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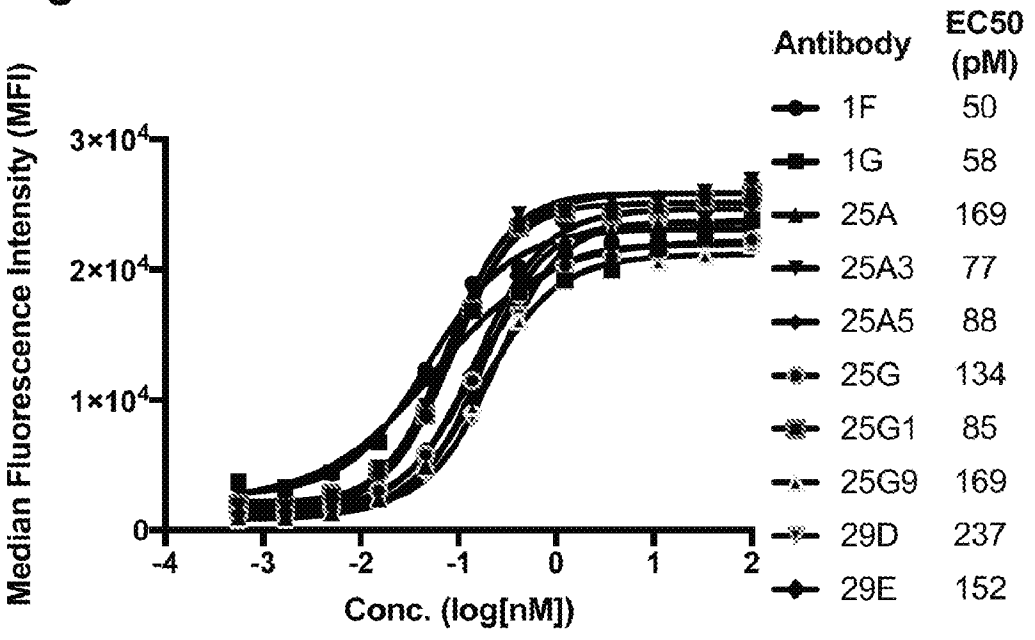
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(54) Title: ANTI-TISSUE FACTOR ANTIBODIES, ANTIBODY-DRUG CONJUGATES, AND RELATED METHODS

Figure 1A



(57) Abrégé/Abstract:
Provided herein are antibodies that specifically bind to human tissue factor (TF), anti-TF antibody-drug conjugates (ADCs), and compositions comprising the antibodies or ADCs. Also provided herein are methods of making and using the antibodies or ADCs, such as therapeutic and diagnostic methods.

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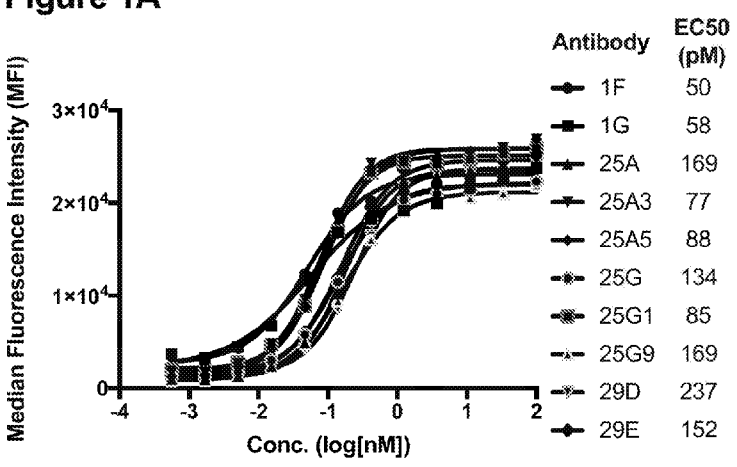
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(54) Title: ANTI-TISSUE FACTOR ANTIBODIES, ANTIBODY-DRUG CONJUGATES, AND RELATED METHODS

Figure 1A



(57) Abstract: Provided herein are antibodies that specifically bind to human tissue factor (TF), anti-TF antibody-drug conjugates (ADCs), and compositions comprising the antibodies or ADCs. Also provided herein are methods of making and using the antibodies or ADCs, such as therapeutic and diagnostic methods.

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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ANTI-TISSUE FACTOR ANTIBODIES, ANTIBODY-DRUG CONJUGATES, AND RELATED METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 62/613,545, filed January 4, 2018; 62/613,564, filed January 4, 2018; 62/646,788, filed March 22, 2018; 62/713,797, filed August 2, 2018; and 62/713,804, filed August 2, 2018, each of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Month XX, 20XX, is named XXXXXUS_sequencelisting.txt, and is X,XXX,XXX bytes in size.

BACKGROUND

[0003] 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.

[0004] TF is over-expressed on multiple types of solid tumors. In cancer, TF/FVIIa signaling can support angiogenesis, tumor progression, and metastasis. Increased TF expression can also induce inflammation and/or angiogenesis in many other diseases, including wet age-related macular degeneration (AMD) and diabetic retinopathy.

SUMMARY

[0005] Provided herein are antibodies that specifically bind human Tissue Factor (TF), anti-TF antibody-drug conjugates, and related methods.

[0006] In one aspect, provided herein is an isolated human antibody which binds to the extracellular domain of human Tissue Factor (TF), wherein the antibody binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa.

[0007] In some embodiments, (1) the isolated antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference

antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0008] In some embodiments, (1) the isolated antibody inhibits human thrombin generation to a lesser extent as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0009] In some embodiments, (1) the isolated antibody allows human thrombin generation to a greater extent as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0010] In some embodiments, (1) the isolated antibody inhibits human thrombin generation by a lesser amount as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0011] In some embodiments, (1) the isolated antibody allows human thrombin generation by a greater amount as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0012] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

[0013] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

[0014] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

[0015] In some embodiments, the isolated antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[0016] In some embodiments, the isolated antibody inhibits human thrombin generation to a lesser extent as determined by thrombin generation assay (TGA) compared to a reference

antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[0017] In some embodiments, the isolated antibody allows human thrombin generation to a greater extent as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[0018] In some embodiments, the isolated antibody inhibits human thrombin generation by a lesser amount as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[0019] In some embodiments, the isolated antibody allows human thrombin generation by a greater amount as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[0020] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA). In some embodiments, the antibody does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control. In some embodiments, the antibody does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control. In some embodiments, the antibody does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control. In some embodiments, the antibody allows human thrombin generation as determined by thrombin generation assay (TGA). In some embodiments, the antibody maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control. In some embodiments, the antibody maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control. In some embodiments, the antibody preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control.

[0021] In some embodiments, the antibody binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX. In some embodiments, the antibody does not interfere with the ability of TF:FVIIa to convert FX into FXa.

[0022] In some embodiments, the antibody does not compete for binding to human TF with human FVIIa.

[0023] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), allows human thrombin generation as determined by thrombin generation assay (TGA), binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

[0024] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, allows human thrombin generation as determined by thrombin generation assay (TGA), preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

[0025] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control, does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control, does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, allows human thrombin generation as determined by thrombin generation assay (TGA), maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control, maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control, preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

[0026] In some embodiments, the antibody inhibits FVIIa-dependent TF signaling.

[0027] In some embodiments, the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the

median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N.

[0028] In some embodiments, the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

[0029] In some embodiments, the binding between the isolated antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[0030] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0031] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0032] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence

shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0033] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0034] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0035] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0036] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0037] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID

NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0038] In some embodiments, the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0039] In some embodiments, the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158

of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

[0040] In some embodiments, the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino

acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; the mutation at amino acid residue 68 of the sequence shown in SEQ ID

NO:810 is K68N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[0041] In some embodiments, the antibody binds to cynomolgus TF. In some embodiments, the antibody binds to mouse TF. In some embodiments, the antibody binds to rabbit TF. In some embodiments, the antibody binds to pig TF.

[0042] In some embodiments, the antibody reduces lesion size in a swine choroidal neovascularization (CNV) model.

[0043] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); and (b) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[0044] In some embodiments, the antibody: (a) allows human thrombin generation as determined by thrombin generation assay (TGA); and(b) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[0045] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (c) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell

staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[0046] In some embodiments, the antibody: (a) allows human thrombin generation as determined by thrombin generation assay (TGA); (b) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (c) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[0047] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) binds to cynomolgus TF; (c) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (d) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[0048] In some embodiments, the antibody: (a) allows human thrombin generation as determined by thrombin generation assay (TGA); (b) binds to cynomolgus TF; (c) the

binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (d) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[0049] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) allows human thrombin generation as determined by thrombin generation assay (TGA); (c) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (d) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (e) does not compete for binding to human TF with FVIIa; (f) inhibits FVIIa-dependent TF signaling; (g) binds to cynomolgus TF; (h) binds to mouse TF; and (i) binds to rabbit TF.

[0050] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (c) allows human thrombin generation as determined by thrombin generation assay (TGA); (d) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (f) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (g) does not compete for binding to human TF with FVIIa; (h) inhibits FVIIa-dependent TF signaling; (i) binds to cynomolgus TF; (j) binds to mouse TF; and (k) binds to rabbit TF.

[0051] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak)

compared to an isotype control; (d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) allows human thrombin generation as determined by thrombin generation assay (TGA); (f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (j) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (k) does not compete for binding to human TF with FVIIa; (l) inhibits FVIIa-dependent TF signaling; (m) binds to cynomolgus TF; (n) binds to mouse TF; and (o) binds to rabbit TF.

[0052] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) allows human thrombin generation as determined by thrombin generation assay (TGA); (c) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (d) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (e) does not compete for binding to human TF with FVIIa; (f) inhibits FVIIa-dependent TF signaling; (g) binds to cynomolgus TF; (h) binds to mouse TF; (i) binds to rabbit TF; (j) binds to pig TF; and (k) reduces lesion size in a swine choroidal neovascularization (CNV) model.

[0053] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (c) allows human thrombin generation as determined by thrombin generation assay (TGA); (d) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (f) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (g) does not compete for binding to human TF with FVIIa; (h) inhibits FVIIa-dependent TF signaling; (i) binds to cynomolgus TF; (j) binds to mouse TF; (k) binds to rabbit TF; (l) binds to pig TF; and (m) reduces lesion size in a swine choroidal neovascularization (CNV) model.

[0054] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not reduce the thrombin peak on

a thrombin generation curve (Peak IIa) compared to an isotype control; (c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) allows human thrombin generation as determined by thrombin generation assay (TGA); (f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (j) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (k) does not compete for binding to human TF with FVIIa; (l) inhibits FVIIa-dependent TF signaling; (m) binds to cynomolgus TF; (n) binds to mouse TF; (o) binds to rabbit TF; (p) binds to pig TF; and (q) reduces lesion size in a swine choroidal neovascularization (CNV) model.

[0055] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) allows human thrombin generation as determined by thrombin generation assay (TGA); (f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (j) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (k) does not compete for binding to human TF with FVIIa; (l) inhibits FVIIa-dependent TF signaling; (m) binds to cynomolgus TF; (n) binds to mouse TF; (o) binds to rabbit TF; (p) binds to pig TF; (q) reduces lesion size in a swine choroidal neovascularization (CNV) model; (r) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the

isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (s) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (t) the binding between the isolated antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (u) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (v) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (w) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (x) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of

the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (y) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (z) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (aa) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (bb) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; and(cc) wherein the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0056] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) allows human thrombin generation as determined by thrombin generation assay (TGA); (f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (j) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (k) does not compete for binding to human TF with FVIIa; (l) inhibits FVIIa-dependent TF signaling; (m) binds to cynomolgus TF; (n) binds to mouse TF; (o) binds to rabbit TF; (p) binds to pig TF; (q) reduces lesion size in a swine choroidal neovascularization (CNV) model; (r) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (s) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation K68N of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (t) the binding between the isolated antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (u) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence

shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (v) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (w) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (x) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (y) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (z) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (aa) the binding between the isolated antibody

and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; (bb) the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; and(cc) wherein the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0057] In some embodiments, the antibody competes for binding to human TF with the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0058] In some embodiments, the antibody competes for binding to human TF with the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[0059] In some embodiments, the antibody competes for binding to human TF with the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0060] In some embodiments, the antibody binds to the same human TF epitope bound by the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0061] In some embodiments, the antibody binds to the same human TF epitope bound by the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[0062] In some embodiments, the antibody binds to the same human TF epitope bound by the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0063] In some embodiments, the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea. In some embodiments, the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

[0064] In some embodiments, the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A5-T, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[0065] In some embodiments, the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0066] In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A3. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5-T. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G1. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G9. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B1. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B7. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D7. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D8. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43E. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43Ea.

[0067] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:113 and a V_L sequence of SEQ ID NO:114. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:151 and a V_L sequence of SEQ ID NO:152. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:189 and a V_L sequence of SEQ ID NO:190. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:836 and a V_L sequence of SEQ ID NO:837. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:227 and a V_L sequence of SEQ ID NO:228. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:265 and a V_L sequence of SEQ ID NO:266. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:303 and a V_L sequence of SEQ ID NO:304. In some embodiments, the antibody comprises a V_H

sequence of SEQ ID NO:455 and a V_L sequence of SEQ ID NO:456. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:493 and a V_L sequence of SEQ ID NO:494. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:531 and a V_L sequence of SEQ ID NO:532. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:569 and a V_L sequence of SEQ ID NO:570. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:607 and a V_L sequence of SEQ ID NO:608. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:645 and a V_L sequence of SEQ ID NO:646. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:683 and a V_L sequence of SEQ ID NO:684. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:721 and a V_L sequence of SEQ ID NO:722.

[0068] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

[0069] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:763 and a V_L sequence of SEQ ID NO:764. In some embodiments, the antibody comprises a V_H

sequence of SEQ ID NO:868 and a V_L sequence of SEQ ID NO:869. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:870 and a V_L sequence of SEQ ID NO:871. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:769 and a V_L sequence of SEQ ID NO:770.

[0070] In some embodiments, the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0071] In some embodiments, the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[0072] In some embodiments, the antibody comprises: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0073] In some embodiments, the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0074] In some embodiments, the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[0075] In some embodiments, the antibody consists of: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0076] In another aspect, provided herein is an isolated antibody comprising all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the

antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0077] In some embodiments, the antibody is human, humanized, or chimeric.

[0078] In some embodiments, the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

[0079] In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[0080] In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A3. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5-T. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G1. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G9.

[0081] In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0082] In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B1. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B7. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain

CDRs from the antibody designated 43D. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D7. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D8. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43E. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43Ea.

[0083] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:113 and a V_L sequence of SEQ ID NO:114. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:151 and a V_L sequence of SEQ ID NO:152. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:189 and a V_L sequence of SEQ ID NO:190. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:836 and a V_L sequence of SEQ ID NO:837. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:227 and a V_L sequence of SEQ ID NO:228. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:265 and a V_L sequence of SEQ ID NO:266. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:303 and a V_L sequence of SEQ ID NO:304. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:455 and a V_L sequence of SEQ ID NO:456. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:493 and a V_L sequence of SEQ ID NO:494. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:531 and a V_L sequence of SEQ ID NO:532. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:569 and a V_L sequence of SEQ ID NO:570. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:607 and a V_L sequence of SEQ ID NO:608. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:645 and a V_L sequence of SEQ ID NO:646. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:683 and a V_L sequence of SEQ ID NO:684. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:721 and a V_L sequence of SEQ ID NO:722.

[0084] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784. In some embodiments, the antibody comprises: a VH-CDR1 comprising the

sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

[0085] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:763 and a V_L sequence of SEQ ID NO:764. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:868 and a V_L sequence of SEQ ID NO:869. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:870 and a V_L sequence of SEQ ID NO:871. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:769 and a V_L sequence of SEQ ID NO:770.

[0086] In some embodiments, the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0087] In some embodiments, the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[0088] In some embodiments, the antibody comprises: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the

antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0089] In some embodiments, the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0090] In some embodiments, the antibody consists: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[0091] In some embodiments, the antibody consists: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[0092] In another aspect, provided herein is an isolated antibody that competes for binding to human TF with: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

[0093] In some embodiments, the antibody is human, humanized, or chimeric.

[0094] In some embodiments, the antibody inhibits FVIIa-dependent TF signaling.

[0095] In some embodiments, the antibody binds to cynomolgus TF.

[0096] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0097] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-93 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-98 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and

the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0098] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[0099] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-85 and 92-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[00100] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-93 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-98 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[00101] In some embodiments, the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the isolated antibody and a human TF extracellular domain with amino acid residues

78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-85 and 92-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

[00102] In some embodiments, the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, the antibody designated 43Ea, or the antibody designated 54E. In some embodiments, the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

[00103] In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 1F. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 1G. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 29D. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 29E. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 39A. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 54E.

[00104] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:37 and a V_L sequence of SEQ ID NO:38. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:75 and a V_L sequence of SEQ ID NO:76. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:341 and a V_L sequence of SEQ ID NO:342. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:379 and a V_L sequence of SEQ ID NO:380. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:417 and a V_L sequence of SEQ ID NO:418. In some embodiments,

the antibody comprises a V_H sequence of SEQ ID NO:759 and a V_L sequence of SEQ ID NO:760.

[00105] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:773; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:774; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:775; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:776; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:777; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:778. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:785; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:786; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:787; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:788; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:789; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:790. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:791; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:792; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:793; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:794; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:795; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:796. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:803; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:804; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:805; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:806; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:807; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:808.

[00106] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:761 and a V_L sequence of SEQ ID NO:762. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:765 and a V_L sequence of SEQ ID NO:766. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:767 and a V_L sequence of SEQ ID NO:768. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:771 and a V_L sequence of SEQ ID NO:772.

[00107] In some embodiments, the antibody comprises: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

[00108] In some embodiments, the antibody consists of: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

[00109] In another aspect, provided herein is an isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:773; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:774; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:775; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:776; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:777; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:778.

[00110] In another aspect, provided herein is an isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

[00111] In another aspect, provided herein is an isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:785; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:786; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:787; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:788; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:789; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:790.

[00112] In another aspect, provided herein is an isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:791; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:792; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:793; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:794; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:795; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:796.

[00113] In another aspect, provided herein is an isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

[00114] In another aspect, provided herein is an isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:803; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:804; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:805; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:806; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:807; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:808.

