

and/or drug can be taken up inside a tumor cell or cancer cell through receptor-mediated endocytosis.

[0094] Once inside the cell, one or more specific peptide sequences within the conjugate (e.g., in a linker) are hydrolytically cleaved by one or more tumor-cell or cancer-cell-associated proteases, resulting in release of the drug. The released drug is then free to migrate within the cell and induce cytotoxic or cytostatic or other activities. In some embodiments, the drug is cleaved from the antibody outside the tumor cell or cancer cell, and the drug subsequently penetrates the cell, or acts at the cell surface.

[0095] Examples of drug moieties or payloads are selected from the group consisting of DM1 (maytansine, N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)- or N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine), mc-MMAD (6-maleimidocaproyl-monomethylauristatin-D or N-methyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(1S)-2-phenyl-1-(2-thiazolyl)ethyl]amino]propyl]-1-pyrrolidiny]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl-(9Cl)-L-valinamide), mc-MMAF (maleimidocaproyl-monomethylauristatin F or N-[6-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxohexyl]-N-methyl-L-valyl-L-valyl-(3R,4S,5S)-3-methoxy-5-methyl-4-(methylamino)heptanoyl-(α R, β R,2S)- β -methoxy- α -methyl-2-pyrrolidinepropanoyl-L-phenylalanine) and mc-Val-Cit-PABA-MMAE (6-maleimidocaproyl-Val-eCit(p-aminobenzyloxycarbonyl)-monomethylauristatin E or N-[[[4-[[N-[6-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxohexyl]-L-valyl-N5-(aminocarbonyl)-L-ornithyl]amino]phenyl]methoxy]carbonyl]-N-methyl-L-valyl-N-[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[(1R,2S)-2-hydroxy-1-methyl-2-phenylethyl]amino]-1-methoxy-2-methyl-3-oxopropyl]-1-pyrrolidiny]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl-L-valinamide). DM1 is a derivative of the tubulin inhibitor maytansine while MMAD, MMAE, and MMAF are auristatin derivatives. In some embodiments, the drug moiety is selected from the group consisting of mc-MMAF and mc-Val-Cit-PABA-MMAE. In some embodiments, the drug moiety is a maytansinoid or an auristatin.

[0096] The antibodies or fragments may be conjugated or fused to a therapeutic agent, which may include detectable labels such as radioactive labels, an immunomodulator, a hormone, an enzyme, an oligonucleotide, a photoactive therapeutic or diagnostic agent, a cytotoxic agent, which may be a drug or a toxin, an ultrasound enhancing agent, a non-radioactive label, a combination thereof and other such agents known in the art.

58F9G10 VH	EVQLQQSGPELVKTGASVKISCKASGYSFTGYIIHWVKQSHGKSLEWIGY ISCYNGATSFNQKFKGKATFTVDTSSSTAYMQFNLSLSEDSAVYYCARTE LRGPWFAYWGQGLTVTVSS	15
V1 (CDR grafting)	QVQLVQSGAEVKKPGASVKVSKASGYSFTGYIIHWVRQAPGQGLEWMGY ISSYNAATSFNQKFKGRVTMTTRDTSTSTVYMESSLRSEDTAVYYCARTE LRGPWFAYWGQGLTVTVSS	61
V2 (with back mutations)	QVQLVQSGAEVKKPGASVKVSKASGYSFTGYIIHWVRQAPGQGLEWIGY ISSYNAATSFNQKFKGRVTETVDTSTSTVYMESSLRSEDTAVYYCARTE LRGPWFAYWGQGLTVTVSS	62
V3 (with back mutations)	QVQLVQSGAEVKKPGASVKVSKASGYSFTGYIIHWVKQAPGQGLEWIGY ISSYNAATSFNQKFKGRVTETVDTSTSTVYMEFSSLRSEDTAVYYCARTE LRGPWFAYWGQGLTVTVSS	63
V4 (with back mutations)	QVQLVQSGAEVKKPGASVKISCKASGYSFTGYIIHWVKQAPGQGLEWIGY ISSYNAATSFNQKFKGRATETVDTSTSTAYMEFSSLRSEDSAVYYCARTE LRGPWFAYWGQGLTVTVSS	64

Table 4B. CDR Sequences

CDR	Sequence	SEQ ID NO:
CDR-H1	GYIIH	54
CDR-H2	YISCYNGATSFNQKFKG YISSYNAATSFNQKFKG	60 55
CDR-H3	TELRGPWFAY	56

Table 4C. Humanization of 58F9G10 – VL

Name	Sequence	SEQ ID NO:
58F9G10 VL	QTVLTQSPAISASPGKEVTMTCSASSSVSYMNWYQQKSGTSPKRWIYDT SKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSNNPLTFGAG TKLELK	16
V1 (CDR grafting)	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLIYDT SKLASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQWSNNPLTFGQG TKLEIK	65
V2 (with back mutations)	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRLLIYDT SKLASGVPSRFSGSGSGTDYTLTISLQPEDFATYYCQQWSNNPLTFGQG TKLEIK	66
V3 (with back mutations)	DIQLTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRLLIYDT SKLASGVPSRFSGSGSGTDYTLTISSMQPEDFATYYCQQWSNNPLTFGQG TKLEIK	67

Table 4D. CDR Sequences

CDR	Sequence	SEQ ID NO:
CDR-L1	SASSSVSYMN	57
CDR-L2	DTSKLAS	58
CDR-L3	QQWSNNPLT	59

Table 4E. Humanized antibodies

	VL	VL v1	VL v2	VL V3
VH	58F9G10-XI			
VH v1		58-H1L1	58-H1L2	58-H1L3
VH v2		58-H2L1	58-H2L2	58-H2L3
VH v3		58-H3L1	58-H3L2	58-H3L3
VH v4		58-H4L1	58-H4L2	58-H4L3

D. 6G10D9

Table 5A. Humanization of 6G10D9 – VH

Name	Sequence	SEQ ID NO:
6G10D9 VH	QVQLQQSGAELARPGASVKMSCKASGYTFTT TYTMH WVKQRPQGGLWLG Y INPSSGYTNYNQKFKD KATLTAGKSSSTAYMQLSSLTSEDSAVYYCAS LR SRGYFDY WGQGTTLTVSS	1
V1 (CDR grafting)	QVQLVQSGAEVKKPGASVKVSKASGYTFTT TYTMH WVRQAPQGGLW MGY INPSSGYTNYNQKFKD RVTMTTRDTSTSTVYME LS SLRSEDTAVYYC SRLR SRGYFDY WGQGTLLTVSS	74
V2 (with back mutations)	QVQLVQSGAEVKKPGASVKVSKASGYTFTTYTMHWVRQAPQGGLW LG Y INPSSGYTNYNQKFKDRVTMT AD TSTSTVYME LS SLRSEDTAVYYC AR LR SRGYFDYWGQGTLLTVSS	75
V3 (with back mutations)	QVQLVQSGAEV AK PGASVKVSKASGYTFTTYTMHW KQ APQGGLW LG Y INPSSGYTNYNQKFKDRVTMT AD TSTSTVYME LS SLRSEDTAVYYC AS LR SRGYFDYWGQGTLLTVSS	76
V4 (with back mutations)	QVQLVQSGAEV AK PGASVK MS CKASGYTFTTYTMHW KQ APQGGLW LG Y INPSSGYTNYNQKFKDRVT LTAD TSTSTVYME LS SLRSEDTAVYYC AS LR SRGYFDYWGQGT LL TVSS	77
V5 (with back mutations)	QVQL QQ SGAEV AK PGASVK MS CKASGYTFTTYTMHW KQ RPQGGLW LG Y INPSSGYTNYNQKFKDRVT LTADK STSTVYME LS SLRSEDTAVYYC AS LR SRGYFDYWGQGT LL TVSS	78
V6 (with back mutations)	QVQL QQ SGAEV AK PGASVK MS CKASGYTFTTYTMHW KQ RPQGGLW LG Y INPSSGYTNYNQKFKDR ATLTAGK STSTVYME LS SLRSEDTAVYYC AS LR SRGYFDYWGQGT LL TVSS	79

Table 5B. CDR Sequences

CDR	Sequence	SEQ ID NO:
CDR-H1	TYTMH	~~D0168~~
CDR-H2	YINPSSGYTNYNQKFKD	~~D0269~~
CDR-H3	LRSRGYFDY	~~D0370~~

Table 5C. Humanization of 6G10D9 – VL

Name	Sequence	SEQ ID NO:
6G10D9 VL	DIVMTQSQTFMSTSVGDRVRITCK KASQNVGTAVV WYQQKGTGQSPRLLI YS ASNRYT GVPDRFTGSGSGTDFLTISNMQSEDLADFFC QQYSSYPY TFGG GTKLEIK	2

CLAIMS

What is claimed is:

1. An antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof having binding specificity, conjugated to a cytotoxin, wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein, wherein the antibody or fragment thereof and comprises:

a heavy chain variable region (~~VH~~) comprising ~~heavy chain~~ a complementarity determining regions ~~CDRH1, CDRH2, and CDRH3~~ 1 (HCDR1) amino acid sequence of SEQ ID NO: 42, an HCDR2 amino acid sequence of SEQ ID NO: 43, and an HCDR3 amino acid sequence of SEQ ID NO: 44; and

a light chain variable region (~~VL~~) comprising a complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, respectively, comprise:1 (LCDR1) amino acid sequence of SEQ ID NO: 45, an LCDR2 amino acid sequence of SEQ ID NO: 46, and an LCDR3 amino acid sequence of SEQ ID NO: 47.

- (a) ~~the amino acid sequences of SEQ ID NO:42-47;~~
- (b) ~~the amino acid sequences of SEQ ID NO:29-34;~~
- (c) ~~the amino acid sequences of SEQ ID NO:54-59; or~~
- (d) ~~the amino acid sequences of SEQ ID NO:68-73.~~

2. The ADC of claim 1, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 9, 48, 49, or 50.

3. The ADC of claim 1 or 2, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 10, 51, 52, or 53.

~~42.~~ The ~~ADC antibody or antigen-binding fragment thereof of any one of claims 1-3,~~
wherein

~~the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 9,~~
~~48, 49, or 50; and~~

~~the light chain variable region comprises the amino acid sequence of SEQ ID NO: 10,~~
~~51, 52, or 53~~~~CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, respectively,~~
~~comprise the amino acid sequences of SEQ ID NO:42-47.~~

~~53.~~ The ~~ADC antibody or antigen-binding fragment thereof of any one of claims 1-42,~~
wherein the heavy chain variable region~~VH~~ comprises ~~the an~~ amino acid sequence selected
from the group consisting of SEQ ID NO:9 and 48-50, and the light chain variable region~~VL~~
comprises ~~the an~~ amino acid sequence selected from the group consisting of SEQ ID NO:40
and 51-53.

~~6.~~ An antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding
fragment thereof, conjugated to a cytotoxin, wherein the antibody or the antigen-binding
fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5
member D (GPRC5D) protein and comprises:

a heavy chain variable region comprising a complementarity determining region 1
(HCDR1) amino acid sequence of SEQ ID NO: 29, an HCDR2 amino acid sequence of SEQ
ID NO: 30, and an HCDR3 amino acid sequence of SEQ ID NO: 31; and

a light chain variable region comprising a complementarity determining region 1
(LCDR1) amino acid sequence of SEQ ID NO: 32, an LCDR2 amino acid sequence of SEQ
ID NO: 33, and an LCDR3 amino acid sequence of SEQ ID NO: 34.

~~74.~~ The ~~ADC antibody or antigen-binding fragment thereof of claim 62,~~ wherein the
heavy chain variable region~~VH~~ comprises the amino acid sequence of SEQ ID NO:48, and
the VL comprises the amino acid sequence of SEQ ID NO:51-7, 35, 36, or 37.

5. ~~The antibody or antigen-binding fragment thereof of claim 1, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, respectively, comprise the amino acid sequences of SEQ ID NO:29-34.~~

86. The ADC ~~antibody or antigen-binding fragment thereof~~ of claim 6 or 75, wherein the light chain variable region ~~VH~~ comprises the ~~an~~ amino acid sequence ~~selected from the group consisting of SEQ ID NO:7 and 35-37, and the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 8, and 38, 39, 40, or 41.~~

9. The ADC of any one of claims 6-8, wherein
the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 7, 35, 36, or 37; and
the light chain variable region comprises the amino acid sequence of SEQ ID NO: 8, 38, 39, 40, or 41.

107. The ADC ~~antibody or antigen-binding fragment thereof~~ of any one of claims 6-95, wherein the heavy chain region ~~VH~~ comprises the amino acid sequence of SEQ ID NO: 35, and the light region variable region ~~VL~~ comprises the amino acid sequence of SEQ ID NO: 38.

118. ~~An~~ The antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to a cytotoxin, wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein and comprises: ~~of claim 1, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, respectively, comprise the~~

a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 54, an HCDR2 amino acid sequence of SEQ ID NO: 55 or 60, and an HCDR3 amino acid sequence of SEQ ID NO: 56; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 57, an LCDR2 amino acid sequence of SEQ ID NO: 58, and an LCDR3 amino acid sequences of SEQ ID NO: 54-59.

129. The ADC antibody or antigen-binding fragment thereof of claim 118, wherein the heavy chain variable region ~~VH~~ comprises the an-amino acid sequence selected from the group consisting of SEQ ID NO: 15, 61, 62, 63, or -64,

13. The ADC of claim 11 or 12, wherein the light chain variable region and the ~~VL~~ comprises the an-amino acid sequence selected from the group consisting of SEQ ID NO: 16, and -65, 66, or -67.

14. The ADC of any one of claims 11-13, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 15, 61, 62, 63, or 64 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 16, 65, 66, or 67.

1510. The ADC antibody or antigen-binding fragment thereof of any one of claims 11-148, wherein the heavy chain variable region ~~VH~~ comprises the amino acid sequence of SEQ ID NO: 61, and the light chain variable region ~~VL~~ comprises the amino acid sequence of SEQ ID NO: 65.

1611. The ADC antibody or antigen-binding fragment thereof of any one of claims 11-148, wherein the heavy chain variable region ~~VH~~ comprises the amino acid sequence of SEQ ID NO: 63, and the light chain variable region ~~VL~~ comprises the amino acid sequence of SEQ ID NO: 65.

1712. An ~~The~~ antibody-drug conjugate (ADC), comprising an antibody, -or an antigen-binding fragment thereof conjugated to a cytotoxin of claim 1, wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPC5D) protein and comprises:

a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 69, and an HCDR3 amino acid sequence of SEQ ID NO: 70; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 71, an LCDR2 amino acid sequence of SEQ ID NO: 72, and an LCDR3 CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, respectively, ~~comprise the~~ amino acid sequences of SEQ ID NO: ~~68-73~~.

18. The ADC of claim 17, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 1, 74, 75, 76, 77, 78, or 79.

1913. The ~~ADC antibody or antigen-binding fragment thereof~~ of claim 17 or 1812, wherein the ~~VH comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1 and 74-79, and the VL light chain variable region comprises the an~~ amino acid sequence selected from the group consisting of SEQ ID NO: ~~2, and 80-81, 82, 83, 84, 85, or~~ 86.

20. The ADC of any one of claims 17-19, wherein

the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 1, 74, 75, 76, 77, 78, or 79; and

the light chain variable region comprises the amino acid sequence of SEQ ID NO: 2, 81, 82, 83, 84, 85, or 86.

2144. The ADC antibody or antigen-binding fragment thereof of any one of claims 17-202, wherein the heavy chain variable region VH comprises the amino acid sequence of SEQ ID NO: 76, and the light chain variable region VL comprises the amino acid sequence of SEQ ID NO: 82.

2245. The ADC antibody or antigen-binding fragment thereof of any one of claims 17-202, wherein the heavy chain variable region VH comprises the amino acid sequence of SEQ ID NO: 77, and the light chain variable region VL comprises the amino acid sequence of SEQ ID NO: 82.

16. — ~~The antibody or fragment thereof of any one of claims 1-15, which is humanized.~~

17. — ~~The antibody or fragment thereof of any one of claims 1-16, which is ADCC-competent.~~

18. — ~~The antibody or fragment thereof of any one of claims 1-16, further comprising a cytotoxic drug conjugated to the antibody or fragment thereof.~~

19. — ~~A bispecific antibody, comprising the antigen-binding fragment of any one of claims 1-16, and a second antigen-binding fragment having specificity to a second target protein.~~

20. — ~~The bispecific antibody of claim 19, wherein the second target protein is selected from the group consisting of CD3, CD16, CD19, CD28, CD64 and 4-1BB.~~

21. — ~~The bispecific antibody of claim 19, wherein the second target protein is CD3.~~

23. The ADC of any one of claims 1-22, wherein the cytotoxin is a maytansinoid or an auristatin.

24. The ADC of claim 23, wherein the cytotoxin is selected from the group consisting of maytansine, N2'-deacetyl-N2'-(3-mercapto-l-oxopropyl) or N2'-deacetyl-N2'-(3-mercapto-l-oxopropyl)-maytansine (DM1); monomethylauristatin-D (MMAD); monomethyl auristatin-E (MMAE); and monomethylauristatin-F (MMAF).

25. An antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to monomethyl auristatin-E (MMAE), wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPC5D) protein and comprises:

a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 42, an HCDR2 amino acid sequence of SEQ ID NO: 43, and an HCDR3 amino acid sequence of SEQ ID NO: 44; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 45, an LCDR2 amino acid sequence of SEQ ID NO: 46, and an LCDR3 amino acid sequence of SEQ ID NO: 47.

26. An antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to monomethyl auristatin-E (MMAE), wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPC5D) protein and comprises:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 48;
and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 51.

27. An antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to monomethyl auristatin-E (MMAE), wherein the antibody or

the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPC5D) protein and comprises:

a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 54, an HCDR2 amino acid sequence of SEQ ID NO: 55 or 60, and an HCDR3 amino acid sequence of SEQ ID NO: 56; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 57, an LCDR2 amino acid sequence of SEQ ID NO: 58, and an LCDR3 amino acid sequence of SEQ ID NO: 59.

28. An antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to monomethyl auristatin-E (MMAE), wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPC5D) protein and comprises:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 61;
and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 65.

29. Use of an antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to monomethyl auristatin-E (MMAE), wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPC5D) protein and comprises:

a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 42, an HCDR2 amino acid sequence of SEQ ID NO: 43, and an HCDR3 amino acid sequence of SEQ ID NO: 44; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 45, an LCDR2 amino acid sequence of SEQ ID NO: 46, and an LCDR3 amino acid sequence of SEQ ID NO: 47,

in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a patient having a hematological cancer.

30. Use of an antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to monomethyl auristatin-E (MMAE), wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein and comprises:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 48; and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 51,

in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a patient having a hematological cancer.

31. Use of an antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to monomethyl auristatin-E (MMAE), wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein and comprises:

a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 54, an HCDR2 amino acid sequence of SEQ ID NO: 55 or 60, and an HCDR3 amino acid sequence of SEQ ID NO: 56; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 57, an LCDR2 amino acid sequence of SEQ ID NO: 58, and an LCDR3 amino acid sequence of SEQ ID NO: 59,

in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a patient having a hematological cancer.

32. Use of an antibody-drug conjugate (ADC), comprising an antibody, or an antigen-binding fragment thereof, conjugated to monomethyl auristatin-E (MMAE), wherein the antibody or the antigen-binding fragment thereof binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPCR5D) protein and comprises:

a heavy chain variable region comprising the amino acid sequence of SEQ ID

NO: 61; and

a light chain variable region comprising the amino acid sequence of SEQ ID

NO: 65,

in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a patient having a hematological cancer.

33. Use of the ADC of any one of claims 2-4, 6-10, 12-14, and 16-28 in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a patient having a hematological cancer.

34. The use of any one of claims 29-33, wherein the cancer is multiple myeloma.

35. An antibody or an antigen-binding fragment thereof, that binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPCR5D) protein, comprising:

a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 42, an HCDR2 amino acid sequence of SEQ ID NO: 43, and an HCDR3 amino acid sequence of SEQ ID NO: 44; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 45, an LCDR2 amino acid sequence of SEQ ID NO: 46, and an LCDR3 amino acid sequence of SEQ ID NO: 47.

36. The antibody or an antigen-binding fragment thereof of claim 35, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 9, 48, 49, or 50.

37. The antibody or an antigen-binding fragment thereof of claim 35 or 36, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 10, 51, 52, or 53.

38. The antibody or an antigen-binding fragment thereof of any one of claims 35-37, wherein
the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 9, 48, 49, or 50; and
the light chain variable region comprises the amino acid sequence of SEQ ID NO: 10, 51, 52, or 53.

39. An antibody or an antigen-binding fragment thereof, that binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein, comprising:
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 48;
and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 51.

40. An antibody or an antigen-binding fragment thereof that binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein, comprising:
a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 29, an HCDR2 amino acid sequence of SEQ ID NO: 30, and an HCDR3 amino acid sequence of SEQ ID NO: 31; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 32, an LCDR2 amino acid sequence of SEQ ID NO: 33, and an LCDR3 amino acid sequence of SEQ ID NO: 34.

