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

SUMMARY

The disclosure~~invention~~ provides anti-mesothelin antibodies and immunoconjugates and methods of using the same.

In one aspect, there is provided an isolated antibody that binds to mesothelin, wherein said antibody binds an epitope of SEQ ID NO:43 comprising E153 and D174 and optionally has one or more of the following characteristics: (a) does not exhibit reduced binding to glycosylated forms of mesothelin; (b) does not block binding of mesothelin to MUC16; and (c) binds mesothelin with an affinity of ≤ 5 nM; wherein said antibody comprises (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19; and wherein said antibody further comprises a light chain variable domain comprising a framework FR2 sequence of SEQ ID NO:25 and an FR3 sequence of SEQ ID NO:27.

In one embodiment~~aspect~~, an isolated antibody that binds to mesothelin is provided, wherein the antibody is selected from: (i) an antibody that binds an epitope of SEQ ID NO:43 comprising E153 and D174 and that optionally has one or more of the following characteristics: (a) does not exhibit reduced binding to glycosylated forms of mesothelin; (b) does not block binding of mesothelin to MUC16; and (c) binds mesothelin with an affinity of ≤ 5 nM; (ii) an antibody that binds an epitope of SEQ ID NO:43 comprising E211 and that optionally has one or more of the following characteristics: (a) does not block binding of mesothelin to MUC16; and (b) binds mesothelin with an affinity of ≤ 5 nM; and (iii) an antibody that binds to an epitope within amino acids 1-131 of SEQ ID NO:43 and binds mesothelin with an affinity of ≤ 5 nM. In certain embodiments, the antibody is a monoclonal antibody. In certain embodiments, the antibody is a human, humanized, or chimeric antibody. In certain embodiments, the antibody is an antibody fragment that binds mesothelin. In certain embodiments, the mesothelin is human mesothelin of SEQ ID NO:43.

In certain embodiments, the antibody comprises: (a) (i) HVR-H3 comprising the amino acid sequence of SEQ ID NO:22, (ii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19, and (iii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:21; (b) (i) HVR-H3 comprising the amino acid sequence of SEQ ID NO:39, (ii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:35, and (iii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:37; or (c) HVR-H3, HVR-L3, and HVR-H2 of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464. In certain embodiments, the antibody comprises (a) (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:20, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:22; (b) (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:36, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:37, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:39; or (c) HVR-H1, HVR-H2, and HVR-H3 of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464. In one such embodiment, the antibody comprises (a) (i) HVR-H1

the amino acid sequence of SEQ ID NO:16; (e) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:12; (f) a VH sequence as in (d) and a VL sequence as in (e); (g) a VH sequence having at least 95% sequence identity to the amino acid sequence of the VH sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464; (h) a VL sequence having at least 95% sequence identity to the amino acid sequence of the VL sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464; or (i) a VH sequence as in (g) and a VL sequence as in (h). In one such embodiment, the antibody comprises a VH sequence of SEQ ID NO:8, a VH sequence of SEQ ID NO:16, or a VH sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464. In another such embodiment, the antibody comprises a VL sequence of SEQ ID NO:4, a VL sequence of SEQ ID NO:12, or a VL sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.

In a further embodiment~~aspect~~, the disclosure~~invention~~ provides an antibody comprising (a) a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:4; (b) a VH sequence of SEQ ID NO:16 and a VL sequence of SEQ ID NO:12; (c) a VH sequence and a VL sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464; or (d) the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.

In certain embodiments, an antibody according to any of the above embodiments is an IgG1, IgG2a or IgG2b antibody.

In one aspect, there is provided an antibody comprising a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:4.

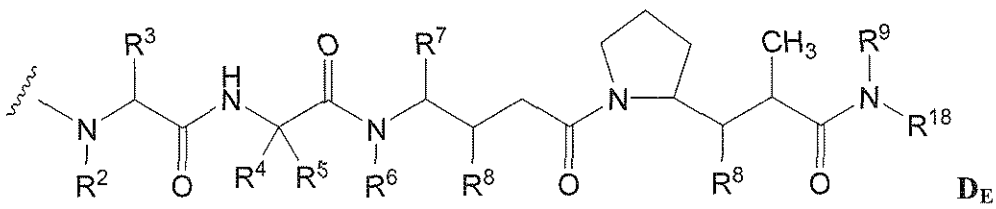
In a further aspect, there is~~the invention~~ provided an isolated nucleic acid encoding the~~an~~ antibody as defined herein~~according to any of the above embodiments~~. In one aspect~~embodiment~~, there is provided a host cell comprising the nucleic acid as defined herein~~is provided~~. In one aspect~~another embodiment~~, there is provided a method of producing an antibody~~is provided, the method~~ comprising culturing the host cell as defined herein so that the antibody is produced.

