CLAIMS

1. An antibody that specifically binds to an epitope within the DSL domain of a DLL3 protein set forth as SEQ ID NO: 3 or 4, wherein the antibody is a chimeric antibody, a CDR-grafted antibody, humanized antibody, or human antibody.

2. The antibody of claim 1, wherein the epitope comprises amino acids G203, R205, and P206 (SEQ ID NO: 10).

3. The antibody of claim 1 or claim 2, which is an internalizing antibody.

4. The antibody of any one of claims 1-3, which is selected from the group consisting of a monoclonal antibody, primatized antibody, multispecific antibody, bispecific antibody, monovalent antibody, multivalent antibody, anti-idiotypic antibody, diabody, Fab fragment, $F(ab')_2$ fragment, Fv fragment, and ScFv fragment; or an immunoreactive fragment thereof.

5. The antibody of any one of claims 1-4, wherein the antibody comprises or competes for binding to human DLL3 protein with an antibody comprising a light chain variable region set forth as SEQ ID NO: 84 and a heavy chain variable region as set forth as SEQ ID NO: 85.

6. The antibody of claim 5 comprising three complementarity determining regions of a light chain variable region set forth as SEQ ID NO: 84, and three complementarity determining regions of a heavy chain variable region set forth as SEQ ID NO: 85.

7. The antibody of claim 5 or claim 6 comprising residues 24-34 of SEQ ID NO: 84 for CDR-L1, residues 50-56 of SEQ ID NO: 84 for CDR-L2, residues 89-97 of SEQ ID NO: 84 for CDR-L3, residues 31-35 of SEQ ID NO: 85 for CDR-H1, residues 50-65 of SEQ ID NO: 85

for CDR-H2 and residues 95-102 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to Kabat.

8. The antibody of claim 5 or claim 6, wherein the antibody comprises residues 23-34 of SEQ ID NO: 84 for CDR-L1, residues 50-56 of SEQ ID NO: 84 for CDR-L2, residues 89-97 of SEQ ID NO: 84 for CDR-L3, residues 26-32 of SEQ ID NO: 85 for CDR-H1, residues 50-58 of SEQ ID NO: 85 for CDR-H2 and residues 95-102 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to Chothia.

9. The antibody of claim 5 or claim 6, wherein the antibody comprises residues 30-36 of SEQ ID NO: 84 for CDR-L1, residues 46-55 of SEQ ID NO: 84 for CDR-L2, residues 89-96 of SEQ ID NO: 84 for CDR-L3, residues 30-35 of SEQ ID NO: 85 for CDR-H1, residues 47-58 of SEQ ID NO: 85 for CDR-H2 and residues 93-101 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to MacCallum.

10. The antibody of claim 5 or claim 6 comprising a light chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 212 and/or a heavy chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 213.

11. The antibody of any one of claims 1-10, wherein the antibody is conjugated, linked, or otherwise associated with a cytotoxic agent.

12. The antibody of claim 11, wherein the cytotoxic agent is a pyrrolobenzodiazepine (PBD), an auristatin, a maytansinoid, a calicheamicin, or a radioisotope.

13. The antibody of claim 12, wherein the cytotoxic agent is a pyrrolobenzodiazepine (PBD).

14. A nucleic acid encoding an amino acid heavy chain variable region or an amino acid light chain variable region of an antibody of any one of claims 1-10.

15. A vector or host cell comprising the nucleic acid of claim 14.

16. A tumor-suppressing antibody drug conjugate of the formula M-[L-D]n, or a pharmaceutically acceptable salt thereof wherein:

M comprises an anti-DLL3 antibody that specifically binds to an epitope within the DSL domain of a DLL3 protein set forth as SEQ ID NO: 3 or 4;

L comprises an optional linker;

D comprises a cytotoxic agent; and

n is an integer from 1 to 20.

17. The antibody drug conjugate of claim 16, wherein the anti-DLL3 antibody specifically binds to an epitope comprising amino acids G203, R205 and P206 (SEQ ID NO: 10).

