bioorthogonal functional group that has been intentionally introduced into the protein. As an example of the latter approach, the Hydrazino-*iso*-Pictet-Spengler (HIPS) conjugation method (**FIG. 1**) takes an advantage of an aldehyde functional group (an "aldehyde tag"), which can be introduced into a protein, such as an antibody, through various means (*e.g.*, by the action of formyl generating enzyme (FGE)), serving as the conjugation handle. The aldehyde group cleanly reacts with the HIPS indole moiety to form a stable carbon-carbon bond that permanently attaches the payload of choice to the protein in a single chemical step.

[0006] There remains a need in the art for ADCs that can target TF to treat, prevent, or alleviate TF-mediated diseases, disorders, or conditions, such as those involving tumor cells expressing TF.

SUMMARY

[0007] The present disclosure provides ADCs comprising an antibody that binds to tissue factor ("TF-ADC"). Such TF-ADCs, in some examples, bind to the same epitope of human TF as an antibody comprising a heavy chain variable region (VH) and a light chain variable region (VL) described herein.

[0008] The present disclosure also provides pharmaceutical compositions comprising a TF-ADC that comprises an antibody or fragment thereof that binds to TF ("TF antibody") and a drug conjugated (directly or indirectly) thereto. Such pharmaceutical compositions, in some examples, include TF-ADCs comprising an antibody or fragment thereof that binds to essentially the same epitope of human TF as an antibody comprising a VH and a VL described herein.

[0009] The present disclosure also provides methods of treating, preventing, or alleviating a TF-mediated disease, disorder, or condition, such as alleviating one or more symptoms of the TF-mediated disease, disorder, or condition with a TF-ADC.

[0010] More specifically, the present disclosure provides a TF-ADC comprising (a) a TF antibody and (b) one or more pyridazine-pyrrolo coupling moieties comprising a drug conjugated to the pyridazine-pyrrolo coupling moiety through a linker, for example, using the Hydrazino-*iso*-Pictet-Spengler (HIPS) conjugation method.

[0011] Traditionally, the HIPS conjugation method has been used to produce conjugates carrying one payload per HIPS moiety per aldehyde tag, which produces antibody conjugates with DAR values of up to 4. In some examples, a TF-ADC as disclosed herein comprises branched HIPS linkers that carry two (or more) molecules of the same or different payload per one HIPS moiety and are therefore capable of conjugating two (or more) small molecule payloads per one aldehyde group in a protein in a single conjugation step (**FIG. 2**).

Consequently, the usage of such branched linkers allows the generation of higher DAR site-specific conjugates (*e.g.*, DAR up to 8) with controlled payload placement, which in the context of therapeutic ADCs would result in larger quantities of pharmaceutical agent delivered to the targeted tissue.

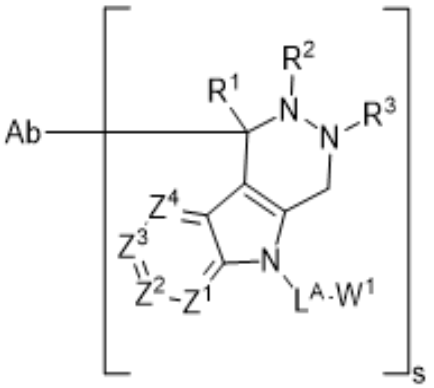
[0012] The present disclosure provides TF-ADC structures, which comprises (a) a TF antibody, (b) a branched HIPS linker, and (c) a drug. The disclosure also encompasses compounds and methods for production of such conjugates, as well as methods of using the conjugates.

[0013] Examples of the present disclosure include a TF-ADC comprising (a) a TF antibody; and (b) one or more pyridazine-pyrrolo coupling moieties comprising one or more drugs conjugated to the pyridazine-pyrrolo coupling moiety via one or more linkers.

[0014] In one aspect, the present disclosure provides for an antibody-drug conjugate (ADC) of Formula (I) comprising:

a. an antibody that binds to tissue factor (TF); and

b. two or more drugs conjugated to a pyridazine-pyrrolo coupling moiety, each via a linker



(I)

wherein:

Ab represents the antibody that binds to TF;

Z^1, Z^2, and Z^4 are each independently CR^4;

Z^3 is $C\text{-}L^B\text{-}W^2$;

R^1, R^2, R^3, and R^4 are each selected from hydrogen and alkyl;

L^A is a first linker comprising:

$$-(T^1\text{-}V^1)_a\text{-}(T^2\text{-}V^2)_b\text{-}(T^3\text{-}V^3)_c\text{-}(T^4\text{-}V^4)_d\text{-}(T^5\text{-}V^5)_e\text{-}(T^6\text{-}V^6)_f\text{-},$$

wherein:

a, b, c, d, e and f are each independently 0 or 1, provided at least one of a, b, c, d, e, and f are 1;

T^1, T^2, T^3, T^4, T^5 and T^6 are each independently selected from 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, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_x-$, 4-amino-piperidine (4AP), meta-amino-benzyloxy (MABO), meta-amino-benzyloxycarbonyl (MABC), para-amino-benzyloxy (PABO), para-amino-benzyloxycarbonyl (PABC), para-aminobenzyl (PAB), para-amino-benzylamino (PABA), para-amino-phenyl (PAP), para-hydroxy-phenyl (PHP), an acetal group, a hydrazine, a disulfide, and an ester, wherein EDA is an ethylene diamine moiety, PEG is a polyethylene glycol, and AA is an amino acid residue or an amino acid analog, wherein 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, and each x is an integer from 1 to 12;

V^1, V^2, V^3, V^4 ,V^5 and V^6 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-, wherein each q is an integer from 1 to 6;

each R^{13} is independently selected from hydrogen, an alkyl, a substituted alkyl, an aryl, and a substituted aryl; and

each R^{15} is independently selected from 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;

L^B is a second linker comprising:

$$-(T^7\text{-}V^7)_g-(T^8\text{-}V^8)_h-(T^9\text{-}V^9)_i-(T^{10}\text{-}V^{10})_j-(T^{11}\text{-}V^{11})_k-(T^{12}\text{-}V^{12})_l-(T^{13}\text{-}V^{13})_m-,$$

wherein:

g, h, i, j, k, 1 and m are each independently 0 or 1, provided that at least one of g, h, i, j, k, l, and m is 1;

T^7, T^8, T^9, T^{10}, T^{11}, T^{12} and T^{13} are each independently selected from a covalent bond, $(C_1\text{-}C_{12})$alkyl, substituted $(C_1\text{-}C_{12})$alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_x-$, 4-amino-piperidine (4AP), meta-amino-benzyloxy (MABO), meta-amino-benzyloxycarbonyl (MABC), para-amino-benzyloxy (PABO), para-amino-benzyloxycarbonyl (PABC), para-aminobenzyl (PAB), para-amino-benzylamino (PABA), para-amino-phenyl (PAP), para-hydroxy-phenyl (PHP), an acetal group, a hydrazine, a disulfide, and an ester, wherein EDA is an ethylene diamine moiety, PEG is a polyethylene glycol, and AA is an amino acid residue or an amino acid analog, wherein 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, and each x is an integer from 1 to 12;

