5T4 ANTIBODY-DRUG CONJUGATES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/341,957, filed May 13, 2022, the disclosure of which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] This application contains a computer readable Sequence Listing which has been submitted in XML file format with this application, the entire content of which is incorporated by reference herein in its entirety. The Sequence Listing XML file submitted with this application is entitled "14529-099-228_SEQ_LISTING.xml", was created on May 9, 2023 and is 125,376 bytes in size.

FIELD

[0003] The present disclosure relates generally to antibody-drug conjugates (ADCs) that bind to 5T4 (*e.g.*, human 5T4) and methods of their use.

BACKGROUND

[0004] 5T4 is an N-glycosylated transmembrane 72 kDa glycoprotein containing eight leucine-rich repeats. 5T4, also known as Wnt-Activated Inhibitory Factor 1 or WAIF1, is often referred to as an oncofetal antigen due to its expression in fetal trophoblast (where it was first discovered) or as trophoblast glycoprotein (TPBG). 5T4 is found in tumors such as colorectal, ovarian, and gastric tumors. Its expression is used as a prognostic aid. 5T4 has very limited expression in normal tissue but is widespread in malignant tumors throughout their development. Although its confined expression would appear to give 5T4 the potential to be a target in cancer therapy, therapeutic success with antibodies, ADCs, and vaccines targeting 5T4 has not yet been achieved.

[0005] There remains a need in the art for ADCs that can target 5T4 to treat, prevent, or alleviate 5T4-mediated diseases, disorders, or conditions, such as those involving tumor cells expressing 5T4.

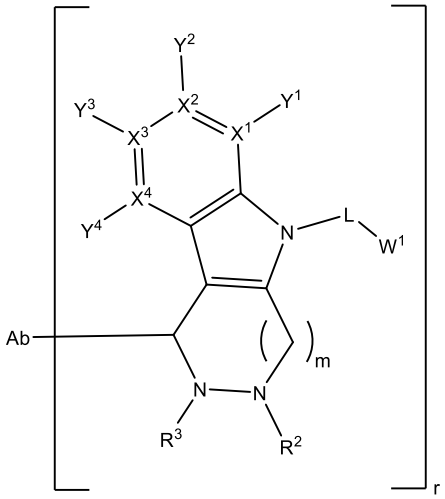
SUMMARY

[0006] The present disclosure provides ADCs comprising an antibody that binds to 5T4 ("5T4-ADC"). Such 5T4-ADCs, in some examples, bind to the same epitope of human 5T4 as an antibody comprising a heavy chain variable region (VH) and a light chain variable region (VL) described herein.

[0007] The present disclosure also provides pharmaceutical compositions comprising a 5T4-ADC that comprises an antibody or fragment thereof that binds to 5T4 and a drug conjugated (directly or indirectly) thereto. Such pharmaceutical compositions, in some examples, include 5T4-ADCs comprising an antibody or fragment thereof that binds to essentially the same epitope of human 5T4 as an antibody comprising a VH and a VL described herein.

[0008] The present disclosure also provides methods of treating, preventing, or alleviating a 5T4-mediated disease, disorder, or condition, such as alleviating one or more symptoms of the 5T4-mediated disease, disorder, or condition with a 5T4-ADC that binds to 5T4.

[0009] More specifically, the present disclosure provides a 5T4-ADC comprising (a) an antibody that binds to 5T4 and (b) one or more pyridazine-pyrrolo coupling moieties comprising a drug conjugated to the pyridazine-pyrrolo coupling moiety through a linker. In some examples, a 5T4-ADC is represented by Formula (IV):



(IV),

wherein

Ab represents the antibody that binds to 5T4;

R^2 and R^3 are each independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; or R^2 and R^3 are cyclically linked to form a 5- or 6-membered heterocyclyl;

L is the linker and is represented by $-(T^1V^1)_a-(T^2V^2)_b-(T^3V^3)_c-(T^4V^4)_d-(T^5V^5)_e-$;

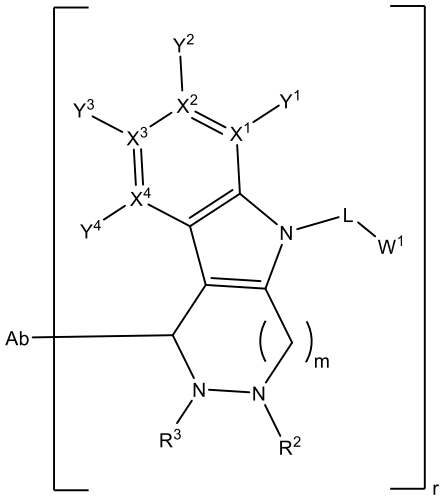
thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; and

R^{13} is independently hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl.

[0009a] In one aspect, the present disclosure provides an antibody-drug conjugate (ADC) of Formula (IV) comprising:

a. an antibody that binds to 5T4; and

b. one or more drugs conjugated to one or more pyridazine-pyrrolo coupling moieties via a linker



(IV)

wherein:

Ab represents the antibody that binds to 5T4;

r is an integer from 1 to 10;

m is 0 or 1;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; or R^2 and R^3 are cyclically linked to form a 5- or 6-membered heterocyclyl;

X^1, X^2, X^3 and X^4 are each independently selected from the group consisting of C, N, O and S;

Y^1, Y^2, Y^3 and Y^4 are each independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, or Y^1 and Y^2, Y^2 and Y^3, or Y^3 and Y^4 are cyclically linked;

W^1 is the drug;

L represents the linker and is $-(T^1V^1)_a-(T^2V^2)_b-(T^3V^3)_c-(T^4V^4)_d-(T^5V^5)_e-$, wherein:

a, b, c, d, and e are each independently 0 or 1, wherein the sum of a, b, c, d, and e is 1 to 5;

T^1, T^2, T^3, T^4, and T^5 each independently comprise C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_h-$, a piperidin-4-amine (P4A-R^{12}), a meta-aminobenzyl carbamate (MABC) group, a meta-aminobenzyloxy (MABO) group, a para-aminiobenzyloxy (PABO) group, a para-aminobenzyl carbamate (PABC) group, a para-aminobenzyl (PAB) group, acetal, a disulfide, a hydrazine, $(AA)_p$-MABC-$(AA)_p$, $(AA)_p$-MABO-$(AA)_p$, $(AA)_p$-PABO-$(AA)_p$, or $(AA)_p$-PABC-$(AA)_p$,

w is an integer from 1 to 20;

n is an integer from 1 to 30;

each p is independently zero or an integer from 1 to 20;

h is an integer from 1 to 12; and

each R^{12} is hydrogen, alkyl, substituted alkyl, a polyethylene glycol moiety, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl,

thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

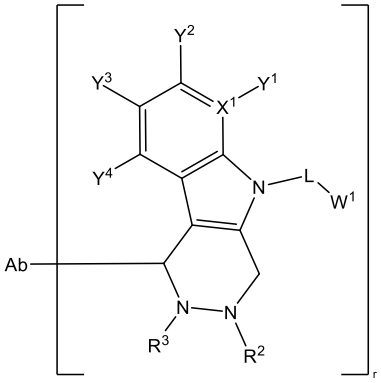
each R^{13} is hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl;

V^1, V^2, V^3, V^4 and V^5 are each independently selected from the group consisting of a covalent bond, -C(=O)-, -NR^{11}-, -C(=O)NR^{11}-, -NR^{11}C(=O)-, -C(=O)O-, -OC(=O)-, -O-, -S-, -S(=O)-, -SO_2-, -SO_2NR^{11}-, -$NR^{11}SO_2$- and -P(=O)OH-, wherein R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, PEG, aryl, and substituted aryl.

[0010] In some examples, the drug is a maytansinoid or an auristatin, such as MMAE or MMAF.

[0011] In some examples, a 5T4-ADC can be represented by Formula (IV), wherein R^2 and R^3 are each alkyl, for example, methyl. In some examples, a 5T4-ADC can be represented by Formula (IV), wherein each of X^1, X^2, X^3, and X^4 are independently C or N.

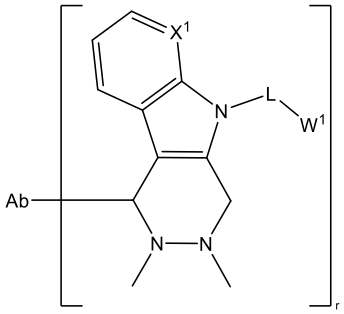
[0012] In some examples, a 5T4-ADC can be represented by Formula (V):



(V),

wherein X^1, Y^1, Y^2, Y^3, Y^4, R^2, R^3, L, and W^1 are as defined herein, such as for Formula (IV).

[0013] In some examples, a 5T4-ADC can be represented by Formula (VI):



(VI),

wherein X^1 is C or N, and L and W^1 are as defined herein, such as for Formula (IV).

[0014] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), or (VI), wherein:

L is the linker and is represented by $-(T^1V^1)_a-(T^2V^2)_b-(T^3V^3)_c-(T^4V^4)_d-(T^5V^5)_e-$;

T^1, T^2, T^3, T^4 and T^5 are each independently C_1-C_6 alkyl, P4A-R^{12}, $(AA)_p$, $(AA)_p$-PABC, or $(PEG)_n$;

V^1, V^2, V^3, V^4 and V^5 are each independently selected from the group consisting of a covalent

bond, -C(=O)-, -NR^{11}-, -C(=O)NR^{11}-, -NR^{11}C(=O)-, -C(=O)O-, -OC(=O)-, -O-, -S-, -S(=O)-, -SO_2-, -SO_2NR^{11}-, -$NR^{11}SO_2$- and -P(=O)OH-;

a, b, c, d, and e are each independently 0 or 1, wherein the sum of a, b, c, d, and e is 1 to 5;

p is an integer from 1 to 20;

n is an integer from 1 to 30;

R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, PEG, aryl, and substituted aryl; and

R^{12} is independently a polyethylene glycol or carboxylic acid-modified polyethylene glycol.

