or a carboxyl protecting group; and

each $R^{4'}$ is independently a hydrogen or a hydroxyl protecting group.

11. The conjugate of claim 9 or 10, wherein

G is  ; and

W is -C(O)NR'-.

12. The conjugate of any one of claims 9-11, wherein L comprises one or more of:

A) a C_1-C_{50} alkylene or a 1 to 50 atom heteroalkylene comprising one or more of:

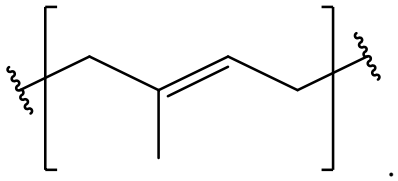
(i) one or more unsaturated bonds;

(ii) a heteroarylene; or

(iii) a C_{1-20} alkyl; or

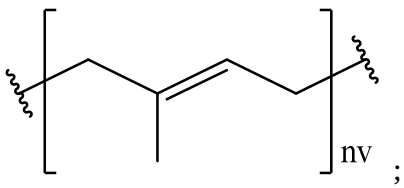
B) at least one isoprenyl group having the structure represented by General Formula IV:

[General Formula IV]

 .

13. The conjugate of claim 12, wherein L comprises an isoprenyl group having a structure represented by General Formula IVa:

[General Formula IVa]

 ;

wherein nv is an integer from 1-20.

14. The conjugate of any one of claims 9-13, wherein L comprises a peptide;
the peptide comprises at least one hydrophilic amino acid comprising a side chain having a moiety that has electric charge in aqueous solution at neutral pH; or
the peptide comprises an amino acid selected from arginine, histidine, aspartate, asparagine, glutamate, glutamine, glycine, lysine, ornithine, proline, serine, and threonine.

15. The conjugate of any one of claims 9-14, wherein L is covalently connected to Ab by a sulfur atom in a cysteine residue of Ab via a thioether bond.

16. The conjugate of any one of claims 9-15, wherein Ab at a C-terminus comprises an amino acid motif that is recognized by an isoprenoid transferase, the isoprenoid transferase is farnesyl protein transferase (FTase) or geranylgeranyl transferase (GGTase), and L is covalently bonded to Ab by a thioether bond and the thioether bond comprises a sulfur atom of a cysteine of the amino acid motif.

17. The conjugate of claim 16, wherein the amino acid motif comprises a CYYX sequence, wherein:
C is cysteine;
each Y is independently an aliphatic amino acid; and
X is selected from glutamine, glutamate, serine, cysteine, methionine, alanine, and leucine.

18. The conjugate of claim 17, wherein
(i) the amino acid motif comprises the CYYX sequence, and each Y is independently selected from alanine, isoleucine, leucine, methionine, and valine; or
(ii) the amino acid motif comprises a CVIM (SEQ ID NO: 22) or CVLL sequence (SEQ ID NO: 23).

19. The conjugate of any one of claims 16-18, wherein at least one of the 1 to 20 amino acids preceding the amino acid motif is glycine.

20. The conjugate of any one of claims 16-19, wherein the amino acid motif has the sequence GGGGGGGCVIM (SEQ ID NO: 19).

21. The conjugate of any one of claims 9-20, wherein L comprises an oxime.

22. The conjugate of claim 21, wherein

L is a 1-50 atom heteroalkylene comprising an oxime; and

(i) the oxygen atom of the oxime is on the side of L linked to W, and
the carbon atom of the oxime is on the side of L linked to Ab; or

(ii) the carbon atom of the oxime is on the side of L linked to W, and
the oxygen atom of the oxime is on the side of L linked to Ab.

23. The conjugate of claim 21 or 22, wherein at least one isoprenyl unit covalently bonds the oxime to Ab.

24. The conjugate of any one of claims 9-23, wherein L comprises a connecting unit represented by General Formula Va or Vb:

[General Formula Va]

$$-(CH_2)_r(V(CH_2)_p)_q-$$

[General Formula Vb]

$$-(CH_2CH_2X)_w-$$

V is a single bond, -O-, -S-, - NR^{21}-, -C(O)NR^{22}-, -NR^{23}C(O)-, -$NR^{24}SO_2$-, or -SO_2NR^{25}-;

X is -O-, C_{1-8} alkylene, or -NR^{21}-;

R^{21}, R^{22}, R^{23}, R^{24}, and R^{25} are each independently hydrogen, C_{1-6} alkyl, C_{1-6} alkyl C_{6-20} aryl, or C_{1-6} alkyl-C_{3-20} heteroaryl;

r is an integer from 0 to 10;

p is an integer from 0 to 10;

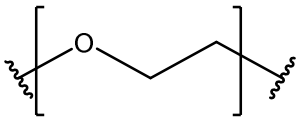
q is an integer from 1 to 20; and

w is an integer from 1 to 20.

