ANTI-Ly6E ANTIBODIES AND IMMUNOCONJUGATES AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of US Provisional Patent Application Serial No. 61/649,775 filed on 21 May 2012, which is fully incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to anti-Ly6E antibodies and immunoconjugates and methods of using the same.

BACKGROUND

[0003] Lymphocyte antigen 6 complex, locus E (Ly6E), also known as retinoic acid induced gene E (RIG-E) and stem cell antigen 2 (SCA-2). It is a GPI linked, 131 amino acid length, ~8.4kDa protein of unknown function with no known binding partners. It was initially identified as a transcript expressed in immature thymocyte, thymic medullary epithelial cells in mice. *RIG-E, a human homolog of the murine Ly-6 family, is induced by retinoic acid during the differentiation of acute promyelocytic leukemia cell*. Mao M., Yu M., Tong J.-H., Ye J., Zhu J., Huang Q.-H., Fu G., Yu L., Zhao S.-Y., Waxman S., Lanotte M., Wang Z.-Y., Tan J.-Z., Chan S.-J., Chen Z. Proc. Natl. Acad. Sci. U.S.A. 93:5910-5914 (1996).

[0004] There is a need in the art for agents that target Ly6E for the diagnosis and treatment of Ly6E-associated conditions, such as cancer. The invention fulfills that need and provides other benefits.

SUMMARY ~~OF THE INVENTION~~

[0005] The ~~invention~~ disclosure provides anti-Ly6E antibodies, immunoconjugates and methods of using the same.

[005a] In one aspect, there is provided an isolated antibody that binds to Ly6E, wherein the antibody binds an epitope within amino acids 21-131 of SEQ ID NO:1 with an affinity of ≤ 4 nM as measured by scatchard analysis.

[0006] In some embodiments, an isolated antibody that binds to Ly6E is provided. In other embodiments the antibody that binds to Ly6E binds to an epitope within amino acids 21-131 of SEQ ID NO:1. In another embodiment, such an antibody binds Ly6E with an affinity of ≤ 4 nM as measured by scatchard analysis. In another embodiment, such an antibody binds Ly6E with an affinity of ≤ 7 nM as measured by surface plasmon resonance (SPR). In yet another embodiment, such an antibody is used as a medicament.

[0007] In one embodiment, an antibody that binds to an epitope within amino acids 21-131 of SEQ ID NO:1 binds with an affinity of ≤ 4 nM as measured by scatchard analysis, or binds Ly6E with an affinity of ≤ 7 nM as measured by SPR is a monoclonal antibody. In another embodiment, such an antibody is a human, humanized, or chimeric antibody.

[0012] In one embodiment, an antibody that binds to an epitope within amino acids 21-131 of SEQ ID NO:1 binds with an affinity of ≤ 4 nM as measured by scatchard analysis, comprises a VH sequence of SEQ ID NO:5 and a VL sequence of SEQ ID NO:3. In another embodiment, an antibody that binds to an epitope within amino acids 21-131 of SEQ ID NO:1 binds with an affinity of ≤ 7 nM as measured by SPR, comprises a VH sequence of SEQ ID NO:5 and a VL sequence of SEQ ID NO:3.

[0013] In one embodiment, an antibody that binds to an epitope within amino acids 21-131 of SEQ ID NO:1 binds with an affinity of ≤ 4 nM as measured by scatchard analysis, which is an IgG1, IgG2a or IgG2b. In one embodiment, an antibody that binds to an epitope within amino acids 21-131 of SEQ ID NO:1 binds with an affinity of ≤ 7 nM as measured by SPR, which is an IgG1, IgG2a or IgG2b.

[0013a] In one aspect, there is provided an antibody comprising a VH sequence of SEQ ID NO:5 and a VL sequence of SEQ ID NO:3.

[0013b] In one aspect, there is provided an isolated nucleic acid encoding the antibody as defined herein.

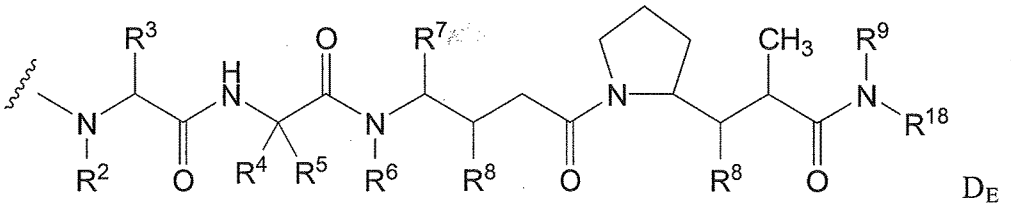
[0013c] In one aspect, there is provided a host cell comprising the nucleic acid as defined herein.

[0014] In one embodiment, isolated nucleic acids encoding an antibody as described herein is provided. In another embodiment, a host cell comprising such an isolated nucleic acid is also provided.

[0014a] In one aspect, there is provided a method of producing an antibody comprising culturing the host cell as defined herein so that the antibody is produced. In yet another embodiment, a method of producing an antibody comprising culturing the host cell comprising an isolated nucleic acid as described herein so that the antibody is produced is also provided.

[0014a] In one aspect, there is provided an immunoconjugate comprising the antibody as defined herein and a cytotoxic agent.

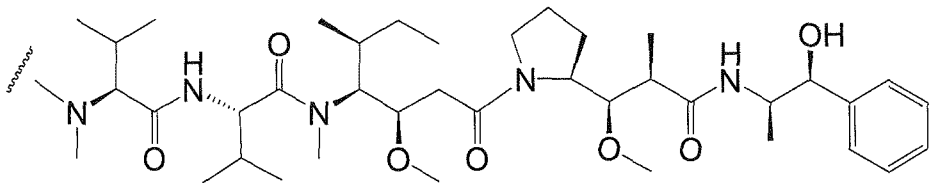
[0015] In one embodiment, an immunoconjugate comprising an antibody as described herein and a cytotoxic agent is provided. In another embodiment, such an immunoconjugate has the formula Ab-(L-D)p, wherein: (a) Ab is an antibody as described herein; (b) L is a linker; (c) D is a drug selected from a maytansinoid, an auristatin, a calicheamicin, a pyrrolobenzodiazepine, and a nemorubicin derivative; and (d) p ranges from 1-8. In some embodiments, such an immunoconjugate has D as an auristatin. In other embodiments, such an immunoconjugate has D having formula D_E:



D_E

wherein R^2 and R^6 are each methyl, R^3 and R^4 are each isopropyl, R^5 is H, R^7 is sec-butyl, each R^8 is independently selected from CH_3, O-CH_3, OH, and H; R^9 is H; and R^{18} is $–C(R^8)_2–C(R^8)_2–$aryl.

[0016] In other embodiments, an immunoconjugate described herein, has as its drug, MMAE having the structure:



[0017] In one embodiment, the immunoconjugate described herein, has D as a pyrrolobenzodiazepine of

[0029] In one embodiment, an immunoconjugate of the ~~invention~~ disclosure as described herein comprises an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:10, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:11, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:12, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:8; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:9. In another embodiment, an immunoconjugate of the ~~invention~~ diclsoure as described herein comprises a VH sequence of SEQ ID NO:5 and a VL sequence of SEQ ID NO:3.