18. The antibody drug conjugate of claim 16 or claim 17, wherein the anti-DLL3 antibody is an internalizing antibody.

19. The antibody drug conjugate of any one of claims 16-18, wherein the anti-DLL3 antibody is selected from the group consisting of a monoclonal antibody, chimeric antibody, CDR-grafted antibody, humanized antibody, human antibody, primatized antibody, multispecific antibody, bispecific antibody, monovalent antibody, multivalent antibody, diabody, Fab fragment, $F(ab')_2$ fragment, Fv fragment, and ScFv fragment; or an immunoreactive fragment thereof that specifically binds to an epitope within the DSL domain of a DLL3 protein set forth as SEQ ID NO: 3 or 4.

20. The antibody drug conjugate of any one of claims 16-19, wherein the anti-DLL3 antibody is a chimeric antibody, CDR-grafted antibody, human antibody, or humanized antibody.

21. The antibody drug conjugate of any one of claims 16-20, wherein the anti-DLL3 antibody comprises or competes for binding to a human DLL3 protein with an antibody

comprising a light chain variable region set forth as SEQ ID NO: 60 and a heavy chain variable region set forth as SEQ ID NO: 61.

22. The antibody drug conjugate of any one of claims 16-21, wherein the anti-DLL3 antibody comprises three CDRs of a light chain variable region set forth as SEQ ID NO: 60 and three CDRs of a heavy chain variable region set forth as SEQ ID NO: 61.

23. The antibody drug conjugate of any one of claims 16-22, wherein the anti-DLL3 antibody comprises residues 23-34 of SEQ ID NO: 60 for CDR-L1, residues 50-56 of SEQ ID NO: 60 for CDR-L2, residues 89-97 of SEQ ID NO: 60 for CDR-L3, residues 26-32 of SEQ ID NO: 61 for CDR-H1, residues 50-58 of SEQ ID NO: 61 for CDR-H2 and residues 95-102 of SEQ ID NO: 61 for CDR-H3, wherein the residues are numbered according to Chothia.

24. The antibody drug conjugate of any one of claims 16-22, wherein the anti-DLL3 antibody comprises residues 30-36 of SEQ ID NO: 60 for CDR-L1, residues 46-55 of SEQ ID NO: 60 for CDR-L2, residues 89-96 of SEQ ID NO: 60 for CDR-L3, residues 30-35 of SEQ ID NO: 61 for CDR-H1, residues 47-58 of SEQ ID NO: 61 for CDR-H2 and residues 93-101 of SEQ ID NO: 61 for CDR-H3, wherein the residues are numbered according to MacCallum.

25. The antibody drug conjugate of any one of claims 16-22, wherein the anti-DLL3 antibody comprises residues 24-34 of SEQ ID NO: 60 for CDR-L1, residues 50-56 of SEQ ID NO: 60 for CDR-L2, residues 89-97 of SEQ ID NO: 60 for CDR-L3, residues 31-35 of SEQ ID NO: 61 for CDR-H1, residues 50-65 of SEQ ID NO: 61 for CDR-H2 and residues 95-102 of SEQ ID NO: 61 for CDR-H3, wherein the residues are numbered according to Kabat.

26. The antibody drug conjugate of any one of claims 16-20, wherein the anti-DLL3 antibody comprises a light chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 210 and a heavy chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 211.

27. The antibody drug conjugate of any one of claims 16-20, wherein the anti-DLL3 antibody comprises or competes for binding to a human DLL3 protein with an antibody comprising a light chain variable region set forth as SEQ ID NO: 84 and a heavy chain variable region set forth as SEQ ID NO: 85.

28. The antibody drug conjugate of any of claims 16-20 or 27, wherein the anti-DLL3 antibody comprises three CDRs of a light chain variable region set forth as SEQ ID NO: 84 and three CDRs of a heavy chain variable region set forth as SEQ ID NO: 85.

29. The antibody drug conjugate of any of claims 16-20, 27 or 28, wherein the anti-DLL3 antibody comprises residues 23-34 of SEQ ID NO: 84 for CDR-L1, residues 50-56 of SEQ ID NO: 84 for CDR-L2, residues 89-97 of SEQ ID NO: 84 for CDR-L3, residues 26-32 of SEQ ID NO: 85 for CDR-H1, residues 50-58 of SEQ ID NO: 85 for CDR-H2 and residues 95-102 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to Chothia.

30. The antibody drug conjugate of any of claims 16-20, 27 or 28, wherein the anti-DLL3 antibody comprises residues 30-36 of SEQ ID NO: 84 for CDR-L1, residues 46-55 of SEQ ID NO: 84 for CDR-L2, residues 89-96 of SEQ ID NO: 84 for CDR-L3, residues 30-35 of SEQ ID NO: 85 for CDR-H1, residues 47-58 of SEQ ID NO: 85 for CDR-H2 and residues 93-101 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to MacCallum.

31. The antibody drug conjugate of any of claims 16-20, 27 or 28, wherein the anti-DLL3 antibody comprises residues 24-34 of SEQ ID NO: 84 for CDR-L1, residues 50-56 of SEQ ID NO: 84 for CDR-L2, residues 89-97 of SEQ ID NO: 84 for CDR-L3, residues 31-35 of SEQ ID NO: 85 for CDR-H1, residues 50-65 of SEQ ID NO: 85 for CDR-H2 and residues 95-102 of SEQ ID NO: 85 for CDR-H3, wherein the residues are numbered according to Kabat.

32. The antibody drug conjugate of any of claims 16-20, wherein the anti-DLL3 antibody comprises a light chain variable region comprising an amino acid sequence set forth as

SEQ ID NO: 212 and a heavy chain variable region comprising an amino acid sequence set forth as SEQ ID NO: 213.

33. The antibody drug conjugate of any one of claims 16-32, wherein D is a pyrrolobenzodiazepine (PBD), an auristatin, a maytansinoid, a calicheamicin, or a radioisotope.

34. The antibody drug conjugate of claim 33, wherein D is a pyrrolobenzodiazepine (PBD).

35. An antibody drug conjugate of the formula M-[L-D]n, or a pharmaceutically acceptable salt thereof, wherein:

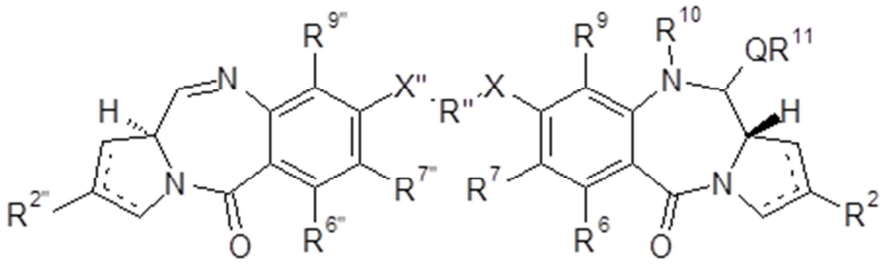
M comprises an anti-DLL3 antibody, wherein the anti-DLL3 antibody is the antibody of any one of claims 1-10;

L comprises a linker;

D comprises pyrrolobenzodiazepine (PBD); and

n is an integer from 1 to 20.

36. The antibody drug conjugate of claim 34 or claim 35, wherein the pyrrolobenzodiazepine comprises a conjugate of formula AC:



AC

wherein:

the dotted lines indicate the optional presence of a double bond, and wherein only one of the dotted lines in a given ring can be a double bond;

R^2 is selected from H, OH, =O, $=CH_2$, CN, R, OR, $=CH\text{-}R^D$, $=C(R^D)_2$, $O\text{-}SO_2\text{-}R$, CO_2R, COR, and halo, where R^D is selected from R, CO_2R, COR, CHO, CO_2H, and halo, preferably wherein R^2 is R;

R^6 and R^9 are each independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo, preferably wherein R^6 and R^9 are H;

R^7 is selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo, preferably wherein R^7 is OR, and preferably wherein R is a C_1 alkyl;

R^{10} is a linker connected to the anti-DLL3 antibody;

Q is selected from O, S and NH, preferably wherein Q is O;

R^{11} is either H, or R or, where Q is O, SO_3M, where M is a metal cation, preferably wherein R^{11} is H;

R and R' are each independently selected from optionally substituted $C_{1\text{-}12}$ alkyl, $C_{3\text{-}20}$ heterocyclyl and $C_{5\text{-}20}$ aryl groups, and optionally in relation to the group NRR', R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring;

X is selected from O, S, and N(H);

$R^{2"}$, $R^{6"}$, $R^{7"}$, $R^{9"}$, and X" are as defined according to R^2, R^6, R^7, R^9, and X, respectively, preferably wherein X and X" are O; and

R″ is a $C_{3\text{-}12}$ alkylene group, which comprises a chain optionally interrupted by one or more heteroatoms, one or more rings, or both one or more heteroatoms and one or more rings, wherein the optional one or more rings are optionally substituted.

37. The antibody drug conjugate of claim 36, wherein:

R^2 is R, wherein R is a $C_{5\text{-}20}$ aryl group;

R^6 and R^9 are H;

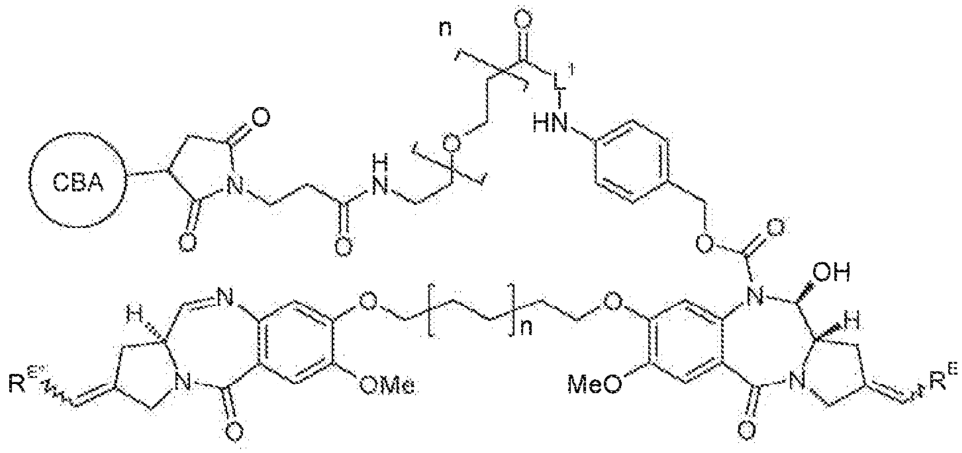
R^7 is OR, wherein R is a C_1 alkyl;

Q is O, and wherein R^{11} is H; and/or

X and X" are O.

38. The antibody drug conjugate of claim 36, comprising the structure:

(i)



wherein:

CBA is a cell binding agent which is the anti-DLL3 antibody,

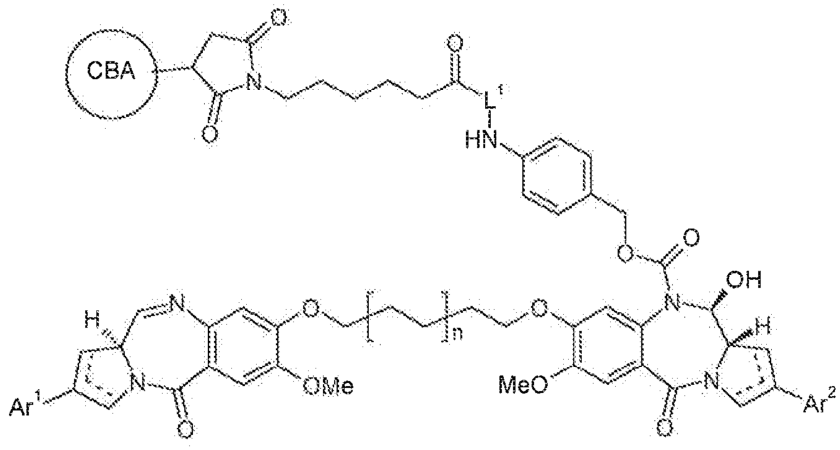
n is 0 or 1,

L^1 is a linker,

and R^E and $R^{E''}$ are each independently selected from H or R^D;

or

(ii)



wherein:

CBA is a cell binding agent which is the anti-DLL3 antibody,

L^1 is a linker,

Ar^1 and Ar^2 are each independently optionally substituted C_{5-20} aryl,

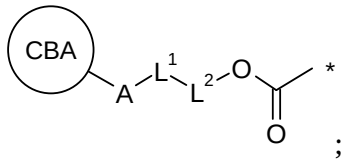
and n is 0 or 1.