25. The conjugate of claim 24, wherein:

(i) q is an integer from 1 to 10;
r and p are each independently an integer of 1 or 2; and
V is -O-; or

(ii) X is -O-.

26. The conjugate of claim 24 or 25, wherein L comprises at least one polyethylene glycol unit represented by 

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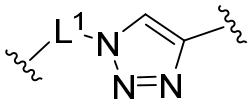
27. The conjugate of claim 26, wherein L comprises an oxime, and the at least one polyethylene glycol unit covalently bonds the oxime to W.

28. The conjugate of any one of claims 9-27, wherein

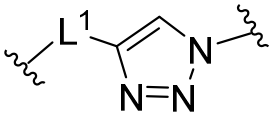
(i) L further comprises a binding unit formed by a reaction between an alkyne and an azide or between an aldehyde or ketone group and hydrazine or hydroxylamine; or

(ii) L further comprises a binding unit represented by General Formula VIa, VIb, VIc, VId, or VIe:

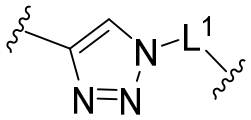
[General Formula VIa]



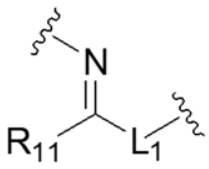
[General Formula VIb]



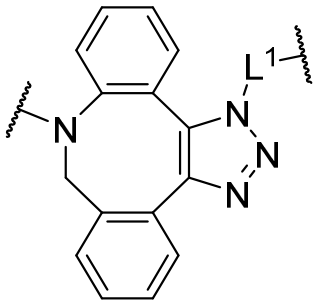
[General Formula VIc]



[General Formula VId]



[General Formula VIe]



wherein

L^1 is each independently a single bond or C_{1-30} alkylene; and

R^{11} is hydrogen or C_{1-10} alkyl.

29. The conjugate of any one of claims 9-28, wherein L is branched and comprises:

i) a branching unit covalently coupled to Ab by a primary linker;

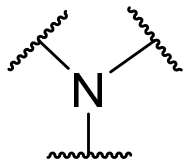
ii) a first branch which couples a first B to the branching unit; and

iiia) a second branch which couples a second B to the branching unit; or

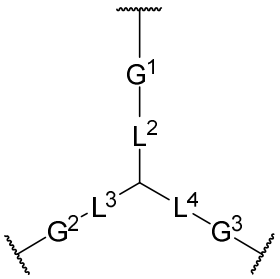
iiib) a second branch, in which an alkyl or heteroalkyl is covalently coupled to the branching unit.

30. The conjugate of claim 29, wherein the branching unit has a structure represented by General Formula VIIa, VIIb, VIId, or VIIe:

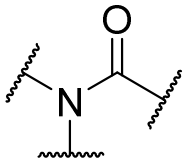
[General Formula VIIa]



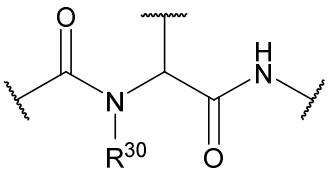
[General Formula VIIb]



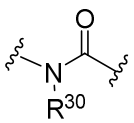
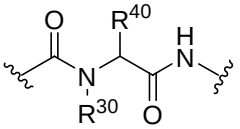
[General Formula VIId]

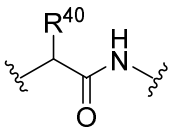
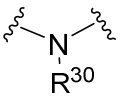


[General Formula VIIe]



wherein

G^1, G^2, and G^3 each independently represents a bond,  ,  ,

 or  ;

R^{30} is hydrogen or C_{1-30} alkyl;

R^{40} is hydrogen or L^5-$COOR^{50}$;

R^{50} is hydrogen or C_{1-30} alkyl;

L^2, L^3, L^4, and L^5 are each independently a bond or $-C_{n'}H_{2n'}-$; and

n' is an integer from 1 to 10.