[0029a] In one aspect, there is provided a pharmaceutical formulation comprising the immunoconjugate as defined herein and a pharmaceutical acceptable carrier.

[0030] In one embodiment, a pharmaceutical formulation comprising the immunoconjugate of the ~~invention~~ disclosure as described herein and a pharmaceutically acceptable carrier is provided. In some embodiments, a pharmaceutical formulation further comprises an additional therapeutic agent. In some embodiments, the additional therapeutic agent is a chemotherapeutic agent, such as, for example, a platinum complex.

[0030a] In one aspect, there is provided the use of an effective amount of the immunoconjugate as defined herein in the manufacture of a medicament for treating an individual having an Ly6E-positive cancer.

[0031] In one embodiment, methods of treating an individual having a Ly6E-positive cancer are provided. In some embodiments, such methods comprise administering a pharmaceutical formulation comprising an immunoconjugate of the ~~invention~~ disclosure as described herein comprising an antibody that binds Ly6E, e.g., as described herein. In other embodiments, the Ly6E-positive cancer is selected from breast cancer, pancreatic cancer, colon cancer, colorectal cancer, melanoma, ovarian cancer, non-small cell lung cancer, or gastric cancer. In some embodiments, a method of the ~~invention~~disclosure comprises administering an additional therapeutic agent to the individual. In some embodiments, the additional therapeutic agent is a chemotherapeutic agent, such as, for example, a platinum complex.

[0031a] In one aspect, there is provided the use of an immunoconjugate as defined herein in the manufacture of a medicament for inhibiting proliferation of an Ly6E-positive cell, wherein the cell is to be exposed to the medicament under conditions permissive for binding of the immunoconjugate to Ly6E on the surface of the cell.

[0032] In some embodiments, methods of inhibiting proliferation of a Ly6E-positive cell are provided. In one embodiment, such methods comprise exposing a Ly6E-positive cell to an immunoconjugate of the ~~invention~~ disclosure as described herein comprising an antibody that binds Ly6E under conditions permissive for binding of the immunoconjugate to Ly6E on the surface of the cell. In some embodiments, an antibody that binds Ly6E is an antibody as described herein. In some embodiments, proliferation of the Ly6E-positive cell is thereby inhibited. In some embodiments, the cell is a breast

cancer cell, pancreatic cancer cell, colon cancer cell, colorectal cancer cell, melanoma cell, ovarian cancer cell, non-small cell lung cancer cell, or gastric cancer cell.

[0032a] In one aspect, there is provided an antibody as defined herein conjugated to a label.

[0033] In one embodiment, an antibody that binds Ly6E as described herein is conjugated to a label. In some embodiments, such a label is a positron emitter. In some embodiments, the positron emitter is ^{89}Zr.

[0033a] In one aspect, there is provided a method of detecting human Ly6E in a biological sample comprising contacting the biological sample with the anti-Ly6E antibody as defined herein under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the biological sample.

[0034] In some embodiments, a method of detecting human Ly6E in a biological sample is provided. In some embodiments, such a method comprises contacting the biological sample with an anti-Ly6E antibody under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the biological sample. In some embodiments, an anti-Ly6E antibody is an antibody described herein. In some embodiments, the biological sample is a breast

cancer sample, pancreatic cancer sample, colon cancer sample, colorectal cancer sample, melanoma sample, ovarian cancer sample, non-small cell lung cancer sample, or gastric cancer sample.

[0034a] In one aspect, there is provided a method for detecting a Ly6E-positive cancer comprising (i) administering a labeled anti-Ly6E antibody to a subject having or suspected of having a Ly6E-positive cancer, wherein the labeled anti-Ly6E antibody comprises the anti-Ly6E antibody as defined herein, and (ii) detecting the labeled anti-Ly6E antibody in the subject, wherein detection of the labeled anti-Ly6E antibody indicates a Ly6E-positive cancer in the subject.

[0035] In one embodiment, a method for detecting a Ly6E-positive cancer is provided. In such embodiments, a method comprises (i) administering a labeled anti-Ly6E antibody to a subject having or suspected of having a Ly6E-positive cancer, and (ii) detecting the labeled anti-Ly6E antibody in the subject, wherein detection of the labeled anti-Ly6E antibody indicates a Ly6E-positive cancer in the subject. In some embodiments, an anti-Ly6E antibody is an antibody described herein. In other embodiments, the Ly6E-positive cancer is selected from breast cancer, pancreatic cancer, colon cancer, colorectal cancer, melanoma, ovarian cancer, non-small cell lung cancer, or gastric cancer. In one embodiment of the method described herein, an antibody that binds Ly6E as described herein is conjugated to a label. In some embodiments, such a label is a positron emitter. In some embodiments, the positron emitter is ^{89}Zr.

[0036] In some embodiments, an isolated antibody that binds to Ly6E is provided for use as a medicament. In other embodiments the antibody that binds to Ly6E binds to an epitope within amino acids 21-131 of SEQ ID NO:1. In another embodiment, such an antibody binds Ly6E with an affinity of ≤ 4 nM as measured by scatchard analysis. In another embodiment, such an antibody binds Ly6E with an affinity of ≤ 7 nM as measured by SPR. In yet another embodiment, such an antibody is used for treating a Ly6E-positive cancer. In some embodiments, such an antibody is used for inhibiting the proliferation of a Ly6E-positive cancer cell. In some embodiments, the Ly6E-positive cancer cell is a breast cancer cell, pancreatic cancer cell, colon cancer cell, colorectal cancer cell, melanoma cell, ovarian cancer cell, non-small cell lung cancer cell, or gastric cancer cell. In some embodiments, use of such an antibody as described herein is used in the manufacture of a medicament. In another embodiment, such use is for a medicament for the treatment of a Ly6E-positive cancer. In yet another embodiment, such use is for inhibiting the proliferation of a Ly6E-positive cancer cell. In some embodiments, the Ly6E-positive cancer cell is a breast cancer cell, pancreatic cancer cell, colon cancer cell, colorectal cancer cell, melanoma cell, ovarian cancer cell, non-small cell lung cancer cell, or gastric cancer cell.

BRIEF DESCRIPTION OF THE FIGURES

[0037] Figure 1 shows a sequence alignment comparing the sequences of Ly6E orthologs from human (SEQ ID NO: 1), Cynomolgus monkey (SEQ ID NO: 2), Rhesus (SEQ ID NO: 35), mouse (SEQ ID NO: 36), and rat species (SEQ ID NO: 37). The percent identity at the amino acid level between these sequences in the extracellular domain (ECD) is shown to be ~96% between human and cynomolgus monkey Ly6E and ~52% between human and rat Ly6E.

[0038] Figure 2 shows a Genelogic profile of Ly6E mRNA expression as further described in Example 1. Measurements were carried out on the Affymetrix U133P chip and are expressed as scaled

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to Ly6E, wherein the antibody binds an epitope within amino acids 21-131 of SEQ ID NO:1 with an affinity of ≤ 4 nM as measured by scatchard analysis.

2. The antibody of claim 1, which is a monoclonal antibody.

3. The antibody of claim 1, which is a human, humanized, or chimeric antibody.

4. The antibody of claim 1, wherein the antibody is internalized in a Ly6E-expressing cell upon binding to said epitope within amino acids 21-131 of SEQ ID NO:1.