39. The antibody drug conjugate of any one of claims 16-38, wherein the linker comprises a cleavable linker, optionally a dipeptide linker.

40. The antibody drug conjugate of claim 39, wherein the dipeptide is Phe-Lys, Val-Ala, Val-Lys, Ala-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit, Phe-Arg, or Trp-Cit.

41. The antibody drug conjugate of claim 40, wherein the dipeptide is Val-Ala.

42. The antibody drug conjugate of any one of claims 16-41, comprising the structure:



;

wherein:

CBA is a cell binding agent, which is the anti-DLL3 antibody M;

A, L^1, and L^2 are components of the linker L;

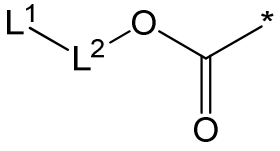
A is a connecting group connecting L^1 to the cell binding agent (CBA);

L^1 is optionally a cleavable linker;

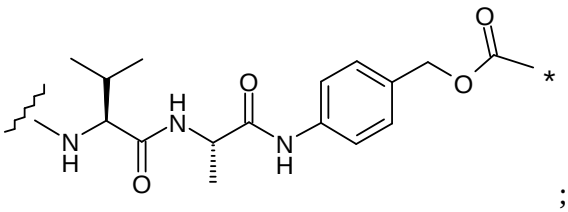
L^2 is a covalent bond or together with the -OC(=O)- group forms a self-immolative linker; and

wherein the linker L is attached to a pyrrolobenzodiazepine (PBD) at the position of the asterisk (*);

and wherein optionally the moiety:



comprises the structure:


;

wherein the wavy line indicates the point of attachment of the structure directly to A or to a remaining portion of L^1 that is further connected to A.

43. An antibody drug conjugate according to any one of claims 16-42 for use as a pharmaceutical product.

44. A pharmaceutical composition comprising an antibody drug conjugate according to any one of claims 16-42.

45. Use of an antibody drug conjugate of the formula M-[L-D]n, or a pharmaceutically acceptable salt thereof, wherein:

M comprises an anti-DLL3 antibody, wherein the anti-DLL3 antibody is the antibody of any one of claims 1-10;

L comprises a linker;

D comprises a cytotoxic agent; and

n is an integer from 1 to 20,

in the preparation of a medicament useful in the treatment of cancer.

46. Use of an antibody drug conjugate of the formula M-[L-D]n, or a pharmaceutically acceptable salt thereof, wherein:

M comprises an anti-DLL3 antibody, wherein the anti-DLL3 antibody is the antibody of any one of claims 1-10;

L comprises a linker;

D comprises a cytotoxic agent; and

n is an integer from 1 to 20,

in the preparation of a medicament useful for reducing the frequency of tumor initiating cells in a subject having cancer.

47. Use of the antibody drug conjugate of claim 45 or claim 46, wherein the cancer comprises a tumor comprising neuroendocrine features, and wherein the tumor is characterized by elevated expression of ASCL1.

48. Use of the antibody drug conjugate of any one of claims 45-47, wherein the tumor shows suppressed Notch signaling.

49. Use of the antibody drug conjugate of any one of claims 45-48, wherein the tumor shows elevated levels of DLL3 and/or HES6 as compared to normal tissue or non-tumorigenic cells.

50. Use of the antibody drug conjugate of any one of claims 45-49, wherein the tumor shows reduced levels of one or more markers selected from the group consisting of HES1, HEY1, JAG1, and Notch receptor.

