ANTI-TISSUE FACTOR ANTIBODY-DRUG CONJUGATES AND RELATED METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application No. 62/870,644, filed on July 3, 2019, the entire contents of which are incorporated by reference herein for all purposes.

SEQUENCE LISTING

[0001.1] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 12, 2020, is named ITI-003WO_SL.txt and is 286,038 bytes in size.

BACKGROUND

[0002] Blood coagulation involves a complex set of processes that result in blood clotting. Tissue factor (TF) plays an important role in these coagulation processes. TF is a cell surface receptor for the serine protease factor VIIa (FVIIa). The TF/FVIIa complex catalyzes conversion of the inactive protease factor X (FX) into the active protease factor Xa (FXa). FXa and its co-factor FVa form the prothrombinase complex, which generates thrombin from prothrombin. Thrombin converts soluble fibrinogen into insoluble strands of fibrin and catalyzes many other coagulation-related processes.

[0003] TF is over-expressed on multiple types of solid tumors. In cancer, TF/FVIIa signaling can support angiogenesis, tumor progression, and metastasis.

SUMMARY

[0004] Provided herein are anti-TF antibody-drug conjugates, and related methods.

[0004a] In one aspect, provided herein is an antibody-drug conjugate comprising:

a. an antigen binding protein (Ab) which binds human Tissue Factor (TF) (SEQ ID NO:810), wherein the Ab comprises three heavy chain complementarity determining regions (CDRs) (a VH-CDR1, a VH-CDR2, and a VH-CDR3) and three light chain CDRs (a VL-CDR1, a VL-CDR2, and a VL-CDR3), wherein

i. the VH-CDR1 comprises the sequence of SEQ ID NO: 872, the VH-CDR2 comprises the sequence of SEQ ID NO: 873, the VH-CDR3 comprises the sequence of SEQ ID NO: 874, the VL-CDR1 comprises the sequence of

SEQ ID NO: 875, the VL-CDR2 comprises the sequence of SEQ ID NO: 876, and the VL-CDR3 comprises the sequence of SEQ ID NO: 877,

ii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25A3,

iii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25A,

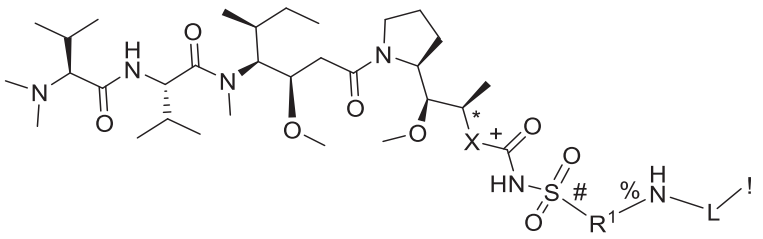
iv. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25A5,

v. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25A5-T, or

vi. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25G1;

and

b. one or more linker-toxin moieties represented by Formula IV:



Formula IV

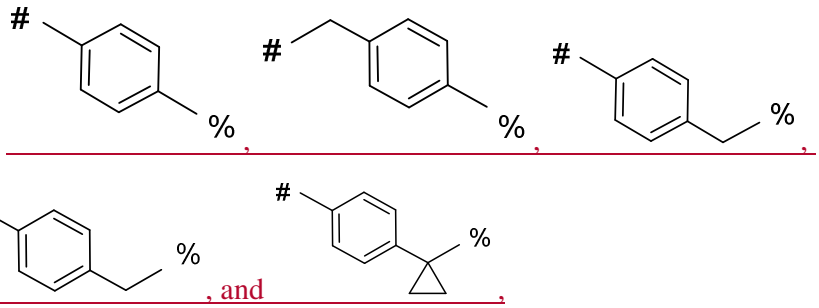
wherein:

X is *-C(O)NHCH(CH_2(R^2))-$^{+}$, wherein * and + represent the respective points of attachment as indicated in Formula IV, or X is absent;

L is a linker;

! represents the point of attachment of L to the Ab, where L is attached to the Ab through a covalent bond;

R^1 is selected from the group consisting of:



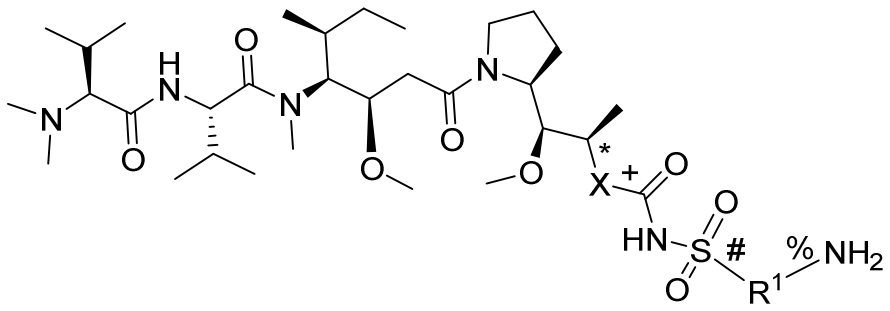
wherein # and % represent the respective points of attachment as indicated in Formula IV; and

R^2 is phenyl.

[0004b] In one aspect, provided herein is the use of the antibody-drug conjugate as described herein or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating or preventing a disease or condition in a subject in need thereof, optionally a human subject, optionally wherein the treating or preventing is treating or delaying the onset of cancer in a subject in need thereof, optionally wherein the cancer is selected from the group consisting of: head and neck cancer, ovarian cancer, gastric cancer, esophageal cancer, cervical cancer, prostate cancer, pancreatic cancer, estrogen receptors negative (ER-) breast cancer, progesterone receptors negative (PR-) breast cancer, HER2 negative (HER2-) triple negative breast cancer, glioblastoma, lung cancer, bladder cancer, melanoma, and kidney cancer, or wherein the disease or condition involves neovascularization, optionally wherein the disease or condition involving neovascularization is cancer, or wherein the disease or condition involves vascular inflammation.

[0004c] In one aspect, provided herein is a process for preparing an antibody-drug conjugate, the process comprising:

(A) reacting a nucleophilic or an electrophilic group on an antigen binding protein (Ab) which binds human Tissue Factor (TF) (SEQ ID NO:810) with a bifunctional linker, or with a first linker component of a bifunctional linker that comprises two or more linker components followed by sequential addition of the remaining linker component(s), to form an Ab-linker intermediate, and reacting the Ab-linker intermediate with the $-NH_2$ group of a compound of general Formula **I**:

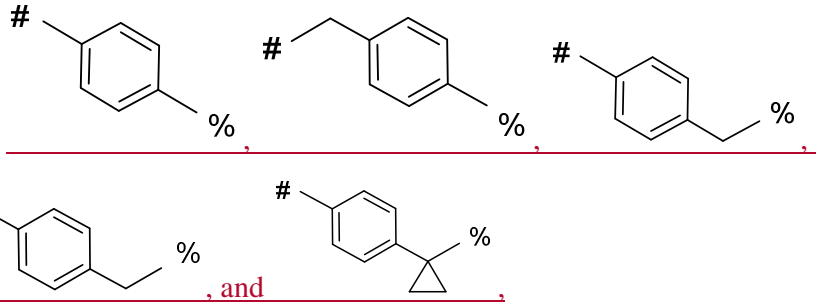


Formula I

wherein:

X is *-C(O)NHCH(CH_2(R^2))-$^{+}$, wherein * and + represent the respective points of attachment as indicated in Formula **I**, or X is absent;

R^1 is selected from the group consisting of:



wherein # and % represent the respective points of attachment as indicated in Formula **I**; and R^2 is phenyl,

to provide the antibody drug conjugate; or

(B) reacting the -NH_2 group on the compound of general Formula **I** with a bifunctional linker, or with a first linker component of a bifunctional linker that comprises two or more linker components followed by sequential addition of the remaining linker component(s), to form a linker-toxin intermediate, and reacting the linker-toxin intermediate with a nucleophilic or an electrophilic group on an Ab which binds human TF (SEQ ID NO: 810) to provide the antibody-drug conjugate, wherein, in (A) or (B),

the Ab comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2, and a VL-CDR3, wherein

i. the VH-CDR1 comprises the sequence of SEQ ID NO: 872, the VH-CDR2 comprises the sequence of SEQ ID NO: 873, the VH-CDR3 comprises the sequence of SEQ ID NO: 874, the VL-CDR1 comprises SEQ ID NO: 875, the VL-CDR2 comprises the sequence of SEQ ID

NO: 876, and the VL-CDR3 comprises the sequence of SEQ ID NO: 877,

ii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25A3,

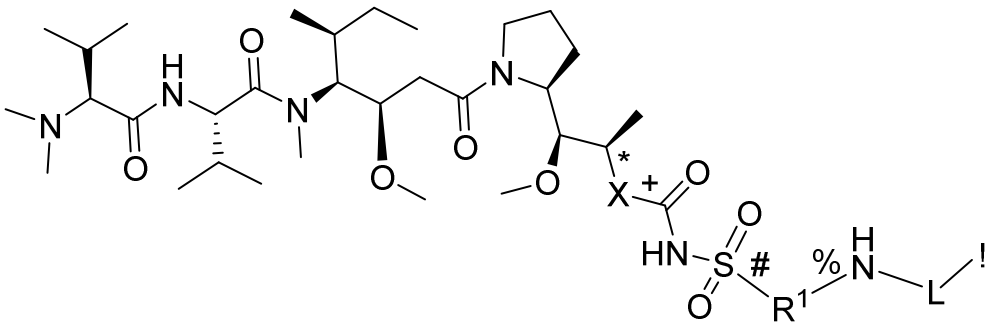
iii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25A,

iv. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25A5,

v. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25A5-T, or

vi. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the Ab designated 25G1;

resulting in the antibody-drug conjugate which comprises one or more moieties represented by Formula IV:



Formula IV

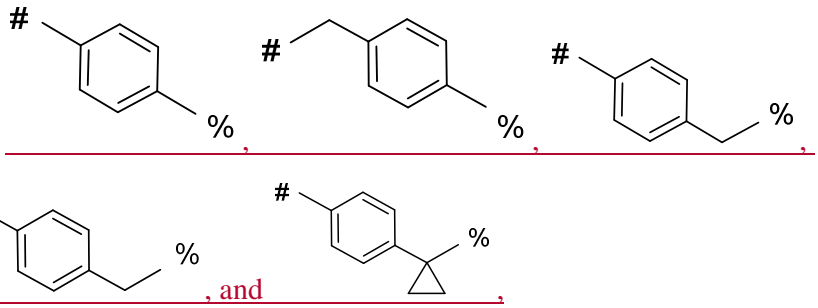
wherein:

X is *-C(O)NHCH($CH_2(R^2)$)-$^{+}$, wherein * and + represent the respective points of attachment as indicated in Formula IV, or X is absent;

L is a linker;

! represents the point of attachment of L to the Ab, where L is attached to the Ab through a covalent bond;

R^1 is selected from the group consisting of:



wherein # and % represent the respective points of attachment as indicated in Formula IV; and

R^2 is phenyl

[0004d] In one aspect, provided herein is a kit comprising: (i) the antibody-drug conjugate as described herein or the pharmaceutical composition as described herein; and (ii) instructions for use,

[0004e] In one aspect, provided herein is the antibody-drug conjugate as described herein or the pharmaceutical composition as described herein for use in therapy.

[0005] Provided herein is an antibody-drug conjugate comprising:

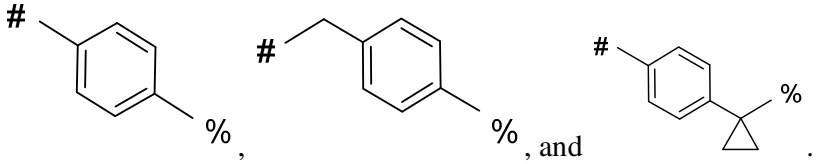
b. an antigen binding protein (Ab) which binds to the extracellular domain of human Tissue Factor (TF) (SEQ ID NO:810), wherein the Ab comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2, and a VL-CDR3, wherein

i. the VH-CDR1 comprises SEQ ID NO: 872, the VH-CDR2 comprises SEQ ID NO: 873, the VH-CDR3 comprises SEQ ID NO: 874, the VL-CDR1 comprises SEQ ID NO: 875, the VL-CDR2 comprises SEQ ID NO: 876, and the VL-CDR3 comprises SEQ ID NO: 877,

ii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A3,

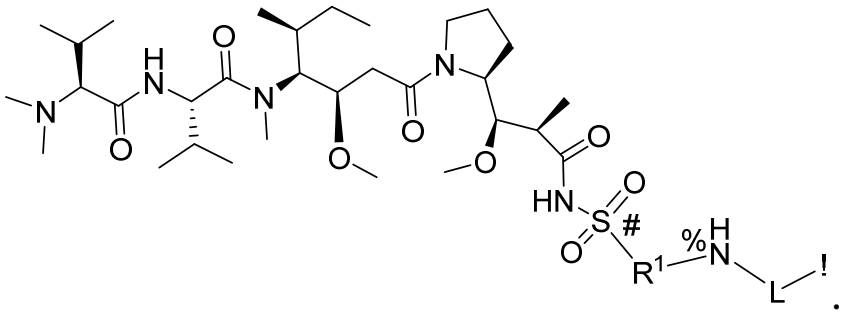
iii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A,

[0006] In some ~~embodiment~~examples, R^1 is selected from the group consisting of:



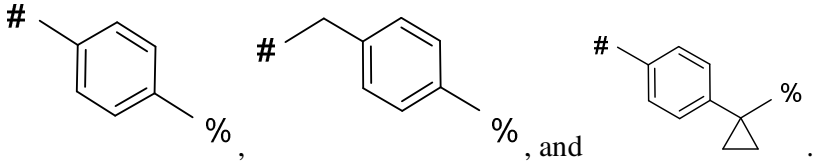
[0007] In some ~~embodiment~~examples, X is absent.

[0008] In some ~~embodiment~~examples, the linker-toxin moiety of Formula IV is represented by Formula V:

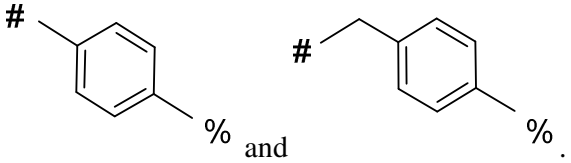


Formula V

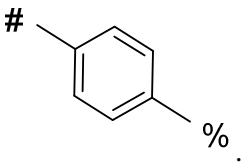
[0009] In some ~~embodiment~~examples, R^1 is selected from the group consisting of:



[0010] In some ~~embodiment~~examples, R^1 is selected from the group consisting of:



[0011] In some ~~embodiment~~examples, R^1 is:



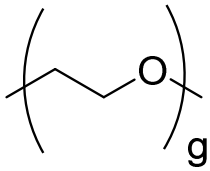
[0012] In some ~~embodiment~~examples, L is a cleavable linker.

[0013] In some ~~embodiment~~examples, L is a peptide-containing linker.

[0014] In some ~~embodiment~~examples, L is a protease-cleavable linker.

[0015] In some ~~embodiment~~examples, L is a linker selected from one of N-(β-maleimidopropyloxy)-N-hydroxy succinimide ester (BMPS), N-(ε-maleimidocaproyloxy) succinimide ester (EMCS), N-[γ-maleimidobutyryloxy]succinimide ester (GMBS), 1,6-hexane-bis-vinylsulfone (HBVS), succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxy-(6-amidocaproate) (LC-SMCC), m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), 4-(4-N-Maleimidophenyl)butyric acid hydrazide (MPBH), succinimidyl 3-(bromoacetamido)propionate (SBAP), succinimidyl iodoacetate (SIA), succinimidyl (4-iodoacetyl)aminobenzoate (SIAB), N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP), succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC), succinimidyl 4-(p-maleimidophenyl)butyrate (SMPB), succinimidyl 6-[(β-maleimidopropionamido)hexanoate] (SMPH), iminothiolane (IT), sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, sulfo-SMPB, and succinimidyl-(4-vinylsulfone)benzoate (SVSB).

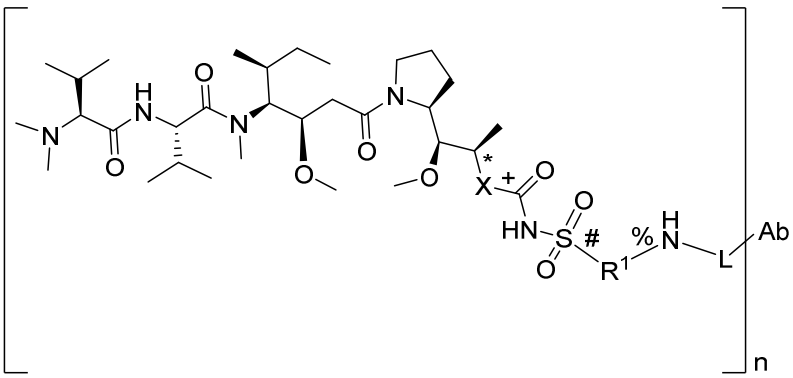
[0016] In some ~~embodiment~~examples, L comprises a poly(ethylene)glycol chain of the formula:



wherein g is an integer from 1-20.

[0017] In some ~~embodiment~~examples, g is 3.

[0018] Provided herein is an antibody-drug conjugate of Formula VI:



Formula VI

wherein:

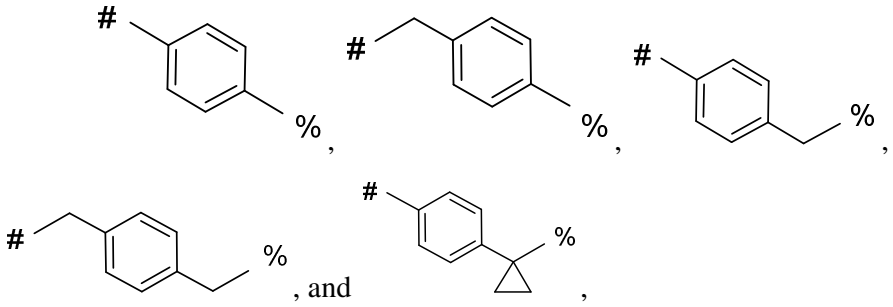
Ab represents a tissue factor (TF) antibody;

n is an integer greater than or equal to 1;

X is *-C(O)NHCH($CH_2(R^2)$)-$^{+}$, wherein * and + represent the respective points of attachment as indicated in Formula VI, or X is absent;

L is a linker;

R^1 is selected from the group consisting of:



, and

wherein # and % represent the respective points of attachment as indicated in Formula VI; and

R^2 is phenyl; and wherein

the Ab comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2, and a VL-CDR3, wherein

i. the VH-CDR1 comprises SEQ ID NO: 872, the VH-CDR2 comprises SEQ ID NO: 873, the VH-CDR3 comprises SEQ ID NO: 874, the VL-CDR1 comprises SEQ ID NO: 875, the VL-CDR2 comprises SEQ ID NO: 876, and the VL-CDR3 comprises SEQ ID NO: 877,

ii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A3,

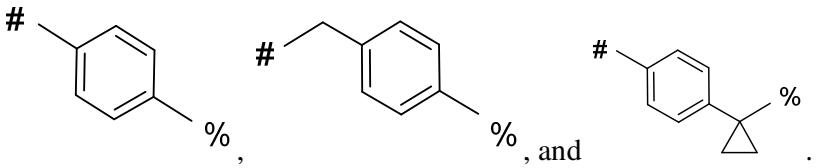
iii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A,

iv. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A5,

v. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A5-T, or

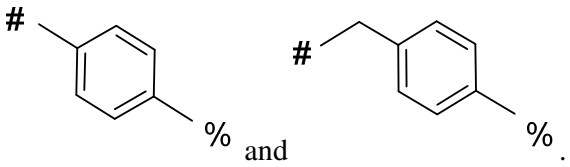
vi. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25G1.