5. The antibody of claim 1, which is an antibody fragment that binds to an epitope within amino acids 21-131 of SEQ ID NO:1.

6. The antibody of claim 1, wherein the antibody comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:12, (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:9, and (c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:11.

7. The antibody of claim 1, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:10, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:11, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:12.

8. The antibody of claim 7, further comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:8; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:9.

9. The antibody of claim 1, comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:8; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:9.

10. The antibody of claim 8, further comprising a light chain variable domain framework FR2 sequence of SEQ ID NO:20 or light chain variable domain framework FR3 of SEQ ID NO:21 or heavy chain variable domain framework FR1 or SEQ ID NO:23, or heavy chain variable domain framework FR2 of SEQ ID NO:24.

11. The antibody of claim 1, comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:5; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:3; or (c) a VH sequence as in (a) and a VL sequence as in (b).

12. The antibody of claim 10, comprising a VH sequence of SEQ ID NO:5.

13. The antibody of claim 10, comprising a VL sequence of SEQ ID NO:3.

14. An antibody comprising a VH sequence of SEQ ID NO:5 and a VL sequence of SEQ ID NO:3.

15. The antibody of claim 1, which is an IgG1, IgG2a or IgG2b.

16. Isolated nucleic acid encoding the antibody of any one of claims 1 to 15.

17. A host cell comprising the nucleic acid of claim 16.

18. A method of producing an antibody comprising culturing the host cell of claim 17 so that the antibody is produced.

19. An immunoconjugate comprising the antibody of any one of claims 1 to 15 and a cytotoxic agent.

20. The immunoconjugate of claim 19 having the formula Ab-(L-D)p, wherein:

(a) Ab is the antibody of any one of claim 1 to 14;

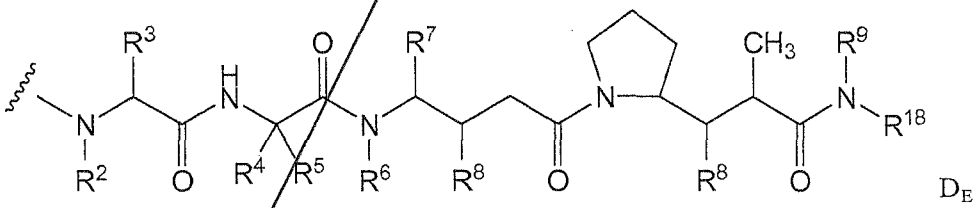
(b) L is a linker;

(c) D is a drug selected from a maytansinoid, an auristatin, a calicheamicin, a pyrrolobenzodiazepine, and a nemorubicin derivative; and

(d) p ranges from 1-8.

21. The immunoconjugate of claim 20, wherein D is an auristatin.

22. The immunoconjugate of claim 21, wherein D has formula D_E

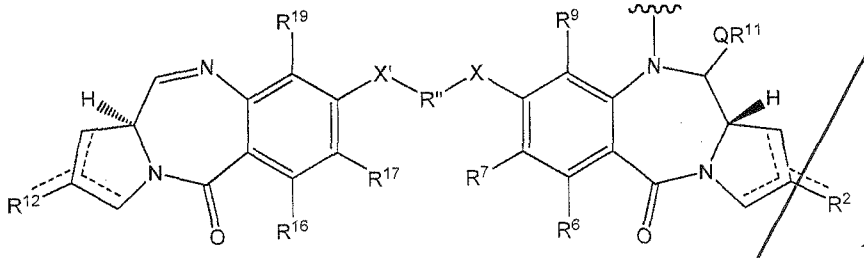


D_E

and wherein R^2 and R^6 are each methyl, R^3 and R^4 are each isopropyl, R^5 is H, R^7 is sec-butyl, each R^8 is independently selected from CH_3, O-CH_3, OH, and H; R^9 is H; and R^{18} is $-C(R^8)_2-C(R^8)_2-$aryl.

23. The immunoconjugate of claim 20, wherein the drug is MMAE.

24. The immunoconjugate of claim 21, wherein D is a pyrrolobenzodiazepine of Formula A:



A;

wherein the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

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

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

R^7 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

Q is independently selected from O, S and NH;

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

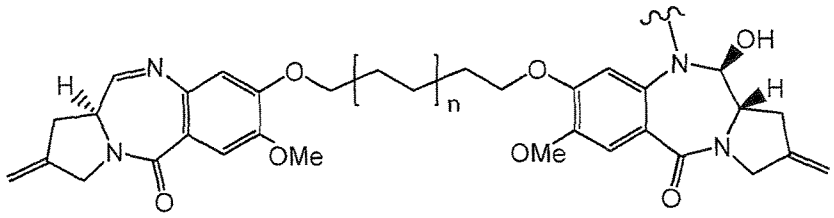
R and R' are each independently selected from optionally substituted C_{1-8} alkyl, C_{3-8} heterocyclyl and C_{5-20} aryl groups, and optionally in relation to the group NRR', R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring;

R^{12}, R^{16}, R^{19} and R^{17} are as defined for R^2, R^6, R^9 and R^7 respectively;

R'' is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms and/or aromatic rings that are optionally substituted; and

X and X' are independently selected from O, S and N(H).

25. The immunoconjugate of claim 24, wherein D has the structure:

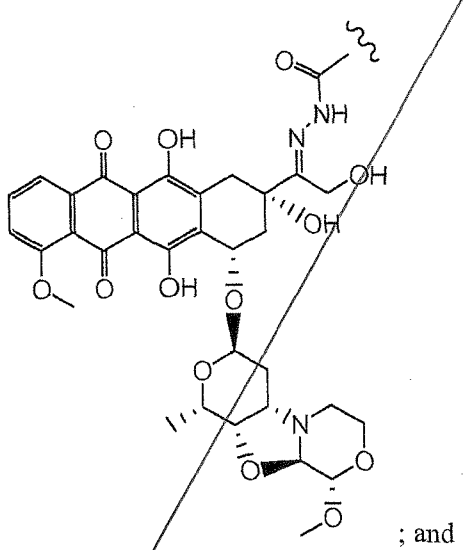


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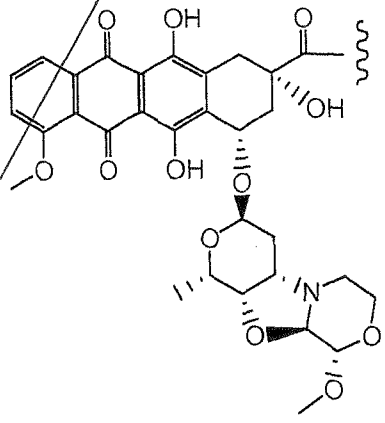
wherein n is 0 or 1.

