Current Protocols in Protein Science (John Wiley & Sons, Inc.), Chapter 15 (Chemical Modifications of Proteins).

Linkers

A linker is a bifunctional compound which can be used to link a drug and an antibody to form an antibody drug conjugate (ADC). Such conjugates are useful, for example, in the formation of immunoconjugates directed against tumor associated antigens. Such conjugates allow the selective delivery of cytotoxic drugs to tumor cells. Suitable linkers include, for example, cleavable and non-cleavable linkers. A cleavable linker is typically susceptible to cleavage under intracellular conditions. Suitable cleavable linkers include, for example, a peptide linker cleavable by an intracellular protease, such as lysosomal protease or an endosomal protease. In exemplary embodiments, the linker can be a dipeptide linker, such as a valine-citrulline (val-cit), a phenylalanine-lysine (phe-lys) linker, or maleimidocaproyl–valine-citrulline-p-aminobenzyloxycarbonyl (vc) linker. Another linker is Sulfosuccinimidyl-4-[N-maleimidomethyl]cyclohexane-1-carboxylate (smcc). Sulfo-smcc conjugation occurs via a maleimide group which reacts with sulfhydryls (thiols, -SH), while its Sulfo-NHS ester is reactive toward primary amines (as found in Lysine and the protein or peptide N-terminus). Yet another linker is maleimidocaproyl (mc). Other suitable linkers include linkers hydrolyzable at a specific pH or a pH range, such as a hydrazone linker. Additional suitable cleavable linkers include disulfide linkers. The linker may be covalently bound to the antibody to such an extent that the antibody must be degraded intracellularly in order for the drug to be released *e.g.* the mc linker and the like.

Linkers of the present invention include maleimidocaproyl–valine-citrulline-p-aminobenzyloxycarbonyl (vc) and maleimidocaproyl (mc), maleimido-heptanoyl (me) and maleimido-Peg6C2 (MalPeg6C2).

Engineered Fc Polypeptide

It has been previously reported that certain residues presumably present on the surface of the CH2 or CH3 domain of the heavy chain of antibodies, or on the constant domain of the light chain, or otherwise accessible, are suitable for the substitution of the naturally-occurring wild type amino acid with, for example, cysteine, and are therefore

length Notch3 (~270 kDa) and cleaved, C-terminal domain containing Notch3 protein fragments at (~80-90 kDa). Notch3 bands at the ~80-90 kDa molecular weights represent the TMIC (Transmembrane and intracellular domain) and/or NEXT (Notch extracellular truncation) proteolytic fragments, as shown in **FIG. 7**. The 1G5 antibodies bind an epitope within amino acids 47-156 of the Notch3 extracellular domain (ECD) and recognize both the uncleaved, full-length (~270kDa) and the cleaved, N-terminal fragment (~210 kDa) (data not shown).

Both the Notch3-ECD (data not shown) and the cleaved C-terminal domain containing Notch3 protein fragments were detected in HCC2429, OVCAR3, MDA-MB-468, N87, MDAMB468/hNotch3 and U2OS/hNotch3, as shown in **FIG. 7**. Further, Notch3 was not detected in the SW900 lung cancer cell line and thus represents a Notch3 negative control cell line.

Example 8

Internalization and Trafficking of Anti-Notch3 Antibodies

Anti-Notch3 antibody-drug conjugates consist of a peptide cleavable maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (vc) linker or a non-cleavable, thioether-based maleimidocaproyl (mc) linker conjugated to a series of cytotoxic agents. Release of payloads from the antibody requires trafficking and localization of the antibody-drug conjugate to lysosomes that possess proteolytic enzymes, such as cathepsin B, to cleave the vc-type linker or late lysosomes for complete catabolism of the antibody in order to release the mc-linked payloads. The internalization and intracellular trafficking of anti-Notch3 antibodies to lysosomal vesicles were monitored by indirect and direct immunofluoresence microscopy-based assays. To directly visual intracellular trafficking of anti-Notch3 antibodies, they were conjugated to fluorescent dyes and incubated with live cells in the presence of pHrodo™ red dextran (Life Technologies) to stain acidic vesicles such as lysosomes. Live cell imaging was performed to identify co-localization of the fluorescence-labeled antibody with lysosomes and other acidic vesicles. Further, indirect immunofluorescence

microscopy-based assays were performed on cells to confirm co-localization of anti-Notch3 antibodies and LAMP1, a lysosomal-associated protein.

A. Internalization and lysosomal trafficking

HCC2429 or MDA-MB-468 cells were cultured in a Lab Tec II 4 chambered coverglass with cover #1.5 borosilicate sterile slides (Thermo Fisher Scientific Inc.). On day 1, pHrodo™ red dextran (Life Technologies) was added to the medium at 10 µg/ml concentration and incubated for 16 hours in order to stain acidic vesicles such as lysosomes. On day 2, cells were washed twice with HBSS++ (Gibco Life Technologies). Anti-Notch3 antibody hu75 was conjugated to Alexa Fluor 488 (hereinafter "hu75-Alexa488") (Life Technologies Protein Labeling kit) and hu28 was directly conjugated to the DyLight650 maleimide reagent (hereinafter "hu28-DyLight650") (Thermo Scientific) according to manufacturer's instructions . Hu75-Alexa488 or hu28-DyLight650 labeled antibodies were added to the cells at a concentration 5 µg/ml in 2% bovine serum albumin (BSA)/HBSS++ for 25 minutes on wet ice. Cells were washed twice with ice cold HBSS++ on ice, placed in 2% BSA/HBSS++ and imaged on a spinning disk CSU-X1M 5000 microscope (Yokogawa) equipped with a eXcelon Evolve 512 camera (Photometrics) and a XL S Series chamber (Zeiss) for temperature, humidity and 5% CO_2 control, from 5 minutes to 12-18 hours. Images were captured every 5 minutes and combined using the Zen CZI file format (Zeiss). A Pearson's correlation coefficient was calculated using the Volocity v6.3 software (PerkinElmer) to determine the degree of colocalization between hu28-DyLight650 and pHrodo™ red dextran.

Once cells were prepared for live cell imaging, the earliest time point that could be assessed was 10 minutes due to set up and optimization of instrument setting for image acquisition. Approximately 10 minutes after cells were place in the humidified, 37°C, 5% CO_2 chamber, hu75-Alexa488 could be observed at the cell surface as well as in several punctuate-like structures inside the cells, as shown in **FIG. 8A**. This result indicates that anti-Notch3 antibody hu75 rapidly underwent internalization upon binding the Notch3 receptor at the cell membrane. At the early time points (10 minutes to about 65 minutes), intracellular anti-Notch3 antibody hu75-Alexa488 and acidic vesicles that were stained with pHrodo™ red dextran appeared as discrete puncta that did not co-

WHAT IS CLAIMED:

1. An isolated antibody, or antigen-binding fragment thereof, that binds to Notch3 comprising:

a VH CDR1, a VH CDR2, and a VH CDR3 of a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13; and

a VL CDR1, a VL CDR2, and a VL CDR3 of a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 25.

2. The isolated antibody, or antigen-binding fragment thereof, of claim 1, wherein the antibody or antigen-binding fragment:

(a) internalizes into a cell,

(b) does not inhibit Notch3 signaling, or

(c) does not activate Notch3 signaling.

3. The isolated antibody, or antigen-binding fragment thereof, of claim 1, wherein the antibody or antigen-binding fragment:

(a) binds to the Lin 12/Notch repeat (LNR)-C and heterodimerization (HD)-1 domains of the Notch3 Negative Regulatory Region (NRR),

(b) does not maintain the Notch3 NRR in an auto-inhibitory conformation, or

(c) does not inhibit S2-cleavage.

4. The isolated antibody, or antigen-binding fragment thereof, of claim 1, comprising:

a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 15 or 16;

a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 19 or 20;

a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 23;

a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 27;

a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 29; and

a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 31.

5. The isolated antibody, or antigen-binding fragment thereof, of claim 1, comprising a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 13 or a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 25.

6. The isolated antibody, or antigen-binding fragment thereof, of claim 5, comprising a heavy chain variable region amino acid sequence of SEQ ID NO: 13.

7. The isolated antibody, or antigen-binding fragment thereof, of claim 6, comprising a heavy chain amino acid sequence of SEQ ID NO: 33.

8. The isolated antibody, or antigen-binding fragment thereof, of claim 5, comprising a light chain variable region amino acid sequence of SEQ ID NO: 25.

9. The isolated antibody, or antigen-binding fragment thereof, of claim 8, comprising a light chain amino acid sequence of SEQ ID NO: 35.

10. An antibody-drug conjugate comprising a cytotoxic agent conjugated to the antibody, or antigen-binding fragment thereof, of claim 1.

11. A pharmaceutical composition comprising the antibody-drug conjugate of claim 10 and a pharmaceutically acceptable carrier.

12. A composition comprising the antibody of claim 1.

13. An isolated antibody, or antigen-binding fragment thereof, that binds to Notch3 comprising:

a VH CDR1, a VH CDR2, and a VH CDR3 of a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 37; and

a VL CDR1, a VL CDR2, and a VL CDR3 of a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 49.

14. The isolated antibody, or antigen-binding fragment thereof, of claim 13, comprising:

a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 39 or 40;

a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 43 or 44;

a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 47;

a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 51;

a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 53; and

a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 55.

15. The isolated antibody, or antigen-binding fragment thereof, of claim 13, comprising a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 37 or a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 49.

16. The isolated antibody, or antigen-binding fragment thereof, of claim 15, comprising a heavy chain variable region amino acid sequence of SEQ ID NO: 37.

17. The isolated antibody, or antigen-binding fragment thereof, of claim 16, comprising a heavy chain amino acid sequence of SEQ ID NO: 57.

18. The isolated antibody, or antigen-binding fragment thereof, of claim 15, comprising a light chain variable region amino acid sequence of SEQ ID NO: 49.

19. The isolated antibody, or antigen-binding fragment thereof, of claim 18, comprising a light chain amino acid sequence of SEQ ID NO: 59.

20. An antibody-drug conjugate comprising a cytotoxic agent conjugated to the antibody, or antigen-binding fragment thereof, of claim 13.

21. A pharmaceutical composition comprising the antibody-drug conjugate of claim 20 and a pharmaceutically acceptable carrier.

22. A composition comprising the antibody of claim 13.

23. An antibody-drug conjugate of the formula:

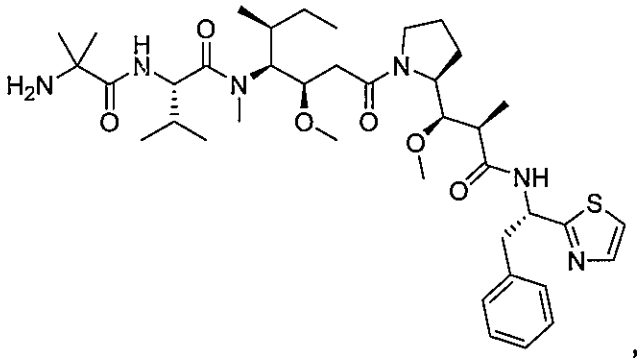
Ab-(L-D)*p*,

or a pharmaceutically acceptable salt thereof wherein:

(a) Ab is an antibody, or antigen-binding fragment thereof, that binds to Notch3;

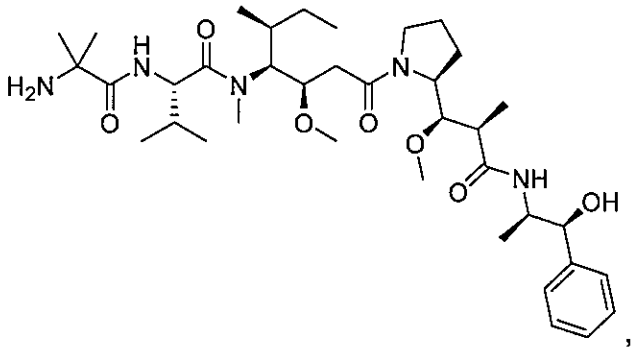
(b) L-D is a linker-drug moiety, wherein L is a linker selected from the group consisting of maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (vc), maleimidocaproyl (mc), maleimido-heptanoyl (me) and maleimido-Peg6C2 (MalPeg6C2), and D is a drug selected from the group consisting of:

(i) 0101 having the formula:



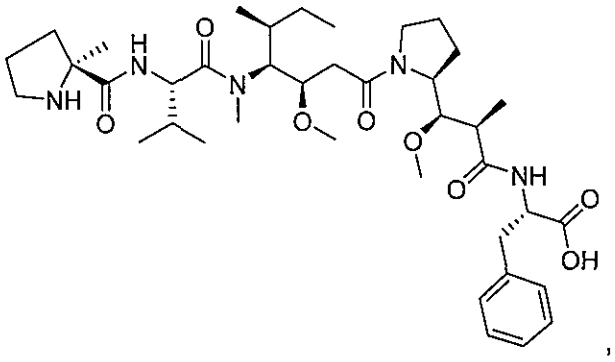
,

(ii) 6780 having the formula:



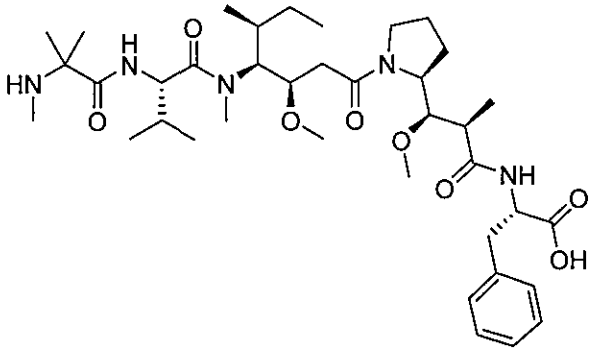
,

(iii) 0131 having the formula:



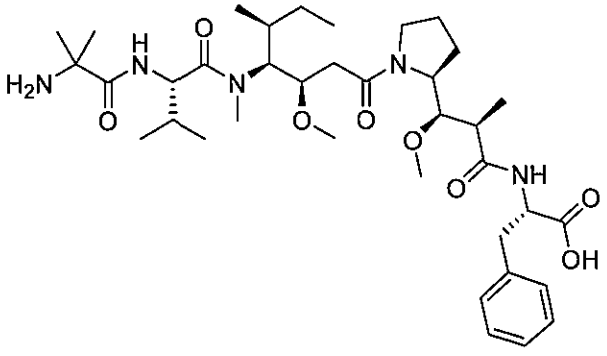
,

(iv) 3377 having the formula:



, and

(v) 8261 having the formula:



; and

(c) *p* is an integer from 1 to 12.