[0019] In some ~~embodiment~~examples, R^1 is selected from the group consisting of:

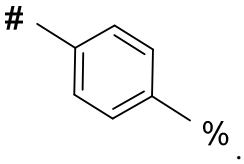


[0020] In some ~~embodiment~~examples, X is absent.

[0021] In some ~~embodiment~~examples, R^1 is selected from the group consisting of:



[0022] In some ~~embodiment~~examples, R^1 is:



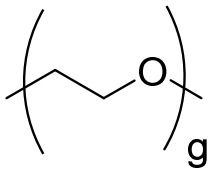
[0023] In some ~~embodiment~~examples, L is a cleavable linker.

[0024] In some ~~embodiment~~examples, L is a peptide-containing linker.

[0025] In some ~~embodiment~~examples, L is a protease-cleavable linker.

[0026] In some ~~embodiment~~examples, L is a linker selected from one of N-(β-maleimidopropyloxy)-N-hydroxy succinimide ester (BMPS), N-(ε-maleimidocaproyloxy) succinimide ester (EMCS), N-[γ-maleimidobutyryloxy]succinimide ester (GMBS), 1,6-hexane-bis-vinylsulfone (HBVS), succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxy-(6-amidocaproate) (LC-SMCC), m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), 4-(4-N-Maleimidophenyl)butyric acid hydrazide (MPBH), succinimidyl 3-(bromoacetamido)propionate (SBAP), succinimidyl iodoacetate (SIA), succinimidyl (4-iodoacetyl)aminobenzoate (SIAB), N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP), succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC), succinimidyl 4-(p-maleimidophenyl)butyrate (SMPB), succinimidyl 6-[(β-maleimidopropionamido)hexanoate] (SMPH), iminothiolane (IT), sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, sulfo-SMPB, and succinimidyl-(4-vinylsulfone)benzoate (SVSB).

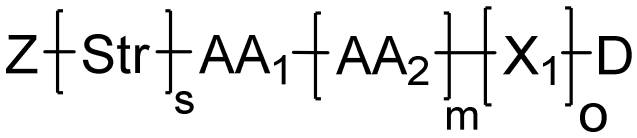
[0027] In some ~~embodiment~~examples, L comprises a poly(ethylene)glycol chain of the formula:



wherein g is an integer from 1-20.

[0028] In some ~~embodiment~~examples, g is 3.

[0029] In some ~~embodiment~~examples, L is represented by Formula VII:



Formula VII

wherein:

Z represents a functional group that binds to a target group of the TF antibody;

D represents the point of attachment to the amino group as indicated in Formula VI;

Str is a stretcher;

AA_1 and AA_2 are each independently an amino acid, wherein AA_1-$[AA_2]_m$ forms a protease cleavage site;

X_1 is a self-immolative group;

s is an integer selected from 0 and 1;

m is an integer selected from the group consisting of 1, 2, 3, and 4;

o is an integer selected from 0, 1, and 2.

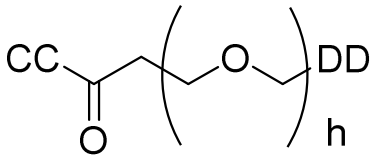
[0030] In some ~~embodiment~~examples, n is an integer selected from the group consisting of 1, 2, 3, 4, and 5.

[0031] In some ~~embodiment~~examples, $[Str]_s$ is selected from the group consisting of alkylene, stretchers based on aliphatic acids, stretchers based on aliphatic diacids, stretchers based on aliphatic amines and stretchers based on aliphatic diamines.

[0032] In some ~~embodiment~~examples, $[Str]_s$ is selected from the group consisting of diglycolate-based stretchers, malonate-based stretchers, caproate-based stretchers and caproamide-based stretchers.

[0033] In some ~~embodiment~~examples, $[Str]_s$ is selected from the group consisting of glycine-based stretchers, polyethylene glycol-based stretchers, and monomethoxy polyethylene glycol-based stretchers.

[0034] In some ~~embodiment~~examples, $[Str]_s$ is:



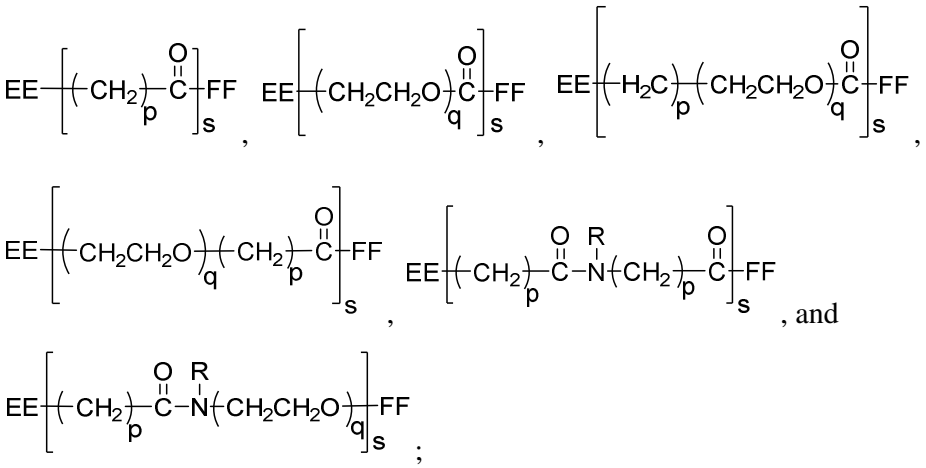
wherein

h is an integer from 1-20,

CC refers to the point of attachment to AA_1; and

DD refers to the point of attachment to Z.

[0035] In some ~~embodiment~~examples, $[Str]_s$ is selected from:



, and

;

wherein:

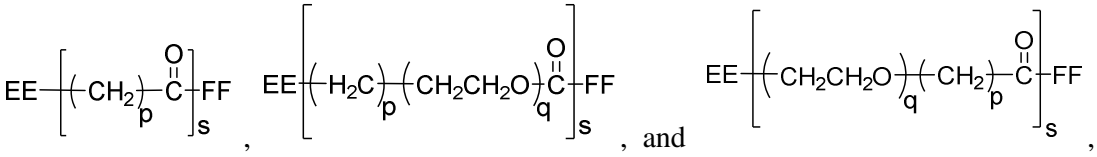
EE and FF represent the points of attachment to Z and AA_1, respectively;

R is selected from hydrogen and C_1-C_6 alkyl;

each occurrence of p is independently an integer from 2 to 10; and

each occurrence of q is independently an integer from 1 to 10.

[0036] In some ~~embodiment~~examples, $[Str]_s$ is selected from the group consisting of:



, and

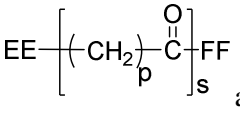
wherein:

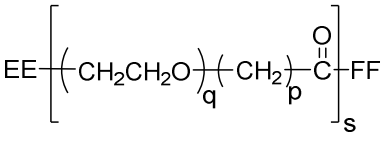
EE and FF represent the points of attachment to Z and AA_1, respectively;

each occurrence of p is independently an integer from 2 to 10; and

each occurrence of q is independently an integer from 1 to 10.

[0037] In some ~~embodiment~~examples, $[Str]_s$ is selected from:



and


,

wherein:

EE and FF represent the points of attachment to Z and AA_1, respectively;

each occurrence of p is independently an integer from 2 to 6, and

q is an integer from 2 to 8.

[0038] In some ~~embodiment~~examples, AA_1-$[AA_2]_m$ is selected from Val-Lys, Ala-Lys, Phe-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Arg, Ala-Phe, Val-Ala, Met-Lys, Asn-Lys, Ile-Pro, Ile-Val, Asp-Val, His-Val, Met-(D)Lys, Asn-(D)Lys, Val-(D)Asp, NorVal-(D)Asp, Ala-(D)Asp, Me_3Lys-Pro, PhenylGly-(D)Lys, Met-(D)Lys, Asn-(D)Lys, Pro-(D)Lys, Met-(D)Lys, Met-Cit-Val, Gly-Cit-Val, (D)Phe-Phe-Lys, (D)Ala-Phe-Lys, Gly-Phe-Leu-Gly (SEQ ID NO: 922), and Ala-Leu-Ala-Leu (SEQ ID NO: 923).

[0039] In some ~~embodiment~~examples, m is selected from 1, 2 and 3.

[0040] In some ~~embodiment~~examples, m is 1.

[0041] In some ~~embodiment~~examples, AA_1-$[AA_2]_m$ is a dipeptide selected from Val-Lys, Ala-Lys, Phe-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit and Trp-Cit.

[0042] In some ~~embodiment~~examples, each X_1 is independently selected from p-aminobenzyloxycarbonyl (PABC), p-aminobenzyl ether (PABE) and methylated ethylene diamine (MED).

[0043] In some ~~embodiment~~examples, s is 1 and h is 3.

[0044] In some ~~embodiment~~examples, s is 1.

[0045] In some ~~embodiment~~examples, o is 0.

[0046] Provided herein is an antibody drug-conjugate comprising a linker-toxin moiety of the Formula VIII:

iv. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A5,

v. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A5-T, or

vi. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25G1,

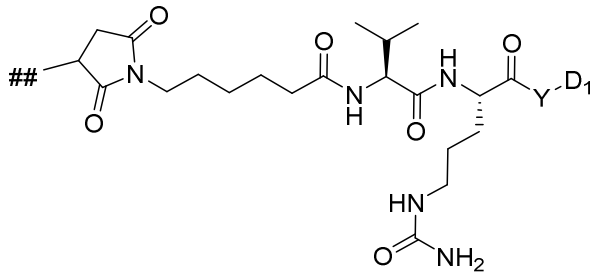
n is an integer greater than or equal to 1, and

the succinimidyl group is attached to the Ab through a covalent bond.

[0048] In some ~~embodiment~~examples, n is selected from the group consisting of 1, 2, 3, 4, and 5.

[0049] In some ~~embodiment~~examples, n is selected from the group consisting of 2, 3, and 4.

[0050] Provided herein is an antibody-drug conjugate comprising a linker as represented by Formula X:



Formula X

wherein:

is the point of attachment to the antibody and the succinimidyl group is attached to the antibody through a covalent bond;

Y is one or more additional linker components, or is absent; and

D_1 is the point of attachment to a cytotoxic agent, and wherein

the Ab comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2, and a VL-CDR3, wherein

i. the VH-CDR1 comprises SEQ ID NO: 872, the VH-CDR2 comprises SEQ ID NO: 873, the VH-CDR3 comprises SEQ ID NO: 874, the VL-CDR1 comprises SEQ ID NO: 875, the VL-CDR2 comprises SEQ ID NO: 876, and the VL-CDR3 comprises SEQ ID NO: 877,

ii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A3,

iii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A,

iv. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A5,

v. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A5-T, or

vi. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25G1.

[0052] In some ~~embodiment~~examples, the cytotoxic agent is selected from the group consisting of a diagnostic agent, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound, or a chemiluminescent compound.

[0053] In some ~~embodiment~~examples, the cytotoxic agent is a cytotoxic payload having an improved safety profile.

[0054] In some ~~embodiment~~examples, the Ab comprises:

a. a VH sequence that is SEQ ID NO: 868 and a VL sequence that is SEQ ID NO: 869,

b. a VH that is SEQ ID NO: 151 and a VL sequence that is SEQ ID NO: 152,

c. a VH sequence that is SEQ ID NO: 113 and a VL sequence that is SEQ ID NO: 114,

d. a VH sequence that is SEQ ID NO: 189 and a VL sequence that is SEQ ID NO: 190,

e. a VH sequence that is SEQ ID NO: 836 and a VL sequence that is SEQ ID NO: 837, or

f. a VH sequence that is SEQ ID NO: 265 and a VL sequence that is SEQ ID NO: 266.

[0055] In some ~~embodiment~~examples, the Ab comprises:

a. a heavy chain sequence that is QVQLVQSGAEVKKPGASVKVSCKASGYTFDx[V/A]YGISWVRQAPGQ

GLEWMGWIAPYx[N/S]GNTNYAQKLQGRVTMTTDTSTSTAYMELRSL
RSDDTAVYYCARDAGTYSPFGYGMDVWGQGTTVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 924)
and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCx[R/Q]ASx[Q/E]SIx[S/N]x[S/N]WLAW
YQQKPGKAPKLLIYKAx[S/Y]x[S/N]LEx[S/Y]GVPSRFSGSGSGTEFTLTI
SSLQPDDFATYYCQx[Q/L]FQx[S/K]LPPFTFGGGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT
EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC (SEQ ID NO: 925),

b. a heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLE
WMGWIAPYSGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTA
VYYCARDAGTYSPFGYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 926) and a light
chain sequence that is
DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLI
YKAYNLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFT
FGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927),

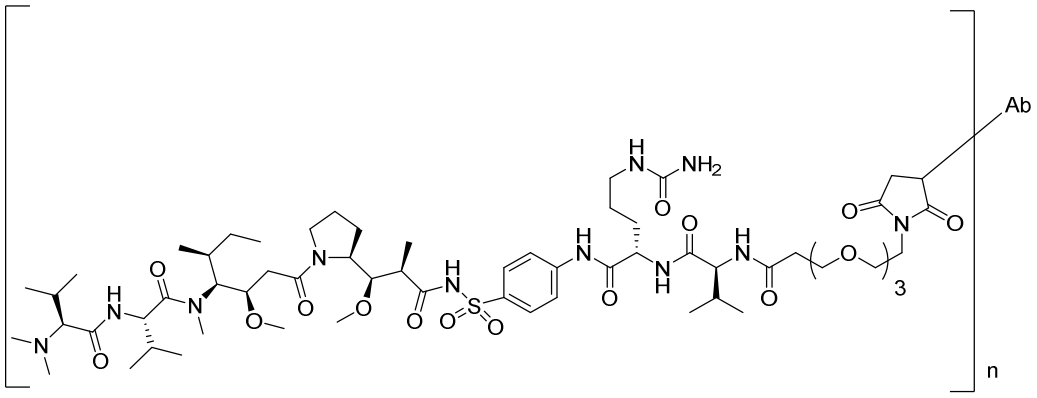
c. a heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWM
GWIAPYSGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC
ARDAGTYSPFGYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPG (SEQ ID NO: 926) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYK
ASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQFQSLPPFTFGGG
TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC (SEQ ID NO: 928),

d. a heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFDAYGISWVRQAPGQGLEWM
GWIAPYSGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC
ARDAGTYSPFGYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPG (SEQ ID NO: 929) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCRASESISNWLAWYQQKPGKAPKLLIYK
AYSLEYGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQFQKLPPFTFGG
GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC (SEQ ID NO: 930),

e. a heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFRSYGISWVRQAPGQGLEWM
GWVAPYSGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC
ARDAGTYSPYGYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPG (SEQ ID NO: 931) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCRASHSIDSWLAWYQQKPGKAPKLLIYK
ASYLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGG
TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC (SEQ ID NO: 932), or

f. a heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWM
GWIAPYSGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC
ARDAGTYSPFGYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPG (SEQ ID NO: 926) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCRASESISNWLAWYQQKPGKAPKLLIYK
AYSLEYGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQFQKLPPFTFGG
GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC (SEQ ID NO: 930).

[0056] Provided herein is an antibody-drug conjugate of Formula IX:



Formula IX

wherein:

Ab is a tissue factor (TF) antibody, wherein the Ab comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2, and a VL-CDR3 from the antibody designated 25A3, and

n is an integer greater than or equal to 1.

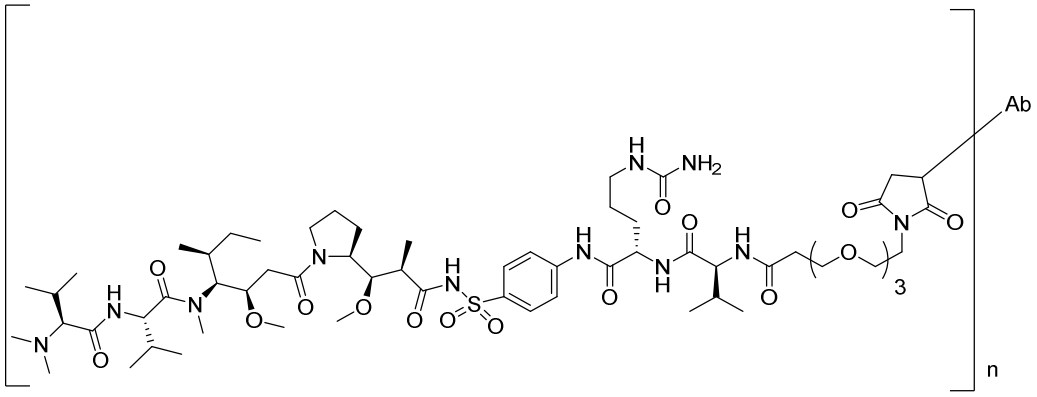
[0057] In some ~~embodiment~~examples, n is selected from the group consisting of 1, 2, 3, 4, and 5.

[0058] In some ~~embodiment~~examples, n is selected from the group consisting of 2, 3, and 4.

[0059] In some ~~embodiment~~examples, the Ab comprises a VH sequence that is SEQ ID NO: 151 and a VL sequence that is SEQ ID NO: 152.

[0060] In some ~~embodiment~~examples, the Ab comprises a full heavy chain sequence that is QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYSGN TNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGMDVWG QGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 926) and a light chain sequence that is DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLESGVPS RFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927).

[0061] Provided herein is an antibody-drug conjugate of Formula **IX**:



Formula IX

wherein:

Ab is a tissue factor (TF) antibody, wherein the Ab comprises a heavy chain sequence that is

QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGW
IAPYSGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAG
TYSPFGYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 926) and

a light chain sequence that is

DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAY
NLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEI
KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR
GEC (SEQ ID NO: 927), and

n is an integer greater than or equal to 1.

[0062] In some ~~embodiment~~examples, n is selected from the group consisting of 1, 2, 3, 4, and 5.

[0063] In some ~~embodiment~~examples, n is selected from the group consisting of 2, 3, and 4.

VNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 926) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLE
SGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927), and

the one or more linker-toxins are attached to the Ab through a covalent bond; and

represents a point of attachment of the linker-toxin to the Ab.

[0067] Provided herein is an antibody-drug conjugate composition comprising the antibody-drug conjugate disclosed herein, wherein the composition comprises a multiplicity of drug-antibody ratio (DAR) species, wherein the average DAR of the composition is 2-4.

[0068] In some ~~embodiment~~examples, the Ab is multispecific.

[0069] In some ~~embodiment~~examples, the Ab is a Fab, Fab', F(ab')2 , Fv, scFv, (scFv)2, single chain antibody molecule, dual variable domain antibody, single variable domain antibody, linear antibody, or V domain antibody.

[0070] In some ~~embodiment~~examples, the antibody comprises a scaffold, optionally wherein the scaffold is Fc, optionally human Fc.

[0071] In some ~~embodiment~~examples, the antibody comprises a heavy chain constant region of a class selected from IgG, IgA, IgD, IgE, and IgM.

[0072] In some ~~embodiment~~examples, the antibody comprises a heavy chain constant region of the class IgG, wherein the heavy chain constant region is from a subclass selected from IgG1, IgG2, IgG3, and IgG4.

[0073] In some ~~embodiment~~examples, the antibody comprises a heavy chain constant region of IgG1.

[0074] In some ~~embodiment~~examples, the Fc comprises one or more modifications, wherein the one or more modifications result in increased half-life, increased antibody-dependent cellular cytotoxicity (ADCC), increased antibody-dependent cellular phagocytosis (ADCP), increased complement-dependent cytotoxicity (CDC), or decreased effector function, compared with the Fc without the one or more modifications.

[0075] Provided herein is a pharmaceutical composition comprising the antibody-drug conjugate as disclosed herein and a pharmaceutically acceptable carrier.

[0076] Provided herein is a method of treating or preventing a disease or condition in a subject in need thereof, comprising administering to the subject an effective amount of the antibody-drug conjugate disclosed herein or the pharmaceutical composition as disclosed herein.

[0077] In some ~~embodiment~~examples, the disease or condition is cancer.

[0078] In some ~~embodiment~~examples, the cancer is selected from the group consisting of: head and neck cancer, ovarian cancer, gastric cancer, esophageal cancer, cervical cancer, prostate cancer, pancreatic cancer, estrogen receptors negative (ER-) breast cancer, progesterone receptors negative (PR-) breast cancer, HER2 negative (HER2-) triple negative breast cancer, glioblastoma, lung cancer, bladder cancer, melanoma, and kidney cancer.

[0079] In some ~~embodiment~~examples, the disease or condition involves neovascularization.

[0080] In some ~~embodiment~~examples, the disease or condition involving neovascularization is cancer.

[0081] In some ~~embodiment~~examples, the disease or condition involves vascular inflammation.

[0082] In some ~~embodiment~~examples, the method further comprises administering one or more additional therapeutic agents to the subject.

[0083] In some ~~embodiment~~examples, the composition further comprises the one or more additional therapeutic agents.

[0084] In some ~~embodiment~~examples, the additional therapeutic agent is formulated in a different pharmaceutical composition.

[0085] In some ~~embodiment~~examples, the additional therapeutic agent is administered prior to administering the composition.

[0086] In some ~~embodiment~~examples, the additional therapeutic agent is administered after administering the composition.

[0087] In some ~~embodiment~~examples, the additional therapeutic agent is administered contemporaneously with the composition.

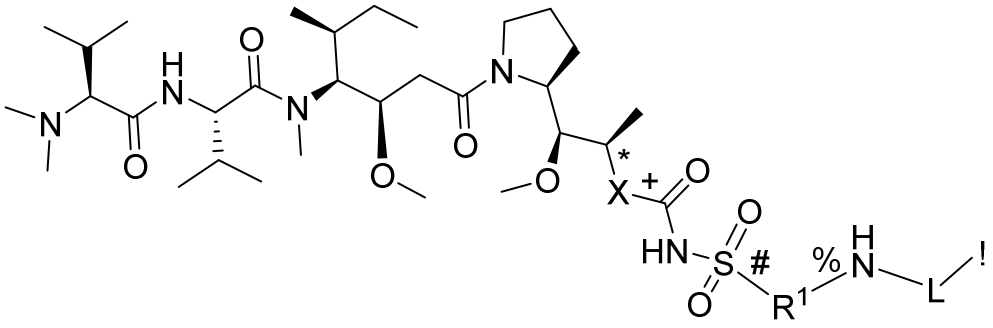
[0088] In some ~~embodiment~~examples, the subject is a human subject.

[0089] Provided herein is a process for preparing an antibody-drug conjugate, the process comprising:

(A) reacting a nucleophilic or an electrophilic group on an antigen binding protein (Ab) which binds to the extracellular domain of human Tissue Factor (TF) (SEQ ID NO:810)

vi. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25G1; and

(b) the antibody-drug conjugate comprises one or more moieties represented by Formula IV:



Formula IV

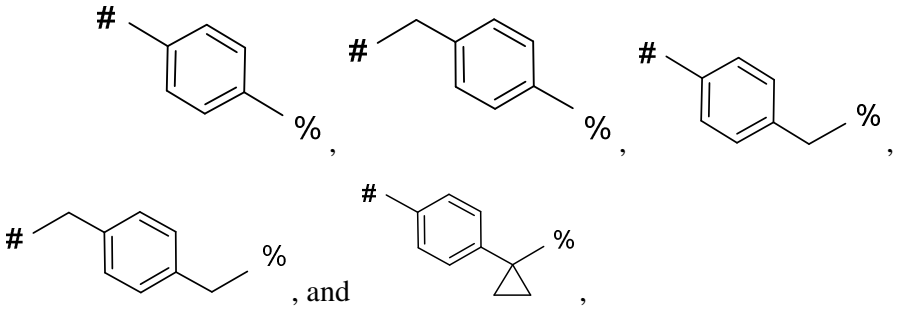
wherein:

X is *-C(O)NHCH($CH_2(R^2)$)-$^{+}$, wherein * and + represent the respective points of attachment as indicated in Formula IV, or X is absent;

L is a linker;

! represents the point of attachment of L to the Ab, where L is attahced to the Ab through a covalent bond;

R^1 is selected from the group consisting of:



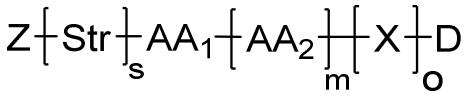
wherein # and % represent the respective points of attachment as indicated in Formula VI; and

R^2 is phenyl.

[0091] In some ~~embodiment~~examples, the nucleophilic or electrophilic group on the Ab is a thiol or an amine.

[0092] In some ~~embodiment~~examples, the process further comprises treating the Ab with a reducing agent to reduce one or more disulfide linkages in the Ab to provide the nucleophilic thiol group.

[0093] In some ~~embodiment~~examples, L is represented by:



Formula VII

wherein:

Z represents a functional group that binds to a target group of the Ab;

D represents the point of attachment to the amino group as indicated in Formula X;

Str is a stretcher;

AA_1 and AA_2 are each independently an amino acid, wherein AA_1-$[AA_2]_m$ forms a protease cleavage site;

X is a self-immolative group;

s is an integer selected from 0 and 1;

m is an integer selected from the group consisting of 1, 2, 3, and 4; and

o is an integer selected from 0, 1, and 2.

[0094] 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

[0095] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

[0096] FIG. 1 shows the structure of the linker-toxin referred to as Linker-Toxin A (also referred to herein as LT-A).

[0097] FIG. 2A shows the structure of a linker-toxin moiety of linker-toxin A (LT-A) as attached to an antibody, where ## represents a point of attachment to a tissue factor (TF) antibody. **FIG. 2B** shows a depiction of an antibody drug conjugate comprising a linker-toxin moiety of Linker-Toxin A (LT-A) and a TF antibody.

[0098] FIG. 3A shows the cell viability as indicated by CTG luminescence and the calculated IC_{50} in TF-positive A431 cells after a 4 h incubation with isotype control or 25A3-

each of which is incorporated by reference in its entirety), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene or FUT8 knockout CHO cells (*see* Yamane-Ohnuki *et al.*, *Biotech. Bioeng.*, 2004, 87: 614-622; Kanda *et al.*, *Biotechnol. Bioeng.*, 2006, 94:680-688; and WO 2003/085107; each of which is incorporated by reference in its entirety).

[00396] In some embodiments, an antibody provided herein is an aglycosylated antibody. An aglycosylated antibody can be produced using any method known in the art or described herein. In some aspects, an aglycosylated antibody is produced by modifying the antibody to remove all glycosylation sites. In some aspects, the glycosylation sites are removed only from the Fc region of the antibody. In some aspects, an aglycosylated antibody is produced by expressing the antibody in an organism that is not capable of glycosylation, such as *E. coli*, or by expressing the antibody in a cell-free reaction mixture.

[00397] In some embodiments, an antibody provided herein has a constant region with reduced effector function compared to a native IgG1 antibody. In some embodiments, the affinity of a constant region of an Fc region of an antibody provided herein for Fc receptor is less than the affinity of a native IgG1 constant region for such Fc receptor.

2.7. Constant Regions, Fc Region and Amino Acid Sequence Variants

[00398] In some embodiments, an antibody provided herein comprises one or more constant regions.

[00399] In some embodiments, the antibody comprises a human Ig constant domain. In some embodiments, the antibody comprises a constant region from a human IgA, IgG, IgE, IgD, or IgM antibody. In some embodiments, the antibody comprises a constant region from human IgG. The human IgG can be human IgG1, human IgG2, human IgG3, or human IgG4.

[00400] In some embodiments, the antibody comprises a human IgG1 CH1 domain. In some embodiments, the human IgG1 CH1 domain sequence is as follows: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV (SEQ ID NO: 933).

[00401] In some embodiments, the human IgG1 CH1 domain is from a particular allotype. Human IgG1 allotypes suitable for any of the antibodies herein are described in http://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/G1m_allotypes.html , which is hereby incorporated by reference in its entirety. In particular embodiments, the allotype is G1m3, also referred to herein as IGHG1*03. The G1m3, also known as IGHG1*03 allotype, is described in

http://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/G1m_allotypes.html , which is hereby incorporated by reference in its entirety.

[00402] In some embodiments, the human IgG1 CH1 region of allotype IGHG1*03 comprises the CH1 domain sequence ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV (SEQ ID NO: 934).

[00403] In some embodiments, an antibody provided herein comprises an Fc region. The Fc region can be from a human IgA, IgG, IgE, IgD, or IgM antibody.

[00404] In some embodiments, the antibody comprises a human IgG Fc region. The human IgG Fc region can be a human IgG1 Fc region, human IgG2 Fc region, human IgG3 Fc region, human IgG4 Fc region.

[00405] In particular embodiments, the antibody comprises a human IgG1 Fc region. The human IgG1 Fc region may comprise a hinge sequence. In some embodiments, the hinge sequence is EPKSCDKTHTCP.

[00406] The human IgG1 Fc region may comprise a human IgG1 CH2 domain sequence. In some embodiments, the human IgG1 CH2 domain sequence is as follows: PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK (SEQ ID NO: 935).

[00407] The human IgG1 Fc region may comprise a human IgG1 CH3 domain sequence. The human IgG1 CH3 domain sequence is as follows: GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 936). In some embodiments, the human IgG1 CH3 domain sequence further comprises a C-terminal lysine (K).

[00408] In some embodiments, the human IgG1 Fc region comprises the following sequence: PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 937). In some embodiments, the human IgG1 Fc region sequence further comprises a C-terminal lysine (K).

[00409] In some embodiments, the human IgG1 Fc region comprises the following sequence: EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV

KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 938). In some embodiments, the human IgG1 Fc region sequence further comprises a C-terminal lysine (K).

[00410] In some embodiments, the human IgG1 Fc region is of a particular allotype. Human IgG1 allotypes suitable for any of the antibodies herein are described in http://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/G1m_allotypes.html , which is hereby incorporated by reference in its entirety. In particular embodiments, the allotype is G1m3, also referred to herein as IGHG1*03. The G1m3, also known as IGHG1*03 allotype, is described in http://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/G1m_allotypes.html , which is hereby incorporated by reference in its entirety.

[00411] In some embodiments, the human IgG1 allotype IGHG1*03 Fc region comprises the following CH2 sequence:
PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK (SEQ ID NO: 935).

[00412] In some embodiments, the human IgG1 allotype IGHG1*03 Fc region comprises the following CH3 sequence:
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 939). In some embodiments, the CH3 region of the human IgG1 allotype IGHG1*03 Fc region further comprises a C-terminal lysine (K).

[00413] In some embodiments, the human IgG1 allotype IGHG1*03 Fc region comprises the following Fc sequence:
PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 940). In some embodiments, the human IgG1 allotype IGHG1*03 Fc region sequence further comprises a C-terminal lysine (K).

[00414] In some embodiments, the human IgG1 allotype IGHG1*03 Fc region comprises the following Fc sequence:
EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV

KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG (SEQ ID NO: 941). In some embodiments, the human IgG1 allotype IGHG1*03 Fc region sequence further comprises a C-terminal lysine (K).

[00415] In certain embodiments, an antibody provided herein comprises an Fc region with one or more amino acid substitutions, insertions, or deletions in comparison to a naturally occurring Fc region. In some aspects, such substitutions, insertions, or deletions yield antibodies with altered stability, glycosylation, or other characteristics. In some aspects, such substitutions, insertions, or deletions yield aglycosylated antibodies.

[00416] In some aspects, the Fc region of an antibody provided herein is modified to yield an antibody with altered affinity for an Fc receptor, or an antibody that is more immunologically inert. In some embodiments, the antibody variants provided herein possess some, but not all, effector functions. Such antibodies may be useful, for example, when the half-life of the antibody is important *in vivo*, but when certain effector functions (*e.g.*, complement activation and ADCC) are unnecessary or deleterious.

[00417] In some embodiments, the Fc region of an antibody provided herein is a human IgG4 Fc region comprising one or more of the hinge stabilizing mutations S228P and L235E. *See* Aalberse *et al.*, *Immunology*, 2002, 105:9-19, incorporated by reference in its entirety. In some embodiments, the IgG4 Fc region comprises one or more of the following mutations: E233P, F234V, and L235A. *See* Armour *et al.*, *Mol. Immunol.*, 2003, 40:585-593, incorporated by reference in its entirety. In some embodiments, the IgG4 Fc region comprises a deletion at position G236.

[00418] In some embodiments, the Fc region of an antibody provided herein is a human IgG1 Fc region comprising one or more mutations to reduce Fc receptor binding. In some aspects, the one or more mutations are in residues selected from S228 (*e.g.*, S228A), L234 (*e.g.*, L234A), L235 (*e.g.*, L235A), D265 (*e.g.*, D265A), and N297 (*e.g.*, N297A). In some aspects, the antibody comprises a PVA236 mutation. PVA236 means that the amino acid sequence ELLG (SEQ ID NO: 920), from amino acid position 233 to 236 of IgG1 or EFLG (SEQ ID NO: 921) of IgG4, is replaced by PVA. *See* U.S. Pat. No. 9,150,641, incorporated by reference in its entirety.

[00419] In some embodiments, the Fc region of an antibody provided herein is modified as described in Armour *et al.*, *Eur. J. Immunol.*, 1999, 29:2613-2624; WO 1999/058572; and/or U.K. Pat. App. No. 98099518; each of which is incorporated by reference in its entirety.

wherein: EE and FF represent the points of attachment to Z and AA_1, respectively; each occurrence of p is independently an integer from 2 to 6, and q is an integer from 2 to 8.

[00521] In some embodiments, in the ADC of general Formula **VI**, where L is a linker of general Formula **VII**, AA_1-$[AA_2]_m$ is selected from Val-Lys, Ala-Lys, Phe-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Arg, Ala-Phe, Val-Ala, Met-Lys, Asn-Lys, Ile-Pro, Ile-Val, Asp-Val, His-Val, Met-(D)Lys, Asn-(D)Lys, Val-(D)Asp, NorVal-(D)Asp, Ala-(D)Asp, Me_3Lys-Pro, PhenylGly-(D)Lys, Met-(D)Lys, Asn-(D)Lys, Pro-(D)Lys, Met-(D)Lys, Met-Cit-Val, Gly-Cit-Val, (D)Phe-Phe-Lys, (D)Ala-Phe-Lys, Gly-Phe-Leu-Gly (SEQ ID NO: 922), and Ala-Leu-Ala-Leu (SEQ ID NO: 923).

[00522] In some embodiments, in the ADC of general Formula **VI**, where L is a linker of general Formula **VII**, s is 1.

[00523] In some embodiments, in the ADC of general Formula **VI**, where L is a linker of general Formula **VII**, o is 0.

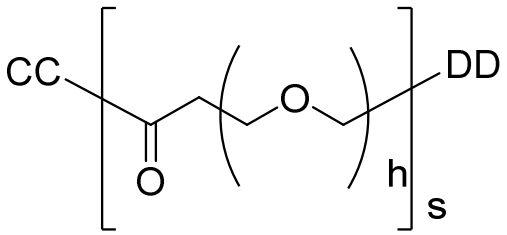
[00524] In some embodiments, in the ADC of general Formula **VI**, where L is a linker of general Formula **VII**, m is selected from 1, 2 and 3.

[00525] In some embodiments, in the ADC of general Formula **VI**, where L is a linker of general Formula **VII**, m is 1.

[00526] In some embodiments, in the ADC of general Formula **VI**, where L is a linker of general Formula **VII**, AA_1-$[AA_2]_m$ is a dipeptide selected from Val-Lys, Ala-Lys, Phe-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit and Trp-Cit.

[00527] In some embodiments, in the ADC of general Formula **VI**, where L is a linker of general Formula **VII**, each X_1 is independently selected from p-aminobenzyloxycarbonyl (PABC), p-aminobenzyl ether (PABE) and methylated ethylene diamine (MED).

[00528] In some embodiments, in the ADC of general Formula **VI**, where L is a linker of general Formula **VII**, and $[Str]_s$ is:



,

s is 1 and h is 3.

[00529] In certain embodiments, the ADC comprises a linker-toxin moiety having the structure of Formula **VIII**:

ii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A3,

iii. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A,

iv. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A5,

v. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25A5-T, or

vi. the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 are from the antibody designated 25G1, n is an integer greater than or equal to 1.

[00532] In some embodiments of the ADC of Formula **IX**, the Ab comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2, and a VL-CDR3 from the antibody designated 25A3.

[00533] In an embodiment, the ADCs described herein comprise an antibody that comprises:

a full heavy chain sequence that is QVQLVQSGAEVKKPGASVKVSCKASGYTFDx[V/A]YGISWVRQAPGQGLEWMGWIAPYx[N/S]GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 924) and a light chain sequence that is DIQMTQSPSTLSASVGDRVTITCx[R/Q]ASx[Q/E]SIx[S/N]x[S/N]WLAWYQQKPGKAPKLLIYKAx[S/Y]x[S/N]LEx[S/Y]GVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQx[Q/L]FQx[S/K]LPPFTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 942),

a heavy chain sequence that is QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYS

GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGM
DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
G (SEQ ID NO: 926) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLESG
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927),

a heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYS
GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGM
DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
G (SEQ ID NO: 926) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGV
PSRFSGSGSGTEFTLTISSLQPDDFATYYCQQFQSLPPFTFGGGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 928),

a heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFDAYGISWVRQAPGQGLEWMGWIAPYS
GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGM
DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI

EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
G (SEQ ID NO: 929) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCRASESISNWLAWYQQKPGKAPKLLIYKAYSLEYG
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQFQKLPPFTFGGGTKVEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 930),

a heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFRSYGISWVRQAPGQGLEWMGWVAPYS
GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPYGYGM
DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
G (SEQ ID NO: 931) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCRASHSIDSWLAWYQQKPGKAPKLLIYKASYLESG
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 932), or

a full heavy chain sequence that is
QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYS
GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGM
DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
G (SEQ ID NO: 926) and a light chain sequence that is
DIQMTQSPSTLSASVGDRVTITCRASESISNWLAWYQQKPGKAPKLLIYKAYSLEYG
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQFQKLPPFTFGGGTKVEIKRTVAAPSV

FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 930).

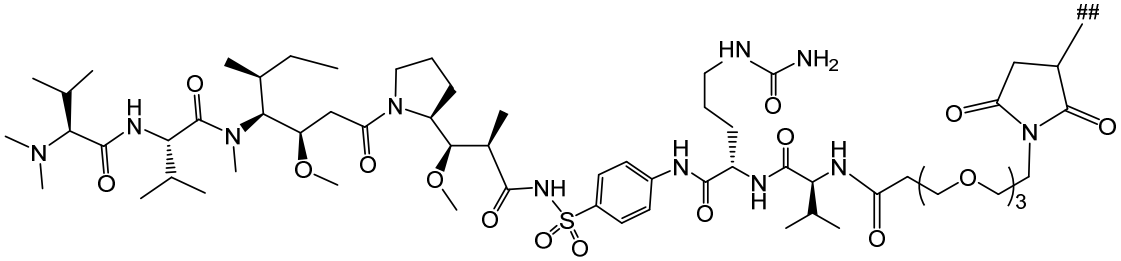
[00534] In an embodiment, the ADCs described herein comprise an antibody that comprises:

a heavy chain sequence that is

QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYS
GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGM
DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
G (SEQ ID NO: 926) and a light chain sequence that is

DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLESG
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927).

[00535] In an embodiment, described herein is an antibody-drug conjugate comprising an antibody (Ab) and one or more linker-toxins of the following structure of Formula **VIII**:



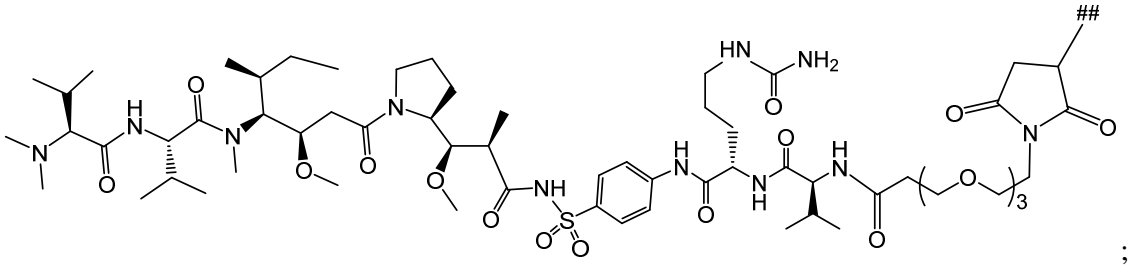
Formula VIII

wherein: Ab is a tissue factor (TF) antibody, wherein the Ab comprises a VH-CDR1, a VH-CDR2, a VH-CDR3, a VL-CDR1, a VL-CDR2, and a VL-CDR3 from the antibody designated 25A3; the one or more linker-toxins are attached to the Ab through a covalent bond; and ## represents a point of attachment of the linker-toxin to the Ab.

[00536] In some embodiments, provided herein is a composition comprising an ADC comprising an antibody (Ab) and one or more linker-toxins of Formula **VIII**. In an

embodiment, the composition comprises a multiplicity of drug-antibody ratio (DAR) species. In some embodiments, the average DAR of the composition is 2-4.

[00537] In an embodiments, provided herein is an antibody-drug conjugate comprising an antibody (Ab) and one or more linker-toxins of the following structure of Formula **VIII**:



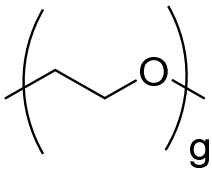
;

wherein:

Ab is a tissue factor (TF) antibody, wherein the Ab comprises a heavy chain sequence that is QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYS GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGM DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G (SEQ ID NO: 926) and a light chain sequence that is DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLESG VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927), the one or more linker-toxins are attached to the Ab through a covalent bond; and ## represents a point of attachment of the linker-toxin to the Ab.

[00538] In another embodiment, described herein is an antibody-drug conjugate composition comprising an ADC of the present disclosure, wherein the composition comprises a multiplicity of drug-antibody ratio (DAR) species, wherein the average DAR of the composition is 2-4.

Linkers



wherein g is an integer from 1-20. In some embodiments, g is 3.

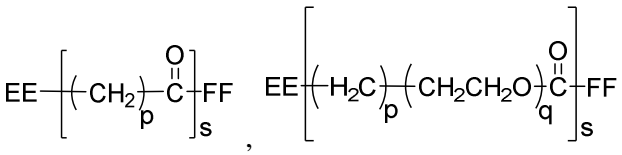
[00548] In certain embodiments, the linker is a cleavable linker comprising a peptide component that includes two or more amino acids and is cleavable by an intracellular protease, such as lysosomal protease or an endosomal protease. A peptide component may comprise amino acid residues that occur naturally and/or minor amino acids and/or non-naturally occurring amino acid analogues, such as citrulline. Peptide components may be designed and optimized for enzymatic cleavage by a particular enzyme, for example, a tumor-associated protease, cathepsin B, C or D, or a plasmin protease.

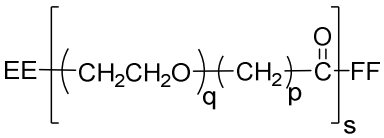
[00549] In certain embodiments, the linker included in the ADCs may be a dipeptide-containing linker, such as a linker containing valine-citrulline (Val-Cit) or phenylalanine-lysine (Phe-Lys). Other examples of suitable dipeptides for inclusion in linkers include Val-Lys, Ala-Lys, Me-Val-Cit, Phe-homoLys, Phe-Cit, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Arg, Ala-Phe, Val-Ala, Met-Lys, Asn-Lys, Ile-Pro, Ile-Val, Asp-Val, His-Val, Met-(D)Lys, Asn-(D)Lys, Val-(D)Asp, NorVal-(D)Asp, Ala-(D)Asp, Me_3Lys-Pro, PhenylGly-(D)Lys, Met-(D)Lys, Asn-(D)Lys, Pro-(D)Lys and Met-(D)Lys. Cleavable linkers may also include longer peptide components such as tripeptides, tetrapeptides or pentapeptides. Examples include, but are not limited to, the tripeptides Met-Cit-Val, Gly-Cit-Val, (D)Phe-Phe-Lys and (D)Ala-Phe-Lys, and the tetrapeptides Gly-Phe-Leu-Gly (SEQ ID NO: 922) and Ala-Leu-Ala-Leu (SEQ ID NO: 923).

[00550] In certain embodiments, the cytotoxic agent is conjugated to the antibody using a linker comprising valine-citrulline (vc).

[00551] Cleavable linkers may optionally further comprise one or more additional components such as self-immolative and self-elimination groups, stretchers or hydrophilic moieties.

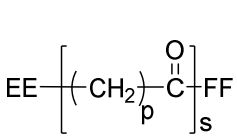
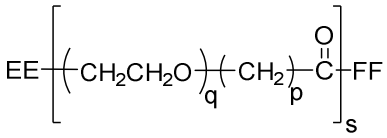
[00552] Self-immolative and self-elimination groups that find use in linkers include, for example, p-aminobenzyloxycarbonyl (PABC) and p-aminobenzyl ether (PABE) groups, and methylated ethylene diamine (MED). Other examples of self-immolative groups include, but are not limited to, aromatic compounds that are electronically similar to the PABC or PABE group such as heterocyclic derivatives, for example 2-aminoimidazol-5-methanol derivatives as described in U.S. Patent No. 7,375,078. Other examples include groups that undergo cyclization upon amide bond hydrolysis, such as substituted and unsubstituted 4-


, and


,

wherein: EE and FF represent the points of attachment to Z and AA_1, respectively; each occurrence of p is independently an integer from 2 to 10; and each occurrence of q is independently an integer from 1 to 10.

[00563] In some embodiments, in the linker of general Formula **VII**, $[Str]_s$ is selected from:


and 
,

wherein: EE and FF represent the points of attachment to Z and AA_1, respectively; each occurrence of p is independently an integer from 2 to 6, and q is an integer from 2 to 8.

[00564] In some embodiments, in the linker of general Formula **VII**, AA_1-$[AA_2]_m$ is selected from Val-Lys, Ala-Lys, Phe-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Arg, Ala-Phe, Val-Ala, Met-Lys, Asn-Lys, Ile-Pro, Ile-Val, Asp-Val, His-Val, Met-(D)Lys, Asn-(D)Lys, Val-(D)Asp, NorVal-(D)Asp, Ala-(D)Asp, Me_3Lys-Pro, PhenylGly-(D)Lys, Met-(D)Lys, Asn-(D)Lys, Pro-(D)Lys, Met-(D)Lys, Met-Cit-Val, Gly-Cit-Val, (D)Phe-Phe-Lys, (D)Ala-Phe-Lys, Gly-Phe-Leu-Gly (SEQ ID NO: 922) and Ala-Leu-Ala-Leu (SEQ ID NO: 923).

[00565] In some embodiments, in the linker of general Formula **VII**, m is 1 (*i.e.* AA_1-$[AA_2]_m$ is a dipeptide).

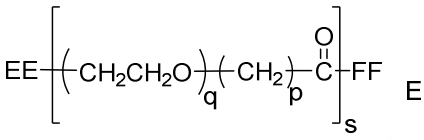
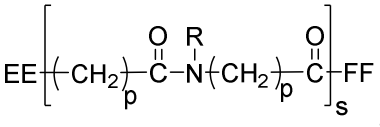
[00566] In some embodiments, in the linker of general Formula **VII**, AA_1-$[AA_2]_m$ is a dipeptide selected from Val-Lys, Ala-Lys, Phe-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit and Trp-Cit.

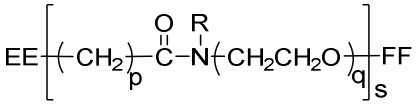
[00567] In some embodiments, in the linker of general Formula **VII**, each X_1 is independently selected from p-aminobenzyloxycarbonyl (PABC), p-aminobenzyl ether (PABE) and methylated ethylene diamine (MED).

[00568] In some embodiments, in the linker of general Formula **VII**, m is 1, 2 or 3.

[00569] In some embodiments, in the linker of general Formula **VII**, s is 1.

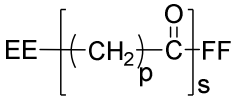
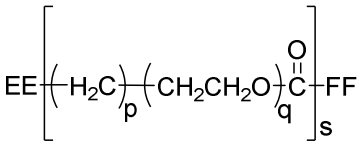
[00570] In some embodiments, in the linker of general Formula **VII**, o is 0.

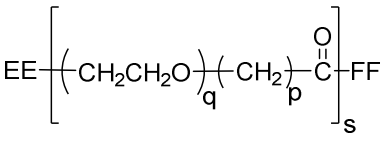


, and


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wherein: EE and FF represent the points of attachment to Z and AA_1, respectively; R is selected from hydrogen and C_1-C_6 alkyl; each occurrence of p is independently an integer from 2 to 10; and each occurrence of q is independently an integer from 1 to 10.

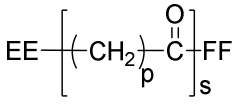
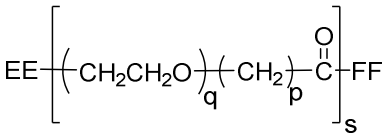
[00584] In some embodiments, in the linker of general Formula **XII**, $[Str]_s$ is selected from the group consisting of:



, and


,

wherein: EE and FF represent the points of attachment to Z and AA_1, respectively; each occurrence of p is independently an integer from 2 to 10; and each occurrence of q is independently an integer from 1 to 10.

[00585] In some embodiments, in the linker of general Formula **XII**, $[Str]_s$ is selected from:


and

,

wherein: EE and FF represent the points of attachment to Z and AA_1, respectively; each occurrence of p is independently an integer from 2 to 6, and q is an integer from 2 to 8.

[00586] In some embodiments, in the linker of general Formula **XII**, AA_1-$[AA_2]_m$ is selected from Val-Lys, Ala-Lys, Phe-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Arg, Ala-Phe, Val-Ala, Met-Lys, Asn-Lys, Ile-Pro, Ile-Val, Asp-Val, His-Val, Met-(D)Lys, Asn-(D)Lys, Val-(D)Asp, NorVal-(D)Asp, Ala-(D)Asp, Me_3Lys-Pro, PhenylGly-(D)Lys, Met-(D)Lys, Asn-(D)Lys, Pro-(D)Lys, Met-(D)Lys, Met-Cit-Val, Gly-Cit-Val, (D)Phe-Phe-Lys, (D)Ala-Phe-Lys, Gly-Phe-Leu-Gly (SEQ ID NO: 922) and Ala-Leu-Ala-Leu (SEQ ID NO: 923).

Group	VH Domain Consensus (SEQ ID NO)	VL Domain Consensus (SEQ ID NO)
	MELRSLRSDDTAVYYCARDAGTYSPYGY GMDVWGQGTTVTVSS (SEQ ID NO:870)	TISSLQPDDFATYYCQx[Q/L/R]FQSLPPFTF GGGTKVEIK (SEQ ID NO:871)

Table 21: Consensus CDRs

Antibody Group		Lineage 25A	Lineage 25G
VH CDR Seq.*	*VH CDR1*	GYTFDx[V/A]YGIS (SEQ ID NO:872)	GYTFRSYGIS (SEQ ID NO:878)
	VH CDR2	WIAPYx[N/S]GNTNYAQKLQG (SEQ ID NO:873)	WVAPYx[N/S]GNTNYAQKLQG (SEQ ID NO:879)
	VH CDR3	DAGTYSPFGYGMDV (SEQ ID NO:874)	DAGTYSPYGYGMDV (SEQ ID NO:880)
VL CDR Seq.*	*VL CDR1*	x[R/Q]ASx[Q/E]SIx[S/N]x[S/N]WLA (SEQ ID NO:875)	x[R/Q]ASx[Q/H]SIx[S/D]SWLA (SEQ ID NO:881)
	VL CDR2	KAx[S/Y]x[S/N]LEx[S/Y] (SEQ ID NO:876)	x[K/S]ASx[S/Y]LES (SEQ ID NO:882)
	VL CDR3	Qx[Q/L]FQx[S/K]LPPFT (SEQ ID NO:877)	Qx[Q/L/R]FQSLPPFT (SEQ ID NO:883)

*Exemplary CDR sequences encompass amino acids as determined by Kabat plus Chothia

Table 22: Antibody sequences

variable regions in bold; cysteines involved in drug conjugation underlined

Clone	HEAVY CHAIN	LIGHT CHAIN
25A	**QVQLVQSGAEVKKPGASVKVSCKASGY TFDVYGISWVRQAPGQGLEWMGWIAP YSGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCARDAGTYSPFG YGMDVWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 926)	**DIQMTQSPSTLSASVGDRVTITCRASQSIS SWLAWYQQKPGKAPKLLIYKASSLESG VPSRFSGSGSGTEFTLTISSLQPDDFATYY CQQFQSLPPFTFGGGTKVEIK**RTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 928)
25A3	**QVQLVQSGAEVKKPGASVKVSCKASGY TFDVYGISWVRQAPGQGLEWMGWIAP YSGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCARDAGTYSPFG YGMDVWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSR	**DIQMTQSPSTLSASVGDRVTITCQASQSI NNWLAWYQQKPGKAPKLLIYKAYNLES GVPSRFSGSGSGTEFTLTISSLQPDDFAT YYCQLFQSLPPFTFGGGTKVEIK**RTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC (SEQ ID NO: 927)

Clone	HEAVY CHAIN	LIGHT CHAIN
	WQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 926)	
25A5	**QVQLVQSGAEVKKPGASVKVSCKASGY TFDVYGISWVRQAPGQGLEWMGWIAP YSGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCARDAGTYSPFG YGMDVWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 926)	**DIQMTQSPSTLSASVGDRVTITCRASESIS NWLAWYQQKPGKAPKLLIYKAYSLEYG VPSRFSGSGSGTEFTLTISSLQPDDFATYY CQQFQKLPPFTFGGGTKVEIK**RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 930)
25A5T	**QVQLVQSGAEVKKPGASVKVSCKASGY TFDAYGISWVRQAPGQGLEWMGWIAP YSGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCARDAGTYSPFG YGMDVWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 929)	**DIQMTQSPSTLSASVGDRVTITCRASESIS NWLAWYQQKPGKAPKLLIYKAYSLEYG VPSRFSGSGSGTEFTLTISSLQPDDFATYY CQQFQKLPPFTFGGGTKVEIK**RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 930)
25G	**QVQLVQSGAEVKKPGASVKVSCKASGY TFRSYGISWVRQAPGQGLEWMGWVAP YNGNTNYAQKLQGRVTMTTDTSTSTA YMELRSLRSDDTAVYYCARDAGTYSPY GYGMDVWGQGTTVTVSS**ASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO: 943)	**DIQMTQSPSTLSASVGDRVTITCRASQSIS SWLAWYQQKPGKAPKLLIYKASSLESG VPSRFSGSGSGTEFTLTISSLQPDDFATYY CQQFQSLPPFTFGGGTKVEIK**RTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 928)
25G1	**QVQLVQSGAEVKKPGASVKVSCKASGY TFRSYGISWVRQAPGQGLEWMGWVAP YSGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCARDAGTYSPYG YGMDVWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVS	**DIQMTQSPSTLSASVGDRVTITCRASHSI DSWLAWYQQKPGKAPKLLIYKASYLES GVPSRFSGSGSGTEFTLTISSLQPDDFAT YYCQLFQSLPPFTFGGGTKVEIK**RTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDS

Clone	HEAVY CHAIN	LIGHT CHAIN
	WNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 931)	TYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC (SEQ ID NO: 932)
25G9	**QVQLVQSGAEVKKPGASVKVSCKASGY TFRSYGISWVRQAPGQGLEWMGWVAP YSGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCARDAGTYSPYG YGMDVWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 931)	**DIQMTQSPSTLSASVGDRVTITCQASQSI DSWLAWYQQKPGKAPKLLIYSASYLES GVPSRFSGSGSGTEFTLTISSLQPDDFAT YYCQRFQSLPPFTFGGGTKVEIK**RTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC (SEQ ID NO: 944)
Lineage 25A consensus	**QVQLVQSGAEVKKPGASVKVSCKASGY TFDx[V/A]YGISWVRQAPGQGLEWMG WIAPYx[N/S]GNTNYAQKLQGRVTMTT DTSTSTAYMELRSLRSDDTAVYYCARD AGTYSPFGYGMDVWGQGTTVTVSS**AST KGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKRVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPG (SEQ ID NO: 924)	**DIQMTQSPSTLSASVGDRVTITCx[R/Q]AS x[Q/E]SIx[S/N]x[S/N]WLAWYQQKPGKAP KLLIYKAx[S/Y]x[S/N]LEx[S/Y]GVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQx[Q/L] FQx[S/K]LPPFTFGGGTKVEIK**RTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 942)