41. The antibody or an antigen-binding fragment thereof of claim 40, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 7, 35, 36, or 37.

42. The antibody or an antigen-binding fragment thereof of claim 40 or 41, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 8, 38, 39, 40, or 41.

43. The antibody or an antigen-binding fragment thereof of any one of claims 40-42, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 7, 35, 36, or 37; and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 8, 38, 39, 40, or 41.

44. The antibody or an antigen-binding fragment thereof of any one of claims 40-43, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 35 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 38.

45. An antibody or an antigen-binding fragment thereof that binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein, comprising:
a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 54, an HCDR2 amino acid sequence of SEQ ID NO: 55 or 60, and an HCDR3 amino acid sequence of SEQ ID NO: 56; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 57, an LCDR2 amino acid sequence of SEQ ID NO: 58, and an LCDR3 amino acid sequence of SEQ ID NO: 59.

46. The antibody or an antigen-binding fragment thereof of claim 45, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 15, 61, 62, 63, or 64.

47. The antibody or an antigen-binding fragment thereof of claim 45 or 46, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 16, 65, 66, or 67.

48. The antibody or an antigen-binding fragment thereof of any one of claims 45-47, wherein

the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 15, 61, 62, 63, or 64; and

the light chain variable region comprises the amino acid sequence of SEQ ID NO: 16, 65, 66, or 67.

49. The antibody or an antigen-binding fragment thereof of any one of claims 45-48, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 63 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 65.

50. An antibody or an antigen-binding fragment thereof, that binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein, comprising:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 61; and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 65.

51. An antibody or an antigen-binding fragment thereof that binds specifically to a human G-protein-coupled receptor family C group 5 member D (GPRC5D) protein and comprises:

a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 69, and an HCDR3 amino acid sequence of SEQ ID NO: 70; and

a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 71, an LCDR2 amino acid sequence of SEQ ID NO: 72, and an LCDR3 amino acid sequence of SEQ ID NO: 73.

52. The antibody or an antigen-binding fragment thereof of claim 51, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 1, 74, 75, 76, 77, 78, or 79.

53. The antibody or an antigen-binding fragment thereof of claim 51 or 52, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 2, 81, 82, 83, 84, 85, or 86.

54. The antibody or an antigen-binding fragment thereof of any one of claims 51-53, wherein
the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 1, 74, 75, 76, 77, 78, or 79; and
the light chain variable region comprises the amino acid sequence of SEQ ID NO: 2, 81, 82, 83, 84, 85, or 86.

55. The antibody, or an antigen-binding fragment thereof of any one of claims 51-54, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 76 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 82.

56. The antibody or an antigen-binding fragment thereof of any one of claims 51-54, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 77 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 82.

5722. ~~Use of A method of treating cancer in a patient in need thereof, comprising administering to the patient the antibody or an antigen-binding fragment thereof of any one of claims 394-21 in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a patient having a hematological cancer.~~

58. Use of the antibody or an antigen-binding fragment thereof of claim 50 in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a patient having a hematological cancer.

59. Use of the antibody or an antigen-binding fragment thereof of any one of claims 35-38, 40-49 and 51-56 in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a patient having a hematological cancer.

23. ~~A method of treating cancer in a patient in need thereof, comprising (a) treating a T cell, a natural killer (NK) cell, or a macrophage, *in vitro*, with the antibody or fragment thereof of any one of claims 1-21, and (b) administering the treated cell to the patient.~~

24. ~~The method of claim 23, further comprising, prior to step (a), isolating the T cell, the NK cell, or the macrophage, from an individual.~~

25. — ~~The method of claim 24, wherein the T cell, the NK cell, or the macrophage, is isolated from the patient.~~

26. — ~~The method of claim 23, wherein the T cell is a tumor-infiltrating T lymphocyte, a CD4⁺ T cell, a CD8⁺ T cell, or the combination thereof.~~

27. — ~~The method of any one of claims 22-26, wherein the cancer is a hematological cancer.~~

28. — ~~The method of claim 27, wherein the hematological cancer is a GPRC5D-expressing B-cell cancer.~~

6029. The use of any one method of claims 57-59-28, wherein the hematological GPRC5D-expressing B-cell cancer is multiple myeloma.