26. The immunoconjugate of claim 20, wherein D is a nemorubicin derivative.

27. The immunoconjugate of claim 26, wherein D has a structure selected from:



; and



28. The immunoconjugate of any one of claims 20 to 27, wherein the linker is cleavable by a protease.

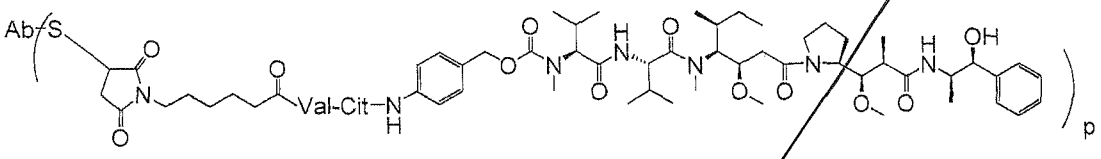
29. The immunoconjugate of claim 28, wherein the linker comprises a val-cit

dipeptide or a Phe-Lys dipeptide.

30. The immunoconjugate of any one of claims 20 to 27, wherein the linker is acid-labile.

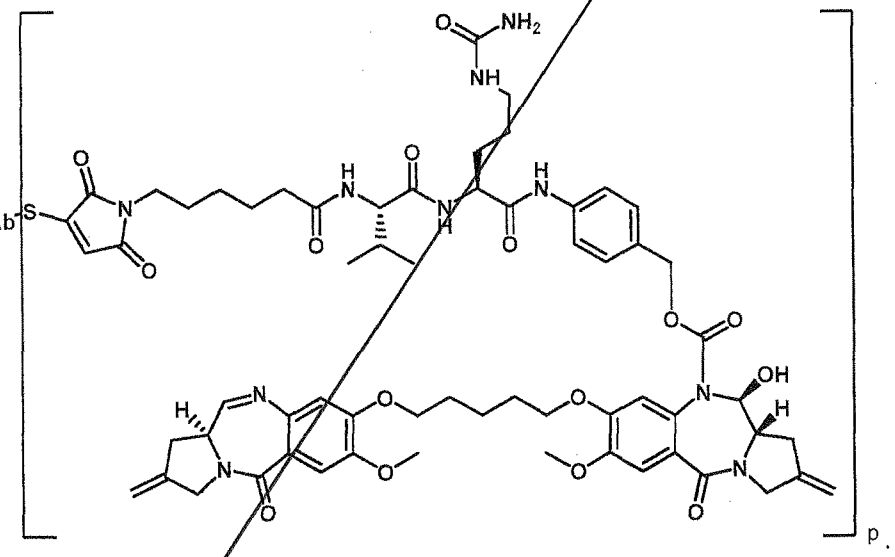
31. The immunoconjugate of claim 30, wherein the linker comprises hydrazone.

32. The immunoconjugate of claim 22 having the formula:

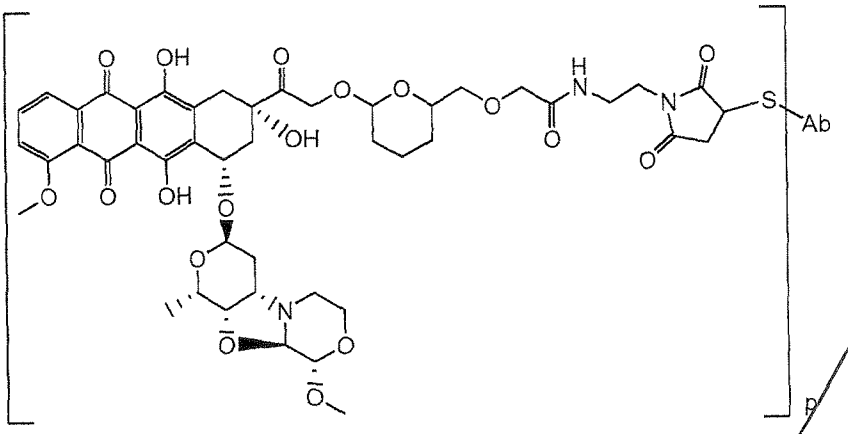


wherein S is a sulfur atom.

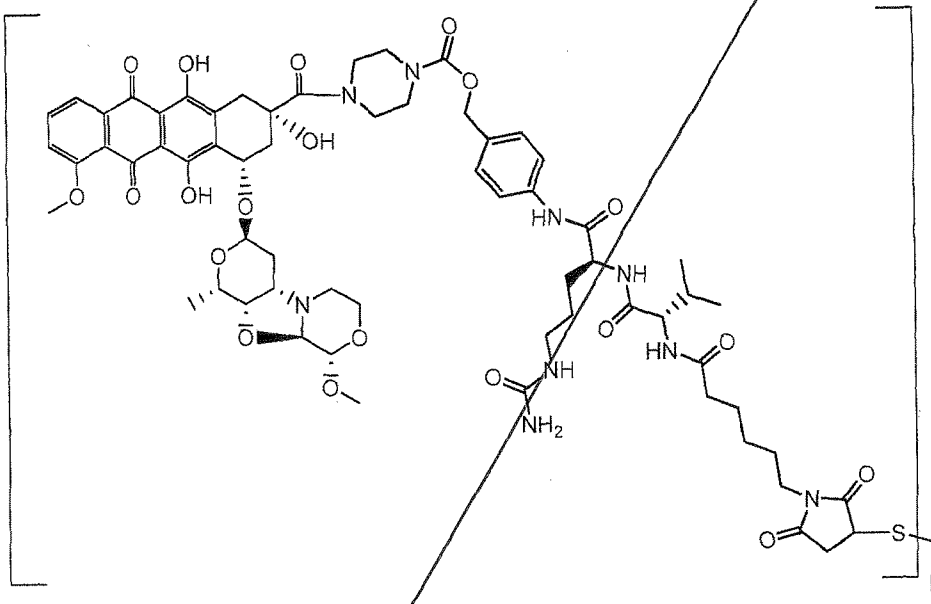
33. The immunoconjugate of claim 25 having the formula:



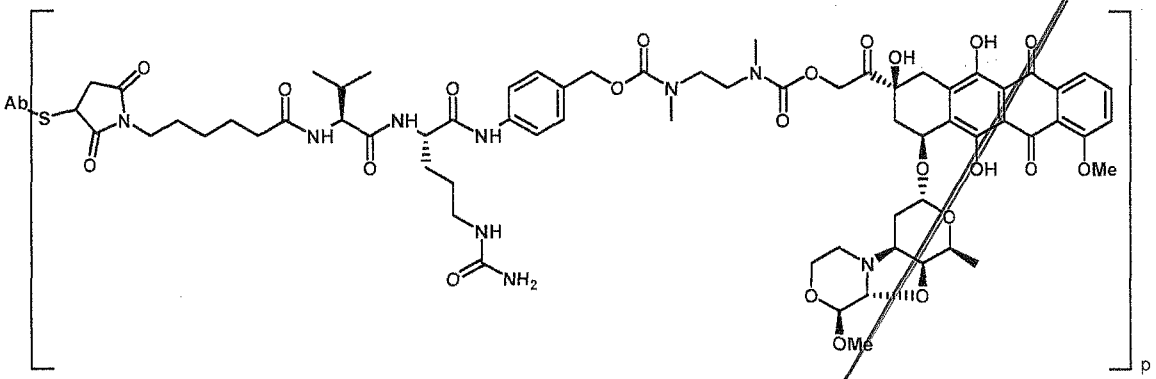
34. The immunoconjugate of claim 27 having a formula selected from:

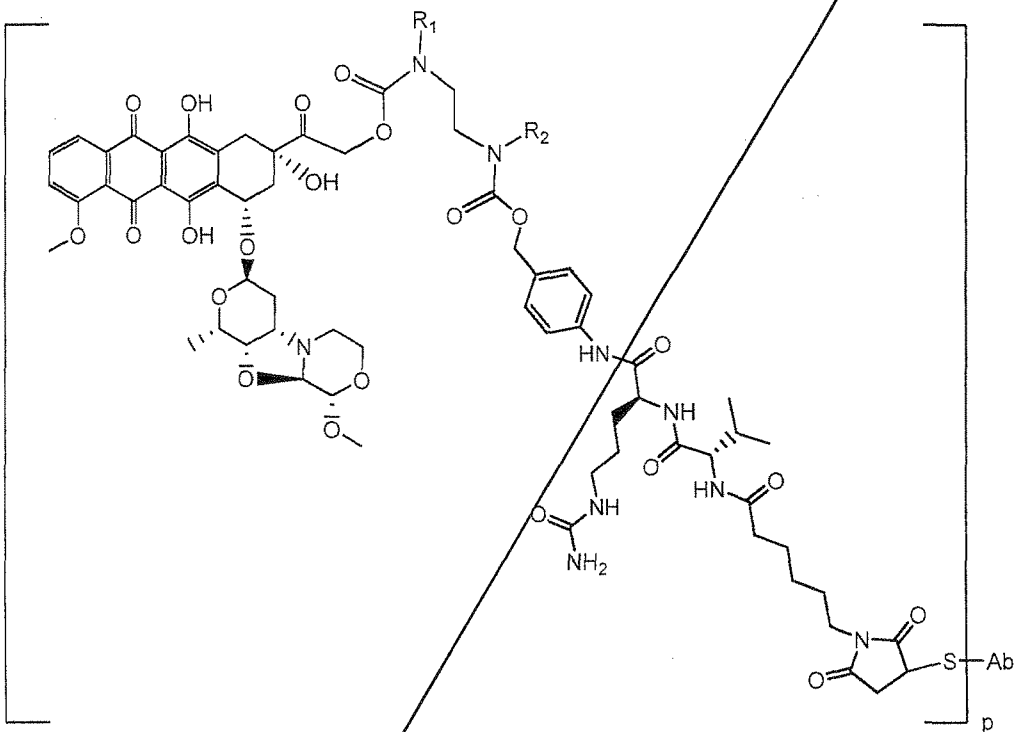


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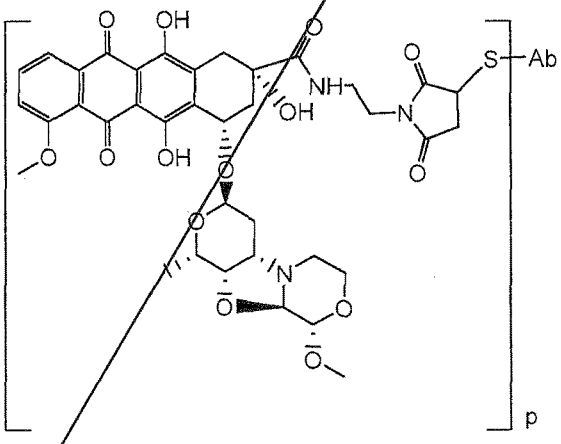


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; and



35. The immunoconjugate of any one of claims 20 to 34, wherein p ranges from 2-5.

36. The immunoconjugate of any one of claims 20 to 35, comprising the antibody of claim 8.

37. The immunoconjugate of any one of claims 20 to 35, comprising the antibody of claim 14.

38. A pharmaceutical formulation comprising the immunoconjugate of any one of claims 20 to 37 and a pharmaceutically acceptable carrier.

39. The pharmaceutical formulation of claim 38, further comprising an additional therapeutic agent.

40. The pharmaceutical formulation of claim 39, wherein the additional therapeutic agent is a platinum complex.

41. A method of treating an individual having an Ly6E-positive cancer, the method comprising administering to the individual an effective amount of the immunoconjugate of any one of claims 20 to 37.

42. The method of claim 41, wherein the Ly6E-positive cancer is selected from a breast cancer, pancreatic cancer, colon cancer, colorectal cancer, melanoma, ovarian cancer, non-small cell lung cancer, or gastric cancer.

43. The method of claim 42, further comprising administering an additional therapeutic agent to the individual.

44. The method of claim 43, wherein the additional therapeutic agent is a platinum complex.

45. A method of inhibiting proliferation of an Ly6E-positive cell, the method comprising exposing the cell to the immunoconjugate of any one of claims 20 to 37 under conditions permissive for binding of the immunoconjugate to Ly6E on the surface of the cell, thereby inhibiting proliferation of the cell.

46. The method of claim 45, wherein the cell is a breast, pancreatic, colon, colorectal, melanoma, ovarian non-small cell lung or gastric cancer cell.

47. The antibody of any one of claims 1 to 15 conjugated to a label.

48. The antibody of claim 47, wherein the label is a positron emitter.

49. The antibody of claim 48, wherein the positron emitter is ^{89}Zr.

50. A method of detecting human Ly6E in a biological sample comprising contacting the biological sample with the anti-Ly6E antibody of any one of claims 1 to 15 under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the biological sample.

51. The method of claim 50, wherein the anti-Ly6E antibody is an antibody as in claim 8 or claim 14.

52. The method of claim 51, wherein the biological sample is a breast cancer sample, a pancreatic cancer sample, a colon cancer sample, a colorectal cancer sample, melanoma cancer sample, ovarian cancer sample, a non-small cell lung cancer sample, or a gastric cancer sample.

53. A method for detecting a Ly6E-positive cancer comprising (i) administering a labeled anti-Ly6E antibody to a subject having or suspected of having a Ly6E-positive cancer, wherein the labeled anti-Ly6E antibody comprises the anti-Ly6E antibody of any one of claims 1 to 15, and (ii) detecting the labeled anti-Ly6E antibody in the subject, wherein detection of the labeled anti-Ly6E antibody indicates a Ly6E-positive cancer in the subject.

54. The method of claim 53, wherein the labeled anti-Ly6E antibody is an antibody as in claim 8 or claim 14 that is labeled.

55. The method of claim 53 or claim 54, wherein the labeled anti-Ly6E antibody comprises an anti-Ly6E antibody conjugated to a positron emitter.

56. The method of claim 56, wherein the positron emitter is ^{89}Zr.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to Ly6E, wherein the antibody binds an epitope within amino acids 21-131 of SEQ ID NO:1 with an affinity of ≤ 4 nM as measured by scatchard analysis.

2. The antibody of claim 1, selected from a group consisting of:

a) an antibody wherein the antibody is a monoclonal antibody;

b) an antibody wherein the antibodyis a human, humanized, or chimeric antibody;

c) an antibody wherein the antibody is internalized in a Ly6E-expressing cell upon binding to said epitope within amino acids 21-131 of SEQ ID NO:1;

d) an antibody wherein the antibody is an antibody fragment that binds to an epitope within amino acids 21-131 of SEQ ID NO:1;

e) an antibody wherein the antibody comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:12, (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:9, and (c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:11;

f) an antibody wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:10, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:11, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:12;

g) an antibody, comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:8; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:9.;

h) an antibody, comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:5; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:3; or (c) a VH sequence as in (a) and a VL sequence as in (b); and

i) an antibody wherein the antibody is an IgG1, IgG2a or IgG2b.

3. The antibody of claim 2(f), further comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:8; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:9.

4. The antibody of claim 3, further comprising a light chain variable domain framework FR2 sequence of SEQ ID NO:20 or light chain variable domain framework FR3 of SEQ ID NO:21 or heavy chain variable domain framework FR1 or SEQ ID NO:23, or heavy chain variable domain framework FR2 of SEQ ID NO:24.

5. The antibody of claim 4, selected from a group consisting of:

a) an antibody comprising a VH sequence of SEQ ID NO:5; and

b) an antibody comprising a VL sequence of SEQ ID NO:3.

6. An antibody comprising a VH sequence of SEQ ID NO:5 and a VL sequence of SEQ ID NO:3.

7. Isolated nucleic acid encoding the antibody of any one of claims 1 to 6.

8. A host cell comprising the nucleic acid of claim 7.

9. A method of producing an antibody comprising culturing the host cell of claim 8 so that the antibody is produced.

10. An immunoconjugate comprising the antibody of any one of claims 1 to 6 and a cytotoxic agent.

11. The immunoconjugate of claim 10 having the formula Ab-(L-D)p, wherein:

(a) Ab is the antibody of any one of claim 1 to 6;

(b) L is a linker;

(c) D is a drug selected from a maytansinoid, an auristatin, a calicheamicin, a pyrrolobenzodiazepine, and a nemorubicin derivative; and

(d) p ranges from 1-8.

12. The immunoconjugate of claim 11 selected from a group consisting of:

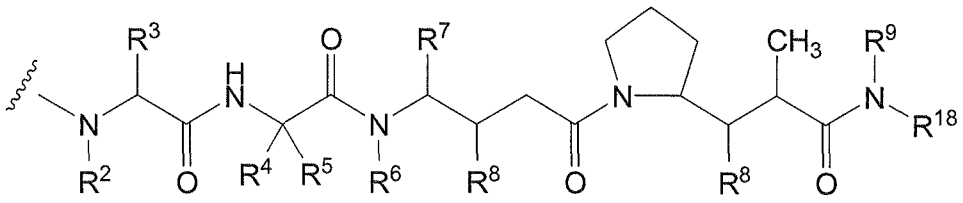
a) an immunoconjugate wherein D is an auristatin;

b) an immunoconjugate wherein the drug is MMAE; and

c) an immunoconjugate wherein D is a nemorubicin derivative.

13. The immunoconjugate of claim 12(a), selected from a group consisting of:

a) an immunoconjugate wherein D has formula D_E

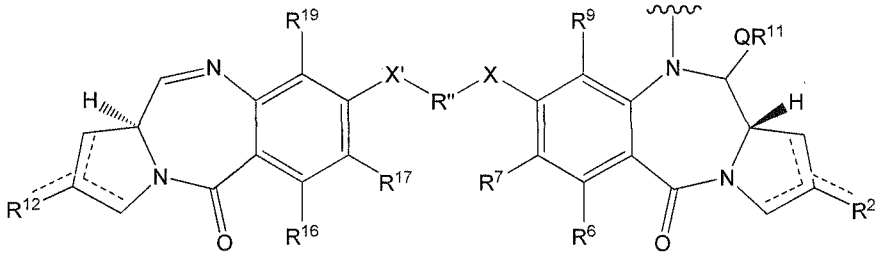


D_E

and wherein R^2 and R^6 are each methyl, R^3 and R^4 are each isopropyl, R^5 is H, R^7 is sec-butyl, each R^8 is independently selected from CH_3, O-CH_3, OH, and H; R^9 is H; and R^{18} is –$C(R^8)_2$–$C(R^8)_2$–aryl and

b) an immunoconjugate wherein D is a pyrrolobenzodiazepine of

Formula A:



A;

wherein the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

R^2 is independently selected from H, OH, =O, =CH_2, CN, R, OR, =CH-R^D, =$C(R^D)_2$, O-SO_2-R, CO_2R and COR, and optionally further selected from halo or dihalo, wherein R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo;

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

R^7 is independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', NO_2, Me_3Sn and halo;

Q is independently selected from O, S and NH;

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

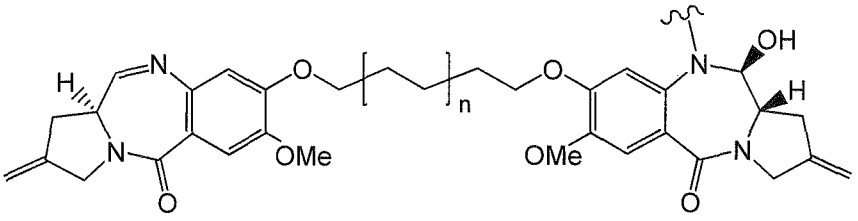
R and R' are each independently selected from optionally substituted C_{1-8} alkyl, C_{3-8} heterocyclyl and C_{5-20} aryl groups, and optionally in relation to the group NRR', R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring;

R^{12}, R^{16}, R^{19} and R^{17} are as defined for R^2, R^6, R^9 and R^7 respectively;

R″ is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms and/or aromatic rings that are optionally substituted; and

X and X' are independently selected from O, S and N(H).

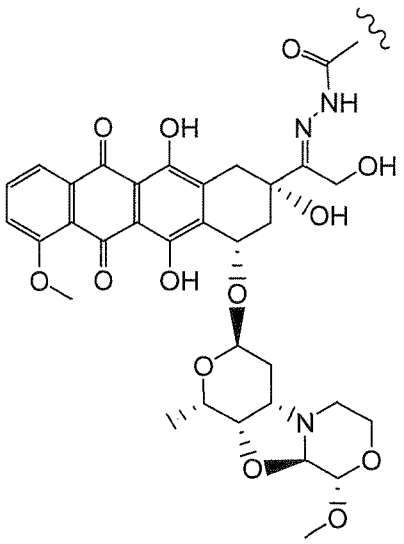
14. The immunoconjugate of claim 13(b), wherein D has the structure:



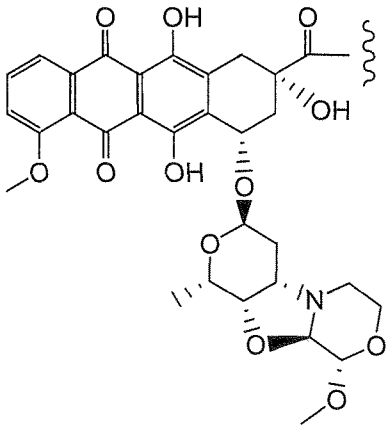
;

wherein n is 0 or 1.

15. The immunoconjugate of claim 12(c), wherein D has a structure selected from:



; and



.

16. The immunoconjugate of any one of claims 11 to 15, selected from a group consisting of:

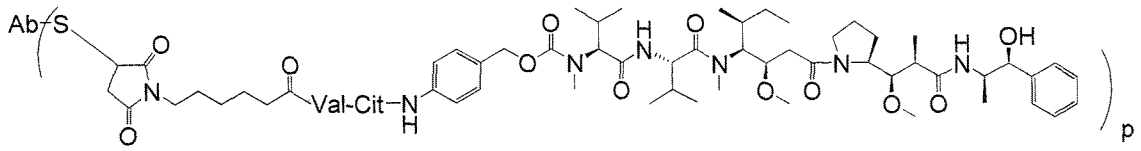
(a) an immunoconjugate wherein the linker is cleavable by a protease; and

(b) an immunoconjugate wherein the linker is acid-labile.

17. The immunoconjugate of claim 16(a), wherein the linker comprises a val-cit dipeptide or a Phe-Lys dipeptide.

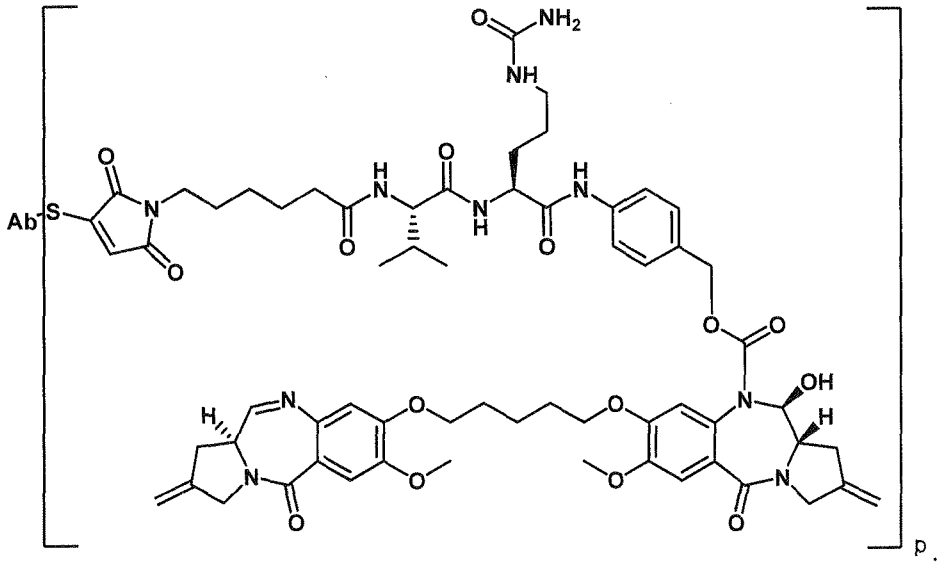
18. The immunoconjugate of claim 16(b), wherein the linker comprises hydrazone.

19. The immunoconjugate of claim 13(a) having the formula:

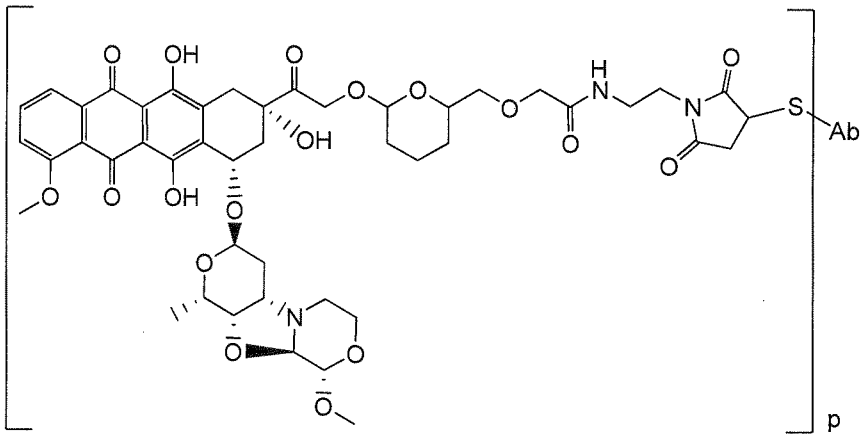


wherein S is a sulfur atom.

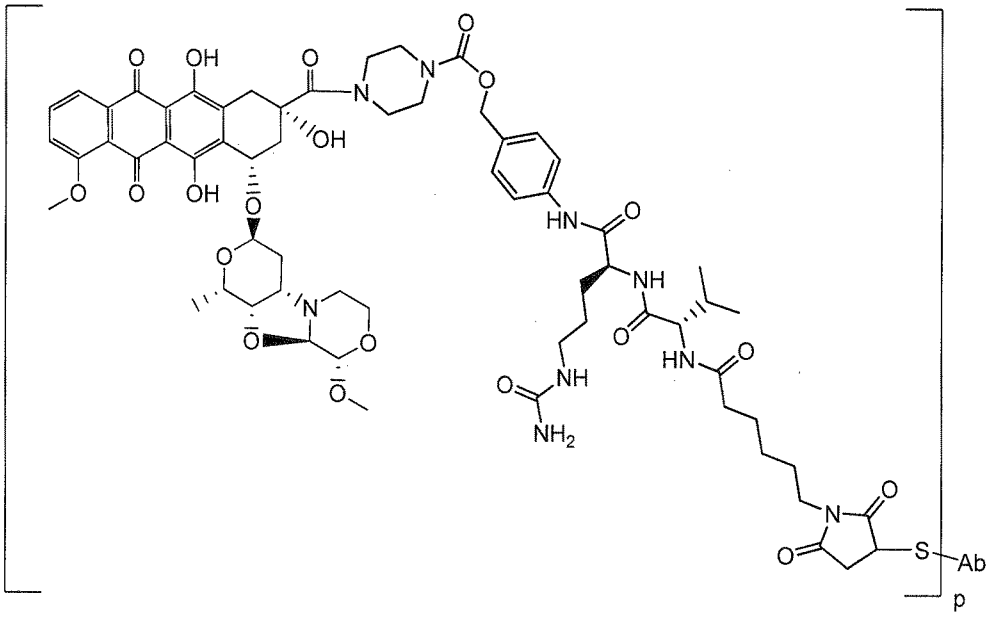
20. The immunoconjugate of claim 14 having the formula:



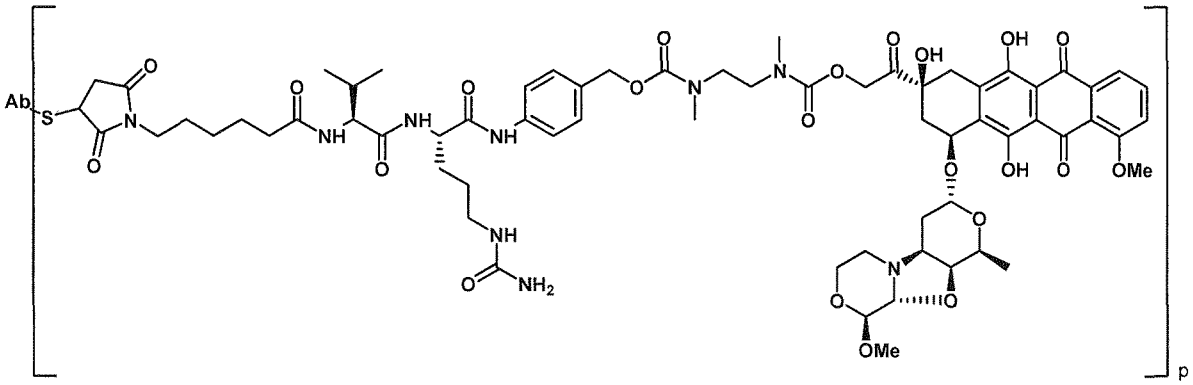
21. The immunoconjugate of claim 15 having a formula selected from:

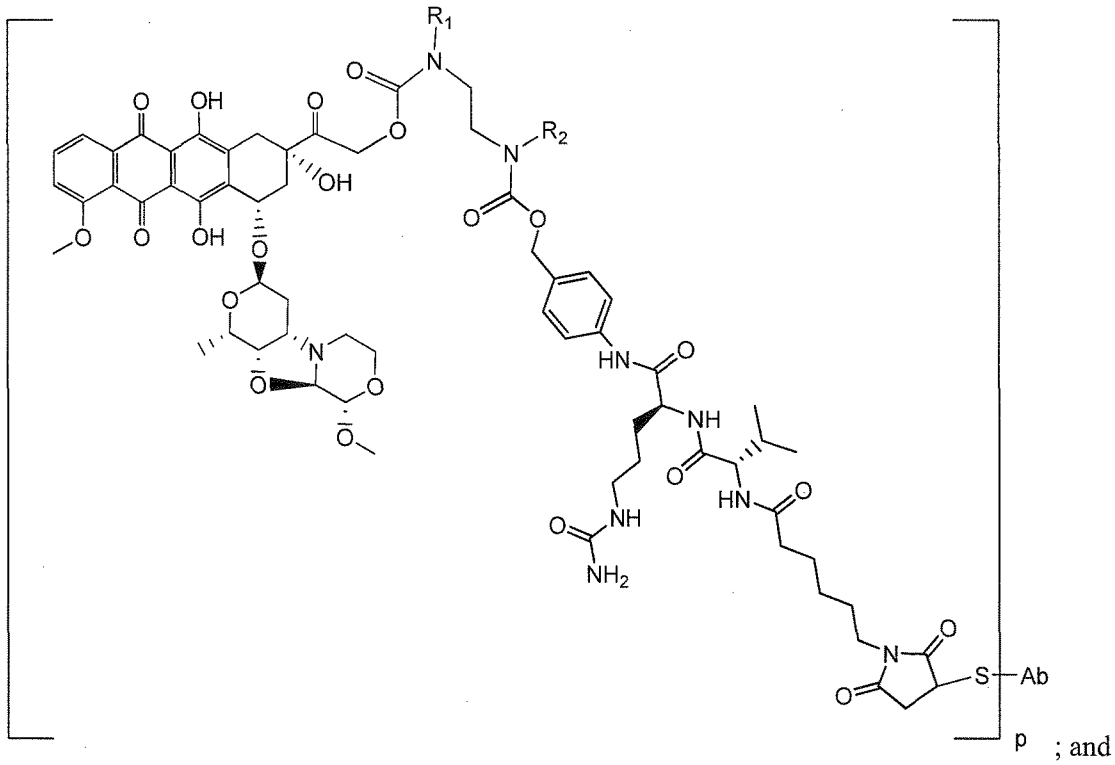


;

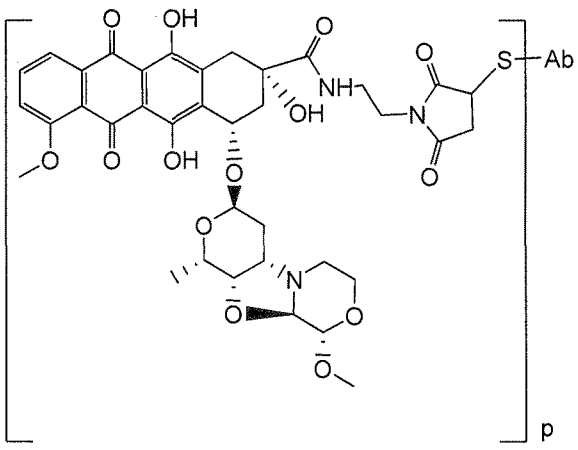


;





; and



22. The immunoconjugate of any one of claims 11 to 21, wherein p ranges from 2-5.

23. The immunoconjugate of any one of claims 11 to 22, selected from a group consisting of:

(a) an immunoconjugate comprising the antibody of claim 3; and

(b) an immunoconjugate comprising the antibody of claim 6.

24. A pharmaceutical formulation comprising the immunoconjugate of any one of claims 11 to 23 and a pharmaceutically acceptable carrier.

25. The pharmaceutical formulation of claim 24, further comprising an additional therapeutic agent.

26. The pharmaceutical formulation of claim 25, wherein the additional therapeutic agent is a platinum complex.

27. Use of an effective amount of the immunoconjugate of any one of claims 11 to 23 in the manufacture of a medicament for treating an individual having an Ly6E-positive cancer.

28. The use of claim 27, wherein the Ly6E-positive cancer is selected from a breast cancer, pancreatic cancer, colon cancer, colorectal cancer, melanoma, ovarian cancer, non-small cell lung cancer, or gastric cancer.

29. The use of claim 28, wherein the medicament is to be further administered with an additional therapeutic agent to the individual.

30. The use of claim 29, wherein the additional therapeutic agent is a platinum complex.

31. Use of the immunoconjugate of any one of claims 11 to 23 in the manufacture of a medicament for inhibiting proliferation of an Ly6E-positive cell, wherein the cell is to be exposed to the medicament under conditions permissive for binding of the immunoconjugate to Ly6E on the surface of the cell.

32. The use of claim 31, wherein the cell is a breast, pancreatic, colon, colorectal, melanoma, ovarian non-small cell lung or gastric cancer cell.

33. The antibody of any one of claims 1 to 6 conjugated to a label.

34. The antibody of claim 33, wherein the label is a positron emitter.

35. The antibody of claim 34, wherein the positron emitter is ^{89}Zr.

36. A method of detecting human Ly6E in a biological sample comprising contacting the biological sample with the anti-Ly6E antibody of any one of claims 1 to 6 under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the biological sample.

37. The method of claim 36, wherein the anti-Ly6E antibody is an antibody as in claim 3 or claim 6.

38. The method of claim 37, wherein the biological sample is a breast cancer sample, a pancreatic cancer sample, a colon cancer sample, a colorectal cancer sample, melanoma cancer sample, ovarian cancer sample, a non-small cell lung cancer sample, or a gastric cancer sample.

39. A method for detecting a Ly6E-positive cancer comprising (i) administering a labeled anti-Ly6E antibody to a subject having or suspected of having a Ly6E-positive cancer, wherein the labeled anti-Ly6E antibody comprises the anti-Ly6E antibody of any one of claims 1 to 6, and (ii) detecting the labeled anti-Ly6E antibody in the subject, wherein detection of the labeled anti-Ly6E antibody indicates a Ly6E-positive cancer in the subject.

40. The method of claim 39, wherein the labeled anti-Ly6E antibody is an antibody as in claim 3 or claim 6 that is labeled.

41. The method of claim 39 or claim 40, wherein the labeled anti-Ly6E antibody comprises an anti-Ly6E antibody conjugated to a positron emitter.

42. The method of claim 41, wherein the positron emitter is ^{89}Zr.