24. A pharmaceutical composition comprising the antibody-drug conjugate of claim 23 and a pharmaceutically acceptable carrier.

25. The antibody-drug conjugate of claim 23, wherein Ab comprises: a VH CDR1, a VH CDR2, and a VH CDR3 of a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13; and a VL CDR1, a VL CDR2, and a VL

CDR3 of a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 25; or a VH CDR1, a VH CDR2, and a VH CDR3 of a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 37; and a VL CDR1, a VL CDR2, and a VL CDR3 of a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 49.

26. The antibody-drug conjugate of claim 23, wherein Ab comprises: a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 15 or 16; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 19 or 20; a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 23; a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 29; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 31; or a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 39 or 40; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 43 or 44; a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 47; a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 51; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 53; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 55.

27. The antibody-drug conjugate of claim 26, wherein Ab comprises: a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 13 or a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 25; or a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 37 or a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 49.

28. The antibody-drug conjugate of claim 27, wherein Ab comprises a heavy chain variable region amino acid sequence of SEQ ID NO: 13; or a heavy chain variable region amino acid sequence of SEQ ID NO: 37.

29. The antibody-drug conjugate of claim 28, wherein Ab comprises a heavy chain amino acid sequence of SEQ ID NO: 33; or a heavy chain amino acid sequence of SEQ

ID NO: 57.

30. The antibody-drug conjugate of claim 27, wherein Ab comprises a light chain variable region amino acid sequence of SEQ ID NO: 25 or a light chain variable region amino acid sequence of SEQ ID NO: 49.

31. The antibody-drug conjugate of claim 30, wherein Ab comprises a light chain amino acid sequence of SEQ ID NO: 35; or a light chain amino acid sequence of SEQ ID NO: 59.

32. An antibody-drug conjugate of the formula:

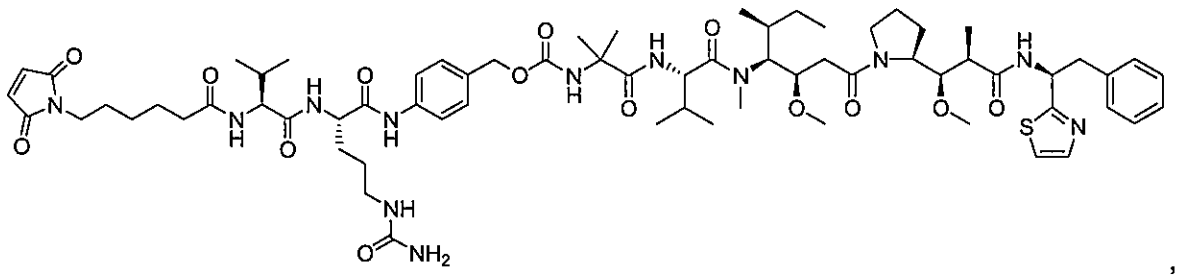
Ab-(L-D)*p*,

or a pharmaceutically acceptable salt thereof wherein:

(a) Ab is an antibody, or antigen-binding fragment thereof, that binds to Notch3;

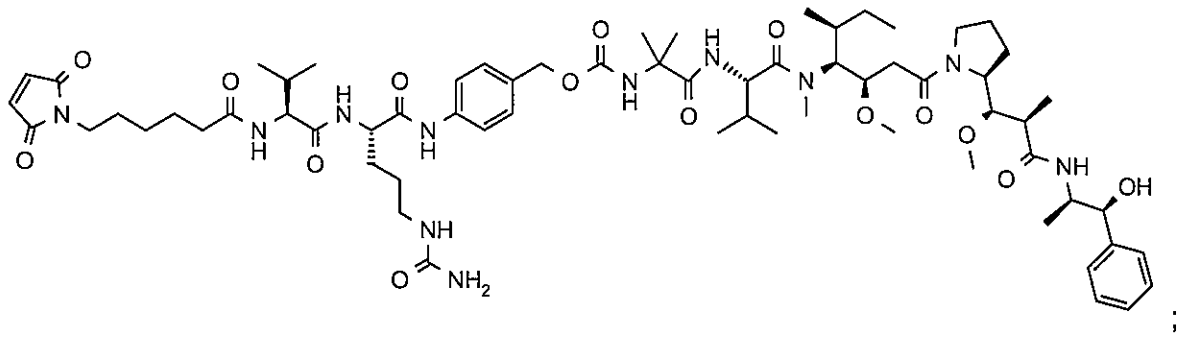
(b) L-D is a linker-drug moiety, wherein L is a linker, and D is a drug, wherein L-D is selected from the group consisting of:

vc0101 having the formula:



,

and vc6780 having the formula:



;

and

(c) *p* is an integer from 1 to 12.