[0015] In further examples, a 5T4-ADC can be represented by Formula (IV), (V), or (VI), wherein:

a, b, c, d, and e are each independently 0 or 1, wherein the sum of a, b, c, d, and e is 1 to 5;

p is an integer from 1 to 20;

n is an integer from 1 to 30;

L is the linker and is represented by -$(T^1V^1)_a$-$(T^2V^2)_b$-$(T^3V^3)_c$-$(T^4V^4)_d$-$(T^5V^5)_e$-;

T^1 is C_1-C_6 alkyl;

T^2, T^3, T^4, and T^5 are each independently $(PEG)_n$, C_1-C_6 alkyl, $(AA)_p$, P4A-R^{12}, $(AA)_p$-(PABO-R^{16})-$(AA)_p$, $(AA)_p$-(PABC-R^{16})-$(AA)_p$, $(AA)_p$-(PABO-R^{16}), or $(AA)_p$-(PABC-R^{16});

V^1, V^2, V^3, V^4, and V^5 are each independently -CO- or -NR^{11};

R^{11} is independently hydrogen or alkyl;

R^{12} is independently a carboxylic acid-modified polyethylene glycol; and

R^{16} is hydrogen.

[0016] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), or (VI), wherein:

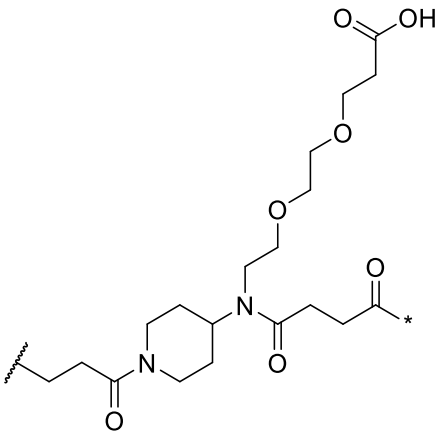
L is -(C_1-C_6 alkyl)-(V^1)-(P4A-R^{12})-(V^2)-(C_1-C_6 alkyl)-(V^3)-;

V^1, V^2, and V^3 are each independently -CO- or -NR^{11}-;

R^{11} is independently hydrogen or C_1-C_6 alkyl; and

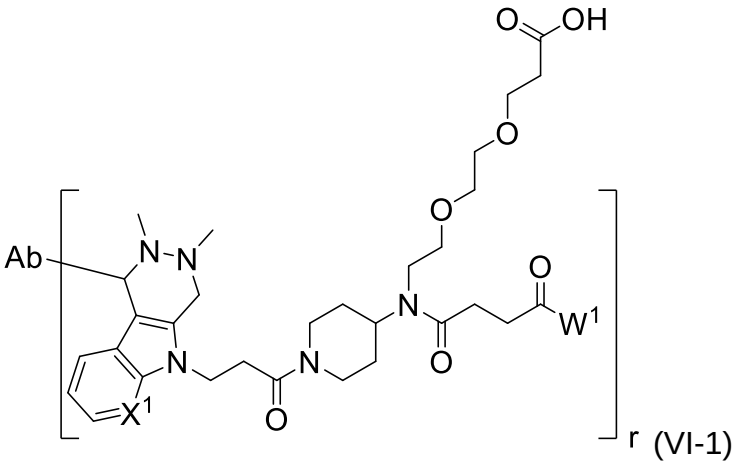
R^{12} is a carboxylic acid-modified polyethylene glycol moiety.

[0017] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), or (VI), wherein L is:



wherein ~~~ represents the point of attachment to the nitrogen of the pyridazine-pyrrolo coupling moiety and * represents the point of attachment to W^1.

[0018] In some examples, a 5T4-ADC can be represented by Formula (VI-1):



(VI-1)

wherein:

Ab represents the antibody that binds to 5T4;

r is an integer from 1 to 10;

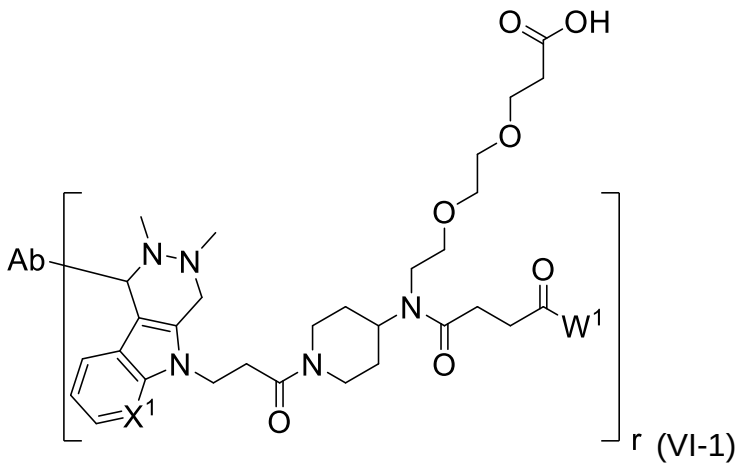
X^1 is C or N; and

W^1 is the drug.

[0018a] In another aspect, the present disclosure provides an antibody-drug conjugate (ADC) of Formula (VI-1) comprising:

a. an antibody that binds to 5T4; and

b. one or more drugs conjugated to one or more pyridazine-pyrrolo coupling moieties via a linker



(VI-1)

wherein:

Ab represents the antibody that binds to 5T4;
r is an integer from 1 to 10;
X^1 is C or N; and
W^1 is the drug.

[0019] In some examples, a 5T4-ADC can be represented by Formula (VI-1), wherein the drug is a maytansinoid or an auristatin, such as MMAE. In some examples, a 5T4-ADC can be represented by Formula (VI-1), wherein X^1 is C and W^1 is maytansine or deacylated maytansine. In some examples, a 5T4-ADC can be represented by Formula (VI-1), wherein X^1 is N and W^1 is MMAE.

[0020] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), or (VI), wherein:

L is (C_1-C_6 alkyl)-V^1-(AA)-V^2-$(PEG)_n$-V^3-$((AA)_p$-(PABC-R^{16}))-V^4-(C_1-C_6 alkyl)-V^5;

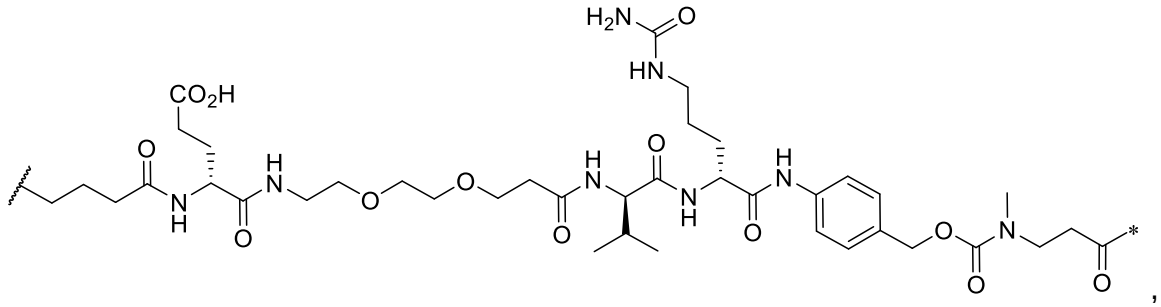
V^1, V^2, V^3, V^4 and V^5 are each independently selected from the group consisting of -CO- and -NR^{11}-;

R^{11} is independently hydrogen or C_1-C_6 alkyl;

R^{16} is hydrogen; and

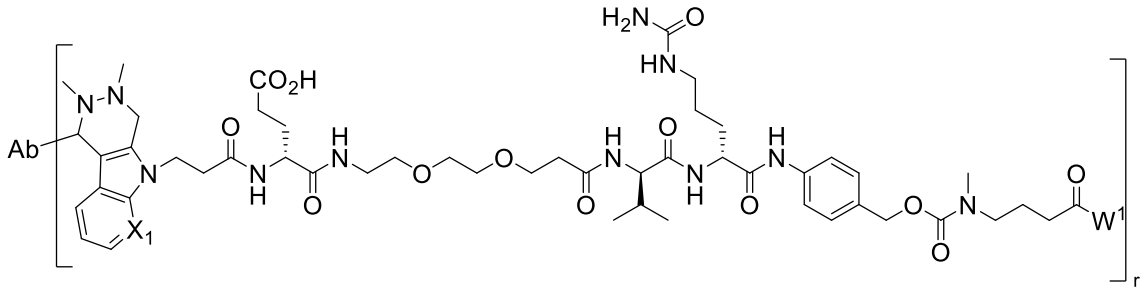
n and p are each independently an integer from 1 to 20;

[0021] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), or (VI), wherein L is:



wherein ~~~ represents the point of attachment to the nitrogen of the pyridazine-pyrrolo coupling moiety; and * represents the point of attachment to W^1.

[0022] In some examples, a 5T4-ADC can be represented by Formula (VI-2):



(VI-2)

wherein:

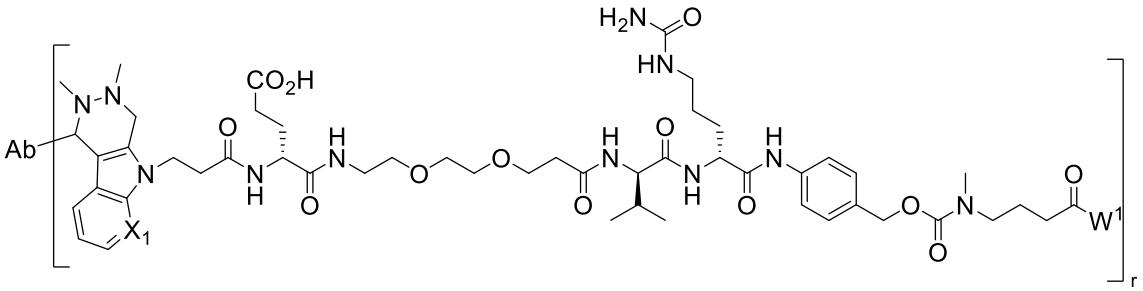
Ab represents the antibody that binds to 5T4;

r is an integer from 1 to 10;

X^1 is C or N; and

W^1 is the drug.

[0022a] In another aspect, the present disclosure provides an antibody-drug conjugate (ADC) comprising an antibody that binds to 5T4 conjugated to one or more drugs via one or more pyridazine-pyrrolo coupling moieties, as represented by Formula (VI-2):



(VI-2)

wherein:

Ab represents the antibody that binds to 5T4;

r is an integer from 1 to 10;

X^1 is C or N; and

W^1 is the drug.

[0023] In some examples, a 5T4-ADC can be represented by Formula (VI-2), wherein the drug is a maytansinoid or an auristatin, such as MMAE. In some examples, a 5T4-ADC can be represented by Formula (VI-2) wherein X^1 is C and W^1 is maytansine or deacylated maytansine.

thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

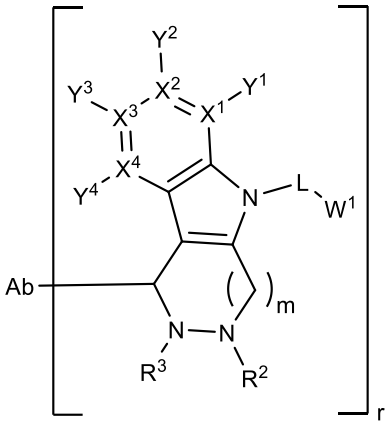
R^{13} is independently hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl; and

R^{15} is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carboxyl, carboxyl ester, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[0024a] In another aspect, the present disclosure provides an antibody-drug conjugate (ADC) of Formula (IV) comprising:

a. an antibody that binds to 5T4; and

b. one or more drugs conjugated to one or me pyridazine-pyrrolo coupling moieties via a linker



(IV)

wherein:

Ab represents the antibody that binds to 5T4;

W^1 is the drug;

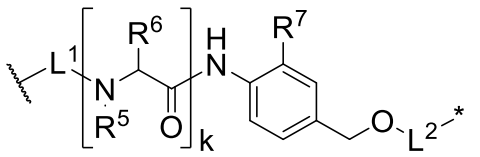
r is an integer from 1 to 10;

m is 0 or 1;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; or R^2 and R^3 are cyclically linked to form a 5- or 6-membered heterocyclyl;

X^1, X^2, X^3, and X^4 are each independently selected from the group consisting of C, N, O and S;

Y^1, Y^2, Y^3, and Y^4 are each independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; or Y^1 and Y^2, Y^2 and Y^3, or Y^3 and Y^4 are cyclically linked;

L is 

,

wherein:

~~~ represents attachment to the nitrogen of the pyridazine-pyrrolo coupling moiety;

* represents attachment to W^1;

each R^5 is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;
~~~

each R^6 is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl;

R^7 is a cleavable moiety;

k is an integer from 1 to 10;

L^1 comprises $-(T^1\text{-}V^1)_a\text{-}(T^2\text{-}V^2)_b\text{-}(T^3\text{-}V^3)_c\text{-}(T^4\text{-}V^4)_d\text{-}$;

L^2 comprises $-(T^5\text{-}V^5)_e\text{-}(T^6\text{-}V^6)_f\text{-}(T^7\text{-}V^7)_g\text{-}(T^8\text{-}V^8)_h\text{-}$;

each of a, b, c, d, e, f, g, and h are independently 1 or 0;

T^1, T^2, T^3 T^4, T^5, T^6, T^7, and T^8 are each independently selected from the group consisting of a covalent bond, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_m\text{-}$, P4A-R^{12}, acetal, a hydrazine, a disulfide, and an ester;

each w is an integer from 1 to 20;

each n is an integer from 1 to 30;

each p is an integer from 1 to 20;

each m is an integer from 1 to 12;

V^1, V^2, V^3, V^4, V^5, V^6, V^7, and V^8 are each independently selected from the group consisting of a covalent bond, -CO-, $-NR^{15}\text{-}$, $-NR^{15}(CH_2)_q\text{-}$, $-NR^{15}(C_6H_4)\text{-}$, $-CONR^{15}\text{-}$, $-NR^{15}CO\text{-}$, -C(O)O-, -OC(O)-, -O-, -S-, -S(O)-, $-SO_2\text{-}$, $-SO_2NR^{15}\text{-}$, $-NR^{15}SO_2\text{-}$, and -P(O)OH-;

each q is an integer from 1 to 6;

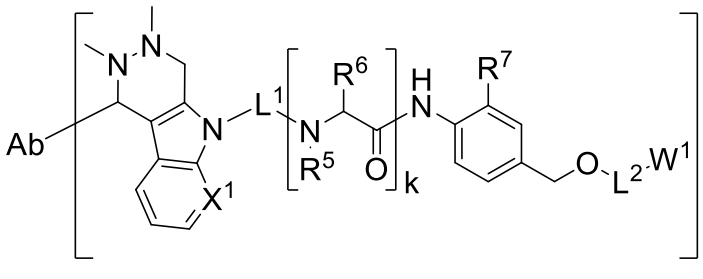
R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, a polyethylene glycol moiety, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl;

each R^{13} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl; and

each R^{15} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carboxyl, carboxyl ester, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

[0025] In some examples, a 5T4-ADC can be represented by Formula (IV) wherein R^2 and R^3 are each alkyl, for example, methyl. In some examples, a 5T4-ADC can be represented by Formula (IV) wherein each of X^1, X^2, X^3, and X^4 are independently C or N.

[0026] In some examples, a 5T4-ADC can be represented by Formula (VI-3):



(VI-3),

wherein:

Ab represents the antibody that binds to 5T4;

X^1 is C, N, O, or S;

R^5 is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

R^6 is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

R^7 is a cleavable moiety;

L^1 comprises $-(T^1\text{-}V^1)_a\text{-}(T^2\text{-}V^2)_b\text{-}(T^3\text{-}V^3)_c\text{-}(T^4\text{-}V^4)_d\text{-}$;

L^2 comprises $-(T^5\text{-}V^5)_e\text{-}(T^6\text{-}V^6)_f\text{-}(T^7\text{-}V^7)_g\text{-}(T^8\text{-}V^8)_h\text{-}$;

T^1, T^2, T^3 T^4, T^5, T^6, T^7, and T^8 are each independently a covalent bond, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted

heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_m-$, P4A-R^{12}, acetal, a hydrazine, a disulfide, or an ester;

V^1, V^2, V^3, V^4, V^5, V^6, V^7, and V^8 are each independently a covalent bond, -CO-,
$-NR^{15}-$, $-NR^{15}(CH_2)_q-$, $-NR^{15}(C_6H_4)-$, $-CONR^{15}-$, $-NR^{15}CO-$, -C(O)O-, -OC(O)-, -O-, -S-,
-S(O)-, $-SO_2-$, $-SO_2NR^{15}-$, $-NR^{15}SO_2-$, or -P(O)OH-;

a, b, c, d, e, f, g, and h are each independently 1 or 0;

k is an integer from 1 to 10;

m is independently an integer from 1 to 12;

n is independently an integer from 1 to 30;

p is independently an integer from 1 to 20;

q is independently an integer from 1 to 6;

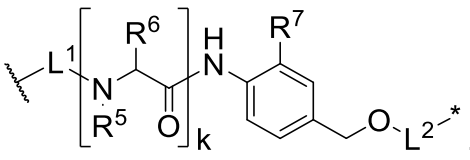
w is independently an integer from 1 to 20;

R^{12} is independently hydrogen, alkyl, substituted alkyl, a polyethylene glycol moiety, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

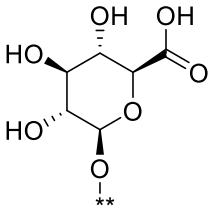
R^{13} is independently hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl; and

R^{15} is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carboxyl, carboxyl ester, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[0027] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), or (IV), wherein:

