

CLAIMS

1. An antibody-drug conjugate comprising an antibody that specifically binds to DLL-3 or antigen binding fragment thereof that is conjugated to a drug via a linker, wherein the antibody or the functional fragment of the antibody is capable of binding to DLL3 and comprises a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein

(a) the V_H comprises a V_H -CDR1 sequence, a V_H -CDR2 sequence, and a V_H -CDR3 sequence selected from the group consisting of

- (i) SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5, respectively;
- (ii) SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, respectively;
- (iii) SEQ ID NO: 23, SEQ ID NO: 24, and SEQ ID NO: 25, respectively; and
- (iv) SEQ ID NO: 33, SEQ ID NO: 34, and SEQ ID NO: 35, respectively; and/or

(b) the V_L comprises a V_L -CDR1 sequence, a V_L -CDR2 sequence, and a V_L -CDR3 sequence selected from the group consisting of

- (i) SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10, respectively;
- (ii) SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20, respectively;
- (iii) SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and
- (iv) SEQ ID NO: 38, SEQ ID NO: 39, and SEQ ID NO: 40, respectively.

2. The antibody-drug conjugate according to claim 1, wherein the antibody comprises a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein the combination of (a) the V_H comprising a V_H -CDR1 sequence, a V_H -CDR2 sequence, and a V_H -CDR3 sequence and (b) the V_L comprising a V_L -CDR1 sequence, a V_L -CDR2 sequence, and a V_L -CDR3 sequence is selected from the group consisting of:

- (i) (a) SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5 and (b) SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10, respectively;

- (ii) (a) SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15 and (b) SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20, respectively;
- (iii) (a) SEQ ID NO: 23, SEQ ID NO: 24, and SEQ ID NO: 25 and (b) SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and
- (iv) (a) SEQ ID NO: 33, SEQ ID NO: 34, and SEQ ID NO: 35 and (b) SEQ ID NO: 38, SEQ ID NO: 39, and SEQ ID NO: 40, respectively.
3. The antibody-drug conjugate according to claim 1 or 2, wherein the antibody comprises a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein:
- (a) the V_H comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 12, SEQ ID NO: 22, and SEQ ID NO: 32; and/or
- (b) the V_L comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 17, SEQ ID NO: 27, and SEQ ID NO: 37.
4. The antibody-drug conjugate according to any one of claims 1-3, wherein the anti-DLL3 antibody comprises a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein: (a) the V_H comprises an amino acid sequence selected from SEQ ID NO: 12, SEQ ID NO: 22 or SEQ ID NO: 32, and (b) the V_L comprises an amino acid sequence selected from SEQ ID NO: 17, SEQ ID NO: 27 or SEQ ID NO: 37.
5. The antibody-drug conjugate according to any one of claims 1-4, wherein the V_H amino acid sequence and the V_L amino acid sequence is selected from the group consisting of:
- SEQ ID NO: 2 and SEQ ID NO: 7 (7-I1-B), respectively;
- SEQ ID NO: 12 and SEQ ID NO: 17 (2-C8-A), respectively;
- SEQ ID NO: 22 and SEQ ID NO: 27 (10-O18-A), respectively; and
- SEQ ID NO: 32 and SEQ ID NO: 37 (6-G23-F), respectively; or

wherein the anti-DLL3 antibody comprises a heavy chain amino acid sequence and a light chain amino acid sequence selected from the group consisting of:

SEQ ID NO: 59 and SEQ ID NO: 62 (H2-C8-A), respectively;
 SEQ ID NO: 60 and SEQ ID NO: 62 (H2-C8-A-2), respectively;
 SEQ ID NO: 61 and SEQ ID NO: 62 (H2-C8-A-3), respectively;
 SEQ ID NO: 67 and SEQ ID NO: 70 (H10-O18-A), respectively;
 SEQ ID NO: 68 and SEQ ID NO: 70 (H10-O18-A-2), respectively;
 SEQ ID NO: 69 and SEQ ID NO: 70 (H10-O18-A-3), respectively;
 SEQ ID NO: 63 and SEQ ID NO: 66 (H6-G23-F), respectively;
 SEQ ID NO: 64 and SEQ ID NO: 66 (H6-G23-F-2), respectively; and
 SEQ ID NO: 65 and SEQ ID NO: 66 (H6-G23-F-3), respectively.

6. The antibody-drug conjugate according to any one of claims 1-5, wherein the antibody comprises:

(a) a light chain immunoglobulin variable domain sequence that is at least 95% identical to the light chain immunoglobulin variable domain sequence of any one of SEQ ID NOs: 7, 17, 27, or 37, or a light chain sequence that is at least 95% identical to the sequence of any one of SEQ ID NOs: 62, 66, or 70; and/or

(b) a heavy chain immunoglobulin variable domain sequence that is at least 95% identical to the heavy chain immunoglobulin variable domain sequence present in any one of SEQ ID NOs: 2, 12, 22, or 32, or a heavy chain sequence that is at least 95% identical to the sequence of any one of SEQ ID NOs: 59, 60, 61, 63, 64, 65, 67, 68, or 69.

