human FcRH5, and detecting whether a complex is formed between the anti-FcRH5 antibody and a naturally occurring human FcRH5 in the biological sample. In some embodiments, the anti-FcRH5 antibody binds an isoform c-specific region of the extracellular domain of FcRH5c. In some embodiments, the anti-FcRH5 antibodies binds Ig-like domain 9 of FcRH5c. In some embodiments, the anti-FcRH5 antibody is an antibody described herein.

In some embodiments, a method for detecting an FcRH5-positive cancer is provided. In some such embodiments, a method comprises (i) administering a labeled anti-FcRH5 antibody to a subject having or suspected of having an FcRH5-positive cancer, and (ii) detecting the labeled anti-FcRH5 antibody in the subject, wherein detection of the labeled anti-FcRH5 antibody indicates an FcRH5-positive cancer in the subject. In some embodiments, the anti-FcRH5 antibody binds an isoform c-specific region of the extracellular domain of FcRH5c. In some embodiments, the anti-FcRH5 antibodies binds Ig-like domain 9 of FcRH5c. In some embodiments, an anti-FcRH5 antibody is an antibody described herein.

In one aspect, there is provided the use of a labeled anti-FcRH5 antibody in the manufacture of a medicament for detecting an FcRH5-positive cancer in a subject having or suspected of having a FcRH5-positive cancer, wherein the labeled anti-FcRH5 antibody comprises the anti-FcRH5 antibody as disclosed herein, wherein detection of the labeled anti-FcRH5 antibody indicates a FcRH5-positive cancer in the subject.

In one aspect, there is provided an isolated anti-FcRH5 antibody that binds an isoform c-specific region of the extracellular domain of FcRH5c (amino acids 743-850 of SEQ ID NO:1), wherein the antibody does not significantly bind another Ig-like domain of FcRH5.

In one aspect, there is provided a pharmaceutical formulation comprising the antibody as described herein and/or the immunoconjugate as described herein and a pharmaceutically acceptable carrier.

In one aspect there is provided use of an antibody as described herein and/or immunoconjugate as described herein in the manufacture of a medicament for inhibiting proliferation of an FcRH5-positive cell, wherein the FcRH5-positive cell is to be exposed to the anti-FcRH5 antibody and/or immunoconjugate under conditions permissive for binding of the antibody and/or immunoconjugate to FcRH5 on the surface of the FcRH5-positive cell, thereby inhibiting proliferation of the FcRH5-positive cell.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1(A) depicts the three major isoforms of FcRH5, FcRH5a (IRTA2a; UniProt Identifier Q96RD9-3), FcRH5b (IRTA2b; UniProt Identifier Q96RD9-4), and FcRH5c (IRTA2c; UniProt Identifier Q96RD9-1). The Ig-like domains are numbered and correspond to the amino acid sequence of UniProt Identifier Q69RD9-1 (SEQ ID NO:1): Ig-like domain 1 (aa ("amino acid") 23-100), Ig-like domain 2 (aa 105-185), Ig-like domain 3 (aa 188-271), Ig-like domain 4 (287-373), Ig-like domain 5 (aa 380-466), Ig-like domain 6 (aa 490-555), Ig-like domain 7 (aa 568-652), Ig-like domain 8 (aa 658-731), and Ig-like domain 9 (aa 754-835). FIG. 1(B) depicts part of FcRH5 (SEQ ID NO:136) and the structure and homology of FcRH5 amino acids 735 to 977 of FcRH5c (SEQ ID NO:2).

FIG. 2 shows binding of FcRH5 antibodies to SVT2 cells transfected with (A) human FcRH5 and (B) cyno FcRH5, in different concentrations.

FIG. 3 shows binding of FcRH5 antibodies to (A) EJM cells or (B) OPM2 cells transfected with human FcRH5, and binding of subclone supernatants (C) 5A10.1, (D) 5F1.1, (E) 3G7.1, and (F) 6D2.2 to MOLP2 cells which express FcRH5 endogenously.

FIG. 4 shows (A) binding of FcRH5 subclone supernatants to 293 cells transfected with WT or (B) mutant FcRH5 with deletion of 4 membrane proximal extracellular domains.

FIG. 5 shows binding of (A) the FcRH5 antibodies to FcRH5a by ELISA, and (B) binding of subclone supernatants to human B cells.

FIG. 6 shows binding of FcRH5 subclone supernatants to SVT2 cells transfected with (A) FcRH1, (B) FcRH2, (C) FcRH3, or (D) FcRH4.

FIG. 7 shows the binding of FcRH5 antibody subclone supernatants to NK cells.

FIG. 8 shows (A) killing activity of FcRH5 bisFabs, FcRH5-TDB (clone 10A8) and (B) HER2-TDB and (C) killing activity of FcRH5-bisFabs and (D) FcRH5-TDBs on FcRH5 transfected 293 cells.

WHAT IS CLAIMED IS:

1) An isolated anti-FcRH5 antibody that binds an isoform c-specific region of the extracellular domain of FcRH5c (amino acids 743-850 of SEQ ID NO:1), wherein the antibody does not significantly bind another Ig-like domain of FcRH5.

2) The antibody of any one of claim 1, wherein the antibody comprises:

(a) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:38, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:62, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:86, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:2, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:14, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:26;

(b) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 39, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:63, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:87, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:3, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:15, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:27;

(c) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:40, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:64, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:88, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:4, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:16, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:28;

(d) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:41, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:65, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:89, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:17, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:29;

(e) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:42, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:66, and an HVR-H3

comprising the amino acid sequence of SEQ ID NO:90, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:6, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:30;

(f) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:43, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:67, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:91, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:7, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:19, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:31;

(g) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:44, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:68, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:92, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:8, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:20, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:32;

(h) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:45, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:69, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:93, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:9, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:21, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:33;

(i) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:46, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:70, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:94, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:10, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:22, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:34;

(j) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:47, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:71, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:95, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:11, an HVR-L2 comprising the amino acid

sequence of SEQ ID NO:23, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:35;

(k) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:48, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:72, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:96, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:12, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:24, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:36; or

(l) a heavy chain comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:49, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:73, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:97, and a light chain comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO:13, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:25, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:37.

3) The antibody of claim 1 or 2, wherein the antibody comprises:

a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:111 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 110;

b) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:113 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:112;

c) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:115 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:114;

d) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:117 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:116;

e) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:119 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:118;

f) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:121 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:120;

g) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:123 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:122;

h) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:125 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:124;

i) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:127 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 126;

j) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:129 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:128;

k) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:131 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:130;

l) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:133 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:132; or

m) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:135 and a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:134.

4) The antibody of any of claims 1-3, wherein the antibody comprises:

a) a VH sequence of SEQ ID NO:111 and a VL sequence of SEQ ID NO:110;

b) a VH sequence of SEQ ID NO:113 and a VL sequence of SEQ ID NO:112;

c) a VH sequence of SEQ ID NO:115 and a VL sequence of SEQ ID NO:114;

d) a VH sequence of SEQ ID NO:117 and a VL sequence of SEQ ID NO:116;

e) a VH sequence of SEQ ID NO:119 and a VL sequence of SEQ ID NO:118;

f) a VH sequence of SEQ ID NO:121 and a VL sequence of SEQ ID NO:120;

g) a VH sequence of SEQ ID NO:123 and a VL sequence of SEQ ID NO:122;
h) a VH sequence of SEQ ID NO:125 and a VL sequence of SEQ ID NO:124;
i) a VH sequence of SEQ ID NO:127 and a VL sequence of SEQ ID NO:126;
j) a VH sequence of SEQ ID NO:129 and a VL sequence of SEQ ID NO:128;
k) a VH sequence of SEQ ID NO:131 and a VL sequence of SEQ ID NO:130;
l) a VH sequence of SEQ ID NO:133 and a VL sequence of SEQ ID NO:132; or
m) a VH sequence of SEQ ID NO:135 and a VL sequence of SEQ ID NO:134.

5) The antibody of any one of claims 1-4, wherein the antibody is a monoclonal antibody.

6) The antibody of any one of claims 1-5, wherein the antibody is a human, humanized, or chimeric antibody.

7) The antibody of any one of claims 1-6, wherein the antibody is an antibody fragment that binds FcRH5.