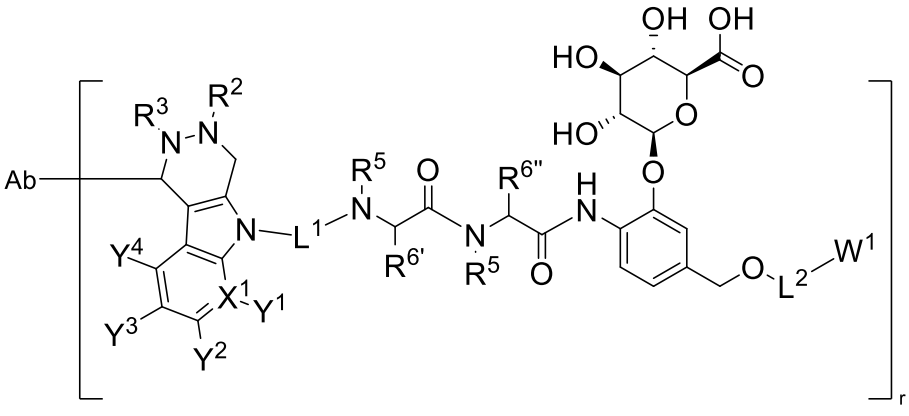
L is ;

R^5, R^6, L^1, L^2, and k are as defined herein, such as for Formula (VI-3); and



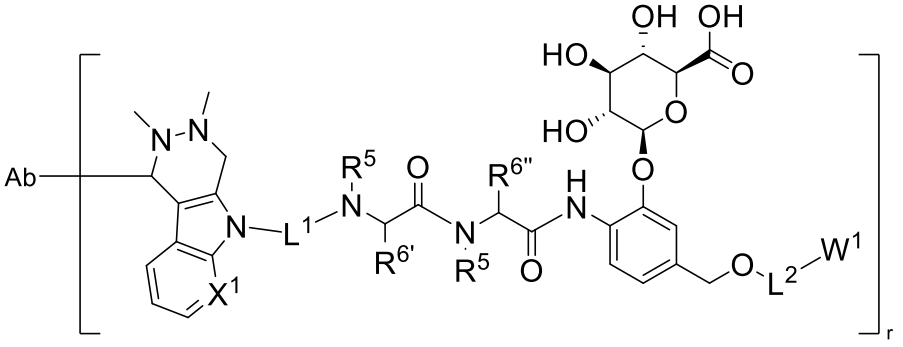
R^7 is , wherein ** represents the point of attachment to the phenyl group described herein, such as in Formula (VI-3), (V-4), or (VI-4).

[0028] In some examples, a 5T4-ADC can be represented by Formula (V-5):



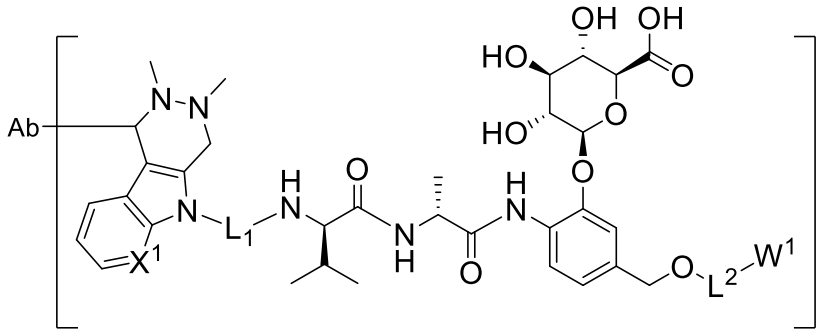
(V-5), wherein Ab, L^1, L^2, R^2, R^3, R^5, X^1, Y^1, Y^2, Y^3, Y^4, W^1, and r are as defined herein, such as for Formula (VI-3) and $R^{6'}$ and $R^{6''}$ are each independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[0029] In some examples, a 5T4-ADC can be represented by Formula (VI-5):



(VI-5), wherein Ab, L^1, L^2, R^5, W^1, and r are as defined herein, such as for Formula (VI-3) and $R^{6'}$ and $R^{6''}$ are each independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl and wherein X^1 is C or N.

[0030] In some examples, a 5T4-ADC can be represented by Formula (VI-6):



(VI-6), wherein Ab, L^1, L^2, W^1, and r are as defined herein, such as for Formula (VI-3) and wherein X^1 is C or N.

[0031] In some examples, a 5T4-ADC can be represented by Formula (VI-3), (V-5), (VI-5), or (VI-6), wherein:

L^1 comprises $-(T^1\text{-}V^1)_a\text{-}(T^2\text{-}V^2)_b\text{-}(T^3\text{-}V^3)_c\text{-}$;

T^1, T^2, and T^3 are each independently selected from the group consisting of $C_1\text{-}C_{12}$ alkyl, $(PEG)_n$, and $(AA)_p$;

V^1, V^2, and V^3 are each independently –C(=O)- or $-NR^{11}-$;

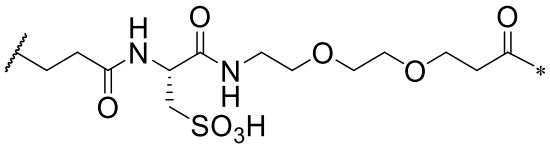
a, b, and c are each 1;

n is independently an integer from 1 to 10;

p is independently an integer from 1 to 10;

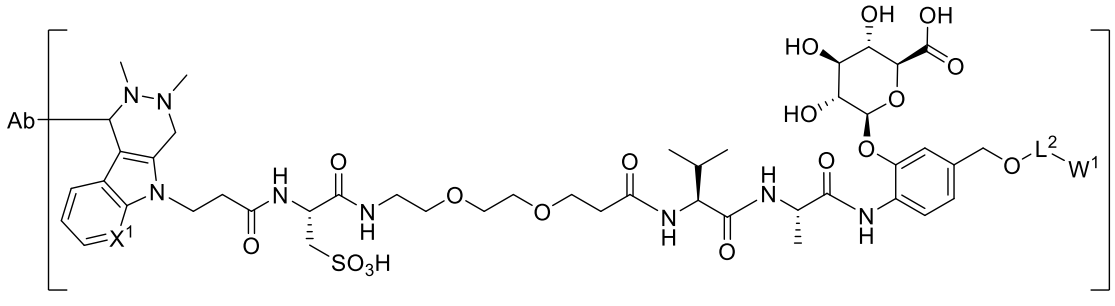
R^{11} is independently hydrogen, alkyl, substituted alkyl, a polyethylene glycol moiety, aryl, or substituted aryl.

[0032] In some examples, a 5T4-ADC can be represented by Formula (VI-3), (V-5), (VI-5), or (VI-6), wherein L^1 is



wherein ~~~ represents the point of attachment to the nitrogen of a pyridazine-pyrrolo coupling moiety, and wherein * represents the point of attachment to terminal nitrogen in the linker, as described herein, such as is shown in Formula (VI-6).

[0033] In some examples, a 5T4-ADC can be represented by Formula (VI-7):



(VI-7), wherein Ab, L^1, L^2, W^1, and r are as defined herein, such as for Formula (VI-3) and wherein X^1 is C or N.

[0034] In some examples, a 5T4-ADC can be represented by Formula (VI-7) wherein L^2 is a carbonyl group. In some examples, a 5T4-ADC can be represented by Formula (VI-7) wherein X^1 is N and W^1 is MMAE.

[0035] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises: (i) a VH CDR1, a VH CDR2, and a VH CDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO:25 and a VL CDR1, a VL CDR2, and a VL CDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO:26; (ii) a VH CDR1, a VH CDR2, and a VH CDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO:44 and a VL CDR1, a VL CDR2, and a VL CDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO:45; or (iii) a VH CDR1, a VH CDR2, and a VH CDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO:62 and a VL CDR1, a VL CDR2, and a VL CDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO:63.

[0036] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises: (a) a VH region comprising (1) a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:1, 7, 12, 13, and 18; (2) a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:2, 8, 14, 19, and 24; and (3) a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:3, 9, 15, and 20; and (b) a VL region comprising (1) a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:4, 10, 16, and 21; (2)a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:5, 11, and 22; and (3) a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:6, 17, and 23.

[0037] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises: (i) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:1, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6; or (ii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:7, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:8, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:9; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6; or (iii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6; or (iv) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:13, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:14, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:15; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:17; or (v) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:19, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:20; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:21, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:22, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:23; or (vi) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:1, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3; and a VL region

comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6.

[0038] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises: (a) a VH region comprising (1) a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:27, 31, 34, 35, and 39; (2) a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:28, 32, 36, 40, and 43; and (3) a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:29, 33, 37, and 41; and (b) a VL region comprising (1) a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:4, 10, 16, and 21; (2) a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:5, 11, and 22; and (3) a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:30, 38, and 42.

[0039] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises (i) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:27, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:28, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:29; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:30; or (ii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:32, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:33; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:30; or (iii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:28, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:29; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising

the amino acid sequence of SEQ ID NO:30; or (iv) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:38; or (v) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:40, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:41; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:21, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:22, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:42; or (vi) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:27, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:43, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:29; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:30.

[0040] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises: (a) a VH region comprising (1) a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:46, 50, 53, 13, and 57; (2) a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:47, 51, 54, 58, and 61; and (3) a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:48, 52, 55, and 59; and (b) a VL region comprising (1) a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:4, 10, 16, and 21; (2) VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:5, 11, and 22; and (3) a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:49, 56, and 60.

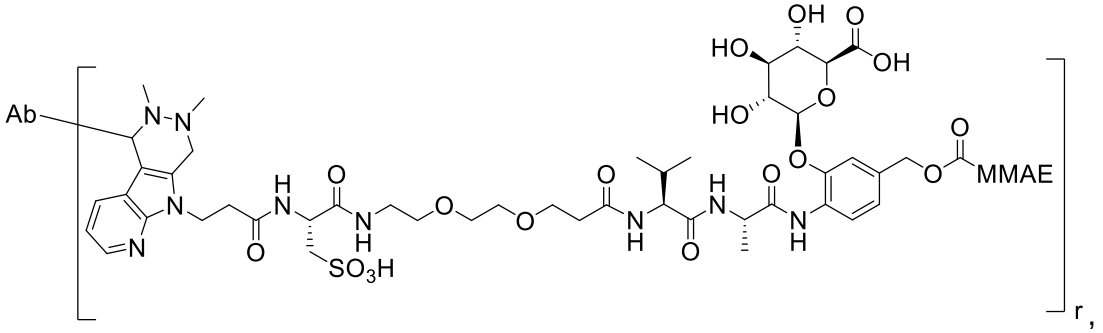
[0041] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises: (i) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VH CDR2 comprising the amino acid sequence of

[0042] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises a framework 1 (FR1), a framework 2 (FR2), a framework 3 (FR3) and/or a framework 4 (FR4) sequence as set forth in any one of SEQ ID NOs:25, 26, 44, 45, 62, and 63.

[0043] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises human framework sequences.

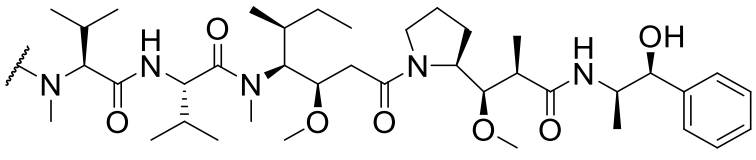
[0044] In some examples, a 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) wherein the antibody (Ab) comprises (i) a VH comprising the amino acid sequence of SEQ ID NO:25 and a VL comprising the amino acid sequence of SEQ ID NO:26; (ii) a VH comprising the amino acid sequence of SEQ ID NO:44 and a VL comprising the amino acid sequence of SEQ ID NO:45; or (iii) a VH comprising the amino acid sequence of SEQ ID NO:62 and a VL comprising the amino acid sequence of SEQ ID NO:63.

[0044a] In another aspect, the present disclosure provides an antibody-drug conjugate (ADC) of Formula (VIb-82):



wherein r is 1 or 2;

MMAE is



(W-2);

and

Ab represents the antibody that binds to 5T4, and Ab comprises:

(i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 97 and a light chain comprising the amino acid sequence of SEQ ID NO: 95, or

(ii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 93 and a light chain comprising the amino acid sequence of SEQ ID NO: 91, or

(iii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 99.

[0045] The present disclosure also provides a pharmaceutical composition comprising a 5T4-ADC, wherein the 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) and a pharmaceutically acceptable excipient, wherein the antibody (Ab) is as described in any example described herein. In another aspect, the present disclosure provides a pharmaceutical composition comprising an ADC as described herein and a pharmaceutically acceptable excipient. In some examples, such a pharmaceutical composition can have a drug-to-antibody ratio (DAR) of the 5T4-ADC of about 1 to about 10, for example, a DAR of about 1 to about 4, about 1 to about 2, about 1.5 to about 2, or about 1.75 to about 1.9.

[0046] The present disclosure also provides a method for treating a cancer or a tumor in a subject comprising administering to the subject the 5T4-ADC, wherein the 5T4-ADC can be represented by Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) or the pharmaceutical composition comprising a 5T4-ADC of Formula (IV), (V), (VI), (VI-1), (VI-2), (VI-3), (V-5), (VI-5), (VI-6), or (VI-7) and a pharmaceutically acceptable excipient, wherein the antibody (Ab) is as described in any example herein.

[0046a] In another aspect, the present disclosure provides use of the antibody-drug conjugate as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of a cancer or a tumor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0047] FIG. 1 provides an exemplary synthesis of the linker-drug of Formula VIa-21 as Scheme 1.

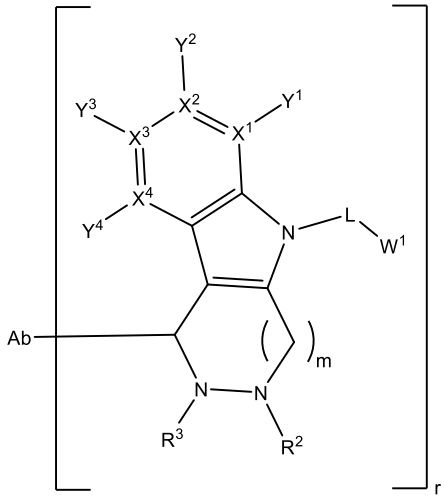
CLAIMS

What is claimed is:

1. An antibody-drug conjugate (ADC) of Formula (IV) comprising:

a. an antibody that binds to 5T4; and

b. one or more drugs conjugated to one or more pyridazine-pyrrolo coupling moieties via a linker



(IV)

wherein:

Ab represents the antibody that binds to 5T4;

r is an integer from 1 to 10;

m is 0 or 1;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; or R^2 and R^3 are cyclically linked to form a 5- or 6-membered heterocyclyl;

X^1, X^2, X^3 and X^4 are each independently selected from the group consisting of C, N, O and S;

Y^1, Y^2, Y^3 and Y^4 are each independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted

alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, or Y^1 and Y^2, Y^2 and Y^3, or Y^3 and Y^4 are cyclically linked;

W^1 is the drug;

L represents the linker and is $-(T^1V^1)_a-(T^2V^2)_b-(T^3V^3)_c-(T^4V^4)_d-(T^5V^5)_e-$, wherein:

a, b, c, d, and e are each independently 0 or 1, wherein the sum of a, b, c, d, and e is 1 to 5;

T^1, T^2, T^3, T^4, and T^5 each independently comprise C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_h-$, a piperidin-4-amine (P4A-R^{12}), a meta-aminobenzyl carbamate (MABC) group, a meta-aminobenzyloxy (MABO) group, a para-aminiobenzyloxy (PABO) group, a para-aminobenzyl carbamate (PABC) group, a para-aminobenzyl (PAB) group, acetal, a disulfide, a hydrazine, $(AA)_p$-MABC-$(AA)_p$, $(AA)_p$-MABO-$(AA)_p$, $(AA)_p$-PABO-$(AA)_p$, or $(AA)_p$-PABC-$(AA)_p$,

w is an integer from 1 to 20;

n is an integer from 1 to 30;

each p is independently zero or an integer from 1 to 20;

h is an integer from 1 to 12; and

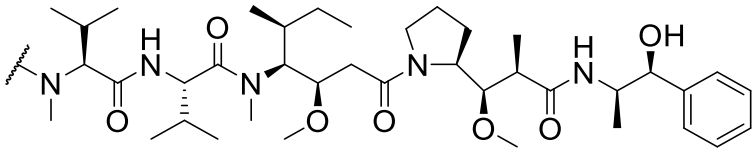
each R^{12} is hydrogen, alkyl, substituted alkyl, a polyethylene glycol moiety, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

each R^{13} is hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl;

V^1, V^2, V^3, V^4 and V^5 are each independently selected from the group consisting of a covalent bond, $-C(=O)-$, $-NR^{11}-$, $-C(=O)NR^{11}-$, $-NR^{11}C(=O)-$, $-C(=O)O-$, $-OC(=O)-$, $-O-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-SO_2NR^{11}-$, $-NR^{11}SO_2-$ and $-P(=O)OH-$, wherein R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, PEG, aryl, and substituted aryl.

2. The ADC of claim 1, wherein:

(i)W^1 is selected from the group consisting of a maytansinoid and an auristatin; optionally wherein the auristatin is MMAE which has the following structure (W-2)


(W-2),

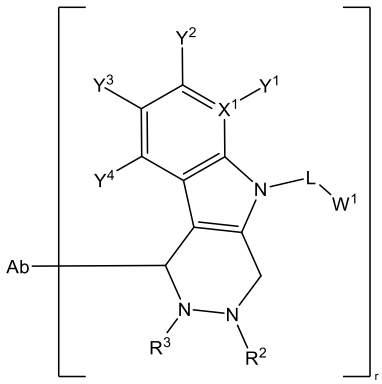
wherein ~~~ indicates the point of attachment between MMAE and the linker L;

(ii) R^2 and R^3 are each alkyl;

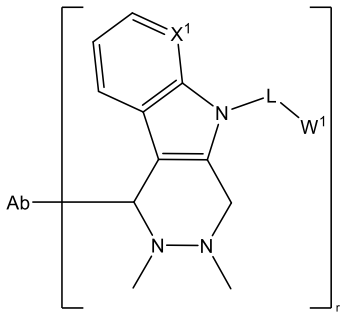
(iii) R^2 and R^3 are each methyl;

(iv) each of X^1, X^2, X^3, and X^4 are independently selected from C and N;

(v) the ADC is represented by Formula (V):


(V);

(vi) the ADC is represented by Formula (VI):


(VI),

wherein X^1 is C or N;

(vii) T^1, T^2, T^3, T^4, and T^5 are each independently selected from the group consisting of C_1-C_6 alkyl, P4A-R^{12}, $(AA)_p$, $(AA)_p$-PABC, and $(PEG)_n$, wherein p is an integer from 1 to 5, and R^{12} is a polyethylene glycol or carboxylic acid-modified polyethylene glycol;

(viii) T^1 is C_1-C_6 alkyl;

T^2, T^3, T^4 and T^5 are each independently selected from $(PEG)_n$, C_1-C_6 alkyl, $(AA)_p$, P4A-R^{12}, $(AA)_p$-(PABO-R^{16})-$(AA)_p$, $(AA)_p$-(PABC-R^{16})-$(AA)_p$, $(AA)_p$-(PABO-R^{16}),

and $(AA)_p$-(PABC-R^{16}), wherein R^{12} is a carboxylic acid-modified polyethylene glycol and R^{16} is hydrogen; and

V^1, V^2, V^3, V^4 and V^5 are each independently selected from -CO- and -NR^{11}-, wherein R^{11} is selected from hydrogen and alkyl;

(ix) L is:

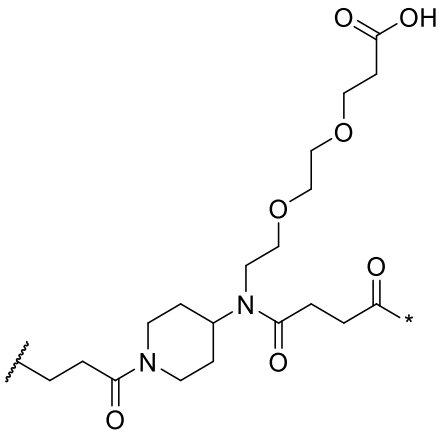
-(C_1-C_6 alkyl)-(V^1)-(P4A-R^{12})-(V^2)-(C_1-C_6 alkyl)-(V^3)-,
wherein:

V^1, V^2, and V^3 are each independently selected from the group consisting of -CO- and -NR^{11}-;

each R^{11} is independently selected from group consisting of hydrogen and C_1-C_6 alkyl; and

R^{12} is a carboxylic acid-modified polyethylene glycol moiety; and/or

(x) L is:



wherein:

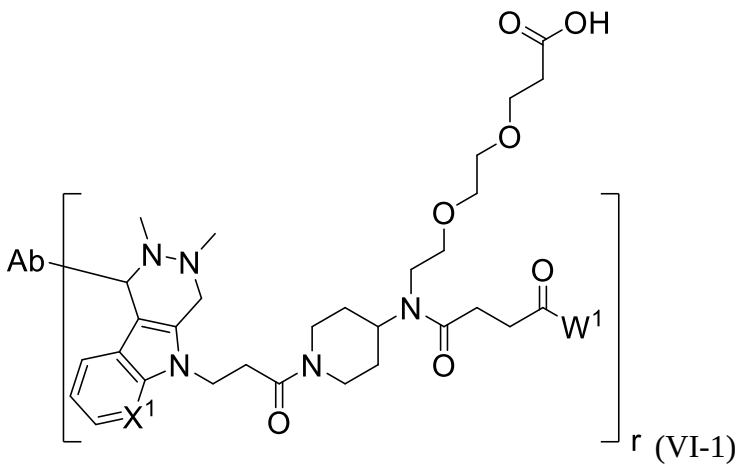
〰 represents attachment to the nitrogen of the pyridazine-pyrrolo coupling moiety; and

* represents attachment to W^1.

3. An antibody-drug conjugate (ADC) of Formula (VI-1) comprising:

a. an antibody that binds to 5T4; and

b. one or more drugs conjugated to one or more pyridazine-pyrrolo coupling moieties via a linker



(VI-1)

wherein:

Ab represents the antibody that binds to 5T4;

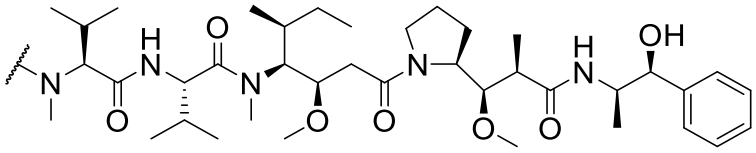
r is an integer from 1 to 10;

X^1 is C or N; and

W^1 is the drug.

4. The ADC of claim 3, wherein:

(i) W^1 is selected from the group consisting of a maytansinoid and an auristatin; optionally wherein the auristatin is MMAE which has the following structure (W-2)



(W-2),

wherein ~~~ indicates the point of attachment between MMAE and the linker L;

(ii) X^1 is C and W^1 is deacyclated maytansine;

(iii) X^1 is N and W^1 is MMAE;

(iv) L is:

$(C_1\text{-}C_6$ alkyl)-V^1-(AA)-V^2-$(PEG)_n$-V^3-$((AA)_p$-(PABC-R^{16}))-V^4-($C_1\text{-}C_6$ alkyl)-V^5,

wherein:

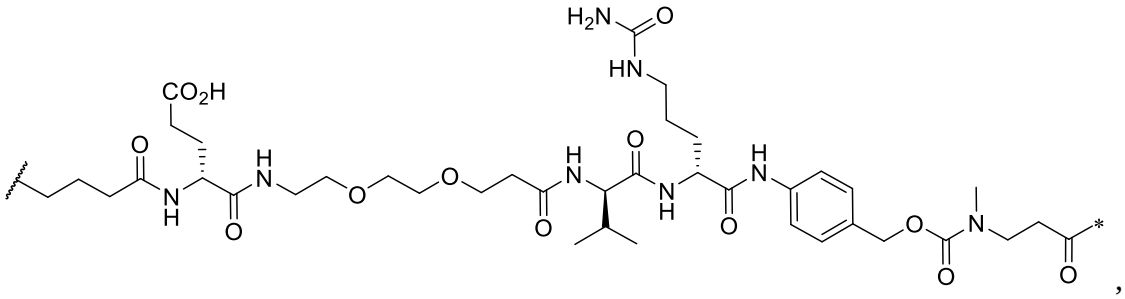
R^{16} is hydrogen;

n and p are each independently an integer from 1 to 20;

V^1, V^2, V^3, V^4 and V^5 are each independently selected from the group consisting of -CO- and -NR^{11}-; and

each R^{11} is independently selected from the group consisting of hydrogen and $C_1\text{-}C_6$ alkyl; and/or

(v) L is:

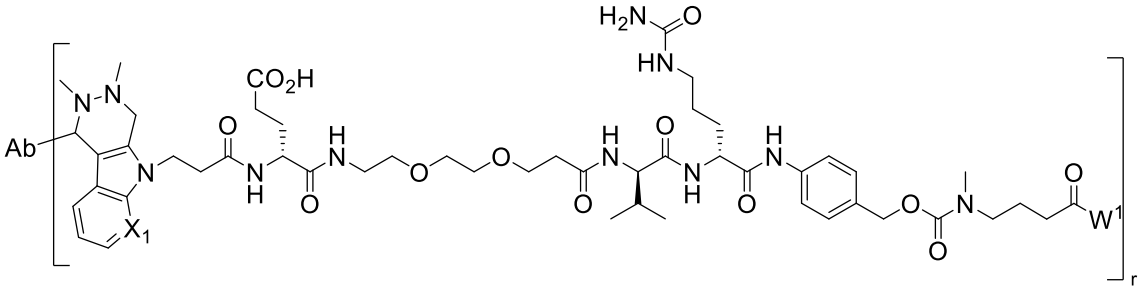


wherein:

〰 represents attachment to the nitrogen of the pyridazine-pyrrolo coupling moiety; and

* represents attachment to W^1.

5. An antibody-drug conjugate (ADC) comprising an antibody that binds to 5T4 conjugated to one or more drugs via one or more pyridazine-pyrrolo coupling moieties, as represented by Formula (VI-2):



(VI-2)

wherein:

Ab represents the antibody that binds to 5T4;

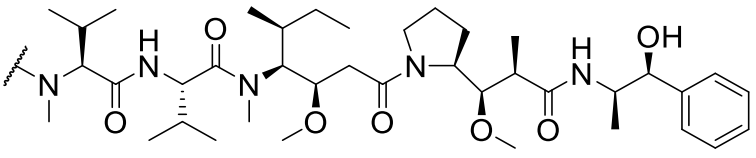
r is an integer from 1 to 10;

X^1 is C or N; and

W^1 is the drug.

6. The ADC of claim 5, wherein:

(i) W^1 is selected from a maytansinoid and an auristatin, optionally wherein the auristatin is MMAE which has the following structure (W-2)



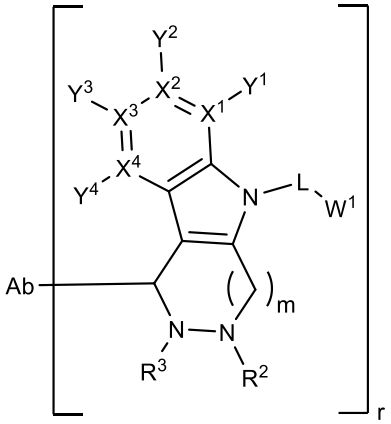
(W-2); and/or

(ii) X^1 is C and W^1 is deacyclated maytansine.

7. An antibody-drug conjugate (ADC) of Formula (IV) comprising:

a. an antibody that binds to 5T4; and

b. one or more drugs conjugated to one or me pyridazine-pyrrolo coupling moieties via a linker



(IV)

wherein:

Ab represents the antibody that binds to 5T4;

W^1 is the drug;

r is an integer from 1 to 10;

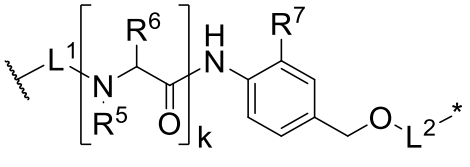
m is 0 or 1;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; or R^2 and R^3 are cyclically linked to form a 5- or 6-membered heterocyclyl;

X^1, X^2, X^3, and X^4 are each independently selected from the group consisting of C, N, O and S;

Y^1, Y^2, Y^3, and Y^4 are each independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted

alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl; or Y^1 and Y^2, Y^2 and Y^3, or Y^3 and Y^4 are cyclically linked;

L is ,

wherein:

〰 represents attachment to the nitrogen of the pyridazine-pyrrolo coupling moiety;

* represents attachment to W^1;

each R^5 is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

each R^6 is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl;

R^7 is a cleavable moiety;

k is an integer from 1 to 10;

L^1 comprises $-(T^1\text{-}V^1)_a\text{-}(T^2\text{-}V^2)_b\text{-}(T^3\text{-}V^3)_c\text{-}(T^4\text{-}V^4)_d\text{-}$;

L^2 comprises $-(T^5\text{-}V^5)_e\text{-}(T^6\text{-}V^6)_f\text{-}(T^7\text{-}V^7)_g\text{-}(T^8\text{-}V^8)_h\text{-}$;

each of a, b, c, d, e, f, g, and h are independently 1 or 0;

T^1, T^2, T^3 T^4, T^5, T^6, T^7, and T^8 are each independently selected from the group consisting of a covalent bond, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_m\text{-}$, P4A-R^{12}, acetal, a hydrazine, a disulfide, and an ester;

each w is an integer from 1 to 20;

each n is an integer from 1 to 30;

each p is an integer from 1 to 20;

each m is an integer from 1 to 12;

V^1, V^2, V^3, V^4, V^5, V^6, V^7, and V^8 are each independently selected from the group consisting of a covalent bond, -CO-, -NR^{15}-, -$NR^{15}(CH_2)_q$-, -$NR^{15}(C_6H_4)$-, -$CONR^{15}$-, -$NR^{15}CO$-, -C(O)O-, -OC(O)-, -O-, -S-, -S(O)-, -SO_2-, -SO_2NR^{15}-, -$NR^{15}SO_2$-, and -P(O)OH-;

each q is an integer from 1 to 6;

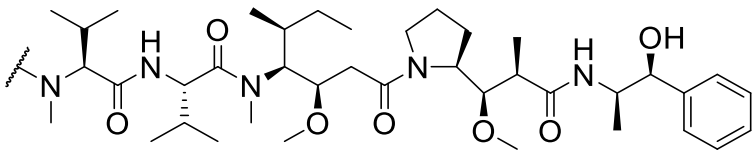
R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, a polyethylene glycol moiety, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, amino, substituted amino, carboxyl, carboxyl ester, acyl, acyloxy, acyl amino, amino acyl, alkylamide, substituted alkylamide, sulfonyl, thioalkoxy, substituted thioalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl;

each R^{13} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl; and

each R^{15} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carboxyl, carboxyl ester, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

8. The ADC of claim 77, wherein:

(i) W^1 is selected from a maytansinoid and an auristatin, optionally wherein the auristatin is MMAE which has the following structure (W-2)



(W-2);

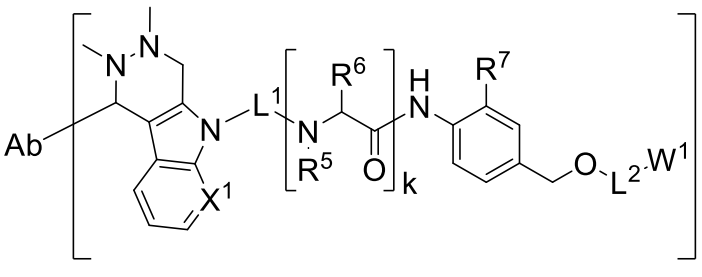
(ii) R^2 and R^3 are each alkyl;

(iii) R^2 and R^3 are each methyl; and/or

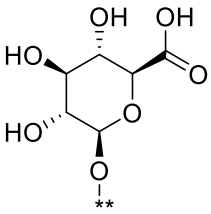
(iv) each of X^1, X^2, X^3, and X^4 are independently selected from C and N.

9. The ADC of claim 7 or 8, represented by:

(i) Formula (VI-3):

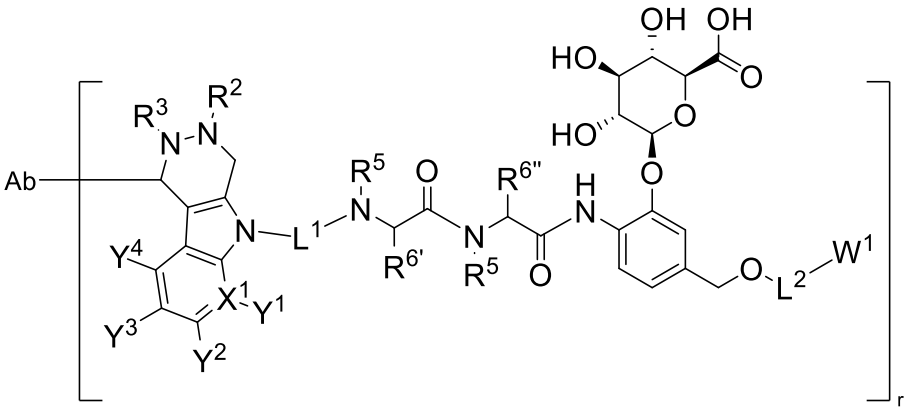


(VI-3),



optionally wherein R^7 is , wherein** represents the point of attachment to the phenyl group in Formula (VI-3);

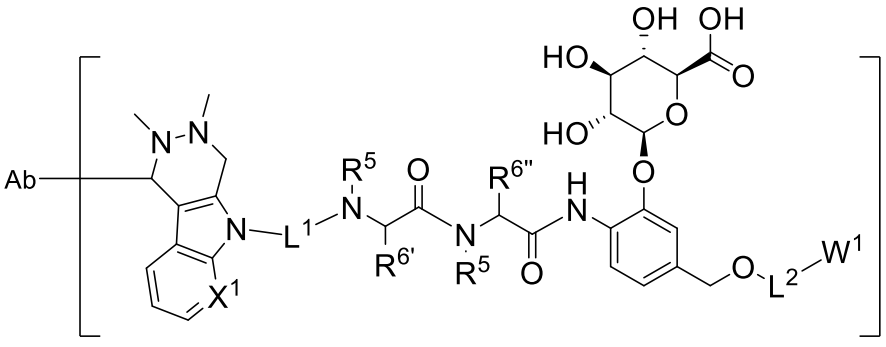
(ii) Formula (V-5):



(V-5),

wherein $R^{6'}$ and $R^{6''}$ are each independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

(iii) Formula (VI-5):

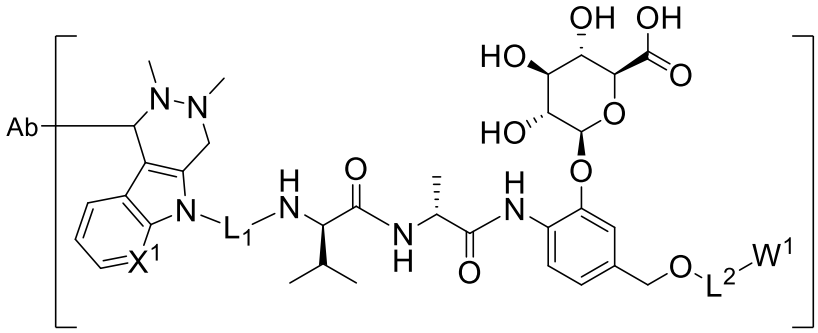


(VI-5),

wherein X^1 is C or N, wherein $R^{6'}$ and $R^{6''}$ are each independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl,

heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl; and/or

(iv) Formula (VI-6):



(VI-6).

10. The ADC of any one of claims 7-9, wherein

(i) L^1 comprises $-(T^1-V^1)_a-(T^2-V^2)_b-(T^3-V^3)_c-(T^4-V^4)_d-$;

a, b, and c are each 1;

d is 0 and therefore T^4 and V^4 are absent;

T^1, T^2, and T^3 are each independently selected from the group consisting of C_1-C_{12} alkyl, $(PEG)_n$, and $(AA)_p$,

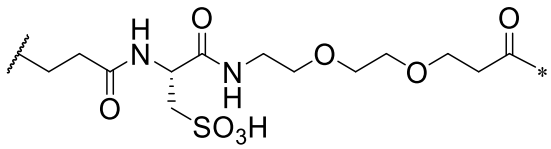
n is an integer from 1 to 10;

p is an integer from 1-10;

V^1, V^2, and V^3 are each independently selected from the group consisting of –C(=O)- and $-NR^{11}-$; and