7. The antibody-drug conjugate according to any one of claims 1-6, further comprising a Fc domain of an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE.

8. The antibody-drug conjugate according to any one of claims 1-7, wherein the anti-DLL3 comprises a heavy chain constant region of SEQ ID NO: 42, 57 or 58.
9. The antibody-drug conjugate of any one of claims 1-8, wherein the antigen binding fragment is selected from the group consisting of Fab, F(ab')₂, Fab', scFv, and Fv.
10. The antibody-drug conjugate of any one of claims 1-8, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, human antibody or a bispecific antibody.
11. The antibody-drug conjugate according to any one of claims 1-10, wherein the antibody comprises:
- (a) a heavy chain comprises amino acid sequence of any one of SEQ ID NOs: 59-61 and a light chain comprises amino acid sequence of any one of SEQ ID NOs: 62;
 - (b) a heavy chain comprises amino acid sequence of any one of SEQ ID NOs: 63-65 and a light chain comprises amino acid sequence of any one of SEQ ID NOs: 66; and/or
 - (c) a heavy chain comprises amino acid sequence of any one of SEQ ID NOs: 67-69 and a light chain comprises amino acid sequence of any one of SEQ ID NOs: 70.
12. The antibody-drug conjugate according to any one of claims 1-11, wherein the antibody comprises:
- (a) a heavy chain comprises amino acid sequence of SEQ ID NO: 60 and a light chain comprises amino acid sequence of SEQ ID NO: 62;
 - (b) a heavy chain comprises amino acid sequence of SEQ ID NO: 64 and a light chain comprises amino acid sequence of SEQ ID NO: 66; or
 - (c) a heavy chain comprises amino acid sequence of SEQ ID NO: 68 and a light chain comprises amino acid sequence of SEQ ID NO: 70.

13. The antibody drug conjugate according to claim 1, wherein the anti-DLL-3 antibody competes with the antibody according to any one of claims 1-12 for binding to DLL-3.
14. The antibody-drug conjugate of any one of claims 1-13, wherein the antibody binds to an epitope present in a mammalian DLL3 polypeptide.
15. The antibody-drug conjugate of claim 14, wherein the epitope is a conformational epitope or a non-conformational epitope.
16. The antibody-drug conjugate of claim 14 or 15, wherein the mammalian DLL3 polypeptide has an amino acid sequence comprising amino acid residues 27-492 of SEQ ID NO: 50 or SEQ ID NO: 51.
17. The antibody-drug conjugate according to any one of claims 1-16, wherein the heavy chain or the light chain has one or two or more modifications or sets of amino acid residues selected from the group consisting of N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amidation of a proline residue, the substitutions of two leucine (L) residues to alanine (A) at position 234 and 235 (EU Numbering) of the heavy chain (LALA), a set of amino acid residues Glu (E) at positions 356 and Met (M) at position 358 (EU Numbering) of the heavy chain, a set of Asp (D) at positions 356 and Leucine (L) at position 358 (EU Numbering) of the heavy chain or any combination thereof, conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids from the carboxyl terminus.
18. The antibody-drug conjugate according to claim 17, wherein one or two amino acids are deleted from the carboxyl terminus of a heavy chain thereof.

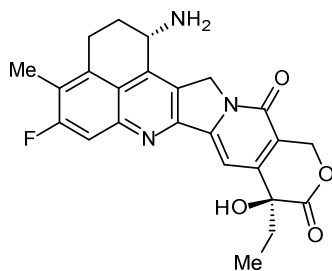
19. The antibody-drug conjugate according to claim 18, wherein one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof.

20. The antibody-drug conjugate according to any one of claims 17-19, wherein a proline residue at the carboxyl terminus of a heavy chain thereof is further amidated.

21. The antibody-drug conjugate according to any one of claims 1-20, wherein antibody comprises a sugar chain modification that is regulated in order to enhance antibody-dependent cellular cytotoxic activity.