V^7, V^8, V^9, V^{10} ,V^{11}, V^{12} and V^{13} 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-, wherein each q is an integer from 1 to 6;

each R^{13} is independently selected from hydrogen, an alkyl, a substituted alkyl, an aryl, and a substituted aryl; and

each R^{15} is independently selected from 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;

s is an integer from 1 to 10;

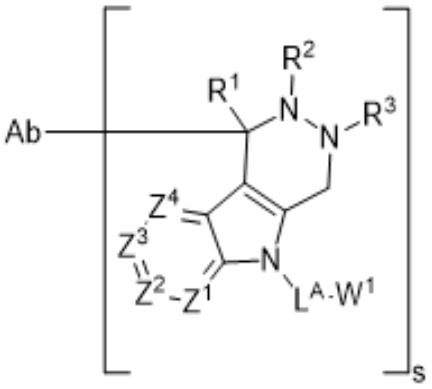
W^1 is a first drug; and

W^2 is a second drug.

[0014a] In some examples, a TF-ADC is represented by Formula (I), the TF-ADC comprising:

a. an antibody that binds to tissue factor (TF); and

b. two or more drugs conjugated to a pyridazine-pyrrolo coupling moiety, each via a linker



(I)

wherein:

Ab represents the antibody that binds to TF;

Z^1, Z^2, and Z^4 are each independently CR^4;

Z^3 is $C\text{-}L^B\text{-}W^2$;

R^1, R^2, R^3, and R^4 are each selected from hydrogen and alkyl;

L^A is a first linker comprising:

$$-(T^1\text{-}V^1)_a\text{-}(T^2\text{-}V^2)_b\text{-}(T^3\text{-}V^3)_c\text{-}(T^4\text{-}V^4)_d\text{-}(T^5\text{-}V^5)_e\text{-}(T^6\text{-}V^6)_f\text{-},$$

wherein:

amino-benzyloxycarbonyl (PABC), para-aminobenzyl (PAB), para-amino-benzylamino (PABA), para-amino-phenyl (PAP), para-hydroxy-phenyl (PHP), an acetal group, a hydrazine, a disulfide, and an ester, wherein EDA is an ethylene diamine moiety, PEG is a polyethylene glycol, and AA is an amino acid residue or an amino acid analog, wherein 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, and each x is an integer from 1 to 12;

V^7, V^8, V^9, V^{10} ,V^{11}, V^{12} and V^{13} 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-, wherein each q is an integer from 1 to 6;

each R^{13} is independently selected from hydrogen, an alkyl, a substituted alkyl, an aryl, and a substituted aryl; and

each R^{15} is independently selected from 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;

s is an integer from 1 to 10;

W^1 is a first drug; and

W^2 is a second drug.

[0015] In some examples, Z^1 is CR^4.

[0016] In some examples, Z^3 is $C\text{-}L^B\text{-}W^2$.

[0017] In some examples, one or both of W^1 and W^2 are camptothecin analogues, for example, belotecan.

[0018] In some examples, L^A comprises:

$$-(T^1\text{-}V^1)_a\text{-}(T^2\text{-}V^2)_b\text{-}(T^3\text{-}V^3)_c\text{-}(T^4\text{-}V^4)_d\text{-}(T^5\text{-}V^5)_e\text{-}(T^6\text{-}V^6)_f-,$$

wherein

a, b, c, d, e and f are each independently 0 or 1, provided at least one of a, b, c, d, e, and f is 1;

T^1, T^2, T^3, T^4, T^5 and T^6 are each independently selected from a covalent bond, $(C_1\text{-}C_{12})$alkyl, substituted $(C_1\text{-}C_{12})$alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_x-$, 4-amino-piperidine (4AP), meta-amino-benzyloxy (MABO), meta-amino-benzyloxycarbonyl (MABC), para-amino-benzyloxy (PABO), para-amino-benzyloxycarbonyl (PABC), para-aminobenzyl (PAB), para-amino-benzylamino (PABA),

para-amino-phenyl (PAP), para-hydroxy-phenyl (PHP), an acetal group, a hydrazine, a disulfide, and an ester, wherein EDA is an ethylene diamine moiety, PEG is a polyethylene glycol, and AA is an amino acid residue or an amino acid analog, wherein 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, and each x is an integer from 1 to 12;

V^1, V^2, V^3, V^4 ,V^5 and V^6 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-, wherein each q is an integer from 1 to 6;

each R^{13} is independently selected from hydrogen, an alkyl, a substituted alkyl, an aryl, and a substituted aryl; and

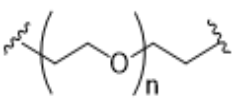
each R^{15} is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carboxyl, carboxyl ester, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

[0019] In some examples of L^A:

T^1 is selected from a (C_1-C_{12})alkyl and a substituted (C_1-C_{12})alkyl;

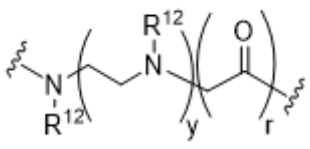
T^2, T^3, T^4, T^5 and T^6 are each independently selected from a covalent bond, (C_1-C_{12})alkyl, substituted (C_1-C_{12})alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, -$(CR^{13}OH)_x$-, 4-amino-piperidine (4AP), MABO, MABC, PABO, PABC, PAB, PABA, PAP, PHP, an acetal group, a hydrazine, and an ester; and

V^1, V^2, V^3, V^4 ,V^5 and V^6 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-; wherein:

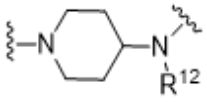
$(PEG)_n$ is 

, where n is an integer from 1 to 30;

EDA is an ethylene diamine moiety having the following structure:



, where y is an integer from 1 to 6 and r is 0 or 1;

4-amino-piperidine (4AP) is  ; and

each R^{12} is independently selected from hydrogen, an alkyl, a substituted alkyl, a polyethylene glycol moiety, an aryl and a substituted aryl, wherein any two adjacent R^{12} groups may be cyclically linked to form a piperazinyl ring;

In further examples, a, b, c, and d are each 1; and

e and f are 0.

[0020] In some examples, T^1, T^2, T^3, T^4, T^5 and T^6 are each optionally substituted with a glycoside.

[0021] In some examples, MABO, MABC, PABO, PABC, PAB, PABA, PAP and PHP are each optionally substituted with a glycoside.

[0022] In some examples, the glycoside is selected from a glucuronide, a galactoside, a glucoside, a mannoside, a fucoside, O-GlcNAc, and O-GalNAc.

[0023] In some examples, L^A is a linker wherein:

T^1 is $(C_1\text{-}C_{12})$alkyl and V^1 is -CONH-;

T^2 is substituted $(C_1\text{-}C_{12})$alkyl and V^2 is -CO-;

T^3 is $(AA)_p$ and V^3 is absent;

T^4 is PABC and V^4 is absent;

p is an integer from 1 to 10;

a, b, c, and d are each 1; and

e and f are each 0.

[0024] In further examples, the PABC is substituted with a glycoside, for example, a hydrogen of PABC is replaced with a glycoside, such as a glucuronide, a galactoside, a glucoside, a mannoside, a fucoside, O-GlcNAc, and O-GalNAc.

[0025] In some examples, L^B comprises:

$$-(T^7\text{-}V^7)_g\text{-}(T^8\text{-}V^8)_h\text{-}(T^9\text{-}V^9)_i\text{-}(T^{10}\text{-}V^{10})_j\text{-}(T^{11}\text{-}V^{11})_k\text{-}(T^{12}\text{-}V^{12})_l\text{-}(T^{13}\text{-}V^{13})_m\text{-},$$

wherein

g, h, i, j, k, 1 and m are each independently 0 or 1, provided at least one of g, h, i, j, k, 1 and m is 1;

T^7, T^8, T^9, T^{10}, T^{11}, T^{12} and T^{13} are each independently selected from a covalent bond, $(C_1\text{-}C_{12})$alkyl, substituted $(C_1\text{-}C_{12})$alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_x$-, 4-amino-piperidine (4AP), meta-amino-benzyloxy

(MABO), meta-amino-benzyloxycarbonyl (MABC), para-amino-benzyloxy (PABO), para-amino-benzyloxycarbonyl (PABC), para-aminobenzyl (PAB), para-amino-benzylamino (PABA), para-amino-phenyl (PAP), para-hydroxy-phenyl (PHP), an acetal group, a hydrazine, a disulfide, and an ester, wherein EDA is an ethylene diamine moiety, PEG is a polyethylene glycol, and AA is an amino acid residue or an amino acid analog, wherein 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, and each x is an integer from 1 to 12;

V^7, V^8, V^9, V^{10} ,V^{11}, V^{12} and V^{13} 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-, wherein each q is an integer from 1 to 6;

each R^{13} is independently selected from hydrogen, an alkyl, a substituted alkyl, an aryl, and a substituted aryl; and

each R^{15} is independently selected from 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.

[0026] In some examples, T^7, T^8, T^9, T^{10}, T^{11}, T^{12} and T^{13} are each optionally substituted with a glycoside.

[0027] In some examples, MABO, MABC, PABO, PABC, PAB, PABA, PAP and PHP are each optionally substituted with a glycoside.

[0028] In some examples, the glycoside is selected from a glucuronide, a galactoside, a glucoside, a mannoside, a fucoside, O-GlcNAc, and O-GalNAc.

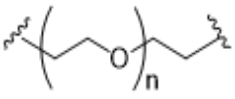
[0029] In some examples of L^B:

T^7 is a covalent bond;

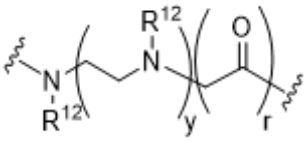
T^8, T^9, T^{10}, T^{11} and T^{12} are each independently selected from a covalent bond, (C_1-C_{12})alkyl, substituted (C_1-C_{12})alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, -$(CR^{13}OH)_x$-, 4-amino-piperidine (4AP), MABO, MABC, PABO, PABC, PAB, PABA, PAP, PHP, an acetal group, a hydrazine, and an ester; and

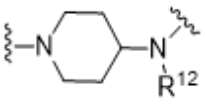
V^7, V^8, V^9, V^{10} ,V^{11} and V^{12} are each independently selected from the group consisting of a covalent bond, -CO-, -NR^{15}-, -$NR^{15}(CH_2)_q$-, -$NR^{15}(C_6H_4)$-, -$CONR^{15}$-, -$NR^{15}CO$-, -C(O)O-, -OC(O)-, -O-, -S-, -S(O)-, -SO_2- , -SO_2NR^{15}-, -$NR^{15}SO_2$-, and -P(O)OH-;

wherein:

$(PEG)_n$ is , where n is an integer from 1 to 30;

EDA is an ethylene diamine moiety having the following structure:

, where y is an integer from 1 to 6 and r is 0 or 1;

4-amino-piperidine (4AP) is ; and

each R^{12} is independently selected from hydrogen, an alkyl, a substituted alkyl, a polyethylene glycol moiety, an aryl and a substituted aryl, wherein any two adjacent R^{12} groups may be cyclically linked to form a piperazinyl ring;

g, h, i, j, and k are each 1; and

l and m is 0.

[0030] In some examples, T^1, T^2, T^3, T^4, T^5, T^6, T^7, T^8, T^9, T^{10}, T^{11}, and T^{12} are each optionally substituted with a glycoside.

[0031] In some examples, MABO, MABC, PABO, PABC, PAB, PABA, PAP and PHP are each optionally substituted with a glycoside.

[0032] In some examples, the glycoside is selected from a glucuronide, a galactoside, a glucoside, a mannoside, a fucoside, O-GlcNAc, and O-GalNAc.

[0033] In some examples, L^B is a linker wherein:

T^7 is absent and V^7 is -NHCO-;

T^8 is $(C_1\text{-}C_{12})$alkyl and V^8 is -CONH-;

T^9 is substituted $(C_1\text{-}C_{12})$alkyl and V^9 is -CO-;

T^{10} is $(AA)_p$ and V^{10} is absent;

T^{11} is PABC and V^{11} is absent;

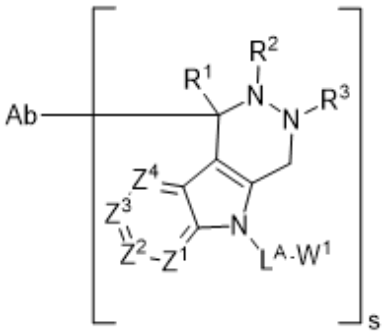
p is an integer from 1 to 10;

g, h, i, j, and k are each 1; and

l and m are each 0.

[0034] In further examples, the PABC is substituted with a glycoside, for example, a hydrogen of PABC is replaced with a glycoside, such as a glucuronide, a galactoside, a glucoside, a mannoside, a fucoside, O-GlcNAc, and O-GalNAc.