8) The antibody of any one of claims 1-7, wherein the antibody is an IgG1, IgG2a or IgG2b antibody.

9) The antibody of any one of claims 1-8, wherein the antibody has one or more of the following characteristics: a) cross reactive with full length human and cyno FcRH5, b) does not cross react with FcRH1, FcRH2, FcRH3, and/or FcRH4, c) binds to endogenous FcRH5, and d) does not cross react with FcRH5a.

10) The antibody of any one of claims 1-9, wherein the antibody is a bispecific antibody.

11) The antibody of claim 10, wherein bispecific antibody binds FcRH5 and CD3.

12) Isolated nucleic acid encoding the antibody of any one of claims 1-11.

13) A host cell comprising the nucleic acid of claim 12.

14) A method of producing an antibody comprising culturing the host cell of claim 13 so that the antibody is produced.

15) An immunoconjugate comprising the antibody of any one of claims 1-11 and a cytotoxic agent.

16) The immunoconjugate of claim 15 having the formula Ab-(L-D)p, wherein:

(a) Ab is the antibody of any one of claim 1 to 36;

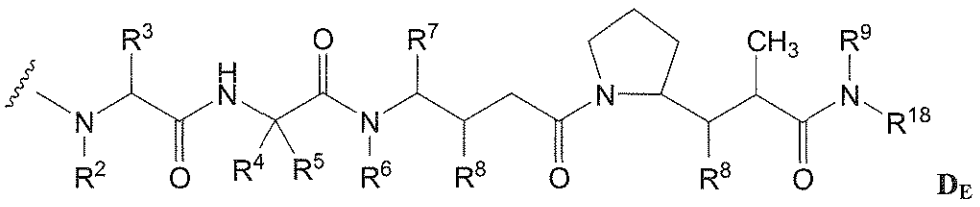
(b) L is a linker;

(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.

17) The immunoconjugate of claim 16, wherein D is an auristatin.

18) The immunoconjugate of claim 17, wherein D has formula D_E

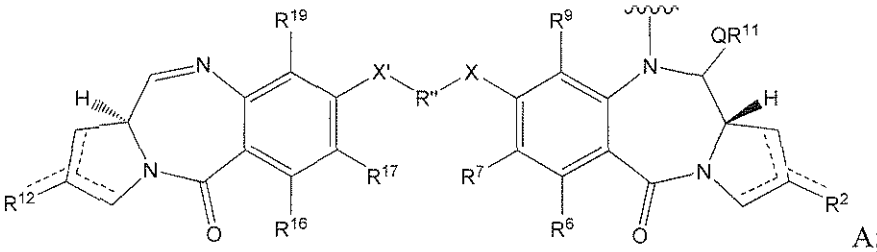


D_E

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.

19) The immunoconjugate of claim 16, wherein the drug is MMAE.

20) The immunoconjugate of claim 16, 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, $=CH\text{-}R^D$, $=C(R^D)_2$, $O\text{-}SO_2\text{-}R$, 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;

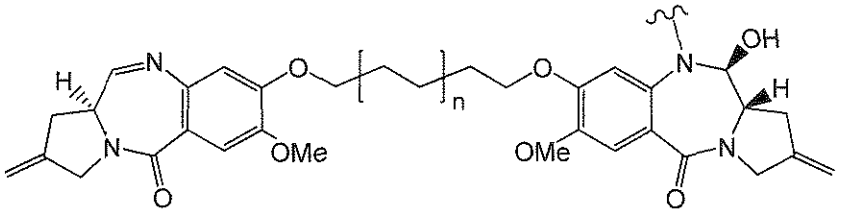
R and R' are each independently selected from optionally substituted C_{1-8} alkyl, C_{3-8} heterocyclyl and C_{5-20} aryl groups, and optionally in relation to the group NRR', R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered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

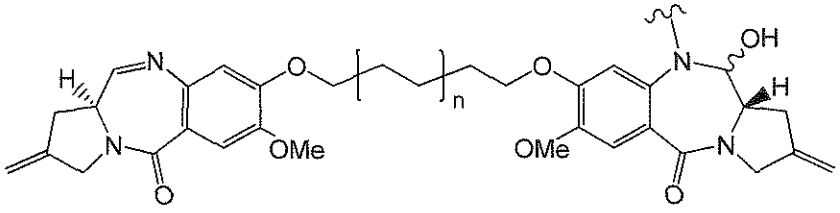
21) The immunoconjugate of claim 20, wherein D has the structure:



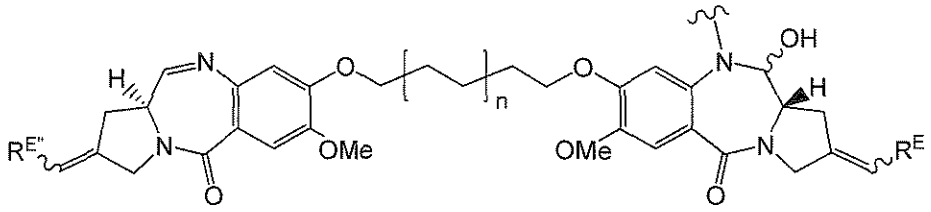
A(II);

wherein n is 0 or 1.

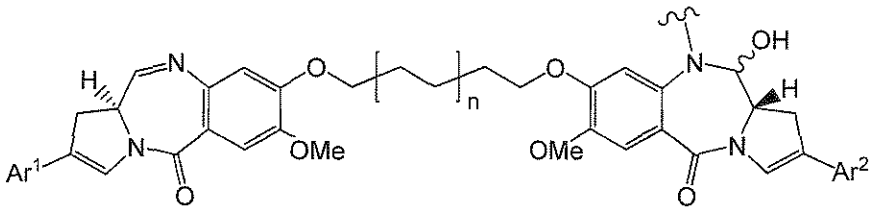
22) The immunoconjugate of claim 20, wherein D has a structure selected from:



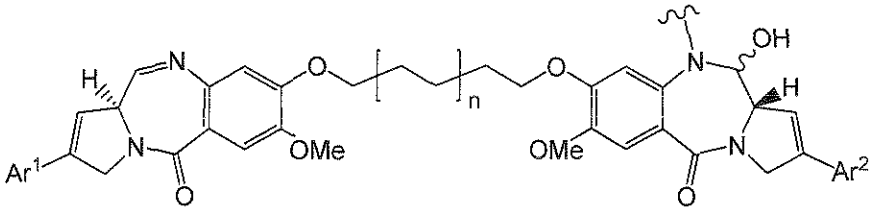
A(I);



A(III);



A(IV); and



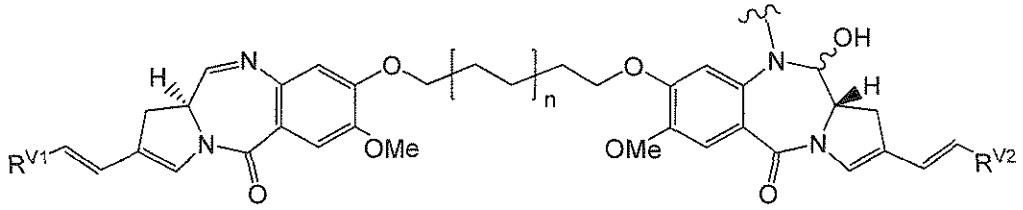
A(V);

wherein R^E and $R^{E''}$ are each independently selected from H or R^D, wherein R^D is independently selected from R, CO_2R, COR, CHO, CO_2H, and halo;

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

wherein n is 0 or 1.

23) The immunoconjugate of claim 16, wherein D is a pyrrolobenzodiazepine of Formula B:



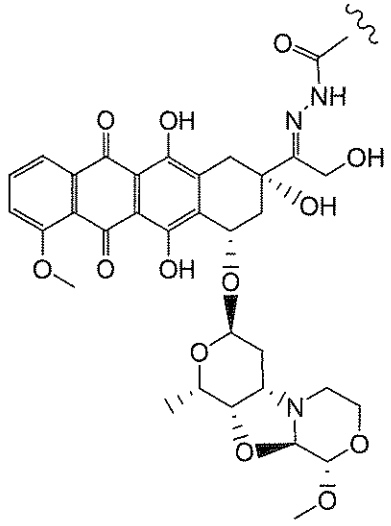
wherein the horizontal wavy line indicates the covalent attachement site to the linker;

R^{V1} and R^{V2} are independently selected from H, methyl, ethyl, phenyl, fluoro-substituted phenyl, and C_{5-6} heterocyclyl; and

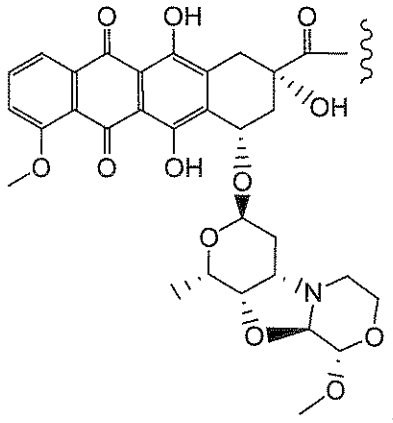
n is 0 or 1.

24) The immunoconjugate of claim 16, wherein D is a nemorubicin derivative.

25) The immunoconjugate of claim 24, wherein D has a structure selected from:



; and



.

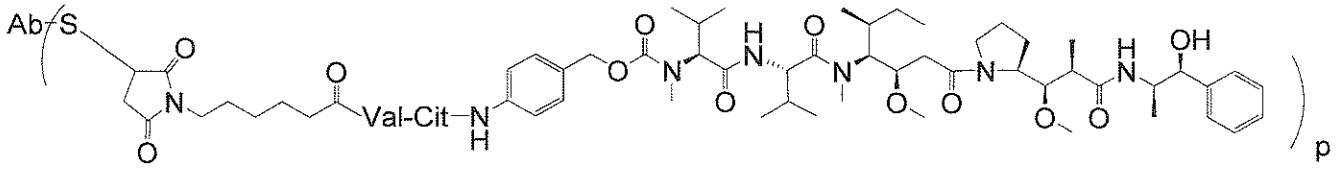
26) The immunoconjugate of any one of claims 16-25, wherein the linker is cleavable by a protease.

27) The immunoconjugate of claim 26, wherein the linker comprises a val-cit dipeptide or a Phe-homoLys dipeptide.

28) The immunoconjugate of any one of claims 16-25, wherein the linker is acid-labile.

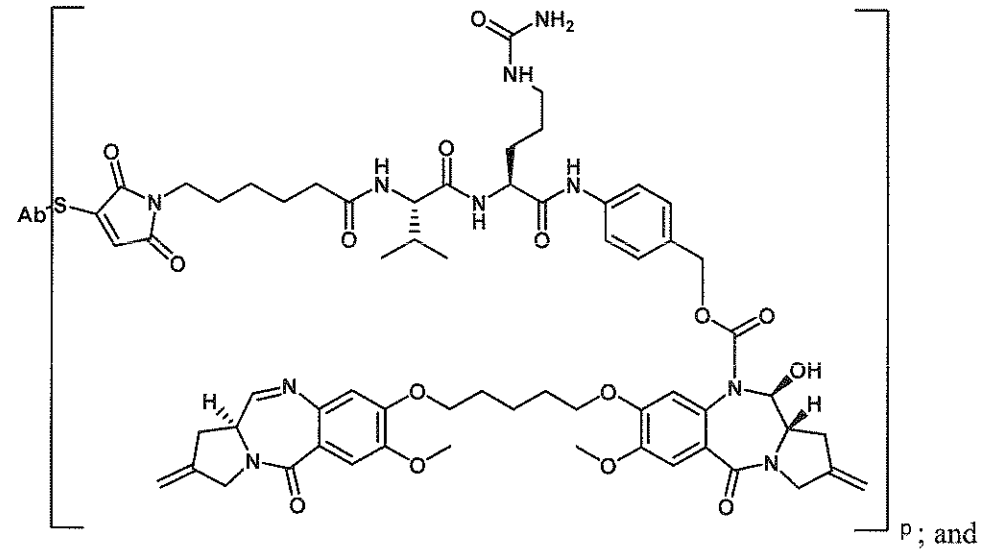
29) The immunoconjugate of claim 28, wherein the linker comprises hydrazone.

30) The immunoconjugate of claim 28 having the formula:

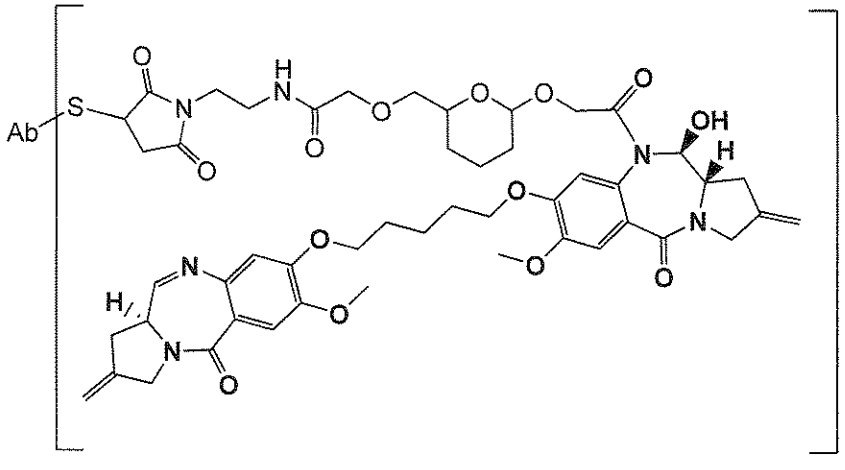


wherein S is a sulfur atom.

31) The immunoconjugate of claim 21 having a formula selected from:

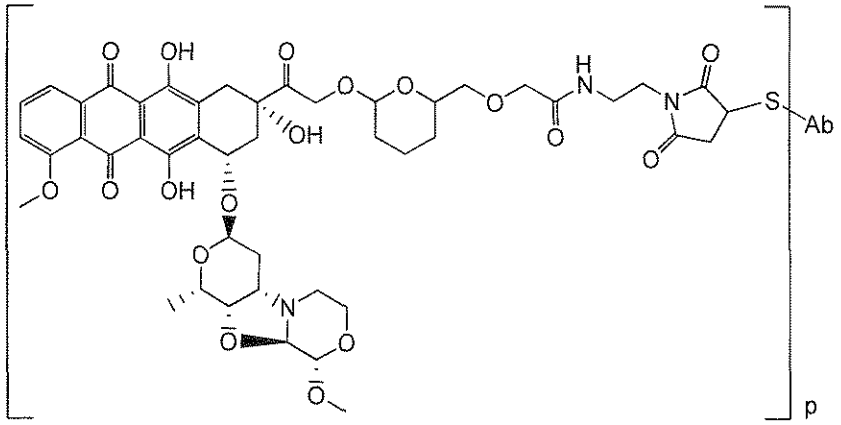


; and

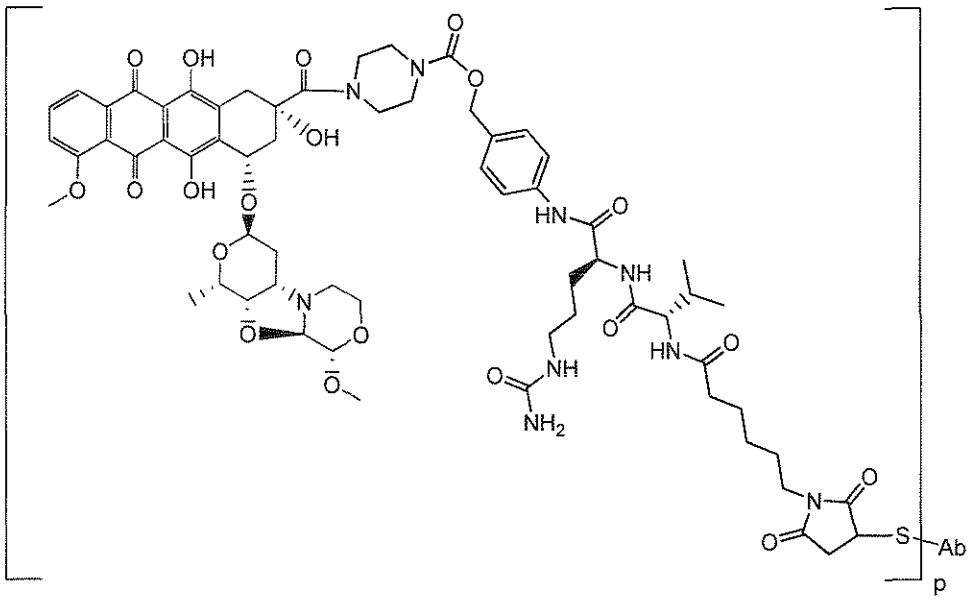


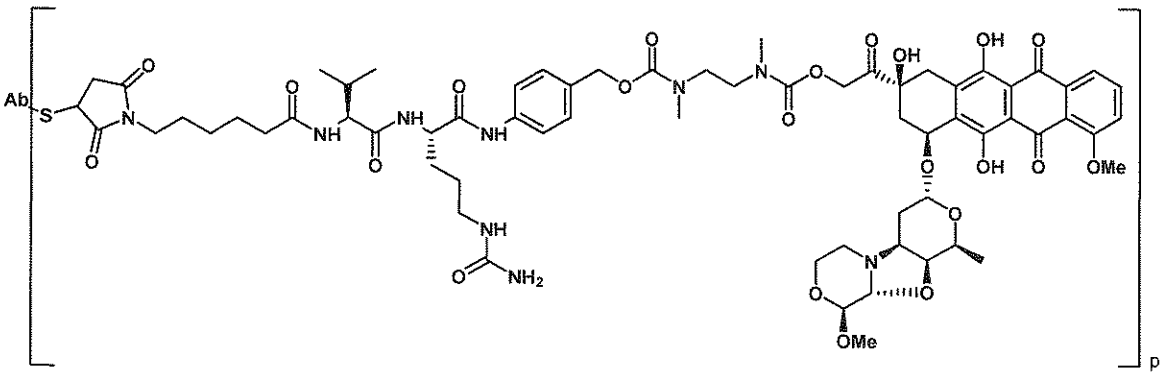
.

32) The immunoconjugate of claim 25 having a formula selected from:

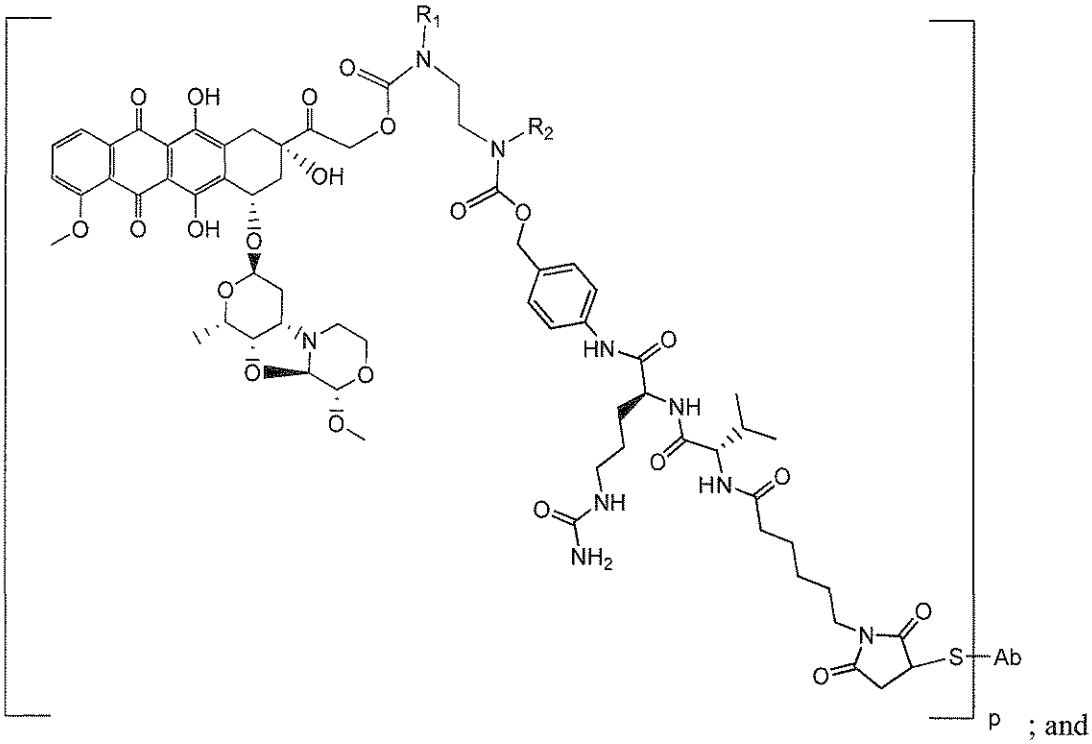


;

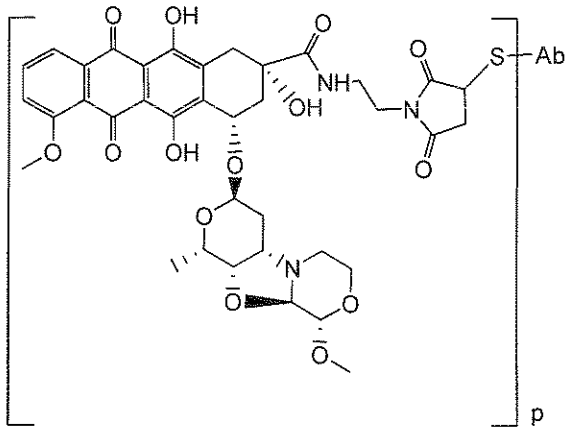




;



; and



33) The immunoconjugate of any one of claims 16-32, wherein p ranges from 2-5.

34) A pharmaceutical formulation comprising the antibody of any one of claims 1-11 and/or the immunoconjugate of any one of claims 15-33 and a pharmaceutically acceptable carrier.

35) The pharmaceutical formulation of claim 34, further comprising an additional therapeutic agent.

36) Use of an effective amount of the antibody of any one of claims 1-11 and/or immunoconjugate of any one of claims 15-33 in the manufacture of a medicament for treating an individual having an FcRH5-positive cancer.

37) The use of claim 36, wherein the FcRH5-positive cancer is a B-cell proliferative disorder.

38) The use of claim 36 or 37, wherein the medicament further comprises an additional therapeutic agent.

39) Use of an antibody of any one of claims 1-11 and/or immunoconjugate of any one of claims 15-33 in the manufacture of a medicament for inhibiting proliferation of an FcRH5-positive cell, wherein the FcRH5-positive cell is to be exposed to the anti-FcRH5 antibody and/or immunoconjugate under conditions permissive for binding of the antibody and/or immunoconjugate to FcRH5 on the surface of the FcRH5-positive cell, thereby inhibiting proliferation of the FcRH5-positive cell.

40) The use of claim 39, wherein the FcRH5-positive cell is a B-cell.

41) The antibody of any one of claims 1-11 conjugated to a label.

42) The antibody of claim 41, wherein the label is a positron emitter.

43) The antibody of claim 42, wherein the positron emitter is ^{89}Zr.

44) A method of detecting human FcRH5 in a biological sample comprising contacting the biological sample with the anti-FcRH5 antibody of any one of claims 1-11 or 41-43 under conditions permissive for binding of the anti-FcRH5 antibody to a naturally occurring human FcRH5, and detecting whether a complex is formed between the anti-FcRH5 antibody and a naturally occurring human FcRH5 in the biological sample.

45) The method of claim 44, wherein the anti-FcRH5 antibody is an antibody as in claim 9 or claim 15.

46) The method of claim 44 or 45, wherein the biological sample is a blood sample.

47) Use of a labeled anti-FcRH5 antibody in the manufacture of a medicament for detecting an FcRH5-positive cancer in a subject having or suspected of having a FcRH5-positive cancer, wherein the labeled anti-FcRH5 antibody comprises the anti-FcRH5 antibody of any one of claims 1-11, wherein detection of the labeled anti-FcRH5 antibody indicates a FcRH5-positive cancer in the subject.

48) The use of 47, wherein the labeled anti-FcRH5 antibody comprises an anti-FcRH5 antibody conjugated to a positron emitter.

49) The use of claim 47 or 48, wherein the positron emitter is ^{89}Zr.