In one~~a further~~ aspect, there is provided an~~An~~ immunoconjugate having the formula Ab-(L-D)p~~is provided~~, wherein:

(a) Ab is an antibody as defined herein~~in any of the above embodiment~~;

(b) L is a linker;

(c) D is a drug of formula D_E



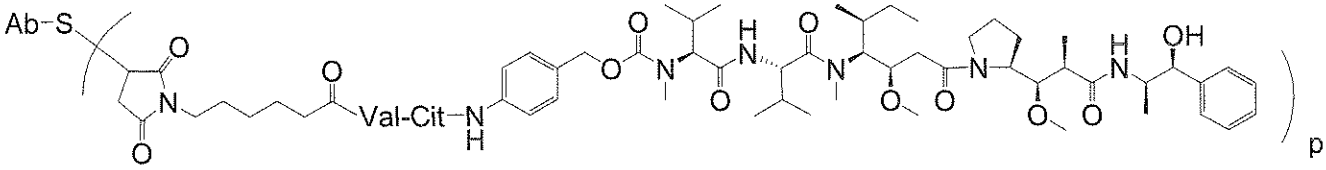
D_E

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

(d) p ranges from 1-8.

In one embodiment, the drug is an auristatin. In one such embodiment, the drug is MMAE. In another embodiment, the linker is cleavable by a protease. In one such embodiment, the linker comprises a val-cit dipeptide.

In a further embodiment, the immunoconjugate has the formula:



wherein S is a sulfur atom. In one such embodiment, p ranges from 2-5. In another such embodiment, the antibody comprises (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:20, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:21, (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:22, (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19. In another such embodiment, the antibody comprises (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:36, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:37, (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:39, (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:33, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:34, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO:35. In another such embodiment, the antibody comprises (a) a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:4. In another such embodiment, the antibody comprises (b) a VH sequence of SEQ ID NO:16 and a VL sequence of SEQ ID NO:12.

In onca ~~further~~ aspect, there is~~the invention~~ provided a pharmaceutical formulation comprising an immunoconjugate as defined herein~~in any of the above embodiments~~ and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical formulation further comprises an additional therapeutic agent. In one such embodiment, the additional therapeutic agent is gemcitabine. In another such embodiment, the additional therapeutic agent is an anti-MUC16 antibody conjugated to a cytotoxic agent.

In a further aspect, there is~~the invention~~ provided an immunoconjugate as defined herein~~in any of the above embodiments~~ for use as a medicament. In one aspect~~certain embodiments~~, there is~~the invention~~ provided an

immunoconjugate as defined hereinin any of the above embodiments for use in treating a mesothelin-positive cancer. In one such embodiment, the mesothelin-positive cancer is selected from pancreatic cancer, ovarian cancer, lung cancer, endometrial cancer, and mesothelioma. In another such embodiment, the mesothelin-positive cancer is a dual-positive cancer.

In onea further aspect, there isthe invention providesd thefor use of an immunoconjugate as defined hereinin any of the above embodiments in the manufacture of a medicament. In one embodiment, the medicament is for treatment of a mesothelin-positive cancer. In one such embodiment, the mesothelin-positive cancer is selected from pancreatic cancer, ovarian cancer, lung cancer, endometrial cancer and mesothelioma. In another such embodiment, the mesothelin-positive cancer is a dual-positive cancer.

In another embodimentaspect, a method of treating an individual having a mesothelin-positive cancer is provided, the method comprising administering to the individual an effective amount of an immunoconjugate as in any of the above embodiments. In one embodiment, the mesothelin-positive cancer is selected from pancreatic cancer, ovarian cancer, lung cancer, endometrial cancer, and mesothelioma. In another embodiment, the mesothelin-positive cancer is a dual-positive cancer. In another embodiment, the method further comprises administering an additional therapeutic agent to the individual. In one such embodiment, the additional therapeutic agent is gemcitabine. In another such embodiment, the additional therapeutic agent is an anti-MUC16 antibody conjugated to a cytotoxic agent.

In one aspect, there is provided an in vitro method of inhibiting proliferation of a mesothelin-positive cell, the method comprising exposing the cell to an immunoconjugate as defined herein under conditions permissive for binding of the immunoconjugate to mesothelin on the surface of the cell, thereby inhibiting proliferation of the cell.

In one aspect, there is provided the of an immunoconjugate as defined herein in the manufacture of a medicament for inhibiting proliferation of a mesothelin-positive cell, wherein the cell is to be exposed to said immunoconjugate under conditions permissive for binding of the immunoconjugate to mesothelin on the surface of the cell, to thereby inhibit proliferation of the cell.

In another embodimentaspect, a method of inhibiting proliferation of a mesothelin-positive cell is provided, the method comprising exposing the cell to an immunoconjugate as in any of the above embodiments under conditions permissive for binding of the immunoconjugate to mesothelin on the surface of the cell, thereby inhibiting proliferation of the cell. In one embodiment, the cell is a pancreatic, ovarian, lung, mesothelioma, or endometrial cell. In another embodiment, the cell is a dual-positive cell.

In oneanother aspect, there isthe invention providesd an antibody as defined hereinin any of the above embodiments, wherein the antibody is conjugated to a label. In one embodiment, the label is a positron emitter. In one such embodiment, the positron emitter is ^{89}Zr.

In another aspect, there is provided a method of detecting human mesothelin in a biological sample is provided, the method comprising contacting the biological sample with an anti-mesothelin antibody as defined hereinin any of the above embodiments under conditions permissive for binding of the anti-mesothelin antibody to a naturally occurring human mesothelin, and detecting whether a complex is formed between the anti-mesothelin antibody and a naturally occurring human mesothelin in the biological sample. In one embodiment, the anti-mesothelin antibody

comprises (a) HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2 and HVR-L3 of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464; (b) a VH sequence and a VL sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464; or (d) the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464. In another embodiment, the biological sample is a pancreatic cancer sample, ovarian cancer sample, lung cancer sample, endometrial cancer sample, or mesothelioma sample. In another embodiment, the method comprises performing immunohistochemistry on a tissue section. In another embodiment, the biological sample is serum.

In a further aspect, there is provided a method for detecting a mesothelin-positive cancer is provided, the method comprising (i) administering a labeled anti-mesothelin antibody, ~~wherein the anti-mesothelin antibody is as in any of the above embodiments~~, to a subject having or suspected of having a mesothelin-positive cancer, wherein the labeled anti-mesothelin antibody comprises an anti-mesothelin antibody as defined herein, and (ii) detecting the labeled anti-mesothelin antibody in the subject, wherein detection of the labeled anti-mesothelin antibody indicates a mesothelin-positive cancer in the subject. In one embodiment, the labeled anti-mesothelin antibody comprises an anti-mesothelin antibody conjugated to a positron emitter. In one such embodiment, the positron emitter is ^{89}Zr.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows that mesothelin is generated by proteolytic cleavage of a precursor protein into a 31 kDa shed component (referred to as megakaryocyte potentiating factor, or MPF) and a 40 kDa mesothelin component. The latter component may remain associated with the cell surface but may also be shed. "CHO" represent the four glycosylation sites, one in MPF and three in mesothelin.

Figure 2 shows a graphic representation of the levels of human mesothelin gene expression in various tissues, as described in Example A.

Figure 3 shows properties of anti-mesothelin monoclonal antibodies isolated as described in Example B.

Figure 4 shows an alignment of the variable light chain region sequences of murine antibody 7D9 (mu7D9) and humanized variants thereof (7D9.v1 and 7D9.v3).

Figure 5 shows an alignment of the variable heavy chain region sequences of murine antibody 7D9 (mu7D9) and humanized variants thereof (7D9.v1 and 7D9.v3).

Figure 6 shows properties of chimeric and humanized variants of 7D9, as described in Example C.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to mesothelin, ~~selected from:~~

~~(i) an~~wherein said antibody ~~that~~ binds an epitope of SEQ ID NO:43 comprising E153 and D174 and ~~that~~ optionally has one or more of the following characteristics:

(a) does not exhibit reduced binding to glycosylated forms of mesothelin;

(b) does not block binding of mesothelin to MUC16; and

(c) binds mesothelin with an affinity of ≤ 5 nM;

~~(ii) an antibody that binds an epitope of SEQ ID NO:43 comprising E211 and that optionally has one or more of the following characteristics:~~

~~(a) does not block binding of mesothelin to MUC16; and~~

~~(b) binds mesothelin with an affinity of ≤ 5 nM;~~

~~and~~

~~(iii) an antibody that binds to an epitope within amino acids 1-131 of SEQ ID NO:43 and binds mesothelin with an affinity of ≤ 5 nM~~

wherein said antibody comprises (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19;

and wherein said antibody further comprises a light chain variable domain comprising a framework FR2 sequence of SEQ ID NO:25 and an FR3 sequence of SEQ ID NO:27.

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, which is an antibody fragment that binds mesothelin.

5. The antibody of claim 1, wherein mesothelin is human mesothelin of SEQ ID NO:43.

6. The antibody of claim 1, wherein the antibody comprises~~:~~

~~(a)~~ (i) HVR-H3 comprising the amino acid sequence of SEQ ID NO:22, (ii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19, and (iii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:21~~;~~

~~(b) (i) HVR-H3 comprising the amino acid sequence of SEQ ID NO:39, (ii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:35, and (iii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:37; or~~

~~(c) HVR-H3, HVR-L3, and HVR-H2 of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.~~

~~7. The antibody of claim 1, wherein the antibody comprises~~

~~(a) (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:20, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:22;~~

~~(b) (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:36, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:37, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:39; or~~

~~(c) HVR-H1, HVR-H2, and HVR-H3 of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.~~

~~8.~~7. The antibody of claim ~~7~~1, comprising:

~~(a)~~ (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:20, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:21, (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:22, (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19~~;~~

~~(b) (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:36, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:37, (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:39, (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:33, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:34, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO:35; or~~

~~(c) HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2 and HVR-L3 of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.~~

~~9. The antibody of claim 1, wherein the antibody comprises~~

~~(a) (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19;~~

~~(b) (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:33, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:34, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:35, or~~

~~(c) HVR-L1, HVR-L2 and HVR-L3 of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.~~

~~10. The antibody of claim 8(a) or 9(a), further comprising a light chain variable domain comprising a framework FR2 sequence of SEQ ID NO:25 and an FR3 sequence of SEQ ID NO:27.~~

~~11.~~8. The antibody of claim 1, wherein the antibody comprises

(a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8;

(b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:4; or

(c) a VH sequence as in (a) and a VL sequence as in (b);

~~(d) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:16;~~

~~(e) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:12;~~

~~(f) a VH sequence as in (d) and a VL sequence as in (e);~~

~~(g) a VH sequence having at least 95% sequence identity to the amino acid sequence of the VH sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464;~~

~~(h) a VL sequence having at least 95% sequence identity to the amino acid sequence of the VL sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464; or~~

~~(i) a VH sequence as in (g) and a VL sequence as in (h)~~.

~~12.~~9. The antibody of claim ~~11~~8, comprising a VH sequence of SEQ ID NO:8~~, a VH sequence of SEQ ID NO:16, or a VH sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464~~.

~~13.~~10. The antibody of claim ~~11~~8, comprising a VL sequence of SEQ ID NO:4~~, a VL sequence of SEQ ID NO:12, or a VL sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464~~.

~~14.~~11. An antibody comprising ~~(a)~~ a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:4~~; (b) a VH sequence of SEQ ID NO:16 and a VL sequence of SEQ ID NO:12; (c) a VH sequence and a VL sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464; or (d) the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464~~.

~~15.~~12. The antibody of claim 1, which is an IgG1, IgG2a or IgG2b antibody.

~~16.~~13. Isolated nucleic acid encoding the antibody of any of claims 1-~~15~~12.

~~17.~~14. A host cell comprising the nucleic acid of claim ~~16~~13.

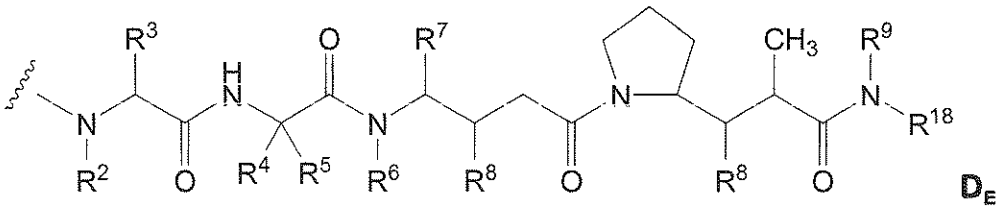
~~18.~~15. A method of producing an antibody comprising culturing the host cell of claim ~~17~~14 so that the antibody is produced.

~~19.~~16. An immunoconjugate having the formula Ab-(L-D)p, wherein:

(a) Ab is an antibody as in any of claims 1-~~15~~12;

(b) L is a linker;

(c) D is a drug of formula 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

(d) p ranges from 1-8.

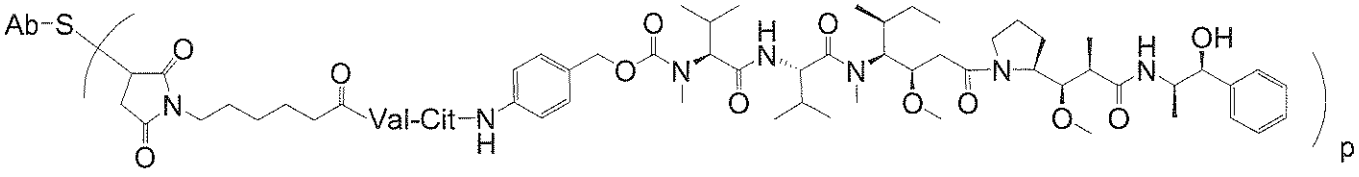
~~20.~~17. The immunoconjugate of claim ~~19~~16, wherein the drug is an auristatin.

~~21.~~18. The immunoconjugate of claim ~~20~~17, wherein the drug is MMAE.

~~22.~~19. The immunoconjugate of claim ~~19~~16, wherein the linker is cleavable by a protease.

~~23.~~20. The immunoconjugate of claim ~~22~~19, wherein the linker comprises a val-cit dipeptide.

~~24.~~21. The immunoconjugate of claim ~~19~~ 16 having the formula:



wherein S is a sulfur atom.

~~25.~~22. The immunoconjugate of claim ~~24~~21, wherein p ranges from 2-5.

~~26.~~23. The immunoconjugate of claim ~~24~~21, comprising the antibody of claim ~~8(a)~~7.

~~27. The immunoconjugate of claim 24, comprising the antibody of claim 8(b).~~

~~28.~~24. The immunoconjugate of claim ~~24~~21, comprising the antibody of claim ~~14(a)~~11.

~~29. The immunoconjugate of claim 24, comprising the antibody of claim 14(b).~~

~~30.~~25. A pharmaceutical formulation comprising an immunoconjugate of any of claims ~~19-29~~16-24 and a pharmaceutically acceptable carrier.

~~31.~~26. The pharmaceutical formulation of claim ~~30~~25, further comprising an additional therapeutic agent.

~~32.~~27. The pharmaceutical formulation of claim ~~31~~26, wherein the additional therapeutic agent is gemcitabine.

~~33.~~28. The pharmaceutical formulation of claim ~~31~~26, wherein the additional therapeutic agent is an anti-MUC16 antibody conjugated to a cytotoxic agent.

~~34.~~29. The immunoconjugate as in any of claims ~~19-29~~16-24 for use as a medicament.

~~35.~~30. The immunoconjugate as in any of claims ~~19-29~~16-24 for use in treating a mesothelin-positive cancer.

~~36.~~31. The immunoconjugate for use as in claim ~~35~~30, wherein the mesothelin-positive cancer is selected from pancreatic cancer, ovarian cancer, lung cancer, endometrial cancer, and mesothelioma.

~~37.~~32. The immunoconjugate for use as in claim ~~35~~30, wherein the mesothelin-positive cancer is a dual-positive cancer.

~~38.~~33. Use of the immunoconjugate as in any of claims ~~19-29~~16-24 in the manufacture of a medicament.

~~39.~~34. The use of claim ~~38~~33, wherein the medicament is for treatment of a mesothelin-positive cancer.

~~40.~~35. The use of claim ~~39~~34, wherein the mesothelin-positive cancer is selected from pancreatic cancer, ovarian cancer, lung cancer, endometrial cancer and mesothelioma.

~~41.~~36. The use of claim ~~39~~34, wherein the mesothelin-positive cancer is a dual-positive cancer.

~~42.~~37. The use of claim ~~39~~34, wherein the medicament is to be administered with an additional therapeutic agent to the individual.

~~43.~~38. The use of claim ~~42~~37, wherein the additional therapeutic agent is gemcitabine.

~~44.~~39. The use of claim ~~42~~37, wherein the additional therapeutic agent is an anti-MUC16 antibody conjugated to a cytotoxic agent.

~~45.~~40. An in vitro method of inhibiting proliferation of a mesothelin-positive cell, the method comprising exposing the cell to an immunoconjugate as in any of claims ~~19-29~~16-24 under

conditions permissive for binding of the immunoconjugate to mesothelin on the surface of the cell, thereby inhibiting proliferation of the cell.

~~46.~~41. The method of claim ~~45~~40, wherein the cell is a pancreatic, ovarian, lung, or endometrial cancer cell or mesothelioma cell.

~~47.~~42. The method of claim ~~45~~40, wherein the cell is a dual-positive cell.

~~48.~~43. An antibody as in any of claims 1-~~15~~ 12 conjugated to a label.

~~49.~~44. The antibody of claim ~~48~~43, wherein the label is a positron emitter.

~~50.~~45. The antibody of claim ~~49~~44, wherein the positron emitter is ^{89}Zr.

~~51.~~46. A method of detecting human mesothelin in a biological sample comprising contacting the biological sample with an anti-mesothelin antibody as in any of claims 1-~~15~~ 12 under conditions permissive for binding of the anti-mesothelin antibody to a naturally occurring human mesothelin, and detecting whether a complex is formed between the anti-mesothelin antibody and a naturally occurring human mesothelin in the biological sample.

~~52. The method of claim 51, wherein the anti-mesothelin antibody is an antibody as in any of claims 8(e), 14(e), and 14(d).~~

~~53.~~47. The method of claim ~~51~~46, wherein the biological sample is a pancreatic cancer sample, ovarian cancer sample, lung cancer sample, endometrial cancer sample, or mesothelioma sample.

~~54.~~48. The method of claim ~~51~~46, wherein the method comprises performing immunohistochemistry on a tissue section.

~~55.~~49. The method of claim ~~51~~46, wherein the biological sample is serum.

~~56.~~50. A method for detecting a mesothelin-positive cancer comprising (i) administering a labeled anti-mesothelin antibody to a subject having or suspected of having a mesothelin-positive cancer, wherein the labeled anti-mesothelin antibody comprises an anti-mesothelin antibody as in any of claims 1-~~15~~12, and (ii) detecting the labeled anti-mesothelin antibody in the subject, wherein detection of the labeled anti-mesothelin antibody indicates a mesothelin-positive cancer in the subject.

~~57.~~51. The method of claim ~~56~~50, wherein the labeled anti-mesothelin antibody is an antibody as in claim 8(a) or 14(a) that is labeled.

~~58.~~52. The method of claim ~~56~~ 50 or claim ~~57~~51, wherein the labeled anti-mesothelin antibody comprises an anti-mesothelin antibody conjugated to a positron emitter.

~~59.~~53. The method of claim ~~58~~52, wherein the positron emitter is ^{89}Zr.

~~60. The antibody of claim 8 comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:20, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID~~

~~NO:21, (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:22, (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19.~~

~~61. The antibody of claim 60, further comprising a light chain variable domain comprising a framework FR2 sequence of SEQ ID NO:25 and an FR3 sequence of SEQ ID NO:27.~~

~~62. The antibody of claim 8 comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:36, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:37, (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:39, (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:33, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:34, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO:35.~~

~~63. The antibody of claim 8 comprising HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2 and HVR-L3 of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.~~

~~64. The antibody of claim 14 comprising a VH sequence of SEQ ID NO:8 and a VL sequence of SEQ ID NO:4.~~

~~65. The antibody of claim 14 comprising a VH sequence of SEQ ID NO:16 and a VL sequence of SEQ ID NO:12.~~

~~66. The antibody of claim 14 comprising a VH sequence and a VL sequence of the antibody produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.~~

~~67. The antibody of claim 14 produced by hybridoma 19C3 having ATCC Accession No. PTA-11464.~~

~~68.~~54. Use of an immunoconjugate as in any of claims ~~19-29~~16-24 in the manufacture of a medicament for inhibiting proliferation of a mesothelin-positive cell, wherein the cell is to be exposed to said immunoconjugate under conditions permissive for binding of the immunoconjugate to mesothelin on the surface of the cell, to thereby inhibit proliferation of the cell.

~~69.~~55. The use of claim ~~68~~54, wherein the cell is a pancreatic, ovarian, lung, or endometrial cancer cell or mesothelioma cell.

~~70.~~56. The use of claim ~~68~~54, wherein the cell is a dual-positive cell.