51. Use of the antibody drug conjugate of any one of claims 45-50, wherein the tumor shows elevated levels of one or more markers selected from the group consisting of neuron-specific enolase (ENO2), CD56 (NCAM1), synaptophysin (SYP), chomogranin A (CHGA), dopa decarboxylase (DDC), PGP9.5 (UCHL1), calcitonin (CALCA), somatostatin (SST), and NK2 homeobox 1 (NKX2-1).

52. Use of the antibody drug conjugate of any one of claims 45-51, wherein the tumor is characterized by a poorly differentiated neuroendocrine phenotype.

53. Use of the antibody drug conjugate of any one of claims 45-52, wherein the cancer is lung cancer, thyroid cancer, prostate cancer, thyroid cancer, genitourinary tract cancer, or kidney cancer.

54. Use of the antibody drug conjugate of any one of claims 45-52, wherein the cancer comprises large cell neuroendocrine carcinoma.

55. Use of the antibody drug conjugate of any one of claims 45-53, wherein the cancer is small cell lung cancer.

56. Use of the antibody drug conjugate of any one of claims 45-55, wherein the cancer comprises a refractory, relapsed, or recurrent tumor.

57. Use of the antibody drug conjugate of claim 56, wherein the recurrent tumor comprises lung cancer.

58. Use of the antibody drug conjugate of claim 57, wherein the recurrent tumor comprises small cell lung cancer.

59. Use of the antibody drug conjugate of claim 57, wherein the recurrent tumor comprises non-small cell lung cancer.

60. Use of the antibody drug conjugate of claim 57 wherein the recurrent tumor comprises large cell neuroendocrine carcinoma.

61. Use of the antibody drug conjugate of any one of claims 57-60, wherein the lung cancer is refractory, relapsed or resistant to a platinum based agent and/or taxane.

62. Use of the antibody drug conjugate of claim 56, wherein the subject has relapsed from chemotherapy.

63. Use of the antibody drug conjugate of any one of claims 45-62, wherein the subject has previously undergone a debulking procedure.

64. Use of the antibody drug conjugate of any one of claims 45-63, wherein the cytotoxic agent is a pyrrolobenzodiazepine (PBD), an auristatin, a maytansinoid, a calicheamicin, or a radioisotope.

65. Use of the antibody drug conjugate of claim 64, wherein the cytotoxic agent is a pyrrolobenzodiazepine (PBD).

66. Use of the antibody drug conjugate of claim 64, wherein the cytotoxic agent is a radioisotope.

67. Use of the antibody drug conjugate of any one of claims 45-66, wherein the antibody drug conjugate is the antibody drug conjugate of any one of claims 16-42.

68. A kit for treating cancer comprising:

(a) one or more containers containing a composition comprising

an antibody drug conjugate of the formula M-[L-D]n, or a pharmaceutically acceptable salt thereof, wherein:

M comprises an anti-DLL3 antibody, wherein the anti-DLL3 antibody is the antibody of any one of claims 1-10;

L comprises an optional linker;

D comprises a cytotoxic agent; and

n is an integer from 1 to 20; and

(b) a label or package insert on or associated with the one or more containers indicating the composition is for treating cancer.

69. The kit of claim 68, wherein D is a pyrrolobenzodiazepine (PBD), an auristatin, a maytansinoid, a calicheamicin, or a radioisotope.

70. The kit of claim 69, wherein D is a pyrrolobenzodiazepine (PBD).

71. A method of making an antibody drug conjugate (ADC) of the formula M-[L-D]n, the method comprising the steps of:

(a) providing a drug D, wherein D comprises a cytotoxic agent;

(b) providing a linker L;

(c) synthesizing a linker-cytotoxic agent [L-D] conjugate;

(d) conjugating the [L-D] conjugate to M, wherein M comprises the anti-DLL3 antibody of any one of claims 1-10;

and wherein the conjugating occurs under conditions where n is an integer from 1 to 20.

72. The method of claim 71, wherein D is a pyrrolobenzodiazepine (PBD), an auristatin, a maytansinoid, a calicheamicin, or a radioisotope.

73. The method of claim 72, wherein D comprises a pyrrolobenzodiazepine (PBD).

74. An antibody drug conjugate (ADC) when prepared according to the method of any one of claims 71 to 73.