33. A pharmaceutical composition comprising the antibody-drug conjugate of claim 32 and a pharmaceutically acceptable carrier.

34. The antibody-drug conjugate of claim 32, wherein Ab comprises: a VH CDR1, a VH CDR2, and a VH CDR3 of a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 13; and a VL CDR1, a VL CDR2, and a VL CDR3 of a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 25; or a VH CDR1, a VH CDR2, and a VH CDR3 of a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 37; and a VL CDR1, a VL CDR2, and a VL CDR3 of a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 49.

35. The antibody-drug conjugate of claim 32, wherein Ab comprises: a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 15 or 16; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 19 or 20; a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 23; a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 29; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 31; or a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 39 or 40; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 43 or 44; a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 47; a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 51; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 53;

and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 55.

36. The antibody-drug conjugate of claim 35, wherein Ab comprises: a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 13 or a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 25; or a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 37 or a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 49.

37. The antibody-drug conjugate of claim 36, wherein Ab comprises a heavy chain variable region amino acid sequence of SEQ ID NO: 13; or a heavy chain variable region amino acid sequence of SEQ ID NO: 37.

38. The antibody-drug conjugate of claim 37, wherein Ab comprises a heavy chain amino acid sequence of SEQ ID NO: 33; or a heavy chain amino acid sequence of SEQ ID NO: 57.

39. The antibody-drug conjugate of claim 36, wherein Ab comprises a light chain variable region amino acid sequence of SEQ ID NO: 25 or a light chain variable region amino acid sequence of SEQ ID NO: 49.

40. The antibody-drug conjugate of claim 39, wherein Ab comprises a light chain amino acid sequence of SEQ ID NO: 35; or a light chain amino acid sequence of SEQ ID NO: 59.

41. An antibody-drug conjugate of the formula:

Ab-(L-D)*p*,

or a pharmaceutically acceptable salt thereof wherein:

(a) Ab is an antibody, or antigen-binding fragment thereof, that binds to Notch3 comprising a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region

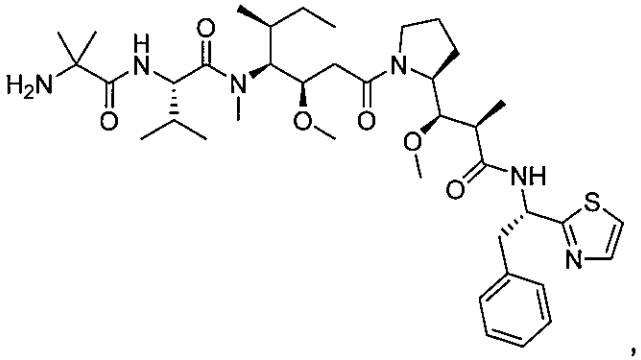
(VH) comprising the amino acid sequence set forth in SEQ ID NO: 13 and a VL CDR1, a VL CDR2 and VL CDR3 of a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 25;

(b) L-D is a linker-drug moiety, wherein L is a linker, and D is a drug; and

(c) p is an integer from 1 to 12.

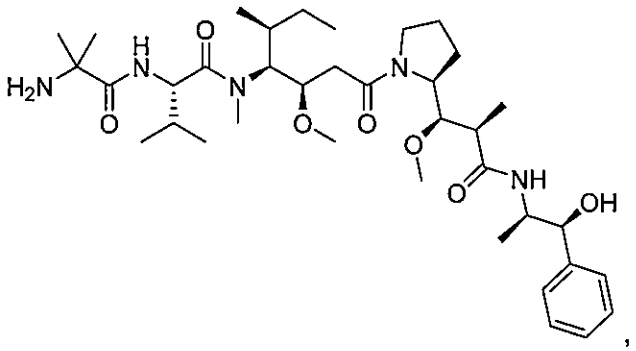
42. The antibody-drug conjugate of claim 41, wherein L is selected from the group consisting of maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (vc), maleimidocaproyl (mc), maleimido-heptanoyl (me) and maleimido-Peg6C2 (MalPeg6C2).

43. The antibody-drug conjugate of claim 42, wherein D is selected from the group consisting of:

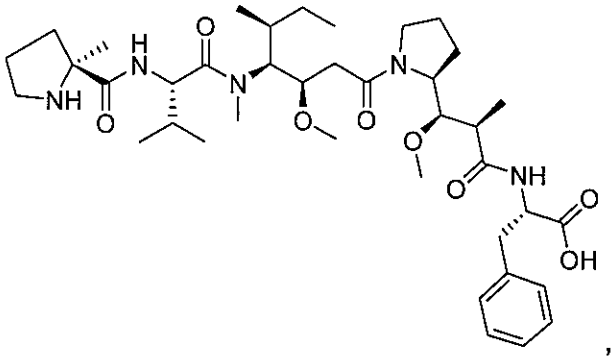


(a) 0101 having the formula:

(b) 6780 having the formula:

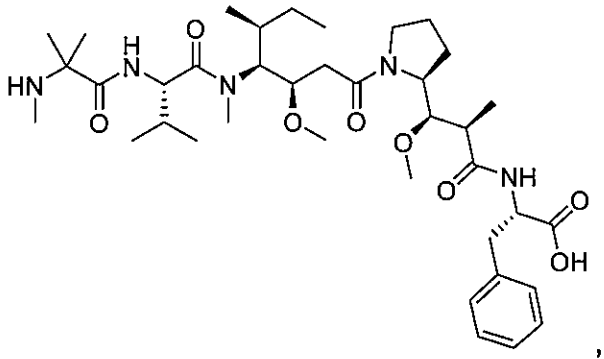


(c) 0131 having the formula:



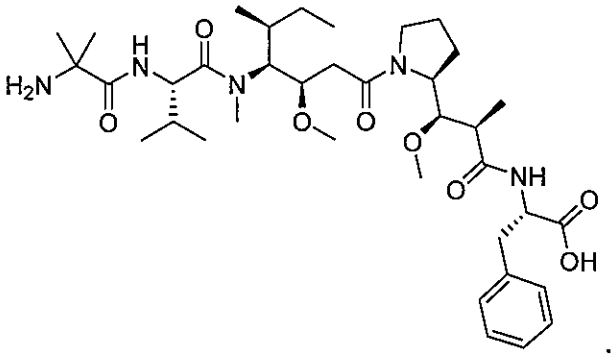
,

(d) 3377 having the formula:



, and

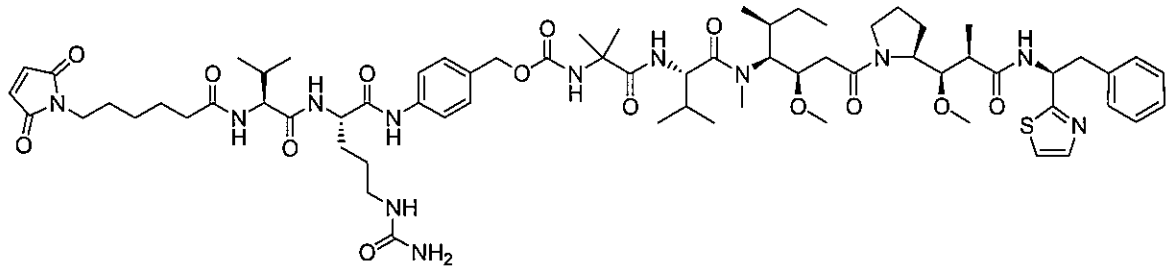
(e) 8261 having the formula:



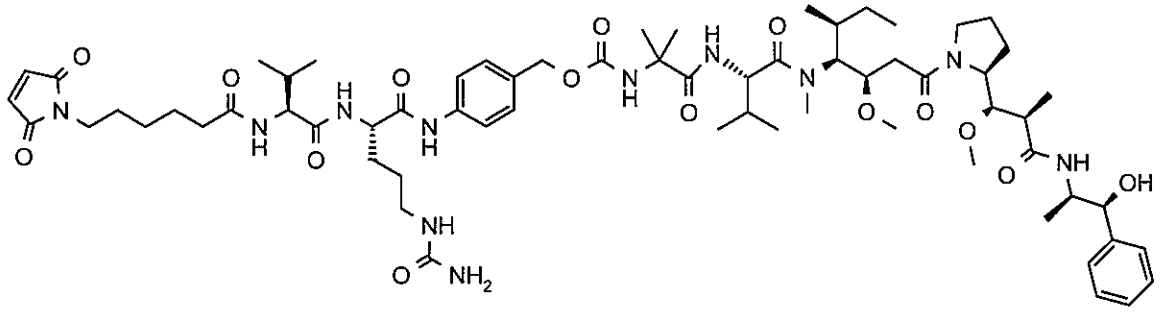
.

44. The antibody-drug conjugate of claim 41, wherein L-D is selected from the group consisting of:

vc0101 having the formula:



and vc6780 having the formula:



45. A pharmaceutical composition comprising the antibody drug conjugate of claim 41 and a pharmaceutically acceptable carrier.

46. The antibody-drug conjugate of claim 41, wherein Ab comprises: a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 15 or 16; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 19 or 20; a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 23; a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 29; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 31.

47. The antibody-drug conjugate of claim 41, wherein Ab comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID

NO: 13 or a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 25.

48. The antibody-drug conjugate of claim 47, wherein Ab comprises a heavy chain variable region amino acid sequence of SEQ ID NO: 13.

49. The antibody-drug conjugate of claim 48, wherein Ab comprises a heavy chain amino acid sequence of SEQ ID NO: 33.

50. The antibody-drug conjugate of claim 47, wherein Ab comprises a light chain variable region amino acid sequence of SEQ ID NO: 25.

51. The antibody-drug conjugate of claim 50, wherein Ab comprises a light chain amino acid sequence of SEQ ID NO: 35.

52. An antibody-drug conjugate of the formula:

Ab-(L-D)*p*,

or a pharmaceutically acceptable salt thereof wherein:

(a) Ab is an antibody, or antigen-binding fragment thereof, that binds to Notch3 comprising a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 37 and a VL CDR1, a VL CDR2 and a VL CDR3 of a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 49;

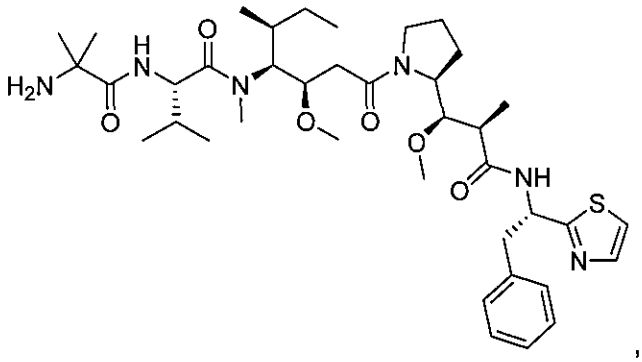
(b) L-D is a linker-drug moiety, wherein L is a linker, and D is a drug; and

(c) p is an integer from 1 to 12.

53. The antibody-drug conjugate of claim 52, wherein L is selected from the group consisting of maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (vc), maleimidocaproyl (mc), maleimido-heptanoyl (me) and maleimido-Peg6C2 (MalPeg6C2).

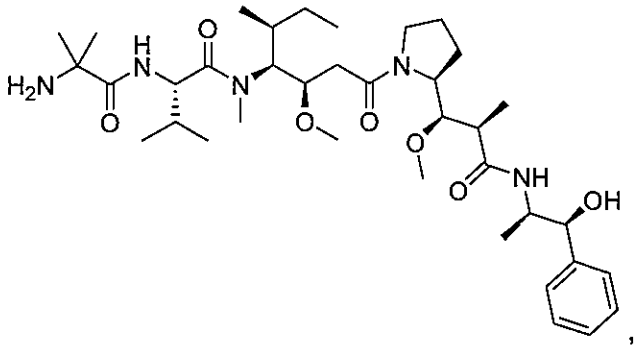
54. The antibody-drug conjugate of claim 53, wherein D is selected from the group consisting of:

(a) 0101 having the formula:



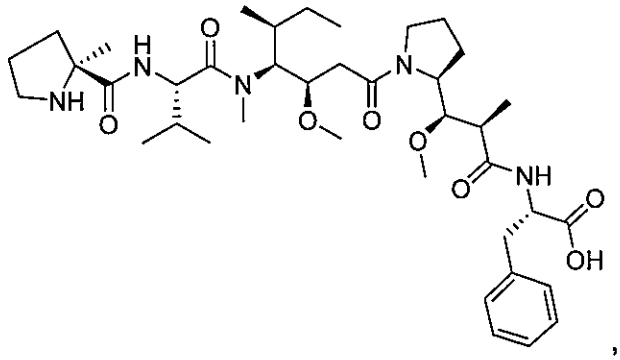
,

(b) 6780 having the formula:



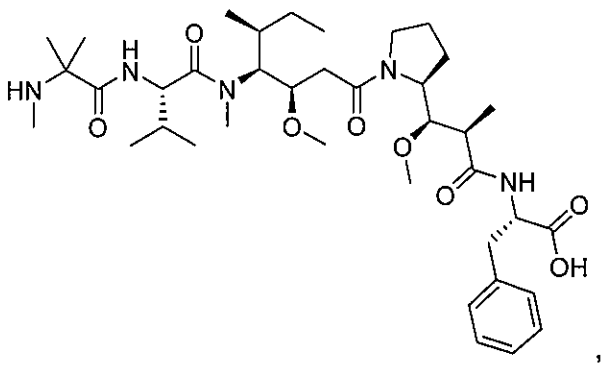
,

(c) 0131 having the formula:



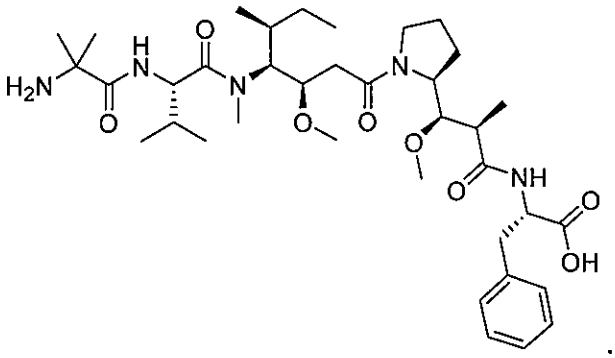
,

(d) 3377 having the formula:



, and

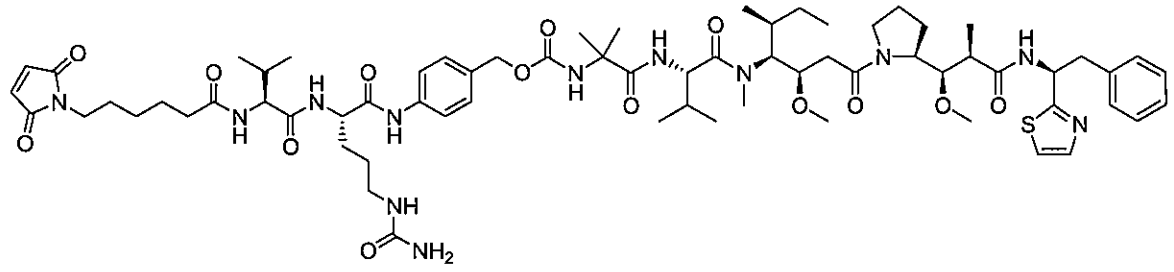
(e) 8261 having the formula:



.

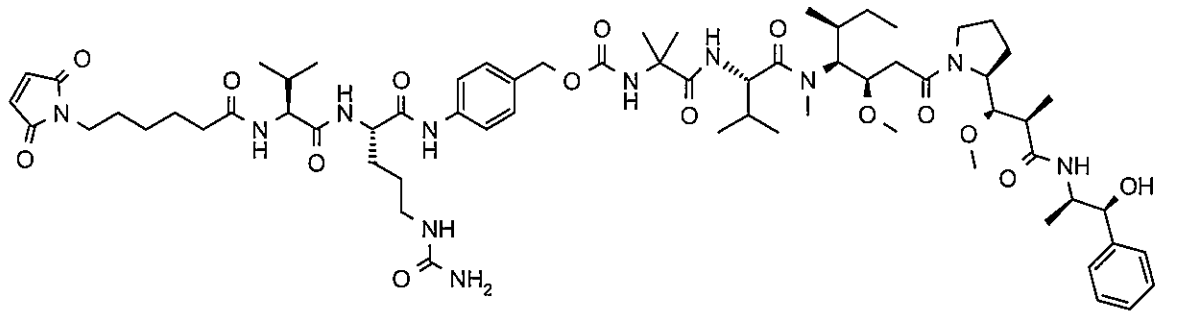
55. The antibody-drug conjugate of claim 52, wherein L-D is selected from the group consisting of:

vc0101 having the formula:



,

and vc6780 having the formula:



56. The antibody-drug conjugate of claim52, wherein Ab comprises: a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 39 or 40; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 43 or 44; a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 47; a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 51; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 53; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 55.

57. The antibody-drug conjugate of claim 52, wherein Ab comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 37 or a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 49.

58. The antibody-drug conjugate of claim 57, wherein Ab comprises a heavy chain variable region amino acid sequence of SEQ ID NO: 37.

59. The antibody-drug conjugate of claim 58, wherein Ab comprises a heavy chain amino acid sequence of SEQ ID NO: 57.

60. The antibody-drug conjugate of claim 57, wherein Ab comprises a light chain variable region amino acid sequence of SEQ ID NO: 49.

61. The antibody-drug conjugate of claim 60, wherein Ab comprises a light chain amino acid sequence of SEQ ID NO: 59.

62. A pharmaceutical composition comprising the antibody-drug conjugate of claim52 and a pharmaceutically acceptable carrier.

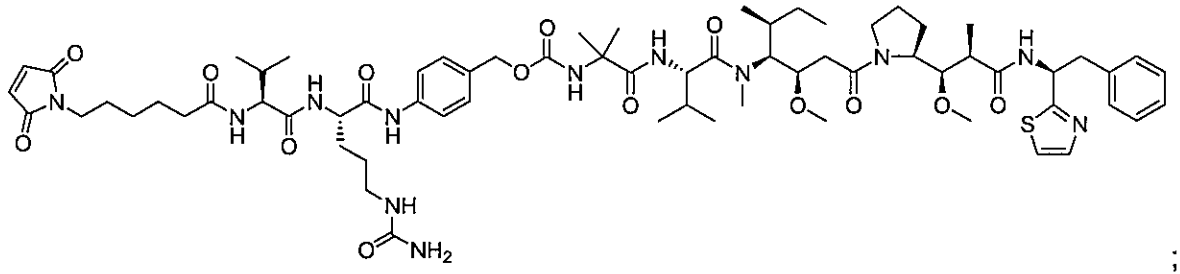
63. An antibody-drug conjugate of the formula:

Ab-(L-D)*p*,

or a pharmaceutically acceptable salt thereof wherein:

(a) Ab is an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region amino acid sequence of SEQ ID NO: 13 and a light chain variable region amino acid sequence of SEQ ID NO 25;

(b) L-D is a linker-drug moiety, wherein L is a linker, and D is a drug, wherein the L-D is vc0101 having the formula



;

and

(c) *p* is an integer from 1 to 12.

64. A pharmaceutical composition comprising the antibody-drug conjugate of claim 63 and a pharmaceutically acceptable carrier.