22. The antibody-drug conjugate according to any one of claims 1-21, wherein the drug is an antitumor compound represented by the following formula:

[Formula 1]



23. The antibody-drug conjugate according to any one of claims 1-22, wherein the antibody is conjugated to the drug via a linker having any structure selected from the group consisting of the following formulas (a) to (f):

(a) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85),

(b) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85),

(c) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85),

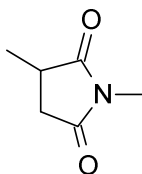
(d) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85),

(e) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85), and

(f) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85),

wherein the antibody is connected to the terminus of -(Succinimid-3-yl-N), the antitumor compound is connected to the carbonyl group of the -CH₂CH₂CH₂-C(=O)- moiety of (a), (b), (e) or (f), the CH₂-O-CH₂-C(=O)- moiety of (c) or the CH₂CH₂-O-CH₂-C(=O)- moiety of (d) with the nitrogen atom of the amino group at position 1 as a connecting position, GGFG (SEQ ID NO: 84) represents an amino acid sequence consisting of glycine-glycine-phenylalanine-glycine (SEQ ID NO: 85) linked through peptide bonds, and -(Succinimid-3-yl-N)- has a structure represented by the following formula:

[Formula 2]



which is connected to the antibody at position 3 thereof and is connected to a methylene group in the linker structure containing this structure on the nitrogen atom at position 1.

24. The antibody-drug conjugate according to any one of claims 1-23, wherein the linker is represented by any formula selected from the group consisting of the following formulas (c), (d) and (e):

(c) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85),

(d) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85), and

(e) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85).

25. The antibody-drug conjugate according to any one of claims 1-24, wherein the linker is represented by the following formula (c) or (e):

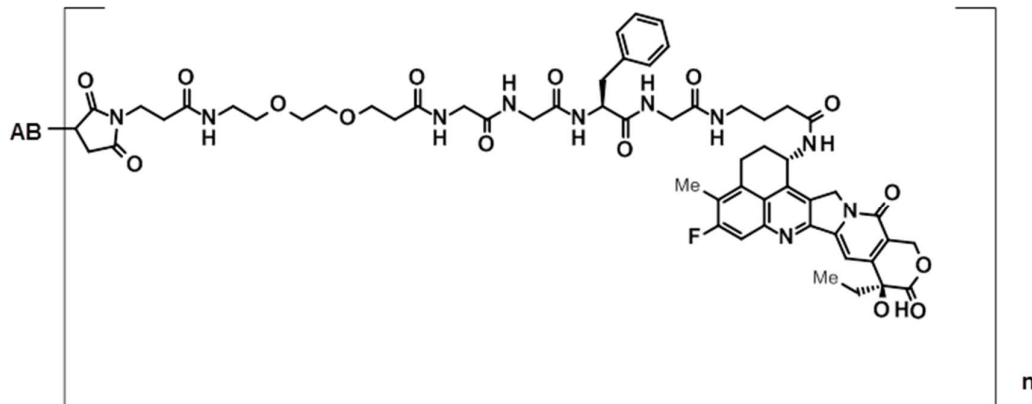
(c) $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(=\text{O})-$

("GGFG" disclosed as SEQ ID NO: 85), and

(e) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)- ("GGFG" disclosed as SEQ ID NO: 85).

26. The antibody-drug conjugate according to any one of claims 1-25, which has a structure represented by the following formula:

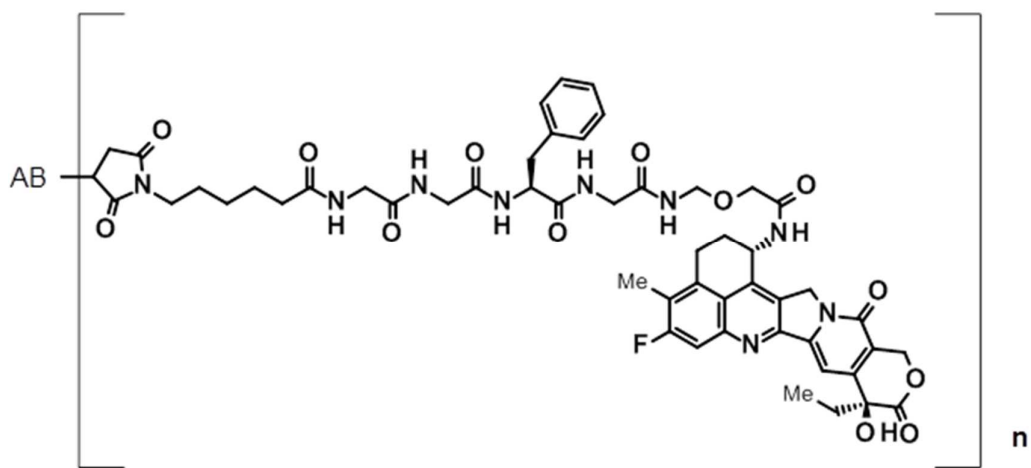
[Formula 3]



wherein AB represents the antibody, n represents the average number of units of the drug-linker structure conjugated to the antibody per antibody, and the antibody is connected to the linker via a sulfhydryl group derived from the antibody.

27. The antibody-drug conjugate according to any one of claims 1-25, which has a structure represented by the following formula:

[Formula 4]



wherein AB represents the antibody, n represents the average number of units of the drug-linker structure conjugated to the antibody per antibody, and the antibody is connected to the linker via a sulfhydryl group derived from the antibody.