[0035] In some examples, a TF-ADC is represented by Formula (I):



(I)

wherein:

Ab represents the antibody that binds to TF;

Z^1, Z^2, and Z^4 are each independently CR^4;

Z^3 is $C\text{-}L^B\text{-}W^2$;

R^1 , R^2, R^3 and R^4 are each selected from hydrogen and $(C_1\text{-}C_{12})$alkyl;

L^A is a first linker wherein:

T^1 is $(C_1\text{-}C_{12})$alkyl and V^1 is -CONH-;

T^2 is substituted $(C_1\text{-}C_{12})$alkyl and V^2 is -CO-;

T^3 is $(AA)_p$ where p is an integer from 1-20 and V^3 is a covalent bond;

T^4 is PABC and V^4 is a covalent bond;

a, b, c, and d are each 1;

e and f are each 0; and

L^B is a second linker wherein

T^7 is a covalent bond and V^7 is -NHCO-;

T^8 is $(C_1\text{-}C_{12})$alkyl and V^8 is -CONH-;

T^9 is substituted $(C_1\text{-}C_{12})$alkyl and V^9 is -CO-;

T^{10} is $(AA)_p$ where p is an integer from 1-20 and V^{10} is a covalent bond;

T^{11} is PABC and V^{11} is a covalent bond; and

g, h, i, j, and k are each 1; and

l and m are each 0;

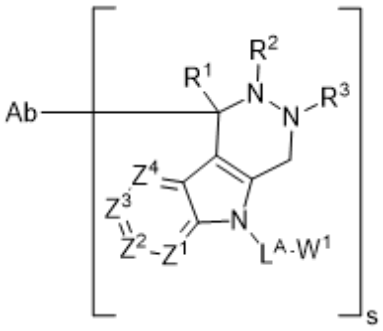
s is an integer from 1 to 10;

W^1 is a first drug; and

W^2 is a second drug.

[0036] In some examples, one or both of W^1 and W^2 are camptothecin analogues, for example, belotecan.

[0037] In some examples, a TF-ADC is represented by Formula (I):



(I)

wherein:

Ab represents the antibody that binds to TF;

Z^1, Z^2, and Z^4 are each independently CR^4;

Z^3 is $C\text{-}L^B\text{-}W^2$;

R^1, R^2, R^3 and R^4 are each selected from hydrogen and $(C_1\text{-}C_{12})$alkyl;

L^A is a linker wherein:

T^1 is $(C_1\text{-}C_6)$alkyl and V^1 is -CONH-;

T^2 is $(C_1\text{-}C_6)$alkylene substituted with -NHCO(PEG)_k, wherein k is an integer from 2 to 10 and V^2 is -CO-;

T^3 is $(AA)_2$ and V^3 is a covalent bond;

T^4 is PABC substituted with a glycoside and V^4 is a covalent bond;

a, b, c, and d are each 1; and

e and f are each 0; and

L^B is a linker wherein

T^7 is a covalent bond and V^7 is -NHCO-;

T^8 is $(C_1\text{-}C_6)$alkyl and V^8 is -CONH-;

T^9 is $(C_1\text{-}C_6)$alkylene substituted with -NHCO(PEG)_k, wherein k is an integer from 2 to 10 and V^9 is -CO-;

T^{10} is $(AA)_2$ and V^{10} is a covalent bond;

T^{11} is PABC substituted with a glycoside and V^{11} is a covalent bond;

g, h, i, j, and k are each 1; and

l and m are each 0;

s is an integer from 1 to 10;

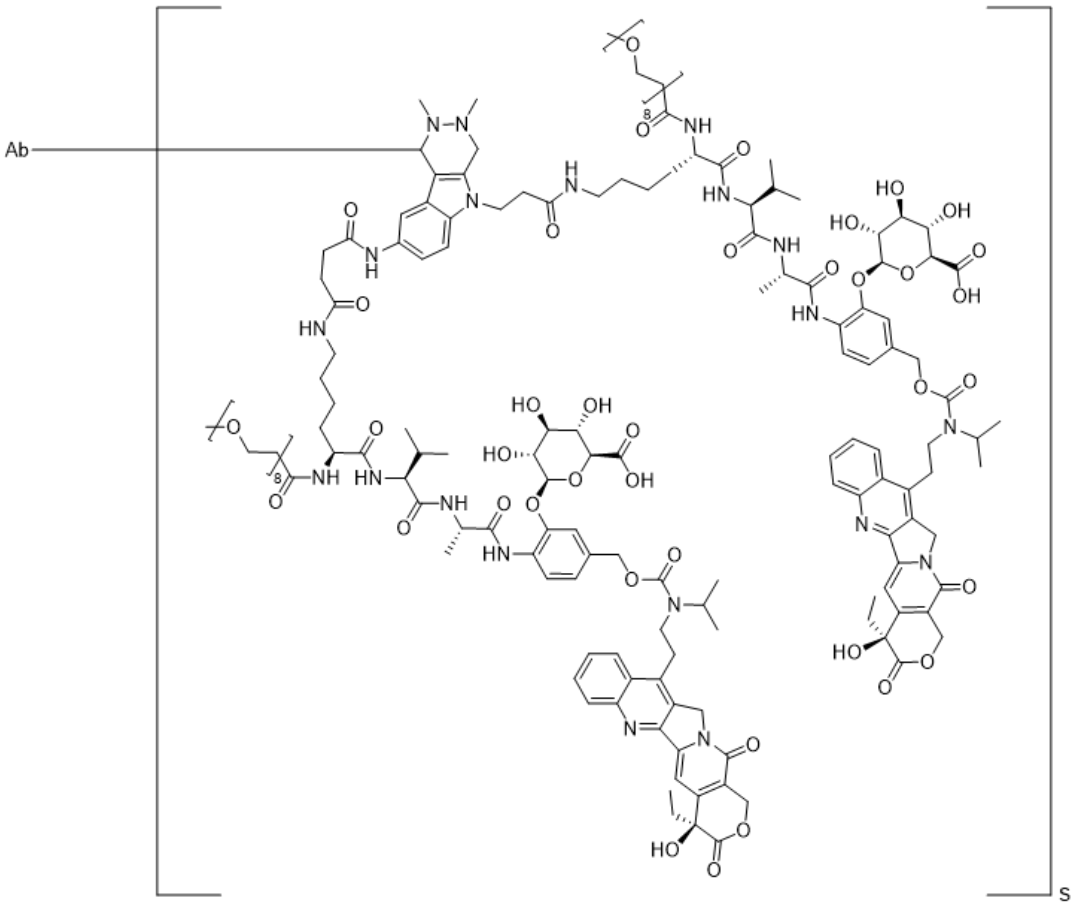
W^1 is a first drug; and

W^2 is a second drug.

[0038] In some examples, the PABC of one or both of T^4 and T^{11} is substituted with a glucuronide. In some examples, one or both of T^1 and T^8 is ethyl. In some examples,

one or both of T^2 and T^9 is C_5 alkylene substituted with -NHCO(PEG)$_k$, where k is an integer from 5-10. In some examples, one or both of W^1 and W^2 are camptothecin analogues, for example, belotecan.

[0039] In another aspect, the present disclosure provides for an ADC represented by Formula (II):



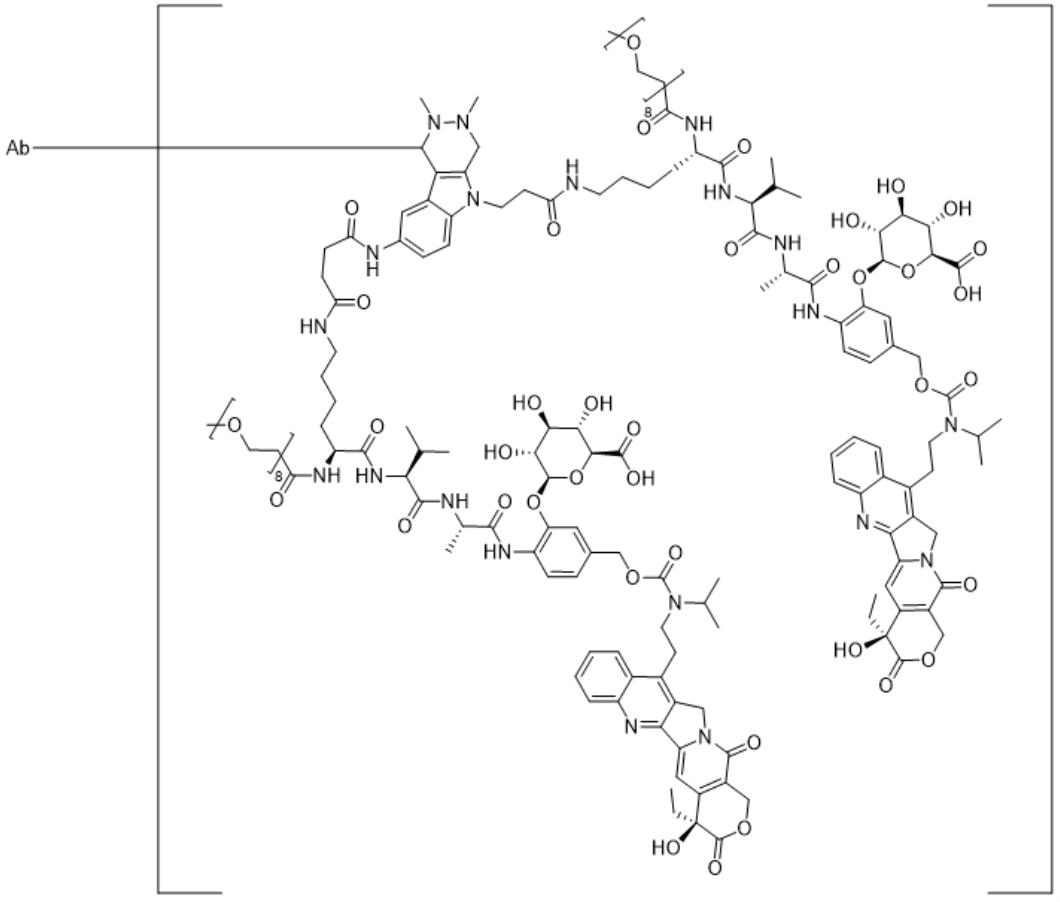
(II),

wherein:

Ab represents the antibody that binds to TF; and

s is an integer from 1 to 10.

[0039a] In some examples, a TF-ADC is represented by Formula (II):



(II),

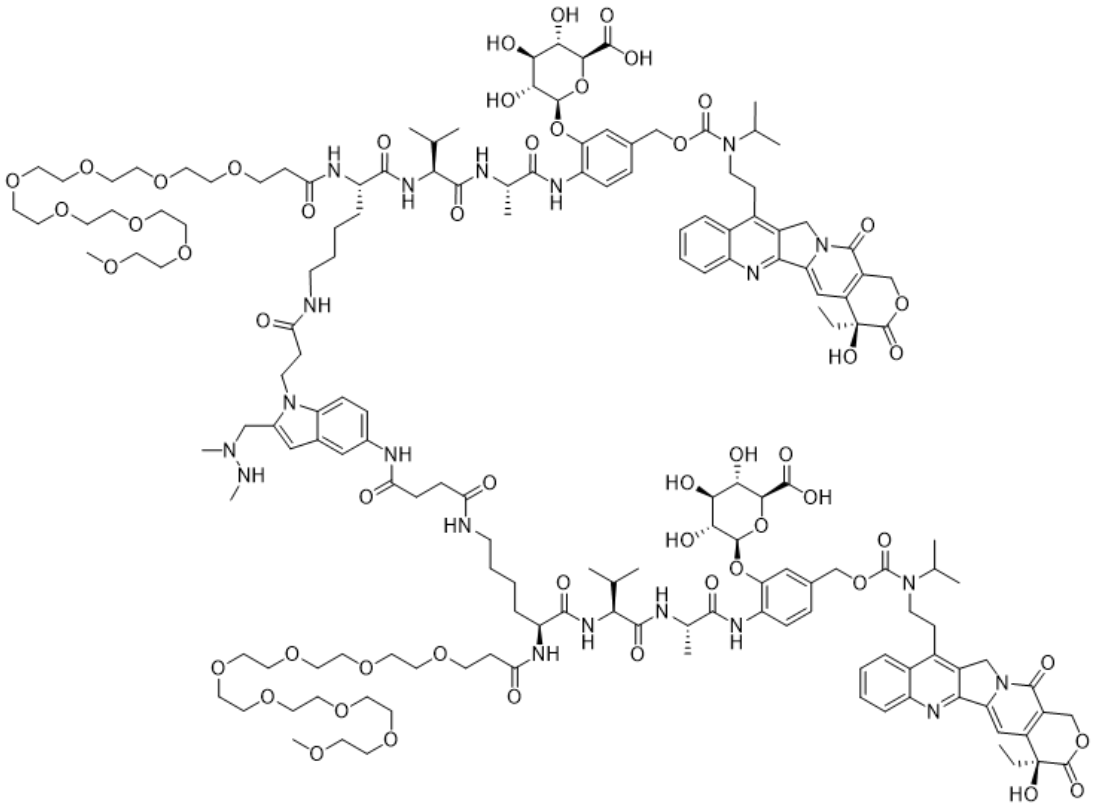
wherein:

Ab represents the antibody that binds to TF; and

s is an integer from 1 to 10.

[0040] In some examples, s is an integer from 1 to 4.

[0041] Formula (II) may be prepared by conjugating one or more linker-payloads of Formula (IIa), shown below, with a TF antibody:



(IIa)

[0042] In some examples, a TF-ADC can be represented by Formula (I) or (II), wherein Ab comprises: 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.

[0043] In some examples, a TF-ADC can be represented by Formula (I) or (II), wherein Ab comprises: 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:41 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:42.

[0044] In some examples, a TF-ADC can be represented by Formula (I) or (II), wherein Ab comprises: (i) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NOs:1, 7, 8, 15, 21, 27, 31, 32, 35, or 39, a VH CDR2 comprising the amino acid sequence of SEQ ID NOs:2, 9, 14, 16, or 22, and a VH CDR3 comprising the amino acid sequence of SEQ ID NOs:3, 10, 17, or 23; and (ii) a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NOs:4, 11, 18, 24, 28, 33, 36, or 40, a VL CDR2 comprising the amino acid sequence of SEQ ID NOs:5, 12, 19, 29, or 37, and a VL CDR3 comprising the amino acid sequence of SEQ ID NOs:6, 13, 20, 30, 34, or 38.

[0045] In some examples, a TF-ADC can be represented by Formula (I) or (II), wherein the Ab competes with any one of the TF antibodies as disclosed herein in binding to TF.

[0046] In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein 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, 41, and 42.

[0047] In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises human framework sequences.

[0048] In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises 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.

[0049] In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:82. Additionally or alternatively, the Ab comprises a VL comprising the amino acid sequence of SEQ ID NO:91. In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:82 and a VL comprising the amino acid sequence of SEQ ID NO:91.

[0050] In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:79. Additionally or alternatively, the Ab comprises a VL comprising the amino acid sequence of SEQ ID NO:91. In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:79 and a VL comprising the amino acid sequence of SEQ ID NO:91.

[0051] In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises (i) a VH comprising the amino acid sequence of SEQ ID NO:41 and a VL comprising the amino acid sequence of SEQ ID NO:42.

[0052] In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:85. Additionally or alternatively, the Ab comprises a VL comprising the amino acid sequence of SEQ ID NO:92. In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:85 and a VL comprising the amino acid sequence of SEQ ID NO:92.

[0053] In some examples, a TF-ADC can be represented by Formula (I) or (II) wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:88. Additionally or alternatively, the Ab comprises a VL comprising the amino acid sequence of SEQ ID NO:92. In some examples, a TF-ADC can be represented by Formula (I) or (II)

wherein Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:88 and a VL comprising the amino acid sequence of SEQ ID NO:92.

[0054] In another aspect, the present disclosure provides for a pharmaceutical composition comprising the ADC as described herein and a pharmaceutically acceptable excipient. The present disclosure also provides a pharmaceutical composition comprising a TF-ADC, wherein the TF-ADC can be represented by Formula (I) or Formula (II) and a pharmaceutically acceptable excipient, wherein the TF antibody (TF Ab or Ab) is as described in any example described herein. In some examples, such a pharmaceutical composition can have a drug-to-antibody ratio (DAR) of the TF-ADC of about 1 to about 20, for example, a DAR of about 2 to about 8, about 1 to about 4, about 2 to about 4, about 3 to about 4, about 4, about 1 to about 8, about 2 to about 8, about 3 to about 8, about 4 to about 8, about 5 to about 8, about 6 to about 8, about 6.5 to about 8, about 6 to about 7, about 6.5 to about 7.5, about 7 to about 8, about 6.5, about 7, about 7.5, or about 8.

[0055] The present disclosure also provides a method for treating a cancer or a tumor in a subject comprising administering to the subject the TF-ADC, wherein the TF-ADC can be represented by Formula (I) or (II) or the pharmaceutical composition comprising a TF-ADC of Formula (I) or (II) and a pharmaceutically acceptable excipient, wherein the TF antibody is as described in any example herein.

[0055a] In yet another aspect, the present disclosure provides for a use of the ADC 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.

[0056] Provided herein is a kit comprising the antibody-drug conjugate as disclosed herein or the pharmaceutical composition as disclosed herein, and instructions for use.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] FIG. 1 shows a schematic drawing of the HIPS ligation for the synthesis of ADCs. Antibodies carrying aldehyde moieties are reacted with a Hydrazino-*iso*-Pictet-Spengler (HIPS) linker and payload to generate a site-specifically conjugated ADC with a stable azacarboline linkage.

[0058] FIG. 2 shows a schematic representation of branched HIPS ligation for the synthesis of ADCs. Antibodies carrying four aldehyde moieties are reacted with a branched HIPS linker to generate ADCs with drug-to-antibody (DAR) value of up to 8, according to embodiments of the present disclosure.

[0059] FIG. 3A shows a graph of total antibody and ADC concentrations for pharmacokinetic (PK) sample analysis. Square: **TF-ADC 6-8** – total mAb measurement; triangle: **TF-ADC 6-8** – total ADC measurement.

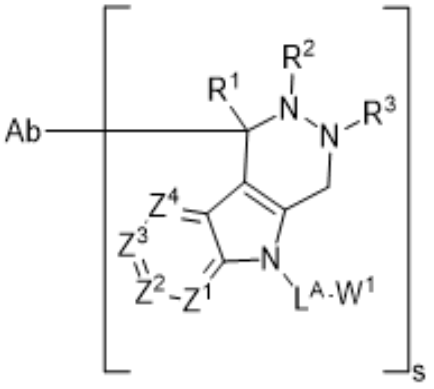
[0060] FIG. 3B shows a graph of total antibody and ADC concentrations for pharmacokinetic (PK) sample analysis. Diamond: **TF-ADC 6-4** – total mAb measurement; star: **TF-ADC 6-4** – total ADC measurement.

WHAT IS CLAIMED IS:

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

a. an antibody that binds to tissue factor (TF); and

b. two or more drugs conjugated to a pyridazine-pyrrolo coupling moiety, each via a linker



(I)

wherein:

Ab represents the antibody that binds to TF;

Z^1, Z^2, and Z^4 are each independently CR^4;

Z^3 is $C\text{-}L^B\text{-}W^2$;

R^1, R^2, R^3, and R^4 are each selected from hydrogen and alkyl;

L^A is a first linker comprising:

$$-(T^1\text{-}V^1)_a\text{-}(T^2\text{-}V^2)_b\text{-}(T^3\text{-}V^3)_c\text{-}(T^4\text{-}V^4)_d\text{-}(T^5\text{-}V^5)_e\text{-}(T^6\text{-}V^6)_f\text{-},$$

wherein:

a, b, c, d, e and f are each independently 0 or 1, provided at least one of a, b, c, d, e, and f are 1;

T^1, T^2, T^3, T^4, T^5 and T^6 are each independently selected from a covalent bond, $(C_1\text{-}C_{12})$alkyl, substituted $(C_1\text{-}C_{12})$alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_x-$, 4-amino-piperidine (4AP), meta-amino-benzyloxy (MABO), meta-amino-benzyloxycarbonyl (MABC), para-amino-benzyloxy (PABO), para-amino-benzyloxycarbonyl (PABC), para-aminobenzyl (PAB), para-amino-benzylamino (PABA), para-amino-phenyl (PAP), para-hydroxy-phenyl (PHP), an acetal group, a hydrazine, a disulfide, and an ester, wherein EDA is an ethylene diamine moiety, PEG is a polyethylene glycol, and AA is an amino acid residue or an amino acid analog, wherein 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, and each x is an integer from 1 to 12;

V^1, V^2, V^3, V^4 ,V^5 and V^6 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-, wherein each q is an integer from 1 to 6;

each R^{13} is independently selected from hydrogen, an alkyl, a substituted alkyl, an aryl, and a substituted aryl; and

each R^{15} is independently selected from 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;

L^B is a second linker comprising:

$$-(T^7\text{-}V^7)_g\text{-}(T^8\text{-}V^8)_h\text{-}(T^9\text{-}V^9)_i\text{-}(T^{10}\text{-}V^{10})_j\text{-}(T^{11}\text{-}V^{11})_k\text{-}(T^{12}\text{-}V^{12})_l\text{-}(T^{13}\text{-}V^{13})_m\text{-},$$

wherein:

g, h, i, j, k, 1 and m are each independently 0 or 1, provided that at least one of g, h, i, j, k, l, and m is 1;

T^7, T^8, T^9, T^{10}, T^{11}, T^{12} and T^{13} are each independently selected from 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, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, -$(CR^{13}OH)_x$-, 4-amino-piperidine (4AP), meta-amino-benzyloxy (MABO), meta-amino-benzyloxycarbonyl (MABC), para-amino-benzyloxy (PABO), para-amino-benzyloxycarbonyl (PABC), para-aminobenzyl (PAB), para-amino-benzylamino (PABA), para-amino-phenyl (PAP), para-hydroxy-phenyl (PHP), an acetal group, a hydrazine, a disulfide, and an ester, wherein EDA is an ethylene diamine moiety, PEG is a polyethylene glycol, and AA is an amino acid residue or an amino acid analog, wherein 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, and each x is an integer from 1 to 12;

V^7, V^8, V^9, V^{10} ,V^{11}, V^{12} and V^{13} 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-, wherein each q is an integer from 1 to 6;

each R^{13} is independently selected from hydrogen, an alkyl, a substituted alkyl, an aryl, and a substituted aryl; and

each R^{15} is independently selected from 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;

s is an integer from 1 to 10;

W^1 is a first drug; and

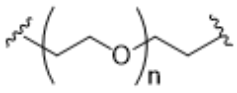
W^2 is a second drug.

2. The ADC of claim 1, wherein:

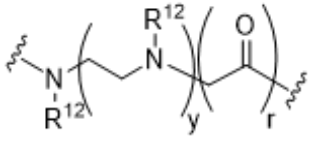
T^1 is selected from a $(C_1\text{-}C_{12})$alkyl and a substituted $(C_1\text{-}C_{12})$alkyl;

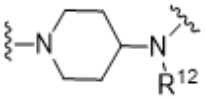
T^2, T^3, T^4, T^5 and T^6 are each independently selected from a covalent bond, $(C_1\text{-}C_{12})$alkyl, substituted $(C_1\text{-}C_{12})$alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_x-$, 4-amino-piperidine (4AP), MABO, MABC, PABO, PABC, PAB, PABA, PAP, PHP, an acetal group, a hydrazine, and an ester; and

V^1, V^2, V^3, V^4 ,V^5 and V^6 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-;

$(PEG)_n$ is ;

EDA is an ethylene diamine moiety having the following structure:

;

4-amino-piperidine (4AP) is ;

each R^{12} is independently selected from hydrogen, an alkyl, a substituted alkyl, a polyethylene glycol moiety, an aryl and a substituted aryl, wherein any two adjacent R^{12} groups may be cyclically linked to form a piperazinyl ring;

q is an integer from 1 to 6;

r is 0 or 1; and

y is an integer from 1 to 6.

3. The ADC of claim 1 or 2, wherein:

T^1 is (C_1-C_{12})alkyl and V^1 is -CONH-;
T^2 is substituted (C_1-C_{12})alkyl and V^2 is -CO-;
T^3 is $(AA)_p$ and V^3 is absent;
T^4 is PABC and V^4 is absent;
p is an integer from 1 to 10; and
a, b, c, and d are each 1; and
e and f are each 0.

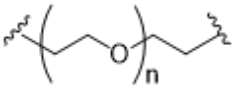
4. The ADC of any one of claims 1-3, wherein:

T^7 is a covalent bond;

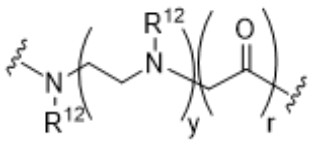
T^8, T^9, T^{10}, T^{11} and T^{12} are each independently selected from a covalent bond, (C_1-C_{12})alkyl, substituted (C_1-C_{12})alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl, $(EDA)_w$, $(PEG)_n$, $(AA)_p$, $-(CR^{13}OH)_x-$, 4-amino-piperidine (4AP), MABO, MABC, PABO, PABC, PAB, PABA, PAP, PHP, an acetal group, a hydrazine, and an ester; and

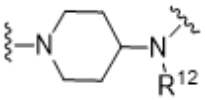
V^7, V^8, V^9, V^{10} ,V^{11} and V^{12} are each independently selected from the group consisting of a covalent bond, -CO-, $-NR^{15}-$, $-NR^{15}(CH_2)_q-$, $-NR^{15}(C_6H_4)-$, $-CONR^{15}-$, $-NR^{15}CO-$, -C(O)O-, -OC(O)-, -O-, -S-, -S(O)-, $-SO_2-$, $-SO_2NR^{15}-$, $-NR^{15}SO_2-$, and -P(O)OH-;

wherein:

$(PEG)_n$ is , where n is an integer from 1 to 30;

EDA is an ethylene diamine moiety having the following structure:

, where y is an integer from 1 to 6 and r is 0 or 1;

4-amino-piperidine (4AP) is ; and

each R^{12} is independently selected from hydrogen, an alkyl, a substituted alkyl, a polyethylene glycol moiety, an aryl and a substituted aryl, wherein any two adjacent R^{12} groups may be cyclically linked to form a piperazinyl ring;

g, h, i, j, and k are each 1; and

l and m is 0.

5. The ADC of any one of claims 1-4, wherein:

T^7 is absent and V^7 is -NHCO-;

T^8 is (C_1-C_{12})alkyl and V^8 is -CONH-;

T^9 is substituted (C_1-C_{12})alkyl and V^9 is -CO-;

T^{10} is $(AA)_p$ and V^{10} is absent;

T^{11} is PABC and V^{11} is absent;

p is an integer from 1 to 10; and

g, h, i, j, and k are each 1; and

l and m are each 0.

6. The ADC of any one of claims 1-5 wherein one or both of T^2 and T^9 is (C_1-C_6)alkylene substituted with -NHCO$(PEG)_k$, wherein k is an integer from 2 to 10.

7. The ADC of any one of claims 1-6, wherein p is 2.

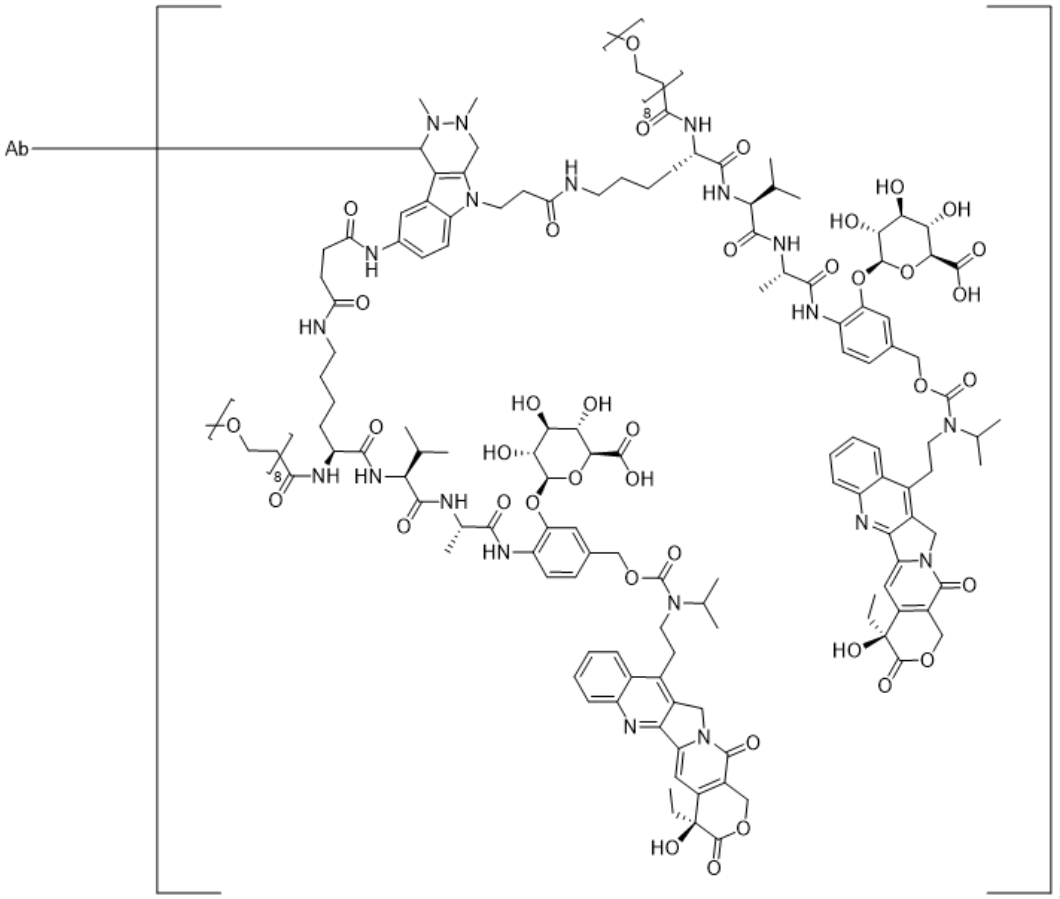
8. The ADC of any one of claims 1-7, wherein s is 2 or 4.

9. The ADC of any one of claims 1-8, wherein one or both of W^1 and W^2 is a camptothecin analog.

10. The ADC of any one of claims 1-9, wherein the camptothecin analog is belotecan.

11. The ADC of any one of claim 1-10, wherein each of W^1 and W^2 is belotecan.

12. An ADC represented by Formula (II):



(II),

wherein:

Ab represents the antibody that binds to TF; and

s is an integer from 1 to 10.

13. The ADC of any one of claims 1-12, wherein 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; or (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:41 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:42.

14. The ADC of any one of claims 1-13, wherein Ab comprises: (i) a VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NOs:1, 7, 8, 15, 21, 27, 31, 32, 35, or 39, a VH CDR2 comprising the amino acid sequence of SEQ ID NOs:2, 9, 14, 16, or 22, and a VH CDR3 comprising the amino acid sequence of SEQ ID NOs:3, 10, 17, or 23; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NOs:4, 11, 18, 24, 28, 33, 36, or 40, a VL CDR2

comprising the amino acid sequence of SEQ ID NOs:5, 12, 19, 29, or 37, and a VL CDR3 comprising the amino acid sequence of SEQ ID NOs:6, 13, 20, 30, 34, or 38.

15. The ADC of any one of claims 1-14, wherein Ab comprises one or more of a framework 1 (FR1), a framework 2 (FR2), a framework 3 (FR3) and a framework 4 (FR4) sequence as set forth in any one of SEQ ID NOs:25, 26, 41, and 42.

16. The ADC of any one of claims 1-14, wherein Ab comprises human framework sequences.

17. The ADC of any one of claims 1-15, wherein Ab comprises 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.

18. The ADC of any one of claims 1-17, wherein the Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:82.

19. The ADC of any one of claims 1-18, wherein the Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:82 and a light chain comprising the amino acid sequence of SEQ ID NO:91.

20. The ADC of any one of claims 1-17, wherein the Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:79.

21. The ADC of any one of claims 1-17 and 20, wherein the Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:79 and a light chain comprising the amino acid sequence of SEQ ID NO:91.

22. The ADC of any one of claims 1-15, wherein Ab comprises: (i) a VH comprising the amino acid sequence of SEQ ID NO:41 and a VL comprising the amino acid sequence of SEQ ID NO:42.

23. The ADC of any one of claims 1-15 and 22, wherein the Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:85.

24. The ADC of any one of claims 1-15 and 22-23, wherein the Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:85 and a light chain comprising the amino acid sequence of SEQ ID NO:92.

25. The ADC of any one of claims 1-15 and 22, wherein the Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:88.

26. The ADC of any one of claims 1-15, 22 and 25, wherein the Ab comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:88 and a light chain comprising the amino acid sequence of SEQ ID NO:92.

27. A pharmaceutical composition comprising the ADC of any one of claims 1-26 and a pharmaceutically acceptable excipient.

28. The pharmaceutical composition of claim 27, characterized by an ADC drug-to-antibody ratio (DAR) of about 1 to about 20.

29. The pharmaceutical composition of claim 27 or 28, wherein the DAR is about 2 to about 8.

30. Use of the ADC of any one of claims 1-18 or the pharmaceutical composition of any one of claims 27-29 in the manufacture of a medicament for the treatment of a cancer or a tumor.

31. The use of claim 30, wherein the cancer or tumor is characterized by expression of tissue factor.

32. The use of claim 30 or 31, wherein the cancer is breast cancer, colon cancer, renal cancer, lung cancer, squamous cell myeloid leukemia, hemangioma, melanoma, astrocytoma, glioblastoma, heart cancer, gastrointestinal cancer, pancreatic cancer, genitourinary cancer, liver cancer, bone cancer, skin cancer, adrenal cancer, or cancer of the nervous system.