31. The conjugate of claim 29 or 30, wherein:

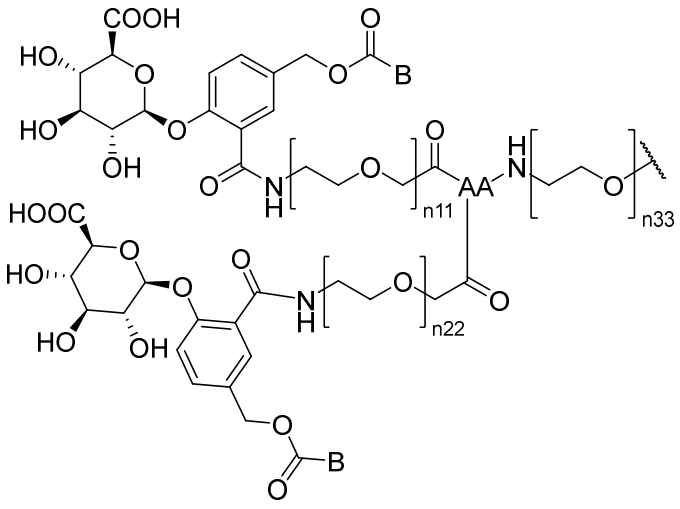
at least one branched L is covalently coupled to Ab; and

at least two B are covalently coupled to the branched L.

32. The conjugate of claim 31, wherein the conjugate comprises 1, 2, 3, or 4 branched L and each branched L is covalently coupled to two B.

33. The conjugate of any one of claims 29-32, wherein the branching unit comprises a lysine residue.

34. The conjugate of any one of claims 1-33, wherein the conjugate comprises a structure represented by:



or a pharmaceutically acceptable salt thereof; wherein

each B is, independently, a camptothecin compound;

n11, n22, and n33 are each independently an integer from 0 to 30; and

AA is a peptide comprising at least two amino acid residues.

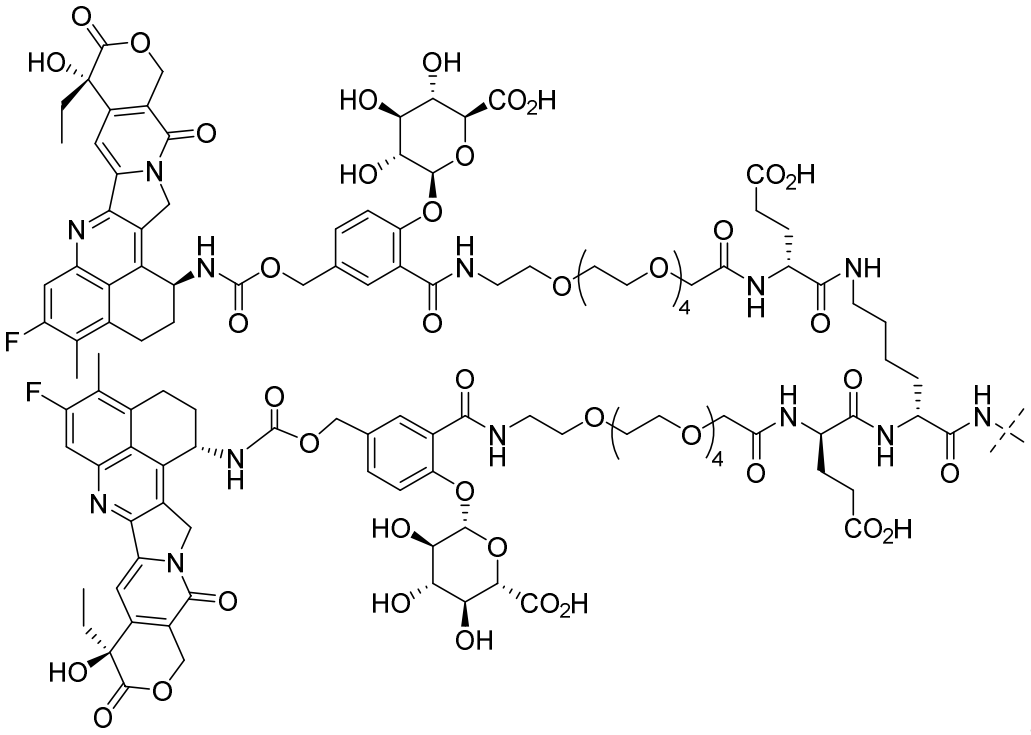
35. The conjugate of any one of claims 1-33, wherein each B is a camptothecin compound.