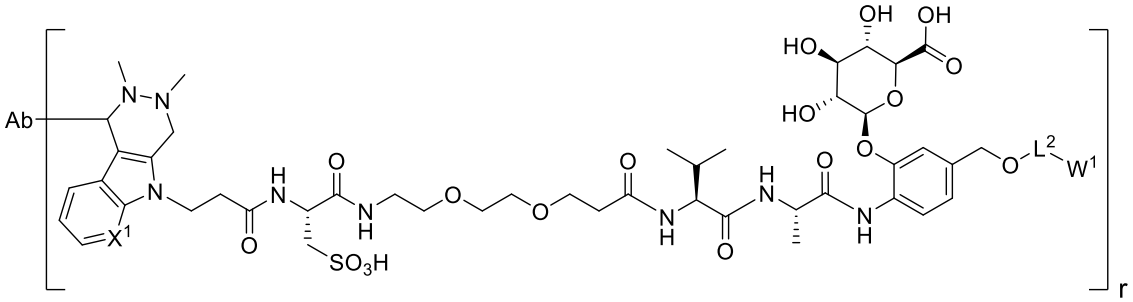
R^{11} is selected from hydrogen, alkyl, substituted alkyl, a polyethylene glycol moiety, aryl, and substituted aryl;

(ii) L^1 is



, wherein 〰 represents the point of attachment to the nitrogen of a pyridazine-pyrrolo coupling moiety and wherein * represents a point of attachment in any direction to a remaining portion of the linker;

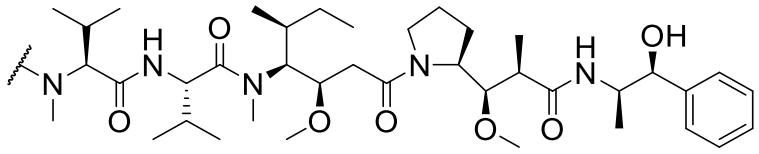
(iii) the ADC is represented by Formula (VI-7):



(VI-7), wherein X^1 is C or N;

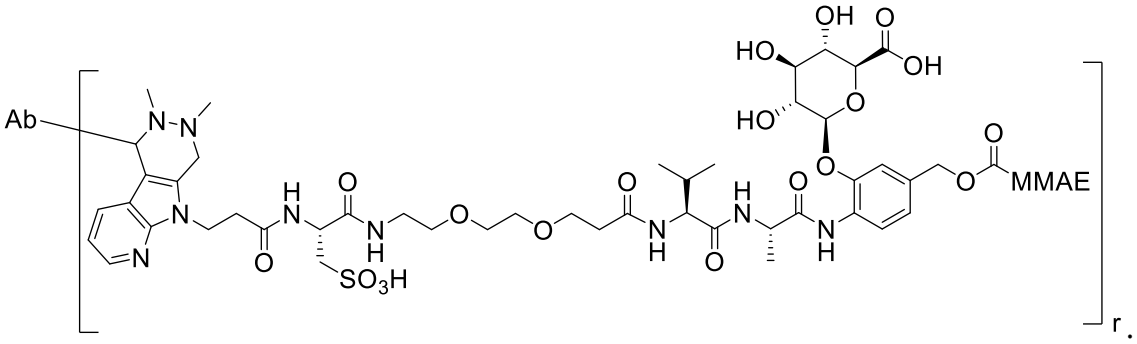
(iv) L^2 is a carbonyl group;

(v) X^1 is N and W^1 is MMAE which has the following structure (W-2)



(W-2); and/or

(vi) the ADC is represented by Formula (VIb-82):



11. The ADC of any one of claims 1-10, wherein the antibody comprises:

(i) a VH CDR1, a VH CDR2, and a VH CDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO:44 and a VL CDR1, a VL CDR2, and a VL CDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO:45;

(ii) (a) a VH region comprising:

(1) a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:27, 31, 34, 35, and 39;

(2) a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:28, 32, 36, 40, and 43; and

(3) a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:29, 33, 37, and 41; and

(b) a VL region comprising:

(1) a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:4, 10, 16, and 21;

(2) a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:5, 11, and 22; and

(3) a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:30, 38, and 42;

(iii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:27, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:28, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:29; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:30;

(iv) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:32, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:33; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:30;

(v) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:28, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:29; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:30;

(vi) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:38;

(vii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:40, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:41; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:21, a VL CDR2

comprising the amino acid sequence of SEQ ID NO:22, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:42;

(viii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:27, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:43, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:29; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:30;

(ix) a VH comprising the amino acid sequence of SEQ ID NO:44 and a VL comprising the amino acid sequence of SEQ ID NO:45; and/or

(x) a heavy chain comprising the amino acid sequence of SEQ ID NO: 97 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

12. The ADC of any one of claims 1-10, wherein the antibody comprises:

(i) a VH CDR1, a VH CDR2, and a VH CDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO:25 and a VL CDR1, a VL CDR2, and a VL CDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO:26;

(ii) (a) a VH region comprising:

(1) a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:1, 7, 12, 13, and 18.

(2) a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:2, 8, 14, 19, and 24; and

(3) a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:3, 9, 15, and 20;

and

(b) a VL region comprising:

(1) a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:4, 10, 16, and 21;

(2) a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:5, 11, and 22; and

(3) a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:6, 17, and 23;

(iii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:1, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2, and a VH

CDR3 comprising the amino acid sequence of SEQ ID NO:3; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6;

(iv) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:7, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:8, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:9; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6;

(v) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6;

(vi) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:13, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:14, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:15; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:17;

(vii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:19, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:20; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:21, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:22, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:23;

(viii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:1, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6;

(ix) a VH comprising the amino acid sequence of SEQ ID NO:25 and a VL comprising the amino acid sequence of SEQ ID NO:26; and/or

(x) a heavy chain comprising the amino acid sequence of SEQ ID NO: 93 and a light chain comprising the amino acid sequence of SEQ ID NO: 91.

13. The ADC of any one of claims 1-10, wherein the antibody comprises:

(i) a VH CDR1, a VH CDR2, and a VH CDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO:62 and a VL CDR1, a VL CDR2, and a VL CDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO:63;

(ii) (a) a VH region comprising:

(1) a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:46, 50, 53, 13, and 57;

(2) a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:47, 51, 54, 58, and 61; and

(3) a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:48, 52, 55, and 59; and

(b) a VL region comprising:

(1) a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs:4, 10, 16, and 21;

(2) a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs:5, 11, and 22; and

(3) a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs:49, 56, and 60;

(iii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:48; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:49;

(iv) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:50, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:51, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:52; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2

comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:49;

(v) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:53, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:48; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:49;

(vi) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:13, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:54, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:55; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:56;

(vii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:57, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:58, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:59; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:21, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:22, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:60;

(viii) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:61, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:48; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:49;

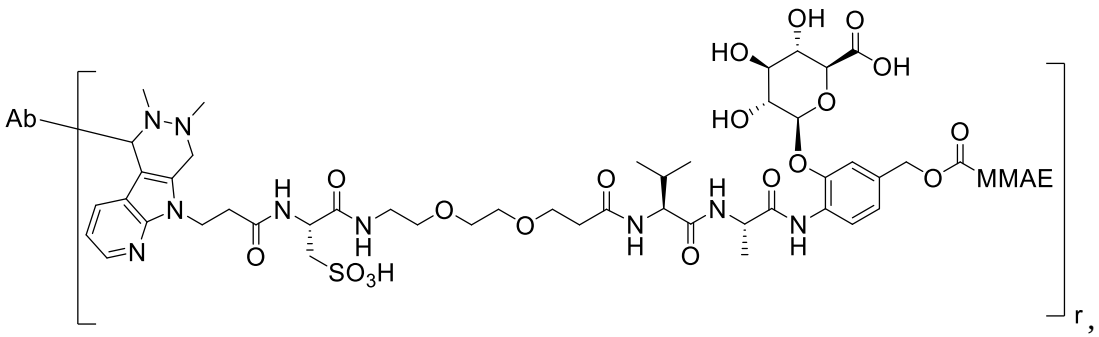
(ix) a VH comprising the amino acid sequence of SEQ ID NO:62 and a VL comprising the amino acid sequence of SEQ ID NO:63; and/or

(x) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 99.

14. The ADC of any one of claims 1-13, wherein the antibody further comprises a framework 1 (FR1), a framework 2 (FR2), a framework 3 (FR3) and/or a framework 4 (FR4) sequence as set forth in any one of SEQ ID NOs:25, 26, 44, 45, 62, and 63.

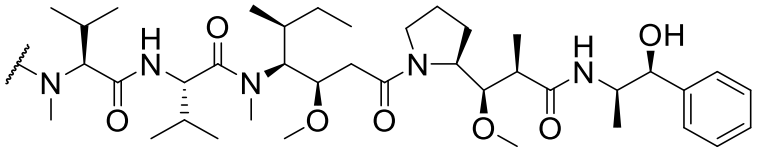
15. The ADC of any one of claims 1-14, wherein the antibody further comprises human framework sequences.

16. An antibody-drug conjugate (ADC) of Formula (VIb-82):



wherein r is 1 or 2;

MMAE is



(W-2);

and

Ab represents the antibody that binds to 5T4, and Ab comprises:

(i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 97 and a light chain comprising the amino acid sequence of SEQ ID NO: 95, or

(ii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 93 and a light chain comprising the amino acid sequence of SEQ ID NO: 91, or

(iii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 99.

17. A pharmaceutical composition comprising an ADC of any one of claims 1-16 and a pharmaceutically acceptable excipient.

18. The pharmaceutical composition of claim 17, wherein the drug-to-antibody ratio of the antibody-drug conjugate is about 1 to about 2.

19. The pharmaceutical composition of claim 18, wherein the drug-to-antibody ratio is about 2.

20. Use of the antibody-drug conjugate of any one of claims 1-16 or the pharmaceutical composition of any one of claims 17-19 in the manufacture of a medicament for the treatment of a cancer or a tumor.