28. The antibody-drug conjugate according to any one of claims 1-27, wherein the antibody is an antibody comprising a light chain comprising a variable domain sequence of SEQ ID NO: 17 and a heavy chain comprising a variable domain sequence of SEQ ID NO: 12.

29. The antibody-drug conjugate according to any one of claims 1-27, wherein the antibody is an antibody comprising a light chain comprising a variable domain sequence of SEQ ID NO: 27 and a heavy chain comprising a variable domain sequence of SEQ ID NO: 22.

30. The antibody-drug conjugate according to any one of claims 1-27, wherein the antibody is an antibody comprising a light chain comprising a variable domain sequence of SEQ ID NO: 37 and a heavy chain comprising a variable domain sequence of SEQ ID NO: 32.

31. The antibody-drug conjugate according to any one of claims 1-27, wherein the antibody is an antibody comprising a light chain comprising a variable domain sequence of SEQ ID NO: 7 and a heavy chain comprising a variable domain sequence of SEQ ID NO: 2.
32. The antibody-drug conjugate according to any one of claims 1-31, wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 1 to 10.
33. The antibody-drug conjugate according to any one of claims 1-32, wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 2 to 8.
34. The antibody-drug conjugate according to any one of claims 1-33, wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 5 to 8.
35. The antibody-drug conjugate according to any one of claims 1-34, wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 7 to 8.
36. A pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 1-35, a salt thereof, or a hydrate of the conjugate or the salt.
37. The pharmaceutical composition according to claim 36, which is an antitumor drug.
38. The pharmaceutical composition according to claim 36 or 37 for use in treating a tumor, wherein the tumor is a tumor expressing DLL3.

39. The pharmaceutical composition according to claim 38, wherein the tumor is small cell lung cancer (SCLC), large cell neuroendocrine carcinoma (LCNEC), neuroendocrine tumors of various tissues including kidney, genitourinary tract (bladder, prostate, ovary, cervix, and endometrium), gastrointestinal tract (stomach, colon), thyroid (medullary thyroid cancer), pancreas and lung, gliomas or pseudo neuroendocrine tumors (pNETs).
40. Use of the antibody-drug conjugate according to any one of claims 1-35, a salt thereof, and a hydrate of the conjugate or the salt, in the manufacture of a medicament for treating a tumor, and wherein said medicament is to be administered to an individual with a tumor.
41. Use of a pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 1-35, a salt thereof, and a hydrate of the conjugate or the salt, and at least one antitumor drug, in the manufacture of a medicament for treating a tumor, and wherein said medicament is to be administered to an individual with a tumor, simultaneously, separately, or continuously.
42. The use according to claim 40 or 41, wherein the tumor is a tumor expressing DLL3.
43. The use according to any one of claims 40-42, wherein the tumor is small cell lung cancer (SCLC), large cell neuroendocrine carcinoma (LCNEC), neuroendocrine tumors of various tissues including kidney, genitourinary tract (bladder, prostate, ovary, cervix, and endometrium), gastrointestinal tract (stomach, colon), thyroid (medullary thyroid cancer), pancreas and lung, gliomas or pseudo neuroendocrine tumors (pNETs).
44. A method for producing an anti-DLL3 antibody-drug conjugate, which comprises the step of reacting an anti-DLL3 antibody or the functional fragment of the antibody with a drug-linker intermediate compound wherein the antibody or the functional fragment of the antibody is capable of binding to DLL3 and comprises a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein

(a) the V_H comprises a V_H -CDR1 sequence, a V_H -CDR2 sequence, and a V_H -CDR3 sequence selected from the group consisting of

- (i) SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5, respectively;
- (ii) SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, respectively;
- (iii) SEQ ID NO: 23, SEQ ID NO: 24, and SEQ ID NO: 25, respectively; and
- (iv) SEQ ID NO: 33, SEQ ID NO: 34, and SEQ ID NO: 35, respectively; and/or

(b) the V_L comprises a V_L -CDR1 sequence, a V_L -CDR2 sequence, and a V_L -CDR3 sequence selected from the group consisting of

- (i) SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10, respectively;
- (ii) SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20, respectively;
- (iii) SEQ ID NO: 28, SEQ ID NO: 29, and SEQ ID NO: 30, respectively; and
- (iv) SEQ ID NO: 38, SEQ ID NO: 39, and SEQ ID NO: 40, respectively.

45. The antibody-drug conjugate according to any one of claims 1-35, a salt thereof, and a hydrate of the conjugate or the salt, for use as a medicament.

46. The pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 1-35, a salt thereof, and a hydrate of the conjugate or the salt, and at least one antitumor drug, for use as a medicament.