36. The conjugate of claim 34 or 35, wherein the camptothecin compound is camptothecin (CPT), hydroxycamptothecin, aminocamptothecin, exatecan, topotecan, belotecan, irinotecan, cositecan, rubitecan, lurtotecan, gimatecan, silatecan, namitecan, homocamptothecin (HomoCPT), diflomotecan, S39625, S38809, S38769, ZBH-01, ZBH-1207, BN80915, CPT211, Dxd, SN-38, or FL118.

37. The conjugate of claim 36, wherein the camptothecin compound is hydroxycamptothecin, aminocamptothecin, exatecan, belotecan, irinotecan, cositecan, rubitecan, lurtotecan, gimatecan, silatecan, namitecan, diflomotecan, Dxd, SN-38, or FL118.

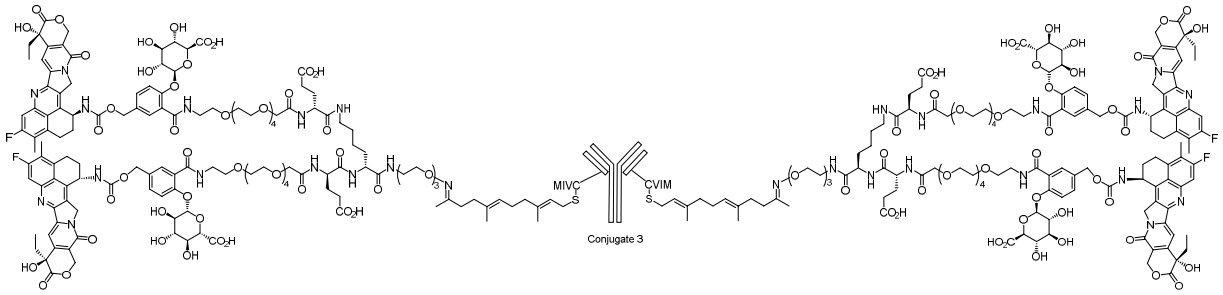
38. The conjugate of claim 37, wherein the camptothecin compound is exatecan.

39. The conjugate of any one of claims 1-38, wherein the conjugate comprises a structure represented by:

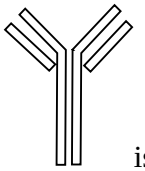


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40. The conjugate of claim 1, wherein the conjugate is:



or a salt thereof, wherein:

 is Ab.

41. The conjugate of claim 40, wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 17 or 20, and a light chain comprising the amino acid sequence of SEQ ID NO: 18.

42. A pharmaceutical composition comprising the conjugate of any one of claims 1-41 and a pharmaceutically acceptable excipient.

43. The conjugate of any one of claims 1-41 or a pharmaceutically acceptable salt thereof, for use in treating or preventing hyperplasia, cancer, or an angiogenic disease.

44. The conjugate for use of claim 43, wherein the conjugate is for use in treating cancer.

45. The conjugate for use of claim 43 or 44, wherein the cancer is lung cancer, small-cell lung cancer, non-small-cell lung cancer, gastrointestinal cancer, colon cancer, intestinal cancer, bowel cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreatic cancer, brain cancer, sarcoma, osteosarcoma, Kaposi’s sarcoma, or melanoma.

46. Use of a conjugate of any one of claims 1-41 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing hyperplasia, cancer, or an angiogenic disease.

47. The use of claim 46, wherein the medicament is for treating cancer.

48. The use of claim 46 or 47, wherein the cancer is lung cancer, small-cell lung cancer, non-small-cell lung cancer, gastrointestinal cancer, colon cancer, intestinal cancer, bowel cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreatic cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, or melanoma.

49. The conjugate of any one of claims 1-41 or a pharmaceutically acceptable salt thereof, for use as a medicament.