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

[0005] The 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~~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, (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.

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

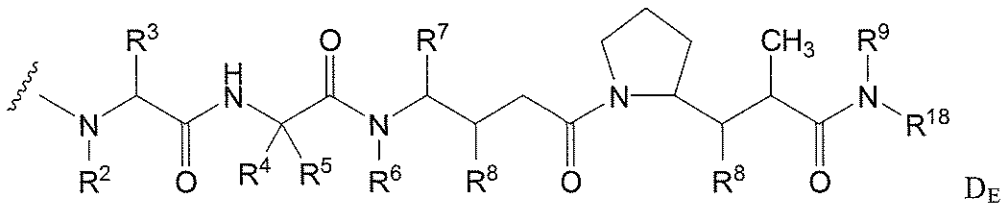
[~~0013c~~0013b] In one aspect, there is provided a host cell comprising the nucleic acid as defined herein.

[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:

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

Table 4

	Scatchard Analysis		Biacore	cell-based Ly6E competitive binding assay	
	hu Ly6E KD (nM)	cyno Ly6E KD (nM)	hu Ly6E KD (nM)	hu Ly6E KD (nM)	cyno Ly6E KD (nM)
Ch 9B12	4	4	6	3-6	5-7
9B12.v12	4	14	7	15-19	16-40

Example 4 - Binding of anti-Ly6E antibody to human and cynomologous Ly6E

[0393] A scatchard analysis was performed to determine affinity and binding sites per cell for the antibodies. Hu.9B12v12 antibody was iodinated several times using the Iodogen method. The radiolabeled Hu.9B12v12 antibody was purified from free ^{125}I-Na by gel filtration using a NAP-5 column and had a range of specific activity of 11.14-16.01 μCi/μg. Competition reaction mixtures of 50 μL containing a fixed concentration of iodinated antibody and decreasing concentrations of unlabeled antibody were placed into 96-well plates. The PC3 cells stably transduced with retrovirus to express either recombinant human or Cynomolgus monkey gD tagged Ly6E were detached from flasks using Sigma Cell Dissociation Solution and were washed with binding buffer (DMEM with 2% FBS, 50 mM HEPES, pH 7.2, and 0.1% sodium azide). The washed cells were added at an approximate density of 200,000 cells in 0.2 mL of binding buffer to the 96-well plates containing the 50-μL competition reaction mixtures. The final concentration of the iodinated antibody in each competition reaction with cells was 200 pM and the final concentration of the unlabeled antibody in the competition reaction with cells varied, starting at 500 nM and then decreasing by 1:2-fold dilution for ten concentrations, and included a zero-added, buffer-only sample. Competition reactions with cells for each concentration of unlabeled antibody were assayed in triplicate. Competition reactions with cells were incubated for 2 hours at room temperature. After the 2-hour incubation, the competition reactions were transferred to a Millipore Multiscreen filter plate and washed four times with binding buffer to separate the free from bound iodinated antibody. The filters were counted on a Wallac Wizard 1470 gamma counter (PerkinElmer Life and Analytical Sciences; Wellesley, MA). The binding data were evaluated using New Ligand software (Genentech), which uses the fitting algorithm of Munson and Rodbard (1980) to determine the binding affinity of the antibody. As shown in Figure 67, Panel A and B and in Table 5, the binding affinity of Hu9B12v12 on human and cynomolgus monkey was estimated at 4.0nM and 7.9nM respectively.

ADC concentrations was added to triplicate wells. Five days later, cell survival was determined using CellTiter-Glo Luminescent Cell Viability Reagent (G7572; Promega Corporation) and with an EnVision 2101 Mutilabel Reader (Perkin-Elmer). For the two cell lines tested, *in vitro* killing efficacy appeared proportional to the expression of Ly6E on the cell surface (Figure ~~6~~7, Panels A and B).