[00115] In another aspect, provided herein is an isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

[00116] In another aspect, provided herein is an isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

[00117] In some embodiments, the antibody binds to human TF with a K_D of less than or equal to 50 nM, 10 nM, 5 nM, 1 nM, 0.5 nM or 0.1 nM, as measured by Octet QK384 or Biacore assay.

[00118] In some embodiments, the antibody is a monoclonal antibody.

[00119] In some embodiments, the antibody is multispecific.

[00120] In some embodiments, the antibody 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.

[00121] In some embodiments, the antibody comprises a scaffold, optionally wherein the scaffold is Fc, optionally human Fc. In some embodiments, the antibody comprises a heavy chain constant region of a class selected from IgG, IgA, IgD, IgE, and IgM. In some embodiments, the antibody comprises a heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4. In some embodiments, the antibody comprises a heavy chain constant region of IgG1.

[00122] In some embodiments, 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.

[00123] In another aspect, provided herein is an isolated antibody that competes for binding to human TF with any antibody above.

[00124] In another aspect, provided herein is an isolated antibody that binds the human TF epitope bound by any antibody above.

[00125] In another aspect, provided herein is an isolated polynucleotide or set of polynucleotides encoding any antibody above, a V_H thereof, a V_L thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof.

[00126] In another aspect, provided herein is a vector or set of vectors comprising the polynucleotide or set of polynucleotides above.

[00127] In another aspect, provided herein is a host cell comprising the polynucleotide or set of polynucleotides above or the vector or set of vectors above.

[00128] In another aspect, provided herein is a method of producing an antibody comprising expressing the antibody with the host cell above and isolating the expressed antibody.

[00129] In another aspect, provided herein is a pharmaceutical composition comprising any antibody above and a pharmaceutically acceptable excipient.

[00130] In another aspect, 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 any antibody above or the pharmaceutical composition above.

[00131] In some embodiments, the disease or condition is cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is cervical cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is kidney cancer.

[00132] In some embodiments, the disease or condition involves neovascularization. In some embodiments, the disease or condition involving neovascularization is age-related

macular degeneration (AMD), diabetic retinopathy, or cancer. In some embodiments, the disease or condition involves vascular inflammation.

[00133] In some embodiments, the method further comprises administering one or more additional therapeutic agents to the subject. In some embodiments, the additional therapeutic agent is formulated in the same pharmaceutical composition as the antibody. In some embodiments, the additional therapeutic agent is formulated in a different pharmaceutical composition from the antibody. In some embodiments, the additional therapeutic agent is administered prior to administering the antibody. In some embodiments, the additional therapeutic agent is administered after administering the antibody. In some embodiments, the additional therapeutic agent is administered contemporaneously with the antibody.

[00134] In another aspect, provided herein is a method of detecting TF in a subject having or suspected of having a disease or condition, the method comprising: (a) receiving a sample from the subject; and (b) detecting the presence or the level of TF in the sample by contacting the sample with any antibody above.

[00135] In some embodiments, the disease or condition is cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is cervical cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is kidney cancer.

[00136] In some embodiments, the disease or condition involves neovascularization. In some embodiments, the disease or condition involving neovascularization is age-related macular degeneration (AMD), diabetic retinopathy, or cancer. In some embodiments, the disease or condition involves vascular inflammation.

[00137] In another aspect, provided herein is a method of detecting TF in a subject having or suspected of having a disease or condition, the method comprising: (a) administering to the subject any antibody above; and (b) detecting the presence or the level of TF in the subject.

[00138] In some embodiments, the disease or condition is cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is

esophageal cancer. In some embodiments, the cancer is cervical cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is kidney cancer.

[00139] In some embodiments, the disease or condition involves neovascularization. In some embodiments, the disease or condition involving neovascularization is age-related macular degeneration (AMD), diabetic retinopathy, or cancer. In some embodiments, the disease or condition involves vascular inflammation.

[00140] In another aspect, provided herein is a kit comprising any antibody above or the pharmaceutical composition above and instructions for use.

[00141] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody binds to the extracellular domain of human Tissue Factor (TF) at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa.

[00142] In some embodiments, (1) the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00143] In some embodiments, (1) the antibody inhibits human thrombin generation to a lesser extent as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00144] In some embodiments, (1) the antibody allows human thrombin generation to a greater extent as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00145] In some embodiments, (1) the antibody inhibits human thrombin generation by a lesser amount as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00146] In some embodiments, (1) the antibody allows human thrombin generation by a greater amount as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and (2) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00147] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

[00148] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 HIcomprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the

sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

[00149] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

[00150] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[00151] In some embodiments, the antibody inhibits human thrombin generation to a lesser extent as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[00152] In some embodiments, the antibody allows human thrombin generation to a greater extent as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[00153] In some embodiments, the antibody inhibits human thrombin generation by a lesser amount as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[00154] In some embodiments, the antibody allows human thrombin generation by a greater amount as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[00155] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA). In some embodiments, the antibody does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control. In some embodiments, the antibody does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control. In some embodiments, the antibody does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an

isotype control. In some embodiments, the antibody allows human thrombin generation as determined by thrombin generation assay (TGA). In some embodiments, the antibody maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control. In some embodiments, the antibody maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control. In some embodiments, the antibody preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control.

[00156] In some embodiments, the antibody binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX. In some embodiments, the antibody does not interfere with the ability of TF:FVIIa to convert FX into FXa.

[00157] In some embodiments, the antibody does not compete for binding to human TF with human FVIIa.

[00158] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), allows human thrombin generation as determined by thrombin generation assay (TGA), binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

[00159] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, allows human thrombin generation as determined by thrombin generation assay (TGA), preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

[00160] In some embodiments, the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control, does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control, does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, allows human thrombin generation as determined by thrombin generation assay (TGA),

maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control, maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control, preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

[00161] In some embodiments, the antibody inhibits FVIIa-dependent TF signaling.

[00162] In some embodiments, the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N.

[00163] In some embodiments, the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

[00164] In some embodiments, the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00165] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the

median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00166] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00167] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00168] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00169] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00170] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the

extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00171] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00172] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00173] In some embodiments, the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00174] In some embodiments, the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding

between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

[00175] In some embodiments, the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain

with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, and wherein the

binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00176] In some embodiments, the antibody binds to cynomolgus TF. In some embodiments, the antibody binds to mouse TF. In some embodiments, the antibody binds to rabbit TF. In some embodiments, the antibody binds to pig TF.

[00177] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); and(b) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00178] In some embodiments, the antibody: (a) allows human thrombin generation as determined by thrombin generation assay (TGA); and(b) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00179] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the

antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (c) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00180] In some embodiments, the antibody: (a) allows human thrombin generation as determined by thrombin generation assay (TGA); (b) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (c) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00181] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) binds to cynomolgus TF; (c) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (d) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in

SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00182] In some embodiments, the antibody: (a) allows human thrombin generation as determined by thrombin generation assay (TGA); (b) binds to cynomolgus TF; (c) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (d) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00183] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) allows human thrombin generation as determined by thrombin generation assay (TGA); (c) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (d) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (e) does not compete for binding to human TF with FVIIa; (f) inhibits FVIIa-dependent TF signaling; (g) binds to cynomolgus TF; (h) binds to mouse TF; and (i) binds to rabbit TF.

[00184] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (c) allows human thrombin generation as determined by thrombin generation assay (TGA); (d) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) binds human TF at a human TF binding site that is distinct from a human TF binding site

bound by human FX; (f) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (g) does not compete for binding to human TF with FVIIa; (h) inhibits FVIIa-dependent TF signaling; (i) binds to cynomolgus TF; (j) binds to mouse TF; and (k) binds to rabbit TF.

[00185] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) allows human thrombin generation as determined by thrombin generation assay (TGA); (f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (j) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (k) does not compete for binding to human TF with FVIIa; (l) inhibits FVIIa-dependent TF signaling; (m) binds to cynomolgus TF; (n) binds to mouse TF; and (o) binds to rabbit TF.

[00186] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) allows human thrombin generation as determined by thrombin generation assay (TGA); (c) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (d) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (e) does not compete for binding to human TF with FVIIa; (f) inhibits FVIIa-dependent TF signaling; (g) binds to cynomolgus TF; (h) binds to mouse TF; (i) binds to rabbit TF; and (j) binds to pig TF.

[00187] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (c) allows human thrombin generation as determined by thrombin generation assay (TGA); (d) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (f) does not interfere with the ability of TF:FVIIa to convert FX into

FXa; (g) does not compete for binding to human TF with FVIIa; (h) inhibits FVIIa-dependent TF signaling; (i) binds to cynomolgus TF; (j) binds to mouse TF; (k) binds to rabbit TF; and (l) binds to pig TF.

[00188] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) allows human thrombin generation as determined by thrombin generation assay (TGA); (f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (j) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (k) does not compete for binding to human TF with FVIIa; (l) inhibits FVIIa-dependent TF signaling; (m) binds to cynomolgus TF; (n) binds to mouse TF; (o) binds to rabbit TF; and (p) binds to pig TF.

[00189] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) allows human thrombin generation as determined by thrombin generation assay (TGA); (f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (j) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (k) does not compete for binding to human TF with FVIIa; (l) inhibits FVIIa-dependent TF signaling; (m) binds to

cynomolgus TF; (n) binds to mouse TF; (o) binds to rabbit TF; (p) binds to pig TF; (q) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (r) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (s) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (t) the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (u) the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (v) the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (w) the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in

SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (x) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (y) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (z) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (aa) the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (bb) the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00190] In some embodiments, the antibody: (a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (e) allows human thrombin generation as determined by thrombin generation assay (TGA); (f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (j) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (k) does not compete for binding to human TF with FVIIa; (l) inhibits FVIIa-dependent TF signaling; (m) binds to cynomolgus TF; (n) binds to mouse TF; (o) binds to rabbit TF; (p) binds to pig TF; (q) the binding between the antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (r) the binding between the antibody and a variant TF extracellular domain comprising a mutation K68N of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (s) the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (t) the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the

median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (u) the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (v) the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (w) the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (x) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (y) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (z) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of

TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (aa) the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (bb) the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00191] In some embodiments, the antibody competes for binding to human TF with the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[00192] In some embodiments, the antibody competes for binding to human TF with the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[00193] In some embodiments, the antibody competes for binding to human TF with the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[00194] In some embodiments, the antibody binds to the same human TF epitope bound by the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[00195] In some embodiments, the antibody binds to the same human TF epitope bound by the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[00196] In some embodiments, the antibody binds to the same human TF epitope bound by the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[00197] In some embodiments, the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea. In some embodiments, the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

[00198] In some embodiments, the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

[00199] In some embodiments, the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[00200] In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A3. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5-T. In some embodiments, the antibody comprises

all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G1. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G9. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B1. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B7. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D7. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D8. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43E. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43Ea.

[00201] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:113 and a V_L sequence of SEQ ID NO:114. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:151 and a V_L sequence of SEQ ID NO:152. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:189 and a V_L sequence of SEQ ID NO:190. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:836 and a V_L sequence of SEQ ID NO:837. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:227 and a V_L sequence of SEQ ID NO:228. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:265 and a V_L sequence of SEQ ID NO:266. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:303 and a V_L sequence of SEQ ID NO:304. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:455 and a V_L sequence of SEQ ID NO:456. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:493 and a V_L sequence of SEQ ID NO:494. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:531 and a V_L sequence of SEQ ID NO:532. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:569 and a V_L sequence of SEQ ID NO:570. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:607 and a V_L sequence of SEQ ID NO:608. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:645

and a V_L sequence of SEQ ID NO:646. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:683 and a V_L sequence of SEQ ID NO:684. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:721 and a V_L sequence of SEQ ID NO:722.

[00202] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

[00203] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:763 and a V_L sequence of SEQ ID NO:764. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:868 and a V_L sequence of SEQ ID NO:869. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:870 and a V_L sequence of SEQ ID NO:871. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:769 and a V_L sequence of SEQ ID NO:770.

[00204] In some embodiments, the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9,

the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea. In some embodiments, the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9. In some embodiments, the antibody comprises: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[00205] In some embodiments, the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea. In some embodiments, the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9. In some embodiments, the antibody consists of: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

[00206] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody competes for binding to human TF with: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

[00207] In some embodiments, the antibody inhibits FVIIa-dependent TF signaling.

[00208] In some embodiments, the antibody binds to cynomolgus TF.

[00209] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the

median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00210] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 78-93 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-98 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00211] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00212] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-85 and 92-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00213] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and the binding between the antibody and a human TF extracellular domain with amino acid residues 78-93 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-98 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00214] In some embodiments, the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between the antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and the binding between the antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-85 and 92-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00215] In some embodiments, the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, the antibody designated 43Ea, or the antibody designated 54E. In some embodiments, the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

[00216] In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 1F. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 1G. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 29D. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 29E. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 39A. In some embodiments, the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 54E.

[00217] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:37 and a V_L sequence of SEQ ID NO:38. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:75 and a V_L sequence of SEQ ID NO:76. In some embodiments, the

antibody comprises a V_H sequence of SEQ ID NO:341 and a V_L sequence of SEQ ID NO:342. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:379 and a V_L sequence of SEQ ID NO:380. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:417 and a V_L sequence of SEQ ID NO:418. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:759 and a V_L sequence of SEQ ID NO:760.

[00218] In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:773; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:774; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:775; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:776; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:777; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:778. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:785; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:786; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:787; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:788; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:789; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:790. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:791; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:792; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:793; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:794; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:795; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:796. In some embodiments, the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:803; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:804; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:805; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:806; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:807; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:808.

[00219] In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:761 and a V_L sequence of SEQ ID NO:762. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:765 and a V_L sequence of SEQ ID NO:766. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:767 and a V_L sequence of SEQ ID NO:768. In some embodiments, the antibody comprises a V_H sequence of SEQ ID NO:771 and a V_L sequence of SEQ ID NO:772.

[00220] In some embodiments, the antibody comprises: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E. In some embodiments, the antibody consists of: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

[00221] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:773; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:774; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:775; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:776; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:777; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:778.

[00222] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

[00223] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:785; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:786; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:787; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:788; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:789; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:790.

[00224] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:791; a VH-CDR2

comprising the sequence set forth in SEQ ID NO:792; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:793; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:794; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:795; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:796.

[00225] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

[00226] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:803; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:804; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:805; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:806; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:807; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:808.

[00227] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

[00228] In another aspect, provided herein is an antibody-drug conjugate comprising: antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising

the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

[00229] In some embodiments, the antibody is human, humanized, or chimeric.

[00230] In some embodiments, the antibody binds to human TF with a K_D of less than or equal to 50 nM, 10 nM, 5 nM, 1 nM, 0.5 nM or 0.1 nM, as measured by Octet QK384 or Biacore assay.

[00231] In some embodiments, the antibody is a monoclonal antibody.

[00232] In some embodiments, the antibody is multispecific.

[00233] In some embodiments, the antibody 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.

[00234] In some embodiments, the antibody comprises a scaffold, optionally wherein the scaffold is Fc, optionally human Fc. In some embodiments, the antibody comprises a heavy chain constant region of a class selected from IgG, IgA, IgD, IgE, and IgM. In some embodiments, the antibody comprises a heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4. In some embodiments, the antibody comprises a heavy chain constant region of IgG1. In some embodiments, 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.

[00235] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody competes for binding to human TF with any antibody above.

[00236] In another aspect, provided herein is an antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody binds the human TF epitope bound by any antibody above.

[00237] In some embodiments, the cytotoxic agent comprises an anti-angiogenic agent, a pro-apoptotic agent, an anti-mitotic agent, an anti-kinase agent, an alkylating agent, a hormone, a hormone agonist, a hormone antagonist, a chemokine, a drug, a prodrug, a toxin, an enzyme, an antimetabolite, an antibiotic, an alkaloid, or a radioactive isotope. In some

embodiments, the cytotoxic agent comprises at least one of: calicheamycin, camptothecin, carboplatin, irinotecan, SN-38, carboplatin, camptothecan, cyclophosphamide, cytarabine, dacarbazine, docetaxel, dactinomycin, daunorubicin, doxorubicin, doxorubicin, etoposide, idarubicin, topotecan, vinca alkaloid, maytansinoid, maytansinoid analog, pyrrolobenzodiazepine, taxoid, duocarmycin, dolastatin, and auristatin.

[00238] In some embodiments, the linker comprises a labile linker, an acid labile linker, a photolabile linker, a charged linker, a disulfide-containing linker, a peptidase-sensitive linker, a β-glucuronide-linker, a dimethyl linker, a thio-ether linker, or a hydrophilic linker. In some embodiments, the linker is a cleavable linker. In some embodiments, the linker is a non-cleavable linker.

[00239] In another aspect, provided herein is a pharmaceutical composition comprising any antibody-drug conjugate above and a pharmaceutically acceptable excipient.

[00240] In another aspect, 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 any antibody-drug conjugate above or the pharmaceutical composition above.

[00241] In some embodiments, the disease or condition is cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is cervical cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is kidney cancer.

[00242] In some embodiments, the method futher comprises administering one or more additional therapeutic agents to the subject. In some embodiments, the additional therapeutic agent is formulated in the same pharmaceutical composition as the antibody-drug conjugate. In some embodiments, the additional therapeutic agent is formulated in a different pharmaceutical composition from the antibody-drug conjugate. In some embodiments, the additional therapeutic agent is administered prior to administering the antibody-drug conjugate. In some embodiments, the additional therapeutic agent is administered after

administering the antibody-drug conjugate. In some embodiments, the additional therapeutic agent is administered contemporaneously with the antibody-drug conjugate.

[00243] In another aspect, provided herein is a method of detecting TF in a subject having or suspected of having a disease or condition, the method comprising: (a) administering to the subject any antibody-drug conjugate above; and (b) detecting the presence or the level of TF in the subject.

[00244] In some embodiments, the disease or condition is cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is cervical cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is kidney cancer.

[00245] In another aspect, provided herein is a kit comprising any antibody-drug conjugate above or the pharmaceutical composition above and instructions for use.

BRIEF DESCRIPTION OF THE DRAWINGS

[00246] 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:

[00247] **Figures 1A and 1B** show binding of anti-TF antibodies to human TF–positive cells. **Figure 1A** shows the median fluorescence intensity (MFI) of antibody bound to HCT-116 cells plotted against concentrations of antibodies from groups 1, 25, and 29 and the reportable cell EC_{50}. **Figure 1B** shows the median fluorescence intensity of antibody bound to HCT-116 cells plotted against concentrations of antibodies from groups 39, 43, and 54 and the reportable cell EC_{50}. The isotype control in **Figure 1B** applies to both **Figures 1A and 1B**.

[00248] **Figures 2A and 2B** show binding of anti-TF antibodies to mouse TF–positive cells. **Figure 2A** shows the median fluorescence intensity (MFI) of antibody bound to CHO cells recombinantly expressing mouse TF (CHO-mTF) plotted against concentrations of antibodies from groups 1, 25, and 29 and the reportable cell EC_{50}. **Figure 2B** shows the

median fluorescence intensity of antibody bound to CHO-mTF cells plotted against concentrations of antibodies from groups 39, 43, and 54 and the reportable cell EC_{50}. The isotype control in **Figure 2B** applies to both **Figures 2A and 2B**.

[00249] **Figures 3A and 3B** show thrombin generation in the presence of anti-TF antibody. **Figure 3A** shows Peak IIa/Thrombin generation (% Peak IIa) as measured by the Thrombin Generation Assay (TGA) without antibody incubation prior to addition of calcium and thrombin substrate in the presence of titrations of anti-TF antibodies from groups 1, 25, 29, 39, 43, and 54. **Figure 3B** shows Peak IIa/Thrombin generation (% Peak IIa) as measured by the Thrombin Generation Assay (TGA) with a 10-min antibody incubation prior to addition of calcium and thrombin substrate in the presence of titrations of anti-TF antibodies from groups 1, 25, 29, 39, 43, and 54.

[00250] **Figures 4A and 4B** show FXa conversion in the presence of anti-TF antibody. **Figure 4A** shows the percentage of FXa conversion (% FXa) by TF:FVIIa in MDA-MB-231 cells in the presence of titrations of anti-TF antibodies from groups 1, 25, and 29. **Figure 4B** shows the percentage of FXa conversion (% FXa) by TF:FVIIa in MDA-MB-231 cells in the presence of titrations of anti-TF antibodies from groups 39, 43, and 54. % FXa conversion at a reported concentration is calculated relative to an antibody-free FXa conversion reaction. The isotype control in **Figure 4B** applies to both **Figures 4A and 4B**.

[00251] **Figures 5A and 5B** show FVIIa binding in the presence of anti-TF antibody. **Figure 5A** shows the percentage of FVIIa binding (% FVIIa) in TF-positive MDA-MB-231 cells in the presence of titrations of anti-TF antibodies from groups 1, 25, and 29. **Figure 5B** shows the percentage of FVIIa binding (% FVIIa) in MDA-MB-231 cells in the presence of titrations of anti-TF antibodies from groups 39, 43, and 54. % FVIIa binding at a reported concentration is calculated relative to antibody-free FVIIa binding. The isotype control in **Figure 5B** applies to both **Figures 5A and 5B**.

[00252] **Figures 6A, 6B, 6C, and 6D** show FVIIa-dependent TF signaling in the presence of anti-TF antibody. **Figure 6A** shows the concentration of IL8 (IL8 conc) in MDA-MB-231 cells in the presence of titrations of anti-TF antibodies from groups 1, 25, and 29. **Figure 6B** shows the concentration of IL8 (IL8 conc) in MDA-MB-231 cells in the presence of titrations of anti-TF antibodies from groups 39, 43, and 54. The control in **Figure 6B** applies to both **Figures 6A and 6B**. **Figure 6C** shows the concentration of GM-CSF (GM-CSF conc) in MDA-MB-231 cells in the presence of titrations of anti-TF antibodies from groups 1, 25, and 29. **Figure 6D** shows the concentration of GM-CSF (GM-CSF conc) in MDA-MB-231 cells

in the presence of titrations of anti-TF antibodies from groups 39, 43, and 54. The control in **Figure 6D** applies to both **Figures 6C and 6D**.

[00253] **Figures 7A and 7B** show internalization of anti-TF antibody by TF-positive cells. **Figure 7A** shows the cell viability of TF-positive A431 cell cultures after the addition of an anti-TF antibody from groups 1, 25, and 29 and a secondary antibody against the human Fc conjugated to mono-methyl auristatin F (MMAF). **Figure 7B** shows the cell viability of TF-positive A431 cell cultures after the addition of an anti-TF antibody from groups 39, 43, and 54 and a secondary antibody against the human Fc conjugated to mono-methyl auristatin F (MMAF). The isotype control in **Figure 7B** applies to both **Figures 7A and 7B**.

[00254] **Figures 8A and 8B** show thrombin generation in the presence of anti-TF antibody. **Figure 8A** shows Peak IIa/Thrombin generation (% Peak IIa) as measured by the Thrombin Generation Assay (TGA) without antibody incubation prior to addition of calcium and thrombin substrate in the presence of titrations of anti-TF antibodies from groups 25, 39, 43, and anti-TF M1593. **Figure 8B** shows Peak IIa/Thrombin generation (% Peak IIa) as measured by the Thrombin Generation Assay (TGA) with a 10-min antibody incubation prior to addition of calcium and thrombin substrate in the presence of titrations of anti-TF antibodies from groups 25, 39, 43, and anti-TF M1593.

[00255] **Figures 9A and 9B** show anti-TF ADC-induced cell death in TF-positive cells. **Figure 9A** shows cell viability of TF-positive A431 cells after a 3-day incubation with titrations of anti-TF antibodies conjugated to MC-vc-PAB-MMAE (DAR of 3-4). **Figure 9B** shows cell viability of TF-positive HPAF-II cells after a 4-day incubation with titrations of anti-TF antibodies conjugated to MC-vc-PAB-MMAE (DAR of 3-4).

[00256] **Figures 10A and 10B** show the effect of anti-TF ADCs on tumor size in xenograft models. **Figure 10A** shows the efficacy of anti-TF ADCs in the A431 xenograft model. **Figure 10B** shows the efficacy of anti-TF ADCs in the HPAF-II xenograft model. The arrows indicate treatments with ADC or vehicle (PBS) dosed at 5 mg/kg once per week for 3 weeks.

[00257] **Figure 11** shows the effect of anti-TF ADCs on tumor size in a head and neck cancer patient-derived xenograft model. The arrows indicate treatments with anti-TF ADC or IgG1 control ADC dosed at 5 mg/kg once per week for 2 weeks.

[00258] **Figures 12A and 12B** show binding of anti-TF antibodies to human TF–positive cancer cells. **Figure 12A** shows the median fluorescence intensity (MFI) of antibody bound to A431 cells plotted against concentrations of antibodies from groups 1, 25, 29, 39, 43, and 54. Reportable cell EC_{50}'s and their 95% confidence intervals are listed. **Figure 12B** shows

the median fluorescence intensity of antibody bound to MDA-MB-231 cells plotted against concentrations of antibodies from groups 25, 29, 39, and 43. Reportable cell EC_{50}'s and their 95% confidence intervals are listed.

[00259] **Figures 13A, 13B and 13C** show thrombin generation in the presence of anti-TF antibody. **Figure 13A** shows the thrombin generation curves in the absence or presence of 100 nM anti-TF antibodies from groups 1, 25, and 29 and previously generated anti-TF antibodies TF-011, 5G9, and 10H10 (samples on plate 1 of **Table 44**). **Figure 13B** shows the thrombin generation curves in the absence or presence of 100 nM anti-TF antibodies from groups 39, 43, and 54 (samples on plate 2 of **Table 44)**. **Figure 13C** shows the peak thrombin concentration in the absence or presence of titrations of anti-TF antibodies. The mean of a triplicate data set is shown. The standard deviation of the mean is listed in **Table 44**.

[00260] **Figures 14A and 14B** show TF:FVIIa-dependent FXa Conversion and FVII binding in the presence of anti-TF antibodies TF-011, 5G9, and 10H10. **Figure 14A** shows TF:FVIIa-dependent conversion of FX into FXa on the cell surface of MDA-MB-231 cells in the absence or presence of titrations of anti-TF antibodies TF-011, 5G9 and 10H10. **Figure 14B** shows FVII binding in the absence or presence of titrations of anti-TF antibodies TF-011, 5G9 and 10H10 after pre-incubation of MDA-MB-231 cells with the anti-TF antibodies. For antibodies that exhibited no less than 25% competition with FVII, the IC_{50} is reported.

[00261] **Figures 15A and 15B** show percent binding (% Binding) of A488-conjugated 25A3 anti-TF antibody to MDA-MB-231 cells after pre-incubation of the cells with titrations of unlabeled competitor antibodies. **Figure 15A** shows percent binding of 25A3 after pre-incubation with unlabeled competitor antibodies from groups 1, 25, 29, 39, 43, and 54. **Figure 15B** shows percent binding of 25A3 after pre-incubation with unlabeled competitor antibodies TF-011, 5G9, and 10H10. The IC_{50} value of antibodies that compete with 25A3 is listed.

[00262] **Figures 16A and 16B** show percent binding (% Binding) of A488-conjugated 43D7 anti-TF antibody to MDA-MB-231 cells after pre-incubation of the cells with titrations of unlabeled competitor antibodies. **Figure 16A** shows percent binding of 43D7 after pre-incubation with unlabeled competitor antibodies from groups 1, 25, 29, 39, 43, and 54. **Figure 16B** shows percent binding of 43D7 after pre-incubation with unlabeled competitor antibodies TF-011, 5G9, and 10H10. The IC_{50} value of antibodies that compete with 43D7 is listed.

[00263] **Figures 17A and 17B** show percent binding (% Binding) of A488-conjugated 39A anti-TF antibody to MDA-MB-231 cells after pre-incubation of the cells with titrations

of unlabeled competitor antibodies. **Figure 17A** shows percent binding of 39A after pre-incubation with unlabeled competitor antibodies from groups 1, 25, 29, 39, 43, and 54. **Figure 17B** shows percent binding of 39A after pre-incubation with unlabeled competitor antibodies TF-011, 5G9, and 10H10. The IC_{50} value of antibodies that compete with 39A is listed.

[00264] **Figures 18A, 18B, and 18C** show the internalization of anti-TF antibodies as measured by cell viability assay and internalization assay. **Figure 18A** shows cell viability of TF-positive A431 cell cultures three days after titrations of anti-TF antibodies. **Figure 18B** shows cell viability of TF-positive A431 cell cultures three days after titrations of anti-TF antibodies complexed with a Fab fragment against the human Fc conjugated to mono-methyl auristatin F (Fab:MMAF). The IC_{50} of the anti-TF antibody Fab:MMAF complexes is listed. **Figure 18C** shows internalization of anti-TF antibodies conjugated to A488. Percent internalization of A488-conjugated anti-TF antibodies at 4 h is listed.

[00265] **Figures 19A, 19B, and 19C** show the binding of anti-TF antibodies and ADCs to human TF-positive HCT-116 cells. **Figure 19A** shows the binding of anti-TF antibodies HCT-116 cells. **Figure 19B** shows the binding of anti-TF ADCs to HCT-116 cells. **Figure 19C** lists reportable cell EC_{50}'s and their 95% confidence intervals.

[00266] **Figures 20A, 20B, and 20C** show cell viability of A431 cells after titrations of anti-TF ADCs. **Figure 20A** shows the cell viability after titrations of anti-TF ADCs with a continuous 72 h incubation. **Figure 20B** shows the cell viability after titrations of anti-TF ADCs with a 4 h incubation followed by removal of excess ADC and culture for another 68 h. **Figure 20C** lists the reportable IC_{50} values of ADCs.

[00267] **Figures 21A, 21B, and 21C** show the effect of FVIIa on the *in vitro* efficacy of anti-TF ADCs. **Figure 21A** shows the cell viability after titrations of anti-TF ADCs with a 4 h incubation followed by removal of excess ADC and culture for another 68 h in the absence of FVIIa. **Figure 21B** shows the cell viability after titrations of anti-TF ADCs with a 4 h incubation followed by removal of excess ADC and culture for another 68 h in the presence of FVIIa. **Figure 21C** lists the reportable IC_{50} values.

[00268] **Figures 22A, 22B, 22C, 22D, and 22E** show cell viability of additional cancer cell lines after titrations of anti-TF ADCs. **Figure 22A** shows the TF copy number in various cell lines with the anti-TF antibody 5G9. The standard error of the mean and the number of measurements (n) are also presented. **Figure 22B** shows the cell viability of HCT-116 cells after 72 h culture in the absence or presence of titrations of anti-TF MMAE ADCs. **Figure 22C** shows the cell viability of CHO cells after 72 h culture in the absence or presence of

titrations of anti-TF MMAE ADCs. **Figure 22D** shows the cell viability of MDA-MB-231 cells after 5-day culture in the absence or presence of titrations of anti-TF MMAE ADCs. **Figure 22E** shows the cell viability of HPAF-II cells after 5-day culture in the absence or presence of titrations of anti-TF MMAE ADCs.

[00269] **Figures 23A and 23B** show staining of the microtubule network after treatment with anti-TF 25A3 MMAE ADC (25A3-vc-MMAE) or isotype control MMAE ADC (isotype ctrl-vc-MMAE). **Figure 23A** shows staining of the microtubule network of A431 cells after treatment. **Figure 23B** shows staining of the microtubule network of HPAF-II cells after treatment. Scale bar, 10 microns.

[00270] **Figures 24A and 24B** show the TF expression after cytokine treatment and the effect of anti-TF ADCs on the viability of cytokine-treated human umbilical vein endothelial cells (HUVECs). **Figure 24A** shows copy numbers of surface TF on HUVECs treated with or without an inflammatory cytokine cocktail for 3, 6, or 20 h prior to analysis. **Figure 24B** shows cell viability of inflammatory cytokine-treated HUVEC cultures after 4 days of culture in the presence of titrations of anti-TF or isotype-control MMAE ADCs.

[00271] **Figures 25A, 25B, and 25C** show the quantitation of the G_2/M arrest in HUVECs or HCT-116 cells treated for 24 h with titrations of anti-TF ADCs. **Figure 25A** shows the percentage of pH3-positive cells (% pH3) with titrations of anti-TF ADCs of HUVECs in the absence of inflammatory cytokines. **Figure 25B** shows the percentage of pH3-positive cells (% pH3) with titrations of anti-TF ADCs of HUVECs in the presence of inflammatory cytokines. **Figure 25C** shows the percentage of pH3-positive cells (% pH3) with titrations of anti-TF ADCs of HCT-116 cells.

[00272] **Figures 26A and 26B** show the percentage of pH3-positive HCT-116 cells analyzed by flow cytometry with or without anti-TF ADC treatment. **Figure 26A** shows the pH3 versus DNA content dot plot after treatment of 10 nM Isotype-vc-MMAE. **Figure 26B** shows the pH3 versus DNA content dot plot after treatment of 10 nM 25A-vc-MMAE.

[00273] **Figures 27A and 27B** show the sensitivity of HUVECs and HCT-116 cells to MMAE. **Figure 27A** shows the percentage of pH3-positive HUVECs (% pH3) in the absence or presence of 24 h of MMAE treatment. **Figure 27B** shows the percentage of pH3-positive HCT-116 cells (% pH3) in the absence or presence of 24 h of MMAE treatment.

[00274] **Figure 28** shows the analysis of Erk phosphorylation by Western blotting with an anti-phospho-Erk1/2 antibody and an anti-Erk1/2 antibody. The values of pErk induction are listed.

[00275] **Figures 29A, 29B, and 29C** show antibody-dependent cellular cytotoxicity (ADCC) reporter luminescence after a 6 h incubation of the reporter Jurkat cell line with TF-positive A431 cells. **Figure 29A** shows the ADCC reporter luminescence in the absence or presence of titrations anti-TF antibodies. **Figure 29B** shows the ADCC reporter luminescence in the absence or presence of titrations anti-TF ADCs. **Figure 29C** lists the ADCC reporter luminescence EC_{50} values for each anti-TF antibody or ADC.

[00276] **Figures 30A and 30B** show *in vivo* efficacy of anti-TF ADCs in HPAF-II xenograft model. **Figure 30A** shows the mean tumor volume after weekly treatment of an anti-TF ADC at 5 mg/kg for 3 weeks. **Figure 30B** shows the mean tumor volume after weekly treatment of an anti-TF ADC at 2 mg/kg for 2 weeks. The mean tumor volumes (Mean) and tumor growth inhibition (TGI) percentages on day 21 are listed. The *P*-values for the mean tumor volume comparison between each ADC and the vehicle control are also listed. In addition, the number of partial regression (PR), complete regression (CR), and tumor-free survivor (TFS) animals at the end of the study (day 59 for **Figure 30A** and day 39 for **Figure 30B**) are also listed.

[00277] **Figures 31A and 31B** show *in vivo* efficacy of anti-TF ADCs in MDA-MB-231 xenograft model. **Figure 31A** shows the mean tumor volume after weekly treatment of an anti-TF ADC at 4 mg/kg for 2 weeks. **Figure 31B** shows the mean tumor volume after weekly treatment of an anti-TF ADC at 2 mg/kg for 2 weeks. The mean tumor volume and tumor growth inhibition on day 25 (**Figure 31A**) and day 27 (**Figure 31B**) are listed. The *P*-values for the mean tumor volume comparison between each ADC and the vehicle control are also listed. In addition, the number of partial regression (PR), complete regression (CR), and tumor-free survivor (TFS) animals at the end of the study (day 49 for **Figure 31A** and day 41 for **Figure 31B**) are also listed.

[00278] **Figure 32** shows the mean tumor volume after weekly treatment of unconjugated anti-TF antibodies at 10 mg/kg for 2 weeks in the HPAF-II xenograft model. The mean tumor volume on day 15 is listed.

[00279] **Figures 33A, 33B, and 33C** show *in vivo* efficacy of anti-TF ADCs in patient-derived xenograft (PDX) models. **Figure 33A** shows the mean tumor volume in the PDX model of a head and neck carcinoma after treatment of an anti-TF ADC. **Figure 33B** shows the mean tumor volume in the PDX model of an ovarian carcinoma after treatment of an anti-TF ADC. **Figure 33C** shows the mean tumor volume in the PDX model of a gastric adenocarcinoma after treatment of an anti-TF ADC. The mean tumor volume and tumor growth inhibition on day 44 (**Figure 33A**), day 15 (**Figure 33B**), and day 25 (**Figure 33C**)

are listed. The *P*-values for the mean tumor volume comparison between each ADC and the isotype control are also listed. In addition, the number of patial responder (PR), complete responder (CR), and tumor free survivor (TFS) animals at the end of the study (day 60 for **Figure 33A** and day 46 for **Figures 33B-C**) are also listed.

[00280] **Figures 34A and 34B** show the change in lesion size after administration of anti-TF antibody in a swine choroidal neovascularization (CNV) model. **Figure 34A** shows the percentage change in lesion size from day 7 (baseline) to day 14 as measured by Fluorescein Angiography (FA) after intravitreal administration of anti-TF antibodies 25G9, 43D8, 1G, and 29D respectively. **Figure 34B** shows the percentage change in lesion size from day 7 (baseline) to day 28 as measured by Fluorescein Angiography (FA) after intravitreal administration of anti-TF antibodies 25G9, 43D8, 1G, and 29D respectively.

[00281] **Figure 35** shows the change in lesion size in a swine choroidal neovascularization (CNV) model from day 7 (baseline) to day 28 as measured by Fluorescein Angiography (FA) after intravitreal administration of anti-TF antibodies 25G9 at 600ug, 2mg and 4mg respectively.

[00282] **Figure 36** shows Clustal Omega alignment of chimeric TF constructs. Rat sequences are highlighted in bold. An "* (asterisk)" indicates positions which have a single, fully conserved residue. A ": (colon)" indicates conservation between groups of strongly similar properties - roughly equivalent to scoring > 0.5 in the Gonnet Percent Accepted Mutation 250 matrix. A ". (period)" indicates conservation between groups of weakly similar properties - roughly equivalent to scoring =< 0.5 and > 0 in the Gonnet Percent Accepted Mutation 250 matrix.

[00283] **Figure 37** shows Clustal Omega alignment of chimeric TF constructs. Human sequences are highlighted in bold. An "* (asterisk)" indicates positions which have a single, fully conserved residue. A ": (colon)" indicates conservation between groups of strongly similar properties - roughly equivalent to scoring > 0.5 in the Gonnet Percent Accepted Mutation 250 matrix. A ". (period)" indicates conservation between groups of weakly similar properties - roughly equivalent to scoring =< 0.5 and > 0 in the Gonnet Percent Accepted Mutation 250 matrix.

[00284] **Figure 38** shows Clustal Omega alignment of chimeric TF constructs. Rat sequences are highlighted in bold. An "* (asterisk)" indicates positions which have a single, fully conserved residue. A ": (colon)" indicates conservation between groups of strongly similar properties - roughly equivalent to scoring > 0.5 in the Gonnet Percent Accepted Mutation 250 matrix. A ". (period)" indicates conservation between groups of weakly similar

properties - roughly equivalent to scoring =< 0.5 and > 0 in the Gonnet Percent Accepted Mutation 250 matrix.

[00285] **Figures 39A-F** show the titration curves of anti-TF antibodies from lineages 25 and 43, h5G9, and 10H10 on select TF constructs. **Figure 39A** shows the titration curves of anti-TF antibodies on human TF construct. **Figure 39B** shows the titration curves of anti-TF antibodies on rat TF construct. **Figure 39C** shows the titration curves of anti-TF antibodies on chimeric human-rat TF construct hTF_K68N. **Figure 39D** shows the titration curves of anti-TF antibodies on chimeric human-rat TF construct hTF_K149N. **Figure 39E** shows the titration curves of anti-TF antibodies on chimeric human-rat TF construct hTF_N171H_T197K. **Figure 39F** shows the titration curves of anti-TF antibodies on chimeric rat-human TF construct r141-194_h.

DETAILED DESCRIPTION

1. Definitions

[00286] Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a difference over what is generally understood in the art. The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodologies by those skilled in the art, such as, for example, the widely utilized molecular cloning methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 4th ed. (2012) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. As appropriate, procedures involving the use of commercially available kits and reagents are generally carried out in accordance with manufacturer-defined protocols and conditions unless otherwise noted.

[00287] As used herein, the singular forms "a," "an," and "the" include the plural referents unless the context clearly indicates otherwise. The terms "include," "such as," and the like are intended to convey inclusion without limitation, unless otherwise specifically indicated.

[00288] As used herein, the term "comprising" also specifically includes embodiments "consisting of" and "consisting essentially of" the recited elements, unless specifically indicated otherwise.

[00289] The term "about" indicates and encompasses an indicated value and a range above and below that value. In certain embodiments, the term "about" indicates the designated

value ± 10%, ± 5%, or ± 1%. In certain embodiments, where applicable, the term "about" indicates the designated value(s) ± one standard deviation of that value(s).

[00290] The terms "Tissue Factor," "TF," "platelet tissue factor," "factor III," "thromboplastin," and "CD142" are used interchangeably herein to refer to TF, or any variants (*e.g.*, splice variants and allelic variants), isoforms, and species homologs of TF that are naturally expressed by cells, or that are expressed by cells transfected with a TF gene. In some aspects, the TF protein is a TF protein naturally expressed by a primate (*e.g.*, a monkey or a human), a rodent (*e.g.*, a mouse or a rat), a dog, a camel, a cat, a cow, a goat, a horse, a pig or a sheep. In some aspects, the TF protein is human TF (hTF; SEQ ID NO:809). In some aspects, the TF protein is cynomolgus TF (cTF; SEQ ID NO:813). In some aspects, the TF protein is mouse TF (mTF; SEQ ID NO:817). In some aspects, the TF protein is pig TF (pTF; SEQ ID NO:824). TF is a cell surface receptor for the serine protease factor VIIa. It is often times constitutively expressed by certain cells surrounding blood vessels and in some disease settings.

[00291] The term "antibody-drug conjugate" or "ADC" refers to a conjugate comprising an antibody conjugated to one or more cytotoxic agents, optionally through one or more linkers. The term "anti-TF antibody-drug conjugate" or "anti-TF ADC" refers to a conjugate comprising an anti-TF antibody conjugated to one or more cytotoxic agents, optionally through one or more linkers.

[00292] The term "cytotoxic agent," as used herein, refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. The cytotoxic agent can be an anti-angiogenic agent, a pro-apoptotic agent, an anti-mitotic agent, an anti-kinase agent, an alkylating agent, a hormone, a hormone agonist, a hormone antagonist, a chemokine, a drug, a prodrug, a toxin, an enzyme, an antimetabolite, an antibiotic, an alkaloid, or a radioactive isotope. Exemplary cytotoxic agents include calicheamycin, camptothecin, carboplatin, irinotecan, SN-38, carboplatin, camptothecan, cyclophosphamide, cytarabine, dacarbazine, docetaxel, dactinomycin, daunorubicin, doxorubicin, doxorubicin, etoposide, idarubicin, topotecan, vinca alkaloid, maytansinoid, maytansinoid analog, pyrrolobenzodiazepine, taxoid, duocarmycin, dolastatin, auristatin, and derivatives thereof.

[00293] A "linker" refers to a molecule that connects one composition to another, e.g., an antibody to an agent. Linkers described herein can conjugate an antibody to a cytotoxic agent. Exemplary linkers include a labile linker, an acid labile linker, a photolabile linker, a charged linker, a disulfide-containing linker, a peptidase-sensitive linker, a □-glucuronide-linker, a

dimethyl linker, a thio-ether linker, and a hydrophilic linker. A linker can be cleavable or non-cleavable.

[00294] The term "immunoglobulin" refers to a class of structurally related proteins generally comprising two pairs of polypeptide chains: one pair of light (L) chains and one pair of heavy (H) chains. In an "intact immunoglobulin," all four of these chains are interconnected by disulfide bonds. The structure of immunoglobulins has been well characterized. *See, e.g.,* Paul, *Fundamental Immunology* 7th ed., Ch. 5 (2013) Lippincott Williams & Wilkins, Philadelphia, PA. Briefly, each heavy chain typically comprises a heavy chain variable region (V_H) and a heavy chain constant region (C_H). The heavy chain constant region typically comprises three domains, abbreviated C_{H1}, C_{H2}, and C_{H3}. Each light chain typically comprises a light chain variable region (V_L) and a light chain constant region. The light chain constant region typically comprises one domain, abbreviated C_L.

[00295] The term "antibody" is used herein in its broadest sense and includes certain types of immunoglobulin molecules comprising one or more antigen-binding domains that specifically bind to an antigen or epitope. An antibody specifically includes intact antibodies (*e.g.*, intact immunoglobulins), antibody fragments, and multi-specific antibodies.

[00296] The term "alternative scaffold" refers to a molecule in which one or more regions may be diversified to produce one or more antigen-binding domains that specifically bind to an antigen or epitope. In some embodiments, the antigen-binding domain binds the antigen or epitope with specificity and affinity similar to that of an antibody. Exemplary alternative scaffolds include those derived from fibronectin (*e.g.*, AdnectinsTM), the β-sandwich (*e.g.*, iMab), lipocalin (*e.g.*, Anticalins®), EETI-II/AGRP, BPTI/LACI-D1/ITI-D2 (*e.g.*, Kunitz domains), thioredoxin peptide aptamers, protein A (*e.g.*, Affibody®), ankyrin repeats (*e.g.*, DARPins), gamma-B-crystallin/ubiquitin (*e.g.*, Affilins), CTLD3 (*e.g.*, Tetranectins), Fynomers, and (LDLR-A module) (*e.g.*, Avimers). Additional information on alternative scaffolds is provided in Binz et al., *Nat. Biotechnol.*, 2005 23:1257-1268; Skerra, *Current Opin. in Biotech.*, 2007 18:295-304; and Silacci et al., *J. Biol. Chem.*, 2014, 289:14392-14398; each of which is incorporated by reference in its entirety.

[00297] The term "antigen-binding domain" means the portion of an antibody that is capable of specifically binding to an antigen or epitope. One example of an antigen-binding domain is an antigen-binding domain formed by a V_H -V_L dimer of an antibody. Another example of an antigen-binding domain is an antigen-binding domain formed by diversification of certain loops from the tenth fibronectin type III domain of an Adnectin. Antigen-binding domains can be found in various contexts including antibodies and chimeric

antigen receptors (CARs), for example CARs derived from antibodies or antibody fragments such as scFvs.

[00298] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a naturally occurring antibody structure and having heavy chains that comprise an Fc region. For example, when used to refer to an IgG molecule, a "full length antibody" is an antibody that comprises two heavy chains and two light chains.

[00299] The term "Fc region" means the C-terminal region of an immunoglobulin heavy chain that, in naturally occurring antibodies, interacts with Fc receptors and certain proteins of the complement system. The structures of the Fc regions of various immunoglobulins, and the glycosylation sites contained therein, are known in the art. *See* Schroeder and Cavacini, *J. Allergy Clin. Immunol.*, 2010, 125:S41-52, incorporated by reference in its entirety. The Fc region may be a naturally occurring Fc region, or an Fc region modified as described in the art or elsewhere in this disclosure.

[00300] The V_H and V_L regions may be further subdivided into regions of hypervariability ("hypervariable regions (HVRs);" also called "complementarity determining regions" (CDRs)) interspersed with regions that are more conserved. The more conserved regions are called framework regions (FRs). Each V_H and V_L generally comprises three CDRs and four FRs, arranged in the following order (from N-terminus to C-terminus): FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4. The CDRs are involved in antigen binding, and influence antigen specificity and binding affinity of the antibody. *See* Kabat et al., *Sequences of Proteins of Immunological Interest 5th ed.* (1991) Public Health Service, National Institutes of Health, Bethesda, MD, incorporated by reference in its entirety.

[00301] A "Complementary Determining Region (CDR)" refers to one of three hypervariable regions (H1, H2 or H3) within the non-framework region of the immunoglobulin (Ig or antibody) VH β-sheet framework, or one of three hypervariable regions (L1, L2 or L3) within the non-framework region of the antibody VL β-sheet framework. CDRs are variable region sequences interspersed within the framework region sequences. CDRs are well recognized in the art and have been defined by, for example, Kabat as the regions of most hypervariability within the antibody variable (V) domains. *See* Kabat et al., *J Biol Chem*, 1977, 252:6609-6616 and Kabat, *Adv Protein Chem*, 1978, 32:1-75, each of which is incorporated by reference in its entirety. CDRs have also been defined structurally by Chothia as those residues that are not part of the conserved β-sheet

framework, and thus are able to adapt different conformations. *See* Chothia and Lesk, *J Mol Biol*, 1987, 196:901-917, incorporated by reference in its entirety. Both the Kabat and Chothia nomenclatures are well known in the art. AbM, Contact and IMGT also defined CDRs. CDR positions within a canonical antibody variable domain have been determined by comparison of numerous structures. *See* Morea et al., *Methods*, 2000, 20:267-279 and Al-Lazikani et al., *J Mol Biol*, 1997, 273:927-48, each of which is incorporated by reference in its entirety. Because the number of residues within a hypervariable region varies in different antibodies, additional residues relative to the canonical positions are conventionally numbered with a, b, c and so forth next to the residue number in the canonical variable domain numbering scheme (Al-Lazikani et al., *supra*). Such terminology is well known to those skilled in the art.

[00302] A number of hypervariable region delineations are in use and are included herein. The Kabat CDRs are based on sequence variability and are the most commonly used. *See* Kabat et al. (1992) *Sequences of Proteins of Immunological Interest*, DIANE Publishing: 2719, incorporated by reference in its entirety. Chothia refers instead to the location of the structural loops (Chothia and Lesk, *supra*). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software. The Contact hypervariable regions are based on an analysis of the available complex crystal structures. The residues from each of these hypervariable regions are noted in **Table 1**.

[00303] More recently, a universal numbering system ImMunoGeneTics (IMGT) Information SystemTM has been developed and widely adopted. *See* Lefranc et al., *Dev Comp Immunol*, 2003, 27:55-77, incorporated by reference in its entirety. IMGT is an integrated information system specializing in immunoglobulins (IG), T cell receptors (TR) and major histocompatibility complex (MHC) of human and other vertebrates. The IMGT CDRs are referred to in terms of both the amino acid sequence and the location within the light or heavy chain. As the "location" of the CDRs within the structure of the immunoglobulin variable domain is conserved between species and present in structures called loops, by using numbering systems that align variable domain sequences according to structural features, CDR and framework residues are readily identified. Correspondence between the Kabat, Chothia and IMGT numbering is also well known in the art (Lefranc et al., *supra*). An Exemplary system, shown herein, combines Kabat and Chothia CDR definitions.

Table 1

	Exemplary (Kabat + Chothia)	Kabat	Chothia	AbM	Contact	IMGT
VH CDR1	26-35	31-35	26-32	26-35	30-35	27-38
VH CDR2	50-65	50-65	52a-55	50-58	47-58	56-65
VH CDR3	95-102	95-102	96-101	95-102	93-101	105-117
VL CDR1	24-34	24-34	26-32	24-34	30-36	27-38
VL CDR2	50-56	50-56	50-52	50-56	46-55	56-65
VL CDR3	89-97	89-97	91-96	89-97	89-96	105-117

[00304] The light chain from any vertebrate species can be assigned to one of two types, called kappa (κ) and lambda (λ), based on the sequence of its constant domain.

[00305] The heavy chain from any vertebrate species can be assigned to one of five different classes (or isotypes): IgA, IgD, IgE, IgG, and IgM. These classes are also designated α, δ, ε, γ, and μ, respectively. The IgG and IgA classes are further divided into subclasses on the basis of differences in sequence and function. Humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[00306] The term "constant region" or "constant domain" refers to a carboxy terminal portion of the light and heavy chain which is not directly involved in binding of the antibody to antigen but exhibits various effector function, such as interaction with the Fc receptor. The terms refer to the portion of an immunoglobulin molecule having a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable domain, which contains the antigen-binding site. The constant domain contains the C_{H1}, C_{H2} and C_{H3} domains of the heavy chain and the C_L domain of the light chain.

[00307] The "EU numbering scheme" is generally used when referring to a residue in an antibody heavy chain constant region (*e.g.*, as reported in Kabat et al., *supra*). Unless stated otherwise, the EU numbering scheme is used to refer to residues in antibody heavy chain constant regions described herein.

[00308] An "antibody fragment" comprises a portion of an intact antibody, such as the antigen-binding or variable region of an intact antibody. Antibody fragments include, for example, Fv fragments, Fab fragments, $F(ab')_2$ fragments, Fab' fragments, scFv (sFv) fragments, and scFv-Fc fragments.

[00309] "Fv" fragments comprise a non-covalently-linked dimer of one heavy chain variable domain and one light chain variable domain.

[00310] "Fab" fragments comprise, in addition to the heavy and light chain variable domains, the constant domain of the light chain and the first constant domain (C_{H1}) of the heavy chain. Fab fragments may be generated, for example, by recombinant methods or by papain digestion of a full-length antibody.

[00311] "F(ab')$_2$" fragments contain two Fab' fragments joined, near the hinge region, by disulfide bonds. F(ab')$_2$ fragments may be generated, for example, by recombinant methods or by pepsin digestion of an intact antibody. The F(ab') fragments can be dissociated, for example, by treatment with ß-mercaptoethanol.

[00312] "Single-chain Fv" or "sFv" or "scFv" antibody fragments comprise a V_H domain and a V_L domain in a single polypeptide chain. The V_H and V_L are generally linked by a peptide linker. *See* Plückthun A. (1994). Any suitable linker may be used. In some embodiments, the linker is a $(GGGGS)_n$ (SEQ ID NO:823). In some embodiments, n = 1, 2, 3, 4, 5, or 6. *See* Antibodies from *Escherichia coli*. In Rosenberg M. & Moore G.P. (Eds.), *The Pharmacology of Monoclonal Antibodies* vol. 113 (pp. 269-315). Springer-Verlag, New York, incorporated by reference in its entirety.

[00313] "scFv-Fc" fragments comprise an scFv attached to an Fc domain. For example, an Fc domain may be attached to the C-terminal of the scFv. The Fc domain may follow the V_H or V_L, depending on the orientation of the variable domains in the scFv (*i.e.*, V_H -V_L or V_L -V_H). Any suitable Fc domain known in the art or described herein may be used.

[00314] The term "single domain antibody" refers to a molecule in which one variable domain of an antibody specifically binds to an antigen without the presence of the other variable domain. Single domain antibodies, and fragments thereof, are described in Arabi Ghahroudi et al., *FEBS Letters*, 1998, 414:521-526 and Muyldermans et al., *Trends in Biochem. Sci.*, 2001, 26:230-245, each of which is incorporated by reference in its entirety. Single domain antibodies are also known as sdAbs or nanobodies.

[00315] A "multispecific antibody" is an antibody that comprises two or more different antigen-binding domains that collectively specifically bind two or more different epitopes. The two or more different epitopes may be epitopes on the same antigen (*e.g.*, a single TF molecule expressed by a cell) or on different antigens (*e.g.*, a TF molecule and a non-TF molecule). In some aspects, a multi-specific antibody binds two different epitopes (*i.e.*, a "bispecific antibody"). In some aspects, a multi-specific antibody binds three different epitopes (*i.e.*, a "trispecific antibody"). In some aspects, a multi-specific antibody binds four different epitopes (*i.e.*, a "quadspecific antibody"). In some aspects, a multi-specific antibody binds five different epitopes (*i.e.*, a "quintspecific antibody"). In some aspects, a multi-

specific antibody binds 6, 7, 8, or more different epitopes. Each binding specificity may be present in any suitable valency. Examples of multispecific antibodies are provided elsewhere in this disclosure.

[00316] A "monospecific antibody" is an antibody that comprises one or more binding sites that specifically bind to a single epitope. An example of a monospecific antibody is a naturally occurring IgG molecule which, while divalent (*i.e.*, having two antigen-binding domains), recognizes the same epitope at each of the two antigen-binding domains. The binding specificity may be present in any suitable valency.

[00317] The term "monoclonal antibody" refers to an antibody from a population of substantially homogeneous antibodies. A population of substantially homogeneous antibodies comprises antibodies that are substantially similar and that bind the same epitope(s), except for variants that may normally arise during production of the monoclonal antibody. Such variants are generally present in only minor amounts. A monoclonal antibody is typically obtained by a process that includes the selection of a single antibody from a plurality of antibodies. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones, yeast clones, bacterial clones, or other recombinant DNA clones. The selected antibody can be further altered, for example, to improve affinity for the target ("affinity maturation"), to humanize the antibody, to improve its production in cell culture, and/or to reduce its immunogenicity in a subject.

[00318] The term "chimeric antibody" refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[00319] "Humanized" forms of non-human antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. A humanized antibody is generally a human antibody (recipient antibody) in which residues from one or more CDRs are replaced by residues from one or more CDRs of a non-human antibody (donor antibody). The donor antibody can be any suitable non-human antibody, such as a mouse, rat, rabbit, chicken, or non-human primate antibody having a desired specificity, affinity, or biological effect. In some instances, selected framework region residues of the recipient antibody are replaced by the corresponding framework region residues from the donor antibody. Humanized antibodies may also comprise residues that are not found in either the recipient antibody or the donor antibody. Such modifications may be made to further refine antibody function. For further details, *see* Jones et al., *Nature*, 1986, 321:522-525; Riechmann et al.,

Nature, 1988, 332:323-329; and Presta, *Curr. Op. Struct. Biol.*, 1992, 2:593-596, each of which is incorporated by reference in its entirety.

[00320] A "human antibody" is one which possesses an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or derived from a non-human source that utilizes a human antibody repertoire or human antibody-encoding sequences (*e.g.*, obtained from human sources or designed *de novo*). Human antibodies specifically exclude humanized antibodies.

[00321] An "isolated antibody" or "isolated nucleic acid" is an antibody or nucleic acid that has been separated and/or recovered from a component of its natural environment. Components of the natural environment may include enzymes, hormones, and other proteinaceous or nonproteinaceous materials. In some embodiments, an isolated antibody is purified to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence, for example by use of a spinning cup sequenator. In some embodiments, an isolated antibody is purified to homogeneity by gel electrophoresis (*e.g.*, SDS-PAGE) under reducing or nonreducing conditions, with detection by Coomassie blue or silver stain. In some embodiments, an isolated antibody may include an antibody *in situ* within recombinant cells, since at least one component of the antibody's natural environment is not present. In some aspects, an isolated antibody or isolated nucleic acid is prepared by at least one purification step. In some embodiments, an isolated antibody or isolated nucleic acid is purified to at least 80%, 85%, 90%, 95%, or 99% by weight. In some embodiments, an isolated antibody or isolated nucleic acid is purified to at least 80%, 85%, 90%, 95%, or 99% by volume. In some embodiments, an isolated antibody or isolated nucleic acid is provided as a solution comprising at least 85%, 90%, 95%, 98%, 99% to 100% antibody or nucleic acid by weight. In some embodiments, an isolated antibody or isolated nucleic acid is provided as a solution comprising at least 85%, 90%, 95%, 98%, 99% to 100% antibody or nucleic acid by volume.

[00322] "Affinity" refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen or epitope). Unless indicated otherwise, as used herein, "affinity" refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen or epitope). The affinity of a molecule X for its partner Y can be represented by the dissociation equilibrium constant (K_D). The kinetic components that contribute to the dissociation equilibrium constant are described in more detail below. Affinity can be measured by common methods known in the art, including those described

herein, such as surface plasmon resonance (SPR) technology (*e.g.*, BIACORE®) or biolayer interferometry (*e.g.*, FORTEBIO®).

[00323] With regard to the binding of an antibody to a target molecule, the terms "bind," "specific binding," "specifically binds to," "specific for," "selectively binds," and "selective for" a particular antigen (*e.g.*, a polypeptide target) or an epitope on a particular antigen mean binding that is measurably different from a non-specific or non-selective interaction (*e.g.*, with a non-target molecule). Specific binding can be measured, for example, by measuring binding to a target molecule and comparing it to binding to a non-target molecule. Specific binding can also be determined by competition with a control molecule that mimics the epitope recognized on the target molecule. In that case, specific binding is indicated if the binding of the antibody to the target molecule is competitively inhibited by the control molecule. In some aspects, the affinity of a TF antibody for a non-target molecule is less than about 50% of the affinity for TF. In some aspects, the affinity of a TF antibody for a non-target molecule is less than about 40% of the affinity for TF. In some aspects, the affinity of a TF antibody for a non-target molecule is less than about 30% of the affinity for TF. In some aspects, the affinity of a TF antibody for a non-target molecule is less than about 20% of the affinity for TF. In some aspects, the affinity of a TF antibody for a non-target molecule is less than about 10% of the affinity for TF. In some aspects, the affinity of a TF antibody for a non-target molecule is less than about 1% of the affinity for TF. In some aspects, the affinity of a TF antibody for a non-target molecule is less than about 0.1% of the affinity for TF.

[00324] The term "k_d" (sec^{-1}), as used herein, refers to the dissociation rate constant of a particular antibody-antigen interaction. This value is also referred to as the k_{off} value.

[00325] The term "k_a" ($M^{-1} \times sec^{-1}$), as used herein, refers to the association rate constant of a particular antibody-antigen interaction. This value is also referred to as the k_{on} value.

[00326] The term "K_D" (M), as used herein, refers to the dissociation equilibrium constant of a particular antibody-antigen interaction. $K_D = k_d/k_a$. In some embodiments, the affinity of an antibody is described in terms of the K_D for an interaction between such antibody and its antigen. For clarity, as known in the art, a smaller K_D value indicates a higher affinity interaction, while a larger K_D value indicates a lower affinity interaction.

[00327] The term "K_A" (M^{-1}), as used herein, refers to the association equilibrium constant of a particular antibody-antigen interaction. $K_A = k_a/k_d$.

[00328] An "affinity matured" antibody is an antibody with one or more alterations (*e.g.*, in one or more CDRs or FRs) relative to a parent antibody (*i.e.*, an antibody from which the altered antibody is derived or designed) that result in an improvement in the affinity of the

antibody for its antigen, compared to the parent antibody which does not possess the alteration(s). In some embodiments, an affinity matured antibody has nanomolar or picomolar affinity for the target antigen. Affinity matured antibodies may be produced using a variety of methods known in the art. For example, Marks et al. (*Bio/Technology*, 1992, 10:779-783, incorporated by reference in its entirety) describes affinity maturation by V_H and V_L domain shuffling. Random mutagenesis of CDR and/or framework residues is described by, for example, Barbas et al., *Proc. Nat. Acad. Sci. U.S.A.*, 1994, 91:3809-3813; Schier et al., *Gene*, 1995, 169:147-155; Yelton et al., *J. Immunol.*, 1995, 155:1994-2004; Jackson et al., *J. Immunol.*, 1995, 154:3310-33199; and Hawkins et al, *J. Mol. Biol.*, 1992, 226:889-896; each of which is incorporated by reference in its entirety.

[00329] "Fc effector functions" refer to those biological activities mediated by the Fc region of an antibody, which activities may vary depending on the antibody isotype. Examples of antibody effector functions include C1q binding to activate complement dependent cytotoxicity (CDC), Fc receptor binding to activate antibody-dependent cellular cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP).

[00330] When used herein in the context of two or more antibodies, the term "competes with" or "cross-competes with" indicates that the two or more antibodies compete for binding to an antigen (*e.g.*, TF). In one exemplary assay, TF is coated on a surface and contacted with a first TF antibody, after which a second TF antibody is added. In another exemplary assay, first a TF antibody is coated on a surface and contacted with TF, and then a second TF antibody is added. If the presence of the first TF antibody reduces binding of the second TF antibody, in either assay, then the antibodies compete with each other. The term "competes with" also includes combinations of antibodies where one antibody reduces binding of another antibody, but where no competition is observed when the antibodies are added in the reverse order. However, in some embodiments, the first and second antibodies inhibit binding of each other, regardless of the order in which they are added. In some embodiments, one antibody reduces binding of another antibody to its antigen by at least 25%, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, or at least 95%. A skilled artisan can select the concentrations of the antibodies used in the competition assays based on the affinities of the antibodies for TF and the valency of the antibodies. The assays described in this definition are illustrative, and a skilled artisan can utilize any suitable assay to determine if antibodies compete with each other. Suitable assays are described, for example, in Cox et al., "Immunoassay Methods," in *Assay Guidance Manual [Internet]*, Updated December 24, 2014 (www.ncbi.nlm.nih.gov/books/NBK92434/; accessed September 29,

2015); Silman et al., *Cytometry*, 2001, 44:30-37; and Finco et al., *J. Pharm. Biomed. Anal.*, 2011, 54:351-358; each of which is incorporated by reference in its entirety. As provided in **Example 8**, antibodies of group 25 and antibodies of group 43 compete with each other for binding to human TF, while antibodies from groups 1, 29, 39, and 54 do not compete for binding to human TF with antibodies of groups 25 and 43.

[00331] As used herein, an antibody that binds specifically to a human antigen is considered to bind the same antigen of mouse origin when a K_D value can be measured on a ForteBio Octet with the mouse antigen. An antibody that binds specifically to a human antigen is considered to be "cross-reactive" with the same antigen of mouse origin when the K_D value for the mouse antigen is no greater than 20 times the corresponding K_D value for the respective human antigen. For example, the antibody M1593 described in U.S Pat. Nos. 8,722,044, 8,951,525, and 8,999,333, each of which is herein incorporated by reference for all purposes, the humanized 5G9 antibody described in Ngo et al., 2007, *Int J Cancer*, 120(6):1261-1267, incorporated by reference in its entirety, and chimeric ALT-836 antibody described in Hong et al, 2012, *J Nucl Med*, 53(11):1748-1754, incorporated by reference in its entirety, do not bind to mouse TF. As provided in **Examples 1 and 2**, TF antibodies from groups 25 and 43 bind to mouse TF, *e.g.*, the TF antibodies 25G, 25G1, 25G9, and 43D8 are cross-reactive with mouse TF.

[00332] As used herein, an antibody that binds specifically to a human antigen is considered to be "cross-reactive" with the same antigen of cynomolgus monkey origin when the K_D value for the cynomolgus monkey antigen is no greater than 15 times the corresponding K_D value for the respective human antigen. As provided in **Example 1**, all tested antibodies from groups 1, 25, 29, 39, 43, and 54 are cross-reactive with cynomolgus monkey TF.

[00333] The term "epitope" means a portion of an antigen that is specifically bound by an antibody. Epitopes frequently include surface-accessible amino acid residues and/or sugar side chains and may have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter may be lost in the presence of denaturing solvents. An epitope may comprise amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding. The epitope to which an antibody binds can be determined using known techniques for epitope determination such as, for example, testing for antibody binding to TF variants with different point-mutations, or to chimeric TF variants.

[00334] Percent "identity" between a polypeptide sequence and a reference sequence, is defined as the percentage of amino acid residues in the polypeptide sequence that are identical to the amino acid residues in the reference sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, MEGALIGN (DNASTAR), CLUSTALW, CLUSTAL OMEGA, or MUSCLE software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[00335] A "conservative substitution" or a "conservative amino acid substitution," refers to the substitution of an amino acid with a chemically or functionally similar amino acid. Conservative substitution tables providing similar amino acids are well known in the art. By way of example, the groups of amino acids provided in **Tables 2-4** are, in some embodiments, considered conservative substitutions for one another.

Table 2: Selected groups of amino acids that are considered conservative substitutions for one another, in certain embodiments.

Acidic Residues	D and E
Basic Residues	K, R, and H
Hydrophilic Uncharged Residues	S, T, N, and Q
Aliphatic Uncharged Residues	G, A, V, L, and I
Non-polar Uncharged Residues	C, M, and P
Aromatic Residues	F, Y, and W

Table 3: Additional selected groups of amino acids that are considered conservative substitutions for one another, in certain embodiments.

Group 1	A, S, and T
Group 2	D and E
Group 3	N and Q
Group 4	R and K
Group 5	I, L, and M
Group 6	F, Y, and W

Table 4: Further selected groups of amino acids that are considered conservative substitutions for one another, in certain embodiments.

Group A	A and G
Group B	D and E
Group C	N and Q

Group D	R, K, and H
Group E	I, L, M, V
Group F	F, Y, and W
Group G	S and T
Group H	C and M

[00336] Additional conservative substitutions may be found, for example, in Creighton, *Proteins: Structures and Molecular Properties* 2nd ed. (1993) W. H. Freeman & Co., New York, NY. An antibody generated by making one or more conservative substitutions of amino acid residues in a parent antibody is referred to as a "conservatively modified variant."

[00337] The term "amino acid" refers to the twenty common naturally occurring amino acids. Naturally occurring amino acids include alanine (Ala; A), arginine (Arg; R), asparagine (Asn; N), aspartic acid (Asp; D), cysteine (Cys; C); glutamic acid (Glu; E), glutamine (Gln; Q), Glycine (Gly; G); histidine (His; H), isoleucine (Ile; I), leucine (Leu; L), lysine (Lys; K), methionine (Met; M), phenylalanine (Phe; F), proline (Pro; P), serine (Ser; S), threonine (Thr; T), tryptophan (Trp; W), tyrosine (Tyr; Y), and valine (Val; V).

[00338] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

[00339] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which an exogenous nucleic acid has been introduced, and the progeny of such cells. Host cells include "transformants" (or "transformed cells") and "transfectants" (or "transfected cells"), which each include the primary transformed or transfected cell and progeny derived therefrom. Such progeny may not be completely identical in nucleic acid content to a parent cell, and may contain mutations.

[00340] The term "treating" (and variations thereof such as "treat" or "treatment") refers to clinical intervention in an attempt to alter the natural course of a disease or condition in a subject in need thereof. Treatment can be performed both for prophylaxis and during the course of clinical pathology. Desirable effects of treatment include preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis.

[00341] As used herein, the term "therapeutically effective amount" or "effective amount" refers to an amount of an antibody or pharmaceutical composition provided herein that, when administered to a subject, is effective to treat a disease or disorder.

[00342] As used herein, the term "subject" means a mammalian subject. Exemplary subjects include humans, monkeys, dogs, cats, mice, rats, cows, horses, camels, goats, rabbits, pigs and sheep. In certain embodiments, the subject is a human. In some embodiments the subject has a disease or condition that can be treated with an antibody provided herein. In some aspects, the disease or condition is a cancer. In some aspects, the disease or condition involves neovascularization or vascular inflammation. In certain aspects, the disease or condition involving neovascularization is age-related macular degeneration (AMD), diabetic retinopathy, or cancer.

[00343] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic or diagnostic products (*e.g.*, kits) that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic or diagnostic products.

[00344] A "chemotherapeutic agent" refers to a chemical compound useful in the treatment of cancer. Chemotherapeutic agents include "anti-hormonal agents" or "endocrine therapeutics" which act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer.

[00345] The term "cytostatic agent" refers to a compound or composition which arrests growth of a cell either *in vitro* or *in vivo*. In some embodiments, a cytostatic agent is an agent that reduces the percentage of cells in S phase. In some embodiments, a cytostatic agent reduces the percentage of cells in S phase by at least about 20%, at least about 40%, at least about 60%, or at least about 80%.

[00346] The term "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective in treating a subject, and which contains no additional components which are unacceptably toxic to the subject in the amounts provided in the pharmaceutical composition.

[00347] The terms "modulate" and "modulation" refer to reducing or inhibiting or, alternatively, activating or increasing, a recited variable.

[00348] The terms "increase" and "activate" refer to an increase of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or greater in a recited variable.

[00349] The terms "reduce" and "inhibit" refer to a decrease of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or greater in a recited variable.

[00350] The term "agonize" refers to the activation of receptor signaling to induce a biological response associated with activation of the receptor. An "agonist" is an entity that binds to and agonizes a receptor.

[00351] The term "antagonize" refers to the inhibition of receptor signaling to inhibit a biological response associated with activation of the receptor. An "antagonist" is an entity that binds to and antagonizes a receptor.

2. TF Antibodies

2.1. TF Binding

[00352] Provided herein are isolated antibodies that specifically bind to TF. In some aspects, the TF is hTF (SEQ ID NO:809). In some aspects, the TF is cTF (SEQ ID NO:813). In some aspects, the TF is mTF (SEQ ID NO:817). In some aspects, the TF is rabbit TF (SEQ ID NO:832). In some aspects, the TF is pTF (SEQ ID NO:824). In some embodiments, the antibodies provided herein specifically bind to hTF (SEQ ID NO:809), cTF (SEQ ID NO:813), mTF (SEQ ID NO:817), rabbit TF (SEQ ID NO:832), and pTF (SEQ ID NO:824). In some embodiments, the antibodies provided herein specifically bind to hTF (SEQ ID NO:809), cTF (SEQ ID NO:813), mTF (SEQ ID NO:817), and pTF (SEQ ID NO:824). In some embodiments, the antibodies provided herein specifically bind to hTF (SEQ ID NO:809), cTF (SEQ ID NO:813), and mTF (SEQ ID NO:817). In some embodiments, the antibodies provided herein specifically bind to hTF (SEQ ID NO:809) and cTF (SEQ ID NO:813). In some embodiments, the antibodies provided herein do not bind mTF (SEQ ID NO:817). In some embodiments, the antibodies provided herein do not bind pTF (SEQ ID NO:824). In some embodiments, the antibodies provided herein do not bind rabbit TF (SEQ ID NO:832).

[00353] In various embodiments, the antibodies provided herein specifically bind to the extracellular domain of human TF (SEQ ID NO:810).

[00354] In some embodiments, the binding between an antibody provided herein and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to

an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N.

[00355] In some embodiments, the binding between an antibody provided herein and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

[00356] In some embodiments, the binding between an antibody provided herein and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00357] In some embodiments, the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00358] In some embodiments, the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00359] In some embodiments, the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody

and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00360] In some embodiments, the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00361] In some embodiments, the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00362] In some embodiments, the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00363] In some embodiments, the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00364] In some embodiments, the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the

sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00365] In some embodiments, the binding between an antibody provided herein and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00366] In some embodiments, the binding between an antibody provided herein and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID

NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and the binding between an antibody provided herein and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

[00367] In some embodiments, the binding between an antibody provided herein and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID

NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; the binding between an antibody provided herein and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and the binding between an antibody provided herein and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody provided herein and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N; and the mutations at

amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

[00368] In some embodiments, the antibodies provided herein are inert in inhibiting human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference antibody M1593, wherein the reference antibody M1593 comprises a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

[00369] In some embodiments, the antibodies provided herein do not inhibit human thrombin generation as determined by thrombin generation assay (TGA). In certain embodiments, the antibodies provided herein allow human thrombin generation as determined by thrombin generation assay (TGA).

[00370] In some embodiments, the antibodies provided herein bind human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX. In certain embodiments, the antibodies provided herein do not interfere with the ability of TF:FVIIa to convert FX into FXa.

[00371] In some embodiments, the antibodies provided herein bind human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa. In certain embodiments, the antibodies provided herein do not compete for binding to human TF with human FVIIa.

[00372] In some embodiments, the antibodies provided herein bind to the extracellular domain of human TF, bind human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa, bind human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, and allow human thrombin generation as determined by thrombin generation assay (TGA).

[00373] In some embodiments, the antibodies provided herein bind to the extracellular domain of human TF, do not inhibit human thrombin generation as determined by thrombin generation assay (TGA), do not interfere with the ability of TF:FVIIa to convert FX into FXa, and do not compete for binding to human TF with human FVIIa.

[00374] In some embodiments, the antibodies provided herein bind to the extracellular domain of human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa, do not inhibit human thrombin generation as determined by thrombin generation assay (TGA), allow human thrombin generation as determined by thrombin generation assay (TGA), bind to human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, do not interfere with the ability of TF:FVIIa to convert FX into FXa, and do not compete for binding to human TF with human FVIIa.

[00375] In some embodiments, the antibodies provided herein inhibit FVIIa-dependent TF signaling.

[00376] In some embodiments, the antibodies provided herein reduce lesion size in a swine choroidal neovascularization (CNV) model.

[00377] In some embodiments, the antibodies provided herein bind to the extracellular domain of human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa, do not inhibit human thrombin generation as determined by thrombin generation assay (TGA), allow human thrombin generation as determined by thrombin generation assay (TGA), bind to human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, do not interfere with the ability of TF:FVIIa to convert FX into FXa, do not compete for binding to human TF with human FVIIa, and bind to cynomolgus and mouse TF.

[00378] In some embodiments, the antibodies provided herein bind to the extracellular domain of human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa, do not inhibit human thrombin generation as determined by thrombin generation assay (TGA), allow human thrombin generation as determined by thrombin generation assay (TGA), bind to human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, do not interfere with the ability of TF:FVIIa to convert FX into FXa, do not compete for binding to human TF with human FVIIa, bind to cynomolgus, mouse, and pig TF, and reduce lesion size in a swine choroidal neovascularization (CNV) model.

[00379] In some embodiments, the antibodies provided herein bind to the extracellular domain of human TF, inhibit FVIIa-dependent TF signaling, and bind to cynomolgus TF.

2.2. Sequences of TF Antibodies

2.2.1. V_H Domains

[00380] In some embodiments, an antibody provided herein comprises a V_H sequence selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:37. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:75. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:113. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:151. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:189. In

some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:836. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:227. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:265. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:303. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:341. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:379. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:417. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:455. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:493. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:531. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:569. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:607. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:645. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:683. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:721. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:759.

[00381] In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759. In some embodiments, an antibody provided herein comprises a V_H sequence provided in SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

2.2.2. V_L Domains

[00382] In some embodiments, an antibody provided herein comprises a V_L sequence selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:38. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:76. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:114. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:152. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:190. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:837. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:228. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:266. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:304. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:342. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:380. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:418. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:456. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:494. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:532. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:570. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:608. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:646. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:684. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:722. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO:760.

[00383] In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_L sequence provided in SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, an antibody provided herein comprises a V_L sequence provided in SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760, with up to 1, 2, 3, 4, 5,

6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

2.2.3. V_H-V_L Combinations

[00384] In some embodiments, an antibody provided herein comprises a V_H sequence selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759 and a V_L sequence selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760.

[00385] In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:37 and a V_L sequence of SEQ ID NO:38. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:75 and a V_L sequence of SEQ ID NO:76. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:113 and a V_L sequence of SEQ ID NO:114. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:151 and a V_L sequence of SEQ ID NO:152. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:189 and a V_L sequence of SEQ ID NO:190. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:836 and a V_L sequence of SEQ ID NO:837. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:227 and a V_L sequence of SEQ ID NO:228. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:265 and a V_L sequence of SEQ ID NO:266. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:303 and a V_L sequence of SEQ ID NO:304. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:341 and a V_L sequence of SEQ ID NO:342. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:379 and a V_L sequence of SEQ ID NO:380. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:417 and a V_L sequence of SEQ ID NO:418. In some embodiments, an antibody provided herein comprises a V_H sequence of

SEQ ID NO:455 and a V_L sequence of SEQ ID NO:456. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:493 and a V_L sequence of SEQ ID NO:494. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:531 and a V_L sequence of SEQ ID NO:532. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:569 and a V_L sequence of SEQ ID NO:570. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:607 and a V_L sequence of SEQ ID NO:608. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:645 and a V_L sequence of SEQ ID NO:646. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:683 and a V_L sequence of SEQ ID NO:684. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:721 and a V_L sequence of SEQ ID NO:722. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO:759 and a V_L sequence of SEQ ID NO:760.

[00386] In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, and a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_L sequence provided in SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, an antibody provided herein comprises a V_H sequence provided in SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions, and a V_L sequence provided in SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

2.2.4. CDRs

[00387] In some embodiments, an antibody provided herein comprises one to three CDRs of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759. In some embodiments, an antibody provided herein comprises two to three CDRs of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759. In some embodiments, an antibody provided herein comprises three CDRs of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759. In some aspects, the CDRs are Exemplary CDRs. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

[00388] In some embodiments, the CDRs are CDRs having at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1, CDR-H2, or CDR-H3 of SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759. In some embodiments, the CDR-H1 is a CDR-H1 of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some embodiments, the CDR-H2 is a CDR-H2 of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some embodiments, the CDR-H3 is a CDR-H3 of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00389] In some embodiments, an antibody provided herein comprises one to three CDRs of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380,

418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, an antibody provided herein comprises two to three CDRs of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, an antibody provided herein comprises three CDRs of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some aspects, the CDRs are Exemplary CDRs. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

[00390] In some embodiments, the CDRs are CDRs having at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1, CDR-L2, or CDR-L3 of SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, the CDR-L1 is a CDR-L1 of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some embodiments, the CDR-L2 is a CDR-L2 of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some embodiments, the CDR-L3 is a CDR-L3 of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00391] In some embodiments, an antibody provided herein comprises one to three CDRs of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759 and one to three CDRs of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, an antibody provided herein comprises two to three CDRs of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151,

189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759 and two to three CDRs of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, an antibody provided herein comprises three CDRs of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759 and three CDRs of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some aspects, the CDRs are Exemplary CDRs. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

[00392] In some embodiments, the CDRs are CDRs having at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1, CDR-H2, or CDR-H3 of SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759 and at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1, CDR-L2, or CDR-L3 of SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760. In some embodiments, the CDR-H1 is a CDR-H1 of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-H2 is a CDR-H2 of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H3 is a CDR-H3 of a V_H domain selected from SEQ ID NOs: 37, 75, 113, 151, 189, 227, 265, 303, 341, 379, 417, 455, 493, 531, 569, 607, 645, 683, 721, and 759, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-L1 is a CDR-L1 of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions; the CDR-L2 is a CDR-L2 of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L3 is a CDR-L3 of a V_L domain selected from SEQ ID NOs: 38, 76, 114, 152, 190, 228, 266, 304, 342, 380, 418, 456, 494, 532, 570, 608, 646, 684, 722, and 760, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed

mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00393] In some embodiments, an antibody provided herein comprises a CDR-H3 selected from SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725, as determined by the Exemplary numbering system. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725. In some embodiments, the CDR-H3 is a CDR-H3 selected from SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00394] In some embodiments, an antibody provided herein comprises a CDR-H2 selected from SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724, as determined by the Exemplary numbering system. In some aspects, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724. In some embodiments, the CDR-H2 is a CDR-H2 selected from SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00395] In some embodiments, an antibody provided herein comprises a CDR-H1 selected from SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723, as determined by the Exemplary numbering system. In some aspects, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723. In some embodiments, the CDR-H1 is a CDR-H1 selected from SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00396] In some embodiments, an antibody provided herein comprises a CDR-H3 selected from SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725 and a CDR-H2 selected from SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724. In some embodiments, an antibody provided herein comprises a CDR-H3 selected from SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725, a CDR-H2 selected from SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724, and a CDR-H1 selected from SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723. In some embodiments, the CDR-H3 is a CDR-H3 selected from SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is

a CDR-H2 selected from SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 selected from SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibody described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00397] In some embodiments, an antibody provided herein comprises a CDR-L3 selected from SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728, as determined by the Exemplary numbering system. In some aspects, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728. In some embodiments, the CDR-L3 is a CDR-L3 selected from SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00398] In some embodiments, an antibody provided herein comprises a CDR-L2 selected from SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727, as determined by the Exemplary numbering system. In some aspects, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727. In some embodiments, the CDR-L2 is a CDR-L2 selected from SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537,

575, 613, 651, 689, and 727, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00399] In some embodiments, an antibody provided herein comprises a CDR-L1 selected from SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726, as determined by the Exemplary numbering system. In some aspects, the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726. In some embodiments, the CDR-L1 is a CDR-L1 selected from SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00400] In some embodiments, an antibody provided herein comprises a CDR-L3 selected from SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728 and a CDR-L2 selected from SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727. In some embodiments, an antibody provided herein comprises a CDR-L3 selected from SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728, a CDR-L2 selected from SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727, and a CDR-L1 selected from SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726. In some embodiments, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272,

310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726. In some embodiments, the CDR-L3 is a CDR-L3 selected from SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 selected from SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 selected from SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00401] In some embodiments, an antibody provided herein comprises a CDR-H3 selected from SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725, a CDR-H2 selected from SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724, a CDR-H1 selected from SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723, a CDR-L3 selected from SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728, a CDR-L2 selected from SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727, and a CDR-L1 selected from SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268,

306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726. In some embodiments, the CDR-H3 is a CDR-H3 selected from SEQ ID NOs: 3, 41, 79, 117, 155, 193, 231, 269, 307, 345, 383, 421, 459, 497, 535, 573, 611, 649, 687, and 725, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 selected from SEQ ID NOs: 2, 40, 78, 116, 154, 192, 230, 268, 306, 344, 382, 420, 458, 496, 534, 572, 610, 648, 686, and 724, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 selected from SEQ ID NOs: 1, 39, 77, 115, 153, 191, 229, 267, 305, 343, 381, 419, 457, 495, 533, 571, 609, 647, 685, and 723, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 selected from SEQ ID NOs: 6, 44, 82, 120, 158, 196, 234, 272, 310, 348, 386, 424, 462, 500, 538, 576, 614, 652, 690, and 728, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 selected from SEQ ID NOs: 5, 43, 81, 119, 157, 195, 233, 271, 309, 347, 385, 423, 461, 499, 537, 575, 613, 651, 689, and 727, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 selected from SEQ ID NOs: 4, 42, 80, 118, 156, 194, 232, 270, 308, 346, 384, 422, 460, 498, 536, 574, 612, 650, 688, and 726, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[00402] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:1, a CDR-H2 of SEQ ID NO:2, a CDR-H3 of SEQ ID NO:3, a CDR-L1 of SEQ ID

NO:4, a CDR-L2 of SEQ ID NO:5, and a CDR-L1 of SEQ ID NO:6, as determined by the Exemplary numbering system.

[00403] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:39, a CDR-H2 of SEQ ID NO:40, a CDR-H3 of SEQ ID NO:41, a CDR-L1 of SEQ ID NO:42, a CDR-L2 of SEQ ID NO:43, and a CDR-L1 of SEQ ID NO:44, as determined by the Exemplary numbering system.

[00404] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:77, a CDR-H2 of SEQ ID NO:78, a CDR-H3 of SEQ ID NO:79, a CDR-L1 of SEQ ID NO:80, a CDR-L2 of SEQ ID NO:81, and a CDR-L1 of SEQ ID NO:82, as determined by the Exemplary numbering system.

[00405] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:115, a CDR-H2 of SEQ ID NO:116, a CDR-H3 of SEQ ID NO:117, a CDR-L1 of SEQ ID NO:118, a CDR-L2 of SEQ ID NO:119, and a CDR-L1 of SEQ ID NO:120, as determined by the Exemplary numbering system.

[00406] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:153, a CDR-H2 of SEQ ID NO:154, a CDR-H3 of SEQ ID NO:155, a CDR-L1 of SEQ ID NO:156, a CDR-L2 of SEQ ID NO:157, and a CDR-L1 of SEQ ID NO:158, as determined by the Exemplary numbering system.

[00407] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:884, a CDR-H2 of SEQ ID NO:885, a CDR-H3 of SEQ ID NO:886, a CDR-L1 of SEQ ID NO:887, a CDR-L2 of SEQ ID NO:888, and a CDR-L1 of SEQ ID NO:889, as determined by the Exemplary numbering system.

[00408] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:191, a CDR-H2 of SEQ ID NO:192, a CDR-H3 of SEQ ID NO:193, a CDR-L1 of SEQ ID NO:194, a CDR-L2 of SEQ ID NO:195, and a CDR-L1 of SEQ ID NO:196, as determined by the Exemplary numbering system.

[00409] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:229, a CDR-H2 of SEQ ID NO:230, a CDR-H3 of SEQ ID NO:231, a CDR-L1 of SEQ ID NO:232, a CDR-L2 of SEQ ID NO:233, and a CDR-L1 of SEQ ID NO:234, as determined by the Exemplary numbering system.

[00410] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:267, a CDR-H2 of SEQ ID NO:268, a CDR-H3 of SEQ ID NO:269, a CDR-L1 of SEQ ID NO:270, a CDR-L2 of SEQ ID NO:271, and a CDR-L1 of SEQ ID NO:272, as determined by the Exemplary numbering system.

[00411] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:305, a CDR-H2 of SEQ ID NO:306, a CDR-H3 of SEQ ID NO:307, a CDR-L1 of SEQ ID NO:308, a CDR-L2 of SEQ ID NO:309, and a CDR-L1 of SEQ ID NO:310, as determined by the Exemplary numbering system.

[00412] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:343, a CDR-H2 of SEQ ID NO:344, a CDR-H3 of SEQ ID NO:345, a CDR-L1 of SEQ ID NO:346, a CDR-L2 of SEQ ID NO:347, and a CDR-L1 of SEQ ID NO:348, as determined by the Exemplary numbering system.

[00413] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:381, a CDR-H2 of SEQ ID NO:382, a CDR-H3 of SEQ ID NO:383, a CDR-L1 of SEQ ID NO:384, a CDR-L2 of SEQ ID NO:385, and a CDR-L1 of SEQ ID NO:386, as determined by the Exemplary numbering system.

[00414] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:419, a CDR-H2 of SEQ ID NO:420, a CDR-H3 of SEQ ID NO:421, a CDR-L1 of SEQ ID NO:422, a CDR-L2 of SEQ ID NO:423, and a CDR-L1 of SEQ ID NO:424, as determined by the Exemplary numbering system.

[00415] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:457, a CDR-H2 of SEQ ID NO:458, a CDR-H3 of SEQ ID NO:459, a CDR-L1 of SEQ ID NO:460, a CDR-L2 of SEQ ID NO:461, and a CDR-L1 of SEQ ID NO:462, as determined by the Exemplary numbering system.

[00416] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:495, a CDR-H2 of SEQ ID NO:496, a CDR-H3 of SEQ ID NO:497, a CDR-L1 of SEQ ID NO:498, a CDR-L2 of SEQ ID NO:499, and a CDR-L1 of SEQ ID NO:500, as determined by the Exemplary numbering system.

[00417] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:533, a CDR-H2 of SEQ ID NO:534, a CDR-H3 of SEQ ID NO:535, a CDR-L1 of SEQ ID NO:536, a CDR-L2 of SEQ ID NO:537, and a CDR-L1 of SEQ ID NO:538, as determined by the Exemplary numbering system.

[00418] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:571, a CDR-H2 of SEQ ID NO:572, a CDR-H3 of SEQ ID NO:573, a CDR-L1 of SEQ ID NO:574, a CDR-L2 of SEQ ID NO:575, and a CDR-L1 of SEQ ID NO:576, as determined by the Exemplary numbering system.

[00419] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:609, a CDR-H2 of SEQ ID NO:610, a CDR-H3 of SEQ ID NO:611, a CDR-L1 of

SEQ ID NO:612, a CDR-L2 of SEQ ID NO:613, and a CDR-L1 of SEQ ID NO:614, as determined by the Exemplary numbering system.

[00420] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:647, a CDR-H2 of SEQ ID NO:648, a CDR-H3 of SEQ ID NO:649, a CDR-L1 of SEQ ID NO:650, a CDR-L2 of SEQ ID NO:651, and a CDR-L1 of SEQ ID NO:652, as determined by the Exemplary numbering system.

[00421] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:685, a CDR-H2 of SEQ ID NO:686, a CDR-H3 of SEQ ID NO:687, a CDR-L1 of SEQ ID NO:688, a CDR-L2 of SEQ ID NO:689, and a CDR-L1 of SEQ ID NO:690, as determined by the Exemplary numbering system.

[00422] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO:723, a CDR-H2 of SEQ ID NO:724, a CDR-H3 of SEQ ID NO:725, a CDR-L1 of SEQ ID NO:726, a CDR-L2 of SEQ ID NO:727, and a CDR-L1 of SEQ ID NO:728, as determined by the Exemplary numbering system.

2.2.5. Consensus Sequences

[00423] In some embodiments, provided herein is a first family of antibodies, wherein an antibody of such family comprises the following six CDR sequences: (a) a CDR-H1 having the sequence G-F-T-F-S-X_1-Y-A-M-X_2, wherein X_1 is D or S and X_2 is A or G (SEQ ID NO:773); (b) a CDR-H2 having the sequence X_3-I-S-G-S-G-G-L-T-Y-Y-A-D-S-V-K-G, wherein X_3 is A or T (SEQ ID NO:774); (c) a CDR-H3 having the sequence APYGYYMDV (SEQ ID NO:775); (d) a CDR-L1 having the sequence RASQSISSWLA (SEQ ID NO:776); (e) a CDR-L2 having the sequence KASSLES (SEQ ID NO:777); and (f) a CDR-L3 having the sequence QQYKSYIT (SEQ ID NO:778). In some embodiments, an antibody of such family comprises a V_H sequence of SEQ ID NO:761 and a V_L sequence of SEQ ID NO:762. In some embodiments, provided herein is an antibody within such first family.

[00424] In some embodiments, provided herein is a second family of antibodies, wherein an antibody of such family comprises the following six CDR sequences: (a) a CDR-H1 having the sequence G-Y-T-F-X_1-X_2-Y-G-I-S, wherein X_1 is D or R and X_2 is S or V (SEQ ID NO:779); (b) a CDR-H2 having the sequence W-X_3-A-P-Y-X_4-G-N-T-N-Y-A-Q-K-L-Q-G, wherein X_3 is I or V and X_4 is S or N (SEQ ID NO:780); (c) a CDR-H3 having the sequence D-A-G-T-Y-S-P-X_5-G-Y-G-M-D-V, wherein X_5 is F or Y (SEQ ID NO:781); (d) a CDR-L1 having the sequence X_6-A-S-X_7-S-I-X_8-X_9-W-L-A, wherein X_6 is R or Q, X_7 is Q, E, or H, X_8 is S, D, or N, and X_9 is S or N (SEQ ID NO:782); (e) a CDR-L2 having the

sequence X_{10}-A-X_{11}-X_{12}-L-E-X_{13}, wherein X_{10} is K or S, X_{11} is S or Y, X_{12} is S, Y, or N, and X_{13} is S or Y (SEQ ID NO:783); and (f) a CDR-L3 having the sequence Q-X_{14}-F-Q-X_{15}-L-P-P-F-T, wherein X_{14} is Q, L, or R, and X_{15} is S or K (SEQ ID NO:784). In some embodiments, an antibody of such family comprises a V_H sequence of SEQ ID NO:763 and a V_L sequence of SEQ ID NO:764. In some embodiments, provided herein is an antibody within such second family.

[00425] In some embodiments, provided herein is a third family of antibodies, wherein an antibody of such family comprises the following six CDR sequences: (a) a CDR-H1 having the sequence G-F-T-F-X_1-S-X_2-G-M-H, wherein X_1 is H or R and X_2 is R or Y (SEQ ID NO:785); (b) a CDR-H2 having the sequence VITYDGINKYYADSVEG (SEQ ID NO:786); (c) a CDR-H3 having the sequence DGVYYGVYDY (SEQ ID NO:787); (d) a CDR-L1 having the sequence KSSQSVLFSSNNKNYLA (SEQ ID NO:788); (e) a CDR-L2 having the sequence WASTRES (SEQ ID NO:789); and (f) a CDR-L3 having the sequence QQFHSYPLT (SEQ ID NO:790). In some embodiments, an antibody of such family comprises a V_H sequence of SEQ ID NO:765 and a V_L sequence of SEQ ID NO:766. In some embodiments, provided herein is an antibody within such third family.

[00426] In some embodiments, provided herein is a fourth family of antibodies, wherein an antibody of such family comprises the following six CDR sequences: (a) a CDR-H1 having the sequence GGTFSSNAIG (SEQ ID NO:791); (b) a CDR-H2 having the sequence SIIPIIGFANYAQKFQG (SEQ ID NO:792); (c) a CDR-H3 having the sequence DSGYYYGASSFGMDV (SEQ ID NO:793); (d) a CDR-L1 having the sequence RASQSVSSNLA (SEQ ID NO:794); (e) a CDR-L2 having the sequence GASTRAT (SEQ ID NO:795); and (f) a CDR-L3 having the sequence EQYNNLPLT (SEQ ID NO:796). In some embodiments, an antibody of such family comprises a V_H sequence of SEQ ID NO:767 and a V_L sequence of SEQ ID NO:768. In some embodiments, provided herein is an antibody within such fourth family.

[00427] In some embodiments, provided herein is a fifth family of antibodies, wherein an antibody of such family comprises the following six CDR sequences: (a) a CDR-H1 having the sequence G-G-S-X_1-S-S-G-X_2-Y-W-S, wherein X_1 is I or L and X_2 is Q or Y (SEQ ID NO:797); (b) a CDR-H2 having the sequence E-I-X_3-X_4-S-G-S-T-R-Y-N-P-S-L-K-S, wherein X_3 is Y or G and X_4 is Y or A (SEQ ID NO:798); (c) a CDR-H3 having the sequence D-X_5-P-Y-Y-Y-X_6-G-G-Y-Y-Y-Y-M-D-V, wherein X_5 is T or A and X_6 is E, G, or D (SEQ ID NO:799); (d) a CDR-L1 having the sequence R-A-S-X_7-S-V-X_8-S-S-X_9-L-A, wherein X_7 is Q, E, or D, X_8 is S or D, and X_9 is Y or F (SEQ ID NO:800); (e) a CDR-L2 having the

sequence G-A-X_{10}-X_{11}-R-X_{12}-X_{13}, wherein X_{10} is S, D, F, or Y, X_{11} is S or T, X_{12} is A or Q, and X_{13} is T or N (SEQ ID NO:801); and (f) a CDR-L3 having the sequence Q-Q-X_{14}-G-V-V-P-Y-T, wherein X_{14} is V, A, or D (SEQ ID NO:802). In some embodiments, an antibody of such family comprises a V_H sequence of SEQ ID NO:769 and a V_L sequence of SEQ ID NO:770. In some embodiments, provided herein is an antibody within such fifth family.

[00428] In some embodiments, provided herein is a sixth family of antibodies, wherein an antibody of such family comprises the following six CDR sequences: (a) a CDR-H1 having the sequence GYTFANYYMH (SEQ ID NO:803); (b) a CDR-H2 having the sequence IINPSGGITVYAQKFQG (SEQ ID NO:804); (c) a CDR-H3 having the sequence GGSKVAALAFDI (SEQ ID NO:805); (d) a CDR-L1 having the sequence QASQDISNSLN (SEQ ID NO:806); (e) a CDR-L2 having the sequence DASNLET (SEQ ID NO:807); and (f) a CDR-L3 having the sequence QQYNFHPLT (SEQ ID NO:808). In some embodiments, an antibody of such family comprises a V_H sequence of SEQ ID NO:771 and a V_L sequence of SEQ ID NO:772. In some embodiments, provided herein is an antibody within such sixth family.

[00429] In some embodiments, provided herein is a seventh family of antibodies, wherein an antibody of such family comprises the following six CDR sequences: (a) a CDR-H1 having the sequence G-Y-T-F-D-X_1-Y-G-I-S, wherein X_1 is V or A (SEQ ID NO:872); (b) a CDR-H2 having the sequence W-I-A-P-Y-X_2-G-N-T-N-Y-A-Q-K-L-Q-G, wherein X_2 is N or S (SEQ ID NO:873); (c) a CDR-H3 having the sequence D-A-G-T-Y-S-P-F-G-Y-G-M-D-V (SEQ ID NO:874); (d) a CDR-L1 having the sequence X_3-A-S-X_4-S-I-X_5-X_6-W-L-A, wherein X_3 is R or Q, X_4 is Q or E, X_5 is S or N, and X_6 is S or N (SEQ ID NO:875); (e) a CDR-L2 having the sequence K-A-X_7-X_8-L-E-X_9, wherein X_7 is S or Y, X_8 is S or N, and X_9 is S or Y (SEQ ID NO:876); and (f) a CDR-L3 having the sequence Q-X_{10}-F-Q-X_{11}-L-P-P-F-T, wherein X_{10} is Q or L, and X_{11} is S or K (SEQ ID NO:877). In some embodiments, an antibody of such family comprises a V_H sequence of SEQ ID NO:868 and a V_L sequence of SEQ ID NO:869. In some embodiments, provided herein is an antibody within such seventh family.

[00430] In some embodiments, provided herein is an eighth family of antibodies, wherein an antibody of such family comprises the following six CDR sequences: (a) a CDR-H1 having the sequence G-Y-T-F-R-S-Y-G-I-S (SEQ ID NO:878); (b) a CDR-H2 having the sequence W-V-A-P-Y-X_1-G-N-T-N-Y-A-Q-K-L-Q-G, wherein X_1 is S or N (SEQ ID NO:879); (c) a CDR-H3 having the sequence D-A-G-T-Y-S-P-Y-G-Y-G-M-D-V (SEQ ID NO:880); (d) a CDR-L1 having the sequence X_2-A-S-X_3-S-I-X_4-S-W-L-A, wherein X_2 is R

or Q, X_3 is Q or H, X_4 is S or D (SEQ ID NO:881); (e) a CDR-L2 having the sequence X_5-A-S-X_6-L-E-S, wherein X_5 is K or S, X_6 is S or Y (SEQ ID NO:882); and (f) a CDR-L3 having the sequence Q-X_7-F-Q-S-L-P-P-F-T, wherein X_7 is Q, L, or R (SEQ ID NO:883). In some embodiments, an antibody of such family comprises a VH sequence of SEQ ID NO:870 and a VL sequence of SEQ ID NO:871. In some embodiments, provided herein is an antibody within such eighth family.

2.2.6. Functional Properties of Antibody Variants

[00431] As described above, and elsewhere in this disclosure, provided herein are antibody variants defined based on percent identity to an illustrative antibody sequence provided herein, or substitution of amino acid residues in comparison to an illustrative antibody sequence provided herein.

[00432] In some embodiments, a variant of an antibody provided herein has specificity for hTF. In some embodiments, a variant of an antibody provided herein has specificity for cTF. In some embodiments, a variant of an antibody provided herein has specificity for mTF. In some embodiments, a variant of an antibody provided herein has specificity for hTF and cTF. In some embodiments, a variant of an antibody provided herein has specificity for hTF and mTF. In some embodiments, a variant of an antibody provided herein has specificity for cTF and mTF. In some embodiments, a variant of an antibody provided herein has specificity for hTF, cTF and mTF.

[00433] In some embodiments, a variant of an antibody that is derived from an illustrative antibody sequence provided herein retains affinity, as measured by K_D, for hTF that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative antibody. In some embodiments, a variant of an antibody that is derived from an illustrative antibody sequence provided herein retains affinity, as measured by K_D, for cTF that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative antibody. In some embodiments, a variant of an antibody that is derived from an illustrative antibody sequence provided herein retains affinity, as measured by K_D, for mTF that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative antibody. In some embodiments, a variant of an antibody that is derived from an illustrative antibody sequence provided herein retains affinity, as measured by K_D, for both hTF and cTF that is within

about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative antibody. In some embodiments, a variant of an antibody that is derived from an illustrative antibody sequence provided herein retains affinity, as measured by K_D, for both hTF and mTF that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative antibody. In some embodiments, a variant of an antibody that is derived from an illustrative antibody sequence provided herein retains affinity, as measured by K_D, for both cTF and mTF that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative antibody. In some embodiments, a variant of an antibody that is derived from an illustrative antibody sequence provided herein retains affinity, as measured by K_D, for all three of hTF, cTF and mTF that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative antibody.

[00434] In some embodiments, a variant of an antibody provided herein retains the ability to inhibit TF signaling, as measured by one or more assays or biological effects described herein. In some embodiments, a variant of an antibody provided herein retains the normal function of TF in the blood coagulation processes.

[00435] In some embodiments, a variant of an antibody provided herein competes for binding to TF with an antibody selected from 1F, 1G, 25A, 25A3, 25A5, 25A5-T, 25G, 25G1, 25G9, 29D, 29E, 39A, 43B, 43B1, 43B7, 43D, 43D7, 43D8, 43E, 43Ea, and 54E, each as provided in **Table 13** of this disclosure. In some embodiments, a variant of an antibody provided herein competes for binding to TF with an antibody selected from 25A, 25A3, 25A5, 25A5-T, 25G, 25G1, and 25G9. In some embodiments, a variant of an antibody provided herein competes for binding to TF with an antibody selected from 43B, 43B1, 43B7, 43D, 43D7, 43D8, 43E, and 43Ea. In some embodiments, a variant of an antibody provided herein competes for binding to TF with an antibody selected from 25A, 25A3, 25A5, 25A5-T, 25G, 25G1, 25G9, 43B, 43B1, 43B7, 43D, 43D7, 43D8, 43E, and 43Ea. In some embodiments, a variant of an antibody provided herein competes for binding to TF with an antibody selected from 1F, 1G, 29D, 29E, 39A, or 54E.

[00436] In some embodiments, a variant of an antibody provided herein allows human thrombin generation as determined by thrombin generation assay (TGA). In some

embodiments, a variant of an antibody provided herein does not inhibit human thrombin generation as determined by thrombin generation assay (TGA).

[00437] In some embodiments, a variant of an antibody provided herein binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX. In some embodiments, a variant of an antibody provided herein does not interfere with the ability of TF:FVIIa to convert FX into FXa.

[00438] In some embodiments, a variant of an antibody provided herein binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa. In some embodiments, a variant of an antibody provided herein does not compete for binding to human TF with human FVIIa.

[00439] In some embodiments, a variant of an antibody provided herein inhibits FVIIa-dependent TF signaling.

[00440] In some embodiments, a variant of an antibody provided herein binds mouse TF (SEQ ID NO:817). In some embodiments, a variant of an antibody provided herein binds mouse TF with an affinity lower (as indicated by higher K_D) than the affinity of the antibody for hTF. In some embodiments, a variant of an antibody provided herein does not bind mTF.

[00441] In some embodiments, a variant of an antibody provided herein binds pig TF (SEQ ID NO:824). In some embodiments, a variant of an antibody provided herein binds pig TF with an affinity lower (as indicated by higher K_D) than the affinity of the antibody for hTF. In some embodiments, a variant of an antibody provided herein does not bind pTF.

[00442] In some embodiments, a variant of an antibody provided herein binds the same epitope of TF as such antibody.

2.2.7. Other Functional Properties of Antibodies

[00443] In some embodiments, an antibody provided herein has one or more of the characteristics listed in the following (a)-(dd): (a) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; (b) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (c) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (d) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (e) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (f) allows human thrombin generation as determined by thrombin generation assay (TGA); (g) maintains the thrombin peak on a thrombin

generation curve (Peak IIa) compared to an isotype control; (h) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (i) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (j) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (k) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (l) does not compete for binding to human TF with human FVIIa; (m) inhibits FVIIa-dependent TF signaling; (n) binds to cynomolgus TF; (o) binds to mouse TF; (p) binds to rabbit TF; (q) binds to pig TF; (r) reduces lesion size in a swine choroidal neovascularization (CNV) model; (s) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (t) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (u) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (v) the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (w) the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the

antibody relative to an isotype control in a live cell staining assay; (x) the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (y) the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (z) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (aa) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (bb) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (cc) the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID

NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (dd) the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, an antibody provided herein has two or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has three or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has four or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has five or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has six or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has seven or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has eight or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has nine or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has ten or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has eleven or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twelve or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has thirteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has fourteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has fifteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has sixteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has seventeen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has eighteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has nineteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has

twenty-one or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-two or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-three of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-four of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-five of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-six of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-seven of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-eight of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-nine of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has all thirty of the characteristics listed in the foregoing (a)-(dd).

[00444] In some embodiments, an antibody provided herein has one or more of the characteristics listed in the following (a)-(dd): (a) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; (b) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (c) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (d) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (e) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (f) allows human thrombin generation as determined by thrombin generation assay (TGA); (g) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (h) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (i) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (j) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (k) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (l) does not compete for binding to human TF with human FVIIa; (m) inhibits FVIIa-dependent TF signaling; (n) binds to cynomolgus TF; (o) binds to mouse TF; (p) binds to rabbit TF; (q) binds to pig TF; (r) reduces lesion size in a swine choroidal neovascularization (CNV) model; (s) the binding between the antibody and a variant TF extracellular domain comprising a

mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (t) the binding between the antibody and a variant TF extracellular domain comprising a mutation K68N of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (u) the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (v) the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (w) the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (x) the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (y) the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular

domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (z) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (aa) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (bb) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (cc) the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (dd) the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay. In some embodiments, an antibody provided herein has two or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has three or more of the characteristics listed in the foregoing (a)-(dd). In some

embodiments, an antibody provided herein has four or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has five or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has six or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has seven or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has eight or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has nine or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has ten or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has eleven or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twelve or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has thirteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has fourteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has fifteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has sixteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has seventeen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has eighteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has nineteen or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-one or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-two or more of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-three of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-four of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-five of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-six of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-seven of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has twenty-eight of the characteristics listed in the foregoing (a)-(dd). In

some embodiments, an antibody provided herein has twenty-nine of the characteristics listed in the foregoing (a)-(dd). In some embodiments, an antibody provided herein has all thirty of the characteristics listed in the foregoing (a)-(dd).

[00445] In some embodiments, an antibody provided herein exhibits a combination of characteristics comprising two or more of characteristics listed in the following (a)-(dd): (a) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; (b) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (c) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (d) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (e) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (f) allows human thrombin generation as determined by thrombin generation assay (TGA); (g) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (h) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (i) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (j) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (k) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (l) does not compete for binding to human TF with human FVIIa; (m) inhibits FVIIa-dependent TF signaling; (n) binds to cynomolgus TF; (o) binds to mouse TF; (p) binds to rabbit TF; (q) binds to pig TF; (r) reduces lesion size in a swine choroidal neovascularization (CNV) model; (s) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (t) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (u) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than

50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (v) the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (w) the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (x) the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (y) the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (z) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (aa) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the

sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (bb) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (cc) the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (dd) the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00446] In some embodiments, an antibody provided herein exhibits a combination of characteristics comprising two or more of characteristics listed in the following (a)-(dd): (a) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; (b) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); (c) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (d) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (e) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (f) allows human thrombin generation as determined by thrombin generation assay (TGA); (g) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control; (h) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control; (i) preserves the

endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control; (j) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX; (k) does not interfere with the ability of TF:FVIIa to convert FX into FXa; (l) does not compete for binding to human TF with human FVIIa; (m) inhibits FVIIa-dependent TF signaling; (n) binds to cynomolgus TF; (o) binds to mouse TF; (p) binds to rabbit TF; (q) binds to pig TF; (r) reduces lesion size in a swine choroidal neovascularization (CNV) model; (s) the binding between the antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (t) the binding between the antibody and a variant TF extracellular domain comprising a mutation K68N of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (u) the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (v) the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (w) the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (x) the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain

amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (y) the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (z) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (aa) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (bb) the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; (cc) the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and (dd) the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of

the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00447] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); and the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00448] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); and the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00449] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; allows human thrombin generation as determined by thrombin generation assay (TGA); and the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00450] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is

distinct from a human TF binding site bound by human FVIIa; allows human thrombin generation as determined by thrombin generation assay (TGA); and the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00451] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00452] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); the binding between the antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00453] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; allows human thrombin generation as determined by thrombin generation assay (TGA); the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00454] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; allows human thrombin generation as determined by thrombin generation assay (TGA); the binding between the antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00455] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); binds to cynomolgus TF; the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of

the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00456] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); binds to cynomolgus TF; the binding between the antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00457] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; allows human thrombin generation as determined by thrombin generation assay (TGA); binds to cynomolgus TF; the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID

NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

[00458] In some embodiments, an antibody provided herein exhibits a combination of the characteristics listed in the following: binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa; allows human thrombin generation as determined by thrombin generation assay (TGA); binds to cynomolgus TF; the binding between the antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

2.3. Affinity and Other Properties of TF Antibodies

2.3.1. Affinity of TF Antibodies

[00459] In some embodiments, the affinity of an antibody provided herein for TF as indicated by K_D, is less than about 10^{-5} M, less than about 10^{-6} M, less than about 10^{-7} M, less than about 10^{-8} M, less than about 10^{-9} M, less than about 10^{-10} M, less than about 10^{-11} M, or less than about 10^{-12} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-12} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-11} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-10} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-9} M. In some embodiments, the affinity of the antibody is between about 10^{-7} M and 10^{-8} M. In some embodiments, the affinity of the antibody is between about 10^{-8} M and 10^{-12} M. In some embodiments, the affinity of the antibody is between about 10^{-8} M and 10^{-11} M. In some embodiments, the affinity of the antibody is between about 10^{-9} M and 10^{-11} M. In some embodiments, the affinity of the antibody is between about 10^{-10} M and 10^{-11} M.

[00460] In some embodiments, the K_D value of an antibody provided herein for cTF is no more than 15× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for cTF is no more than 10× of the K_D value of the antibody

for hTF. In some embodiments, the K_D value of an antibody provided herein for cTF is no more than 8× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for cTF is no more than 5× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for cTF is no more than 3× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for cTF is no more than 2× of the K_D value of the antibody for hTF.

[00461] In some embodiments, the K_D value of an antibody provided herein for mTF is no more than 20× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for mTF is no more than 15× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for mTF is no more than 10× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for mTF is no more than 5× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for mTF is no more than 2× of the K_D value of the antibody for hTF.

[00462] In some embodiments, the affinity of an antibody provided herein for hTF as indicated by K_D measured by Biacore, as set forth in **Table 5** is selected from about 0.31 nM, about 6.20 nM, about 0.36 nM, about 0.08 nM, about 23.0 nM, about 0.94 nM, about 13.3 nM, about 0.47 nM, about 0.09 nM, about 1.75 nM, about 0.07 nM, about 0.14 nM, about 2.09 nM, about 0.06 nM, about 0.15 nM, about 1.46 nM, about 1.60 nM, and about 0.42 nM. In some embodiments, such affinity as indicated by K_D ranges from about 23.0 nM to about 0.06 nM. In some embodiments, such is about 23.0 nM or less.

[00463] In some embodiments, the affinity of an antibody provided herein for hTF as indicated by K_D measured by ForteBio, as set forth in **Table 5** is selected from about 1.28 nM, about 2.20 nM, about 8.45 nM, about 1.67 nM, about 0.64 nM, about 21.9 nM, about 3.97 nM, about 35.8 nM, about 3.30 nM, about 2.32 nM, about 0.83 nM, about 2.40 nM, about 0.96 nM, about 0.86 nM, about 3.84 nM, about 1.02 nM, about 1.61 nM, about 2.52 nM, about 2.28 nM, and about 1.59 nM. In some embodiments, such affinity as indicated by K_D ranges from about 35.8 nM to about 0.64 nM. In some embodiments, such K_D is about 35.8 nM or less.

[00464] In some embodiments, the affinity of an antibody provided herein for cTF as indicated by K_D measured by Biacore, as set forth in **Table 5** is selected from about 0.26 nM, about 5.42 nM, about 0.21 nM, about 0.04 nM, about 18.0 nM, about 0.78 nM, about 16.4 nM, about 5.06 nM, about 0.08 nM, about 5.64 nM, about 0.12 nM, about 0.24 nM, about 5.66 nM, about 0.39 nM, about 5.69 nM, about 6.42 nM, and about 1.83 nM. In some

embodiments, such affinity as indicated by K_D ranges from about 18.0 nM to about 0.04 nM. In some embodiments, such K_D is about 18.0 nM or less.

[00465] In some embodiments, the affinity of an antibody provided herein for cTF as indicated by K_D measured by ForteBio, as set forth in **Table 5** is selected from about 1.43 nM, about 2.70 nM, about 7.65 nM, about 1.36 nM, about 0.76 nM, about 17.5 nM, about 4.99 nM, about 42.9 nM, about 12.0 nM, about 15.0 nM, about 0.57 nM, about 3.40 nM, about 1.05 nM, about 0.94 nM, about 4.12 nM, about 1.11 nM, about 1.96 nM, about 4.07 nM, about 2.71 nM, and about 4.16 nM. In some embodiments, such affinity as indicated by K_D ranges from about 42.9 nM to about 0.57 nM. In some embodiments, such K_D is about 42.9 nM or less.

[00466] In some embodiments, the affinity of an antibody provided herein for mTF as indicated by K_D measured by Biacore, as set forth in **Table 5** is selected from about 5.4 nM, about 2.9 nM, about 21 nM, and about 2.4 nM. In some embodiments, such affinity as indicated by K_D ranges from about 21 nM to about 2.4 nM. In some embodiments, such K_D is about 21 nM or less.

[00467] In some embodiments, the affinity of an antibody provided herein for mTF as indicated by K_D measured by ForteBio, as set forth in **Table 5** is selected from about 263 nM, about 131 nM, about 188 nM, about 114 nM, about 34.2 nM, about 9.16 nM, about 161 nM, about 72.1 nM, about 360 nM, about 281 nM, about 41.4 nM, about 6.12 nM, about 121 nM, and about 140 nM. In some embodiments, such affinity as indicated by K_D ranges from about 360 nM to about 6.12 nM. In some embodiments, such K_D is about 360 nM or less.

[00468] In some embodiments, the affinity of an antibody provided herein for hTF as indicated by EC_{50} measured with human TF-positive HCT-116 cells, as set forth in **Figures 1A and 1B** is selected from about 50 pM, about 58 pM, about 169 pM, about 77 pM, about 88 pM, about 134 pM, about 85 pM, about 237 pM, about 152 pM, about 39 pM, about 559 pM, about 280 pM, about 255 pM, about 147 pM, about 94 pM, about 117 pM, about 687 pM, about 532 pM, and about 239 pM. In some embodiments, such affinity ranges from about 687 pM to about 39 pM. In some embodiments, such EC_{50} is about 687 pM or less.

[00469] In some embodiments, the affinity of an antibody provided herein for mTF as indicated by EC_{50} measured with mouse TF-positive CHO cells, as set forth in **Figures 2A and 2B** is selected from about 455 nM, about 87 nM, about 11 nM, about 3.9 nM, about 3.0 nM, about 3.4 nM, about 255 nM, about 2.9 nM, about 3.6 nM, and about 4.0 nM. In some embodiments, such affinity ranges from about 455 nM to about 2.9 nM. In some embodiments, such EC_{50} is about 455 pM or less.

[00470] In some embodiments, the K_D value of an antibody provided herein for pTF is no more than 20× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for pTF is no more than 15× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for pTF is no more than 10× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for pTF is no more than 5× of the K_D value of the antibody for hTF. In some embodiments, the K_D value of an antibody provided herein for pTF is no more than 2× of the K_D value of the antibody for hTF.

[00471] In some embodiments, the affinity of an antibody provided herein for pTF as indicated by K_D measured by Biacore, as set forth in Table 40 is 3.31 nM or 12.9 nM.

2.3.2. Thrombin Generation in the Presence of TF Antibodies

[00472] In some embodiments, the TF antibodies provided herein do not inhibit human thrombin generation as determined by thrombin generation assay (TGA). In certain embodiments, the TF antibodies provided herein allow human thrombin generation as determined by thrombin generation assay (TGA).

[00473] In some embodiments, the percent peak thrombin generation (% Peak IIa) is at least 40% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 50% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 60% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 70% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 80% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 90% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 95% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 99% in the presence of no less than 100 nM TF

antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA).

[00474] In some embodiments, the % Peak IIa is at least 40% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 50% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 60% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 70% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 80% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 90% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 95% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 99% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA).

[00475] In some embodiments, the % Peak IIa is at least 60% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 70% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 80% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 90% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 95% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % Peak IIa is at least 99% in the presence of no less than 10 nM TF

antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA).

[00476] In some embodiments, the % Peak IIa in the presence of 100 nM TF antibody, as set forth in **Table 6** and **Table 37** is selected from about 99%, about 100%, about 103%, about 64%, about 52%, about 87%, about 96%, about 98%, and about 53% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) without antibody pre-incubation. In some embodiments, such % Peak IIa ranges from about 52% to about 103%. In some embodiments, such % Peak IIa is about 52% or more.

[00477] In some embodiments, the % Peak IIa in the presence of 50 nM TF antibody, as set forth in **Table 6** and **Table 37** is selected from about 99%, about 100%, about 103%, about 67%, about 58%, about 89%, about 96%, about 98%, about 68%, about 62%, and about 88% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) without antibody pre-incubation. In some embodiments, such % Peak IIa ranges from about 58% to about 103%. In some embodiments, such % Peak IIa is about 58% or more.

[00478] In some embodiments, the % Peak IIa in the presence of 10 nM TF antibody, as set forth in **Table 6** and **Table 37** is selected from about 100%, about 99%, about 103%, about 87%, about 83%, about 95%, about 98%, about 86%, and about 96% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) without antibody pre-incubation. In some embodiments, such % Peak IIa ranges from about 83% to about 103%. In some embodiments, such % Peak IIa is about 83% or more.

[00479] In some embodiments, the % Peak IIa in the presence of 100 nM TF antibody, as set forth in **Table 7** and **Table 38** is selected from about 108%, about 105%, about 111%, about 58%, about 47%, about 91%, about 103%, about 109%, about 107%, and about 45% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) with 10 min antibody pre-incubation. In some embodiments, such % Peak IIa ranges from about 45% to about 111%. In some embodiments, such % Peak IIa is about 45% or more.

[00480] In some embodiments, the % Peak IIa in the presence of 50 nM TF antibody, as set forth in **Table 7** and **Table 38** is selected from about 107%, about 104%, about 114%, about 62%, about 49%, about 87%, about 105%, about 109%, about 55%, and about 92% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) with 10 min antibody pre-incubation. In some embodiments, such %

Peak IIa ranges from about 49% to about 114%. In some embodiments, such % Peak IIa is about 49% or more.

[00481] In some embodiments, the % Peak IIa in the presence of 10 nM TF antibody, as set forth in **Table 7** and **Table 38** is selected from about 105%, about 114%, about 76%, about 68%, about 94%, about 108%, about 104%, about 74%, and about 93% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) with 10 min antibody pre-incubation. In some embodiments, such % Peak IIa ranges from about 68% to about 114%. In some embodiments, such % Peak IIa is about 68% or more.

[00482] In some embodiments, the percent endogenous thrombin potential (% ETP) is at least 80% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % ETP is at least 90% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % ETP is at least 95% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % ETP is at least 99% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA).

[00483] In some embodiments, the % ETP is at least 80% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % ETP is at least 90% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % ETP is at least 95% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % ETP is at least 99% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA).

[00484] In some embodiments, the % ETP is at least 80% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % ETP is at least 90% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the %

ETP is at least 95% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA). In some embodiments, the % ETP is at least 99% in the presence of no less than 10 nM TF antibody compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA).

[00485] In some embodiments, the % ETP in the presence of 100 nM TF antibody, as set forth in **Table 6** and **Table 37** is selected from about 108%, about 103%, about 109%, about 100%, about 96%, about 102%, about 105%, and about 92% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) without antibody pre-incubation. In some embodiments, such % ETP ranges from about 92% to about 109%. In some embodiments, such % ETP is about 92% or more.

[00486] In some embodiments, the % ETP in the presence of 50 nM TF antibody, as set forth in **Table 6** and **Table 37** is selected from about 108%, about 103%, about 111%, about 101%, about 97%, about 104%, about 106%, about 93%, about 96%, and about 105% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) without antibody pre-incubation. In some embodiments, such % ETP ranges from about 93% to about 111%. In some embodiments, such % ETP is about 93% or more.

[00487] In some embodiments, the % ETP in the presence of 10 nM TF antibody, as set forth in **Table 6** and **Table 37** is selected from about 106%, about 109%, about 105%, about 104%, about 107%, about 99%, about 101%, and about 102% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) without antibody pre-incubation. In some embodiments, such % ETP ranges from about 99% to about 109%. In some embodiments, such % ETP is about 99% or more.

[00488] In some embodiments, the % ETP in the presence of 100 nM TF antibody, as set forth in **Table 7** and **Table 38** is selected from about 110%, about 104%, about 106%, about 98%, about 95%, about 108%, about 107%, about 96%, about 92%, and about 103% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) with 10 min antibody pre-incubation. In some embodiments, such % ETP ranges from about 92% to about 110%. In some embodiments, such % ETP is about 92% or more.

[00489] In some embodiments, the % ETP in the presence of 50 nM TF antibody, as set forth in **Table 7** and **Table 38** is selected from about 110%, about 106%, about 108%, about 103%, about 96%, about 109%, about 102%, about 104%, about 94%, and about 98%

compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) with 10 min antibody pre-incubation. In some embodiments, such % ETP ranges from about 94% to about 110%. In some embodiments, such % ETP is about 94% or more.

[00490] In some embodiments, the % ETP in the presence of 10 nM TF antibody, as set forth in **Table 7** and **Table 38** is selected from about 107%, about 106%, about 110%, about 103%, about 100%, about 105%, about 102%, and about 101% compared to the control conditions without the antibody, as determined by thrombin generation assay (TGA) with 10 min antibody pre-incubation. In some embodiments, such % ETP ranges from about 100% to about 110%. In some embodiments, such % ETP is about 100% or more.

2.3.3. FXa Conversion in the Presence of TF Antibodies

[00491] In some embodiments, the antibodies provided herein bind human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX. In certain embodiments, the antibodies provided herein do not interfere with the ability of TF:FVIIa to convert FX into FXa.

[00492] In some embodiments, the percentage of FXa conversion (% FXa) is at least 75% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 80% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 85% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 90% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 95% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody.

[00493] In some embodiments, the % FXa is at least 75% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 80% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 85% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 90% in the presence of no less than 50 nM TF antibody compared to the control conditions without the

antibody. In some embodiments, the % FXa is at least 95% in the presence of no less than 50 nM TF antibody compared to the control conditions without the antibody.

[00494] In some embodiments, the % FXa is at least 75% in the presence of no less than 25 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 80% in the presence of no less than 25 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 85% in the presence of no less than 25 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 90% in the presence of no less than 25 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 95% in the presence of no less than 25 nM TF antibody compared to the control conditions without the antibody.

[00495] In some embodiments, the % FXa is at least 75% in the presence of no less than 12.5 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 80% in the presence of no less than 12.5 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 85% in the presence of no less than 12.5 nM TF antibody compared to the control conditions without the antibody. In some embodiments, % FXa is at least 90% in the presence of no less than 12.5 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FXa is at least 95% in the presence of no less than 12.5 nM TF antibody compared to the control conditions without the antibody.

[00496] In some embodiments, the % FXa in the presence of 100 nM TF antibody, as set forth in **Table 8** is selected from about 89%, about 96%, about 116%, about 108%, about 117%, about 105%, about 112%, about 106%, about 103%, about 111%, about 98%, and about 101% compared to the control conditions without the antibody. In some embodiments, such % FXa ranges from about 89% to about 117%. In some embodiments, such % FXa is about 89% or more.

[00497] In some embodiments, the % FXa in the presence of 50 nM TF antibody, as set forth in **Table 8** is selected from about 94%, about 93%, about 78%, about 102%, about 99%, about 104%, about 105%, about 108%, about 107%, about 97%, and about 106% compared to the control conditions without the antibody. In some embodiments, such % FXa ranges from about 78% to about 108%. In some embodiments, such % FXa is about 78% or more.

[00498] In some embodiