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

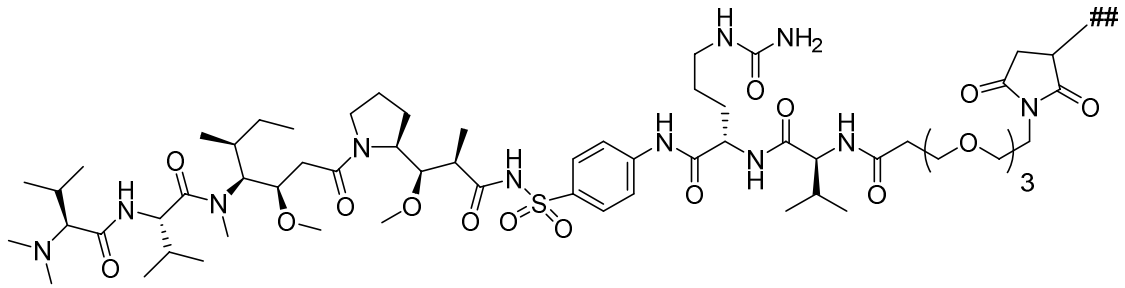
[0004] Provided herein are anti-TF antibody-drug conjugates, and related methods.

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

a. an antigen binding protein (Ab) which binds to the extracellular domain of human Tissue Factor (TF) (SEQ ID NO:810), wherein the Ab comprises a VH-CDR1, a VH-CDR2, and a VH-CDR3 comprising the amino acid sequences of the VH-CDR1, the VH-CDR2, and the VH-CDR3, respectively, as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 151, and a VL-CDR1, a VL-CDR2, and a VL-CDR3 comprising the amino acid sequences of the VL-CDR1, the VL-CDR2, and the VL-CDR3, respectively, as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 152,

and

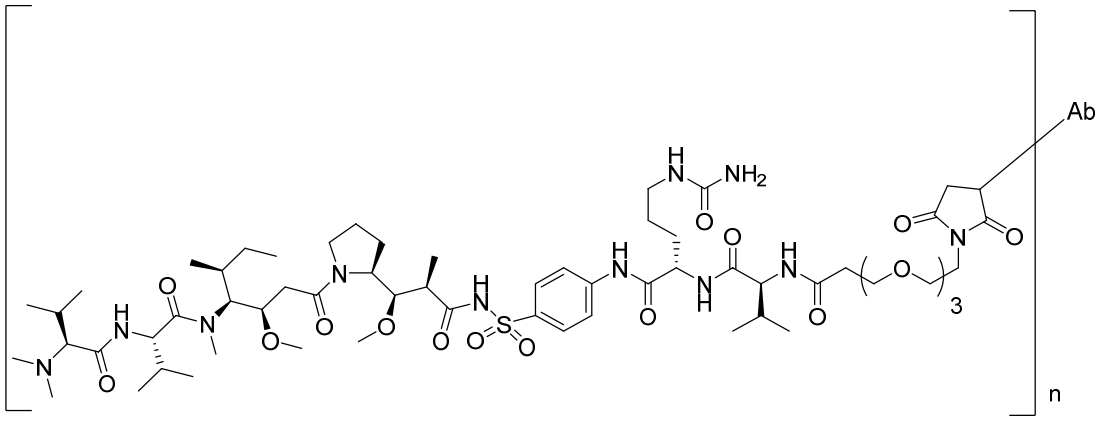
b. one or more linker-toxin moieties represented by Formula VIII:



Formula VIII

wherein ## represents the point of attachment of the linker-toxin moiety to the Ab through a covalent bond.

[0004b] In another aspect, provided herein is an antibody-drug conjugate of Formula IX:



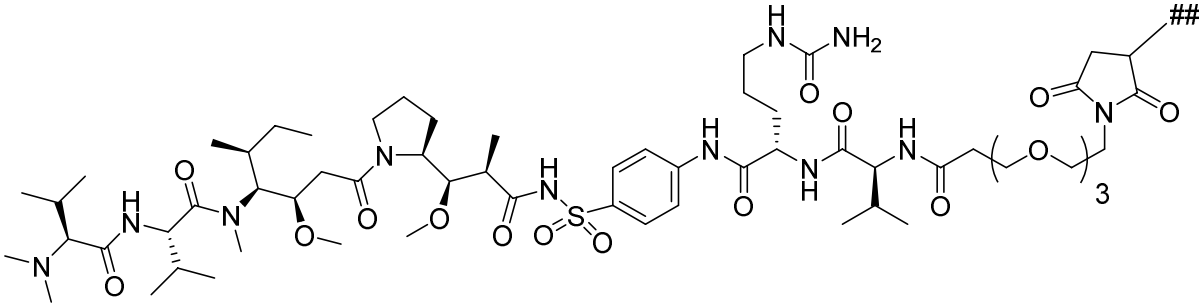
Formula IX

wherein:

n is an integer selected from the group consisting of 2, 3 and 4, and Ab comprises a heavy chain sequence comprising
QVQVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYSG
NTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGMD
VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 926) and a light chain sequence comprising
DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLESG
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927).

[0004c] In another 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 to the extracellular domain of human Tissue Factor (TF) (SEQ ID NO:810) with a linker-toxin moiety represented by Formula VIII:



Formula VIII

wherein ## represents the point of attachment of the linker-toxin moiety to the Ab through a covalent bond

to provide the antibody drug conjugate;

wherein

the Ab comprises a VH-CDR1, a VH-CDR2, and a VH-CDR3 comprising the amino acid sequences of the VH-CDR1, the VH-CDR2, and the VH-CDR3, respectively, as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 151, and a VL-CDR1, a VL-CDR2, and a VL-CDR3 comprising the amino acid sequences of the VL-CDR1, the VL-CDR2, and the VL-CDR3, respectively, as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 152.

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

a. 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,

Table 7: Antibody 25A-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GYTFDVYGIS (SEQ ID NO:77)	VYGIS (SEQ ID NO:83)	GYTFDVY (SEQ ID NO:89)	GYTFDVYGIS (SEQ ID NO:95)	DVYGIS (SEQ ID NO:101)	GYTFDVYG (SEQ ID NO:107)
	VH CDR2	WIAPYNGNTNY AQKLQG (SEQ ID NO:78)	WIAPYNGNTNY AQKLQG (SEQ ID NO:84)	PYNG (SEQ ID NO:90)	WIAPYNGNTN (SEQ ID NO:96)	WMGWIAPYNGN TN (SEQ ID NO:102)	IAPYNGNT (SEQ ID NO:108)
	VH CDR3	DAGTYSPFGYG MDV (SEQ ID NO:79)	DAGTYSPFGYG MDV (SEQ ID NO:85)	AGTYSPFGYGM D (SEQ ID NO:91)	DAGTYSPFGYG MDV (SEQ ID NO:97)	ARDAGTYSPFGY GMD (SEQ ID NO:103)	ARDAGTYSPFGY GMDV (SEQ ID NO:109)
VL CDR Seq.	*VL CDR1*	RASQSISSWLA (SEQ ID NO:80)	RASQSISSWLA (SEQ ID NO:86)	SQSISSW (SEQ ID NO:92)	RASQSISSWLA (SEQ ID NO:98)	SSWLAWY (SEQ ID NO:104)	QSISSW (SEQ ID NO:110)
	VL CDR2	KASSLES (SEQ ID NO:81)	KASSLES (SEQ ID NO:87)	KAS (SEQ ID NO:93)	KASSLES (SEQ ID NO:99)	LLIYKASSLE (SEQ ID NO:105)	KAS (SEQ ID NO:111)
	VL CDR3	QQFQSLPPFT (SEQ ID NO:82)	QQFQSLPPFT (SEQ ID NO:88)	FQSLPPF (SEQ ID NO:94)	QQFQSLPPFT (SEQ ID NO:100)	QQFQSLPPF (SEQ ID NO:106)	QQFQSLPPFT (SEQ ID NO:112)
VH Sequence*: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFDVYGIS**WVRQAPGQGLEWMG**WIAPYNGNTNYAQKLQG**RVTMTTDTSTSTAYMELRSLRSDD TAVYYCAR**DAGTYSPFGYGMDV**WGQGTTVTVSS (SEQ ID NO:113)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**RASQSISSWLA**WYQQKPGKAPKLLIY**KASSLES**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QQFQSLPP FT**FGGGTKVEIK (SEQ ID NO:114)							

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

Table 8: Antibody 25A3-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GYTFDVYGIS (SEQ ID NO:115)	VYGIS (SEQ ID NO:121)	GYTFDVY (SEQ ID NO:127)	GYTFDVYGIS (SEQ ID NO:133)	DVYGIS (SEQ ID NO:139)	GYTFDVYG (SEQ ID NO:145)
	VH CDR2	WIAPYSGNTNY AQKLQG (SEQ ID NO:116)	WIAPYSGNTNY AQKLQG (SEQ ID NO:122)	PYSG (SEQ ID NO:128)	WIAPYSGNTN (SEQ ID NO:134)	WMGWIAPYSG NTN (SEQ ID NO:140)	IAPYSGNT (SEQ ID NO:146)
	VH CDR3	DAGTYSPFGYG MDV (SEQ ID NO:117)	DAGTYSPFGYG MDV (SEQ ID NO:123)	AGTYSPFGYG MD (SEQ ID NO:129)	DAGTYSPFGYG MDV (SEQ ID NO:135)	ARDAGTYSPFG YGMD (SEQ ID NO:141)	ARDAGTYSPFG YGMDV (SEQ ID NO:147)
VL CDR Seq.	*VL CDR1*	QASQSINNWLA (SEQ ID NO:118)	QASQSINNWLA (SEQ ID NO:124)	SQSINNW (SEQ ID NO:130)	QASQSINNWLA (SEQ ID NO:136)	NNWLAWY (SEQ ID NO:142)	QSINNW (SEQ ID NO:148)
	VL CDR2	KAYNLES (SEQ ID NO:119)	KAYNLES (SEQ ID NO:125)	KAY (SEQ ID NO:131)	KAYNLES (SEQ ID NO:137)	LLIYKAYNLE (SEQ ID NO:143)	KAY (SEQ ID NO:149)
	VL CDR3	QLFQSLPPFT (SEQ ID NO:120)	QLFQSLPPFT (SEQ ID NO:126)	FQSLPPF (SEQ ID NO:132)	QLFQSLPPFT (SEQ ID NO:138)	QLFQSLPPF (SEQ ID NO:144)	QLFQSLPPFT (SEQ ID NO:150)
VH Sequence*: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFDVYGIS**WVRQAPGQGLEWMG**WIAPYSGNTNYAQKLQG**RVTMTTDTSTSTAYME LRSLRSDDTAVYYCAR**DAGTYSPFGYGMDV**WGQGTTVTVSS (SEQ ID NO:151)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**QASQSINNWLA**WYQQKPGKAPKLLIY**KAYNLES**GVPSRFSGSGSGTEFTLTISSLQPDDFATYY C**QLFQSLPPFT**FGGGTKVEIK (SEQ ID NO:152)							

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

Table 9: Antibody 25A5-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GYTFDVYGIS (SEQ ID NO:153)	VYGIS (SEQ ID NO:159)	GYTFDVY (SEQ ID NO:165)	GYTFDVYGIS (SEQ ID NO:171)	DVYGIS (SEQ ID NO:177)	GYTFDVYG (SEQ ID NO:183)
	VH CDR2	WIAPYSGNTNY AQKLQG (SEQ ID NO:154)	WIAPYSGNTNY AQKLQG (SEQ ID NO:160)	PYSG (SEQ ID NO:166)	WIAPYSGNTN (SEQ ID NO:172)	WMGWIAPYSG NTN (SEQ ID NO:178)	IAPYSGNT (SEQ ID NO:184)
	VH CDR3	DAGTYSPFGYG MDV (SEQ ID NO:155)	DAGTYSPFGYG MDV (SEQ ID NO:161)	AGTYSPFGYG MD (SEQ ID NO:167)	DAGTYSPFGYG MDV (SEQ ID NO:173)	ARDAGTYSPFG YGMD (SEQ ID NO:179)	ARDAGTYSPFG YGMDV (SEQ ID NO:185)
VL CDR Seq.	*VL CDR1*	RASESISNWLA (SEQ ID NO:156)	RASESISNWLA (SEQ ID NO:162)	SESISNW (SEQ ID NO:168)	RASESISNWLA (SEQ ID NO:174)	SNWLAWY (SEQ ID NO:180)	ESISNW (SEQ ID NO:186)
	VL CDR2	KAYSLEY (SEQ ID NO:157)	KAYSLEY (SEQ ID NO:163)	KAY (SEQ ID NO:169)	KAYSLEY (SEQ ID NO:175)	LLIYKAYSLE (SEQ ID NO:181)	KAY (SEQ ID NO:187)
	VL CDR3	QQFQKLPPFT (SEQ ID NO:158)	QQFQKLPPFT (SEQ ID NO:164)	FQKLPPF (SEQ ID NO:170)	QQFQKLPPFT (SEQ ID NO:176)	QQFQKLPPF (SEQ ID NO:182)	QQFQKLPPFT (SEQ ID NO:188)
VH Sequence*: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFDVYGIS**WVRQAPGQGLEWMG**WIAPYSGNTNYAQKLQG**RVTMTTDTSTSTAYME LRSLRSDDTAVYYCAR**DAGTYSPFGYGMDV**WGQGTTVTVSS (SEQ ID NO:189)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**RASESISNWLA**WYQQKPGKAPKLLIY**KAYSLEY**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC **QQFQKLPPFT**FGGGTKVEIK (SEQ ID NO:190)							

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

Table 10: Antibody 25A5-T-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GYTFDAYGIS (SEQ ID NO:884)	AYGIS (SEQ ID NO:890)	GYTFDAY (SEQ ID NO:896)	GYTFDAYGIS (SEQ ID NO:902)	DAYGIS (SEQ ID NO:908)	GYTFDAYG (SEQ ID NO:914)
	VH CDR2	WIAPYSGNTNY AQKLQG (SEQ ID NO:885)	WIAPYSGNTNY AQKLQG (SEQ ID NO:891)	PYSG (SEQ ID NO:897)	WIAPYSGNTN (SEQ ID NO:903)	WMGWIAPYSG NTN (SEQ ID NO:909)	IAPYSGNT (SEQ ID NO:915)
	VH CDR3	DAGTYSPFGYG MDV (SEQ ID NO:886)	DAGTYSPFGYG MDV (SEQ ID NO:892)	AGTYSPFGYG MD (SEQ ID NO:898)	DAGTYSPFGYG MDV (SEQ ID NO:904)	ARDAGTYSPFG YGMD (SEQ ID NO:910)	ARDAGTYSPFG YGMDV (SEQ ID NO:916)
VL CDR Seq.	*VL CDR1*	RASESISNWLA (SEQ ID NO:887)	RASESISNWLA (SEQ ID NO:893)	SESISNW (SEQ ID NO:899)	RASESISNWLA (SEQ ID NO:905)	SNWLAWY (SEQ ID NO:911)	ESISNW (SEQ ID NO:917)
	VL CDR2	KAYSLEY (SEQ ID NO:888)	KAYSLEY (SEQ ID NO:894)	KAY (SEQ ID NO:900)	KAYSLEY (SEQ ID NO:906)	LLIYKAYSLE (SEQ ID NO:912)	KAY (SEQ ID NO:918)
	VL CDR3	QQFQKLPPFT (SEQ ID NO:889)	QQFQKLPPFT (SEQ ID NO:895)	FQKLPPF (SEQ ID NO:901)	QQFQKLPPFT (SEQ ID NO:907)	QQFQKLPPF (SEQ ID NO:913)	QQFQKLPPFT (SEQ ID NO:919)
VH Sequence*: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFDAYGIS**WVRQAPGQGLEWMG**WIAPYSGNTNYAQKLQG**RVTMTTDTSTSTAYME LRSLRSDDTAVYYCAR**DAGTYSPFGYGMDV**WGQGTTVTVSS (SEQ ID NO:836)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**RASESISNWLA**WYQQKPGKAPKLLIY**KAYSLEY**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC **QQFQKLPPFT**FGGGTKVEIK (SEQ ID NO:837)							

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

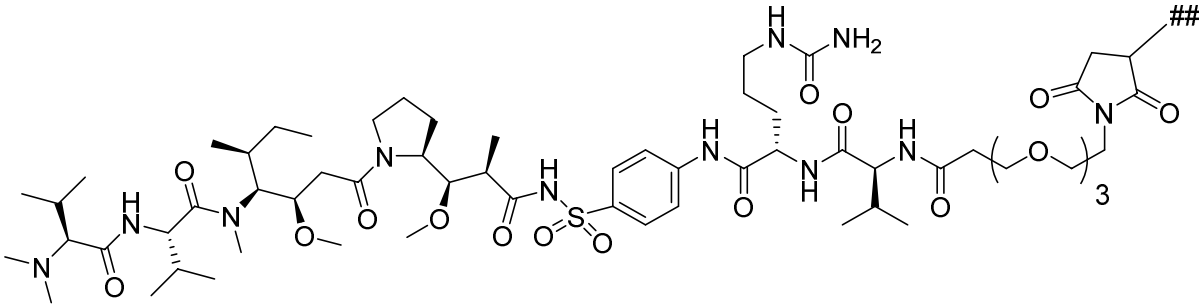
CLAIMS

1. An antibody-drug conjugate comprising:

a. 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, and a VH-CDR3 comprising the amino acid sequences of the VH-CDR1, the VH-CDR2, and the VH-CDR3, respectively, as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 151, and a VL-CDR1, a VL-CDR2, and a VL-CDR3 comprising the amino acid sequences of the VL-CDR1, the VL-CDR2, and the VL-CDR3, respectively, as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 152,

and

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



Formula VIII

wherein ## represents the point of attachment of the linker-toxin moiety to the Ab through a covalent bond.

2. The antibody-drug conjugate of claim 1, wherein the Ab comprises

a VH comprising the amino acid sequence of SEQ ID NO: 151 and a VL comprising the amino acid sequence of SEQ ID NO: 152.

3. The antibody-drug conjugate of claim 1, wherein

(i) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 115, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 116, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 117, the VL-CDR1 comprises the amino acid sequence

of SEQ ID NO: 118, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 119, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 120;

(ii) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 121, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 122, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 123, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 124, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 125, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 126;

(iii) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 127, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 128, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 129, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 130, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 131, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 132;

(iv) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 133, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 134, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 135, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 136, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 137, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 138;

(v) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 139, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 140, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 141, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 142, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 143, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 144; or

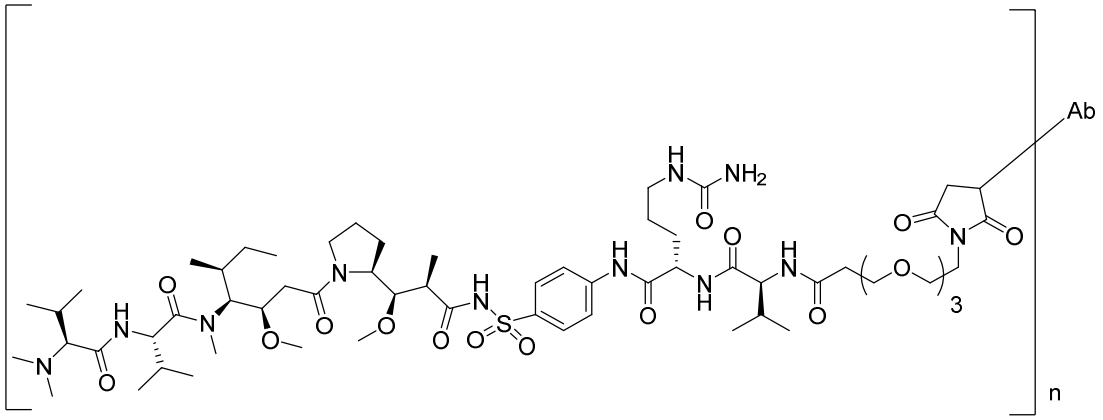
(vi) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 145, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 146, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 147, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 148, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 149, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 150.

4. The antibody-drug conjugate of any one of claims 1-3, wherein the Ab comprises:

a heavy chain sequence comprising
QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLE
WMGWIAPYSGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTA
VYYCARDAGTYSPFGYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSK

STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 926) and a light chain sequence comprising
DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLI
YKAYNLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFT
FGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927).

5. The antibody-drug conjugate of claim 1, wherein the antibody-drug conjugate has Formula IX:



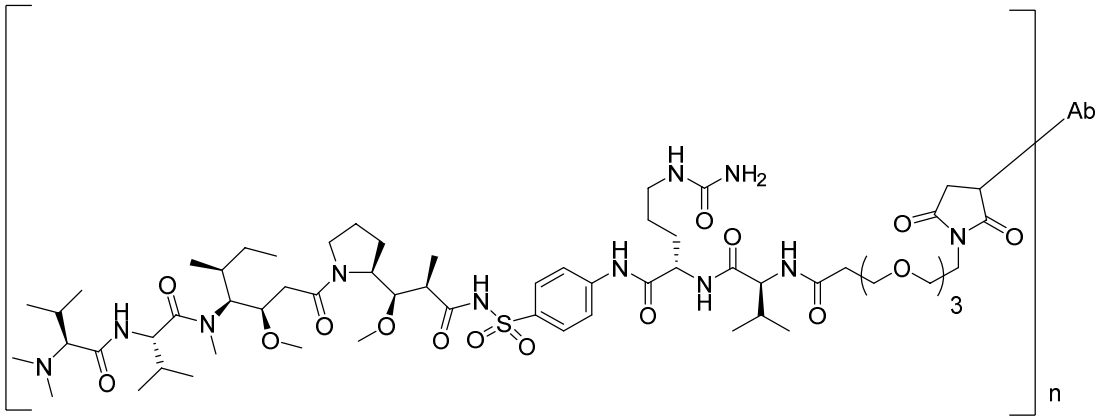
Formula IX

wherein:

the Ab comprises a VH-CDR1, a VH-CDR2, and a VH-CDR3 comprising the amino acid sequences of the VH-CDR1, the VH-CDR2, and the VH-CDR3, respectively, as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 151, and a VL-CDR1, a VL-CDR2, and a VL-CDR3 comprising the amino acid sequences of the VL-CDR1, the VL-CDR2, and the VL-CDR3, respectively, as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 152, and

n is selected from the group consisting of 1, 2, 3, 4, and 5.

6. The antibody-drug conjugate of claim 1, wherein the antibody-drug conjugate has Formula IX:



Formula IX

wherein:

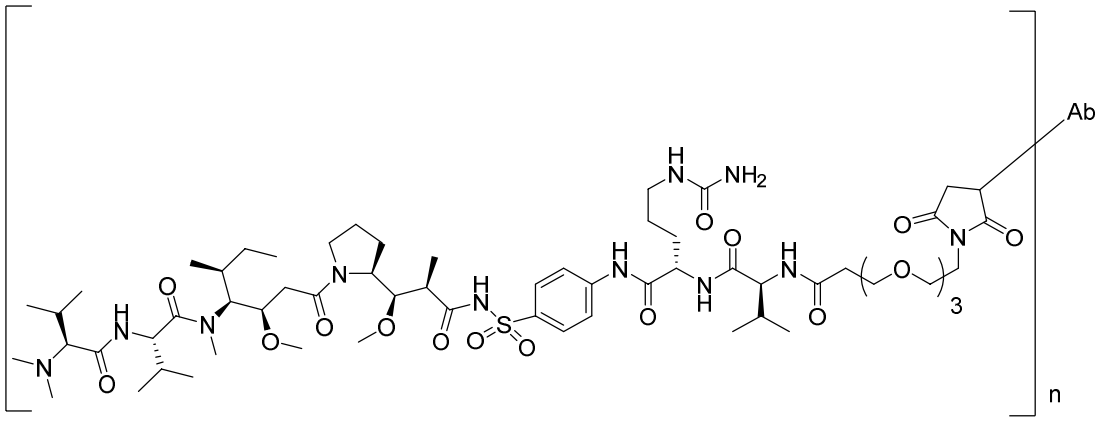
the Ab comprises a variable heavy (VH) sequence shown in SEQ ID NO: 151 and a variable light (VL) sequence shown in SEQ ID NO: 152; and/or

the Ab comprises a heavy chain sequence comprising QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYS GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGM DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G (SEQ ID NO: 926) and a light chain sequence comprising DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLESG VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927),

and

n is an integer selected from the group consisting of 1, 2, 3, 4, and 5.

7. An antibody-drug conjugate of Formula IX:



Formula IX

wherein:

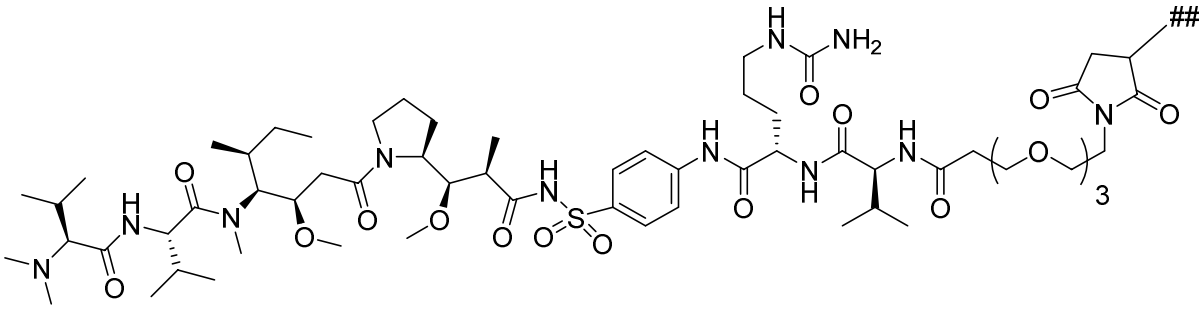
n is an integer selected from the group consisting of 2, 3 and 4, and Ab comprises a heavy chain sequence comprising
QVQVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYSG
NTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGMD
VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 926) and a light chain sequence comprising
DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLESG
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927).

8. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 1-7 and a pharmaceutically acceptable carrier.

9. The pharmaceutical composition of claim 8, wherein the composition comprises a multiplicity of drug-antibody ratio (DAR) species, wherein the average DAR of the composition is 2-4.

10. 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) with a linker-toxin moiety represented by Formula VIII:



Formula VIII

wherein ## represents the point of attachment of the linker-toxin moiety to the Ab through a covalent bond

to provide the antibody drug conjugate;

wherein

the Ab comprises a VH-CDR1, a VH-CDR2, and a VH-CDR3 comprising the amino acid sequences of the VH-CDR1, the VH-CDR2, and the VH-CDR3, respectively, as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 151, and a VL-CDR1, a VL-CDR2, and a VL-CDR3 comprising the amino acid sequences of the VL-CDR1, the VL-CDR2, and the VL-CDR3, respectively, as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 152.

11. The process according to claim 10, wherein:

the nucleophilic or electrophilic group on the Ab is a thiol or an amine.

12. The process of claim 10, wherein the antibody comprises a VH sequence of SEQ ID NO: 151 and a VL sequence of SEQ ID NO: 152.

13. The process of claim 10, wherein

(i) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 115, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 116, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 117, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 118, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 119, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 120;

(ii) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 121, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 122, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 123, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 124, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 125, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 126;

(iii) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 127, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 128, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 129, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 130, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 131, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 132;

(iv) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 133, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 134, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 135, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 136, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 137, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 138;

(v) the VH-CDR1 comprises the amino acid sequence of SEQ ID NO: 139, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 140, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 141, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 142, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 143, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 144; or

(vi) the VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 145, the VH-CDR2 comprises the amino acid sequence of SEQ ID NO: 146, the VH-CDR3 comprises the amino acid sequence of SEQ ID NO: 147, the VL-CDR1 comprises the amino acid sequence of SEQ ID NO: 148, the VL-CDR2 comprises the amino acid sequence of SEQ ID NO: 149, and the VL-CDR3 comprises the amino acid sequence of SEQ ID NO: 150.

14. The process of claim 10, wherein the Ab comprises: a heavy chain sequence comprising QVQLVQSGAEVKKPGASVKVSCKASGYTFDVYGISWVRQAPGQGLEWMGWIAPYS GNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDAGTYSPFGYGM DVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G (SEQ ID NO: 926) and a light chain sequence comprising DIQMTQSPSTLSASVGDRVTITCQASQSINNWLAWYQQKPGKAPKLLIYKAYNLESG VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQLFQSLPPFTFGGGTKVEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 927).