[0397] Flow Cytometry: For fluorescence-activated cell sorting (FACS), cells were harvested in PBS with 2.5 mmol/L EDTA and washed in PBS buffer containing 1% FBS. All subsequent steps were carried out at 4^0C. Cells were incubated for 1 hour each with 3 to 5 μg/mL primary antibodies, followed by the appropriate secondary antibodies. Cells were then analyzed with a FACS Calibur flow cytometer (BD Biosciences) and GeoMean values were obtained. Primary antibodies, Hu.9B12v12 for Ly6E cell surface detection, in-house generated anti-gD mAb for N-Term gD tag detection were used. Alexa 488–conjugated anti-mouse or anti-human IgG fluorescent detection reagent (A11017, A11013; Invitrogen) were used.

Example 7: In vivo efficacy of anti-Ly6E ADC in xenograft mouse model

[0398] Breast cancer cell line, HCC1569 (CRL-2330), pancreatic cancer cell line SU.86.86 (CRL-1837), Chinese Hamster ovary cell line, CHO-K1 (CCl-61) and prostatic cancer cell line PC3 (CRL-1435) were obtained from American Type Culture Collection (ATCC,Manassas, VA). CHO-K1S is a suspension cell line derivative of CHO-K1.The HCC1569 X2 cell line is a derivative of the parental HCC1569 cell line (ATCC, CRL-2330) optimized for growth *in vivo*. Parental HCC1569 cells were injected subcutaneously in the right flank of female Taconic NCr nude mice, one tumor was harvested, minced and grown *in vitro* resulting in the HCC1569 X1 cell line. The HCC1569 X1 line was injected again subcutaneously in the right flank of female Taconic NCr nude mice in an effort to improve the growth of the cell line. A tumor from this study was collected and again adapted for *in vitro* growth to generate the HCC1569 X2 cell line. This cell line and tumors derived from this line express Ly6E.

[0399] Xenograft models: Efficacy of anti-Ly6E antibody drug conjugates (ADCs) was evaluated in xenograft models derived from cell lines described above or in primary patient derived tumor models, the latter experiments were conducted at Oncotest, Freiburg, Germany and in XenTech, Genopole, France.

[0400] All studies conducted at Genentech, South San Francisco, CA were in accordance with the Guide for the Care and Use of Laboratory Animals (Ref: Institute of Laboratory Animal Resources (NIH publication no. 85-23), Washington, DC: National Academies Press; 1996). All experiments conducted at Oncotest were approved by the local authorities, and are conducted according to the guidelines of the German Animal Welfare Act (Tierschutzgesetz). The authorization to use animals in the CERFE facilities of XenTech was obtained by The Direction des Services Vétérinaires, Ministère de l'Agriculture et de la Pêche, France (agreement No. A 91-228-107). The animal care and housing are in accordance with European Convention STE 123. All experiments at XenTech will be performed in accordance with French legislation concerning the protection of laboratory animals and in accordance

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~~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, (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.

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 or antibody fragment ~~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~~e) 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.~~3. The antibody of claim ~~3~~2, 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.~~4. The antibody of claim ~~4~~3, 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.~~5. Isolated nucleic acid encoding the antibody of any one of claims 1 to ~~6~~4.

~~8.~~6. A host cell comprising the nucleic acid of claim ~~7~~5.

~~9.~~7. A method of producing an antibody comprising culturing the host cell of claim ~~8~~6 so that the antibody is produced.

~~10.~~8. An immunoconjugate comprising the antibody of any one of claims 1 to ~~6~~4 and a cytotoxic agent.

~~11.~~9. The immunoconjugate of claim ~~10~~8 having the formula Ab-(L-D)p, wherein:

(a) Ab is the antibody of any one of claim 1 to ~~6~~4;

(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.~~10. The immunoconjugate of claim ~~11~~9 selected from a group consisting of:

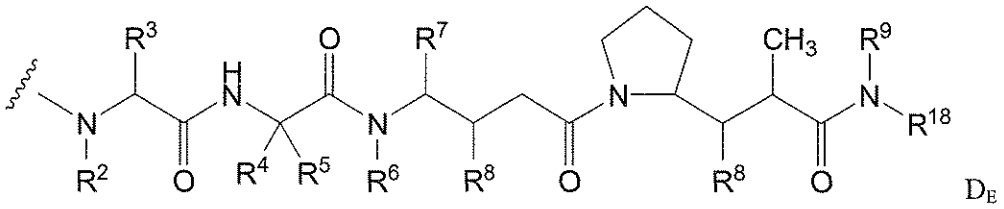
a) an immunoconjugate wherein D is an auristatin;

b) an immunoconjugate wherein the drug is MMAE; and

c) an immunoconjugate wherein D is a nemorubicin derivative.

~~13.~~11. The immunoconjugate of claim ~~12~~10(a), selected from a group consisting of:

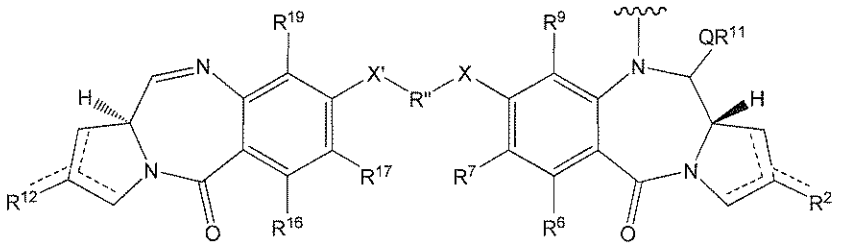
a) an immunoconjugate wherein D has formula D_E



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, $=CH\text{-}R^D$, $=C(R^D)_2$, 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;

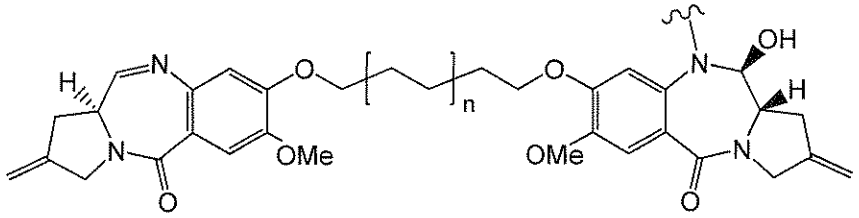
R and R' are each independently selected from ~~optionally substituted~~ C_{1-8} alkyl optionally substituted with one or more groups selected from -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -aryl, -C(O)R', -OC(O)R', -C(O)OR', -C(O)NH_2, -C(O)NHR', -C(O)N(R')$_2$, -NHC(O)R', -SO_3R', -S(O)$_2$R', -S(O)R', -OH, -halogen, -N_3, -NH_2, -NH(R'), -N(R')$_2$ and –CN, where each R' is independently selected from H, -C_1-C_8 alkyl and aryl; C_{3-8} heterocyclyl optionally substituted with up to seven groups selected from -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -aryl, -C(O)R', -OC(O)R', -C(O)OR', -C(O)NH_2, -C(O)NHR', -C(O)N(R')$_2$, -NHC(O)R', -S(O)$_2$R', -S(O)R', -OH, -halogen, -N_3, -NH_2, -NH(R'), -N(R')$_2$ and –CN, wherein each R' is independently selected from H, -C_1-C_8 alkyl and aryl; and C_{5-20} aryl groups optionally substituted with one or more groups selected from -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -aryl, -C(O)R', -OC(O)R', -C(O)OR', -C(O)NH_2, -C(O)NHR', -C(O)N(R')$_2$, -NHC(O)R', -S(O)$_2$R', -S(O)R', -OH, -halogen, -N_3, -NH_2, -NH(R'), -N(R')$_2$ and -CN; wherein each R' is independently selected from H, -C_1-C_8 alkyl and aryl, 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).

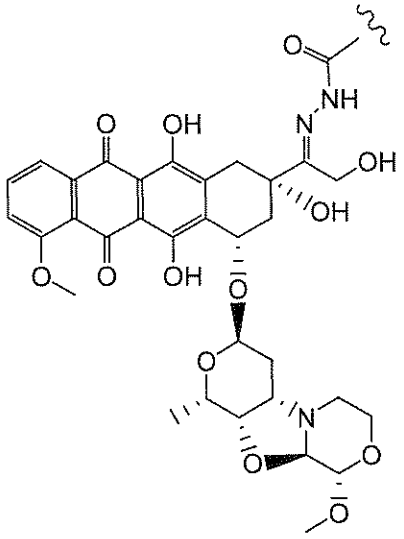
~~14.~~12. The immunoconjugate of claim ~~13~~11(b), wherein D has the structure:



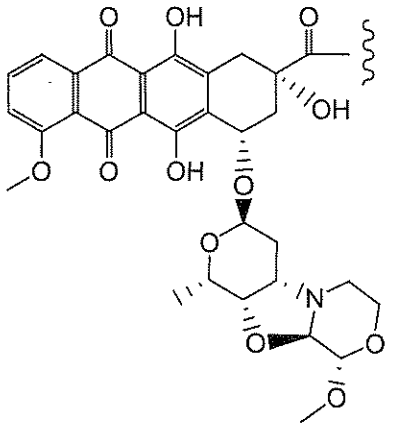
;

wherein n is 0 or 1.

~~15.~~13. The immunoconjugate of claim ~~12~~14(c), wherein D has a structure selected from:



; and



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~~16.~~14. The immunoconjugate of any one of claims ~~11~~9 to ~~15~~13, selected from a group consisting of:

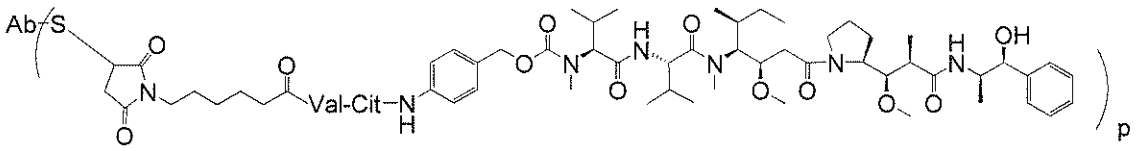
(a) an immunoconjugate wherein the linker is cleavable by a protease; and

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

~~17.~~15. The immunoconjugate of claim ~~16~~14(a), wherein the linker comprises a val-cit dipeptide or a Phe-Lys dipeptide.

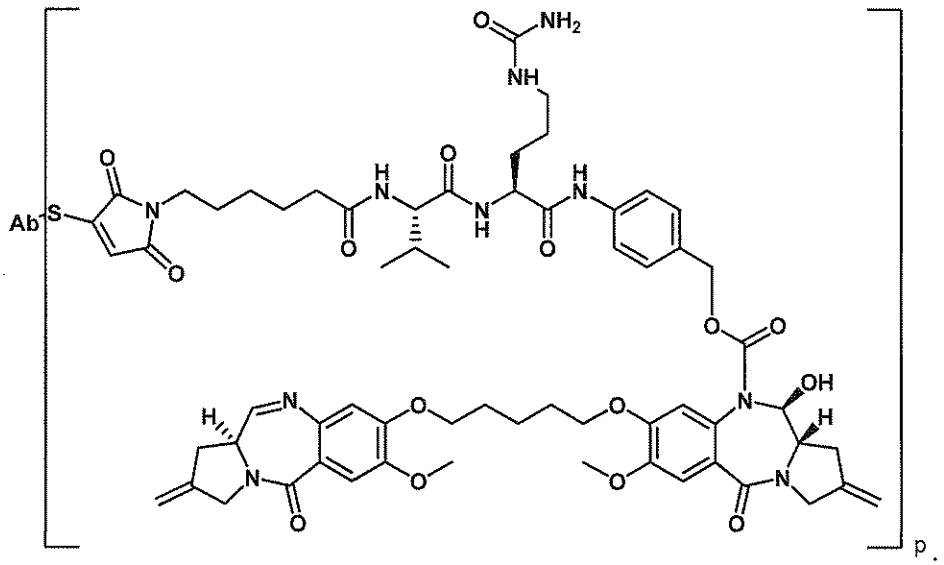
~~18.~~16. The immunoconjugate of claim ~~16~~14(b), wherein the linker comprises hydrazone.

~~19.~~17. The immunoconjugate of claim ~~13~~11(a) having the formula:

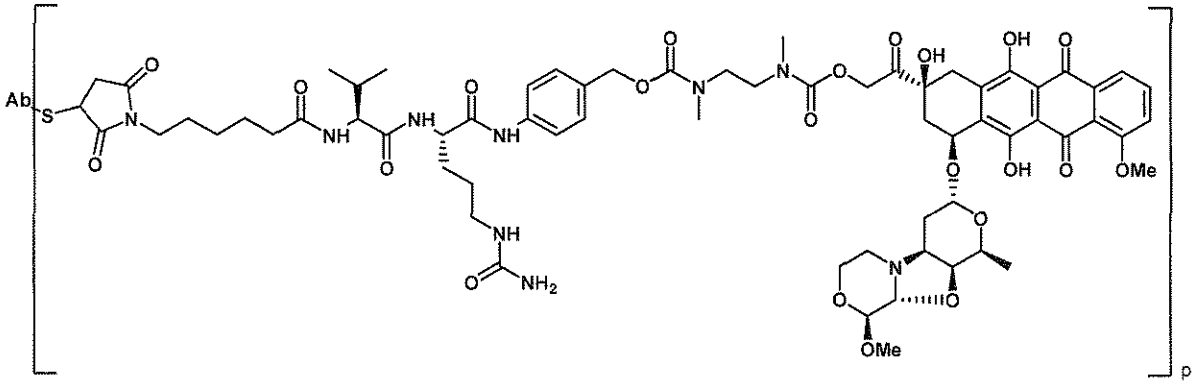


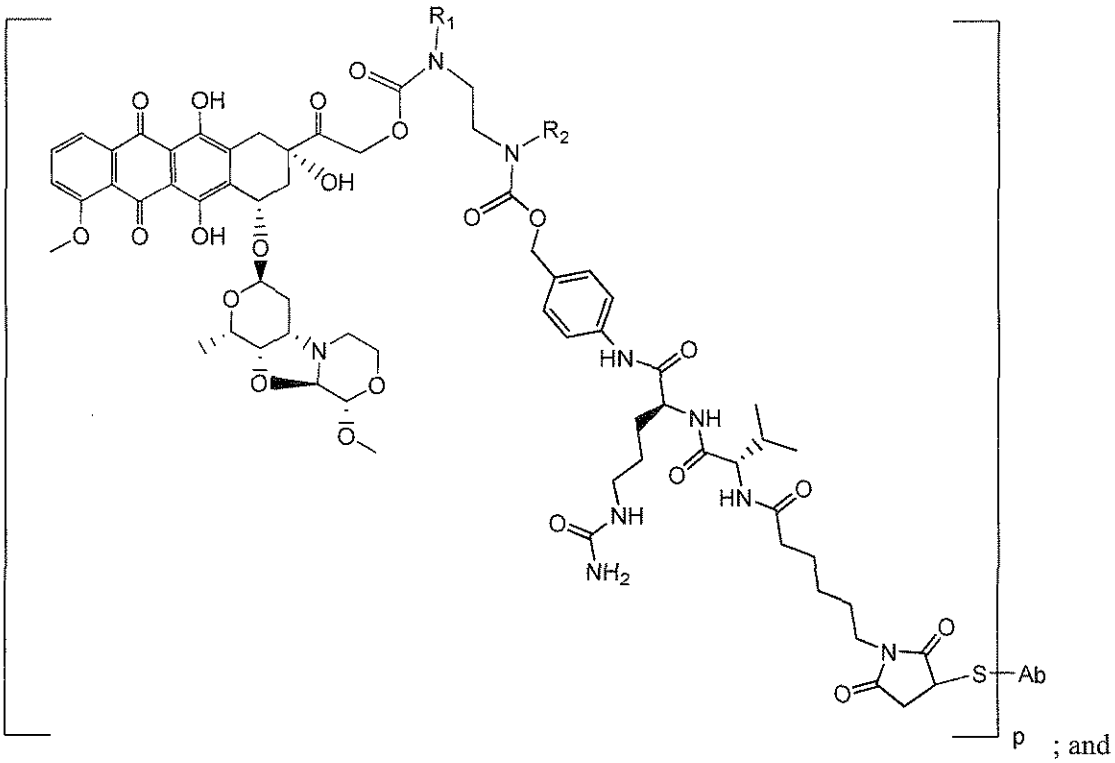
wherein S is a sulfur atom.

~~20.~~18. The immunoconjugate of claim ~~14~~12 having the formula:

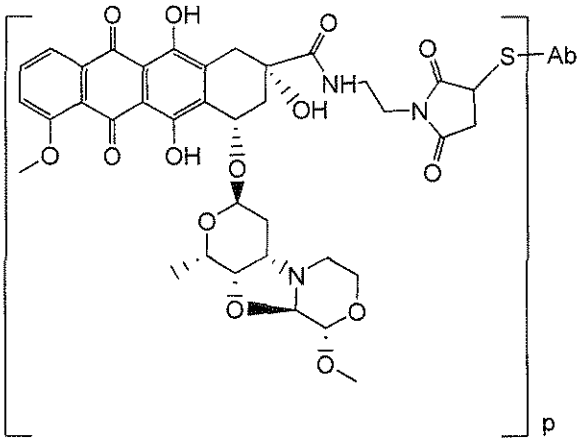


~~21.~~19. The immunoconjugate of claim ~~15~~13 having a formula selected from:





; and



~~22~~20. The immunoconjugate of any one of claims ~~11~~9 to ~~21~~19, wherein p ranges from 2-5.

~~23.~~21. The immunoconjugate of any one of claims ~~11~~ 9 to ~~22~~20, ~~selected from a group consisting of:~~

~~(a) an immunoconjugate~~ comprising the antibody of claim ~~31~~; ~~and~~

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

~~24.~~22. A pharmaceutical formulation comprising the immunoconjugate of any one of claims ~~11~~ 9 to ~~23~~ 21 and a pharmaceutically acceptable carrier.

~~25.~~23. The pharmaceutical formulation of claim ~~24~~22, further comprising an additional therapeutic agent.

~~26.~~24. The pharmaceutical formulation of claim ~~25~~23, wherein the additional therapeutic agent is a platinum complex.

~~27.~~25. Use of an effective amount of the immunoconjugate of any one of claims ~~11~~ 9 to ~~23~~ 21 in the manufacture of a medicament for treating an individual having an Ly6E-positive cancer.

~~28.~~26. The use of claim ~~27~~25, 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.~~27. The use of claim ~~28~~26, wherein the medicament is to be further administered with an additional therapeutic agent to the individual.

~~30.~~28. The use of claim ~~29~~27, wherein the additional therapeutic agent is a platinum complex.

~~31.~~29. Use of the immunoconjugate of any one of claims ~~11~~ 9 to ~~23~~ 21 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.~~30. The use of claim ~~31~~29, wherein the cell is a breast, pancreatic, colon, colorectal, melanoma, ovarian non-small cell lung or gastric cancer cell.

~~33.~~31. The antibody of any one of claims 1 to ~~6~~ 4 conjugated to a label.

~~34.~~32. The antibody of claim ~~33~~31, wherein the label is a positron emitter.

~~35.~~33. The antibody of claim ~~34~~32, wherein the positron emitter is ^{89}Zr.

~~36.~~34. 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~~ 4 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.~~35. The method of claim ~~36~~34, wherein the anti-Ly6E antibody is an antibody as in claim ~~3 or claim 6~~1.

~~38.~~36. The method of claim ~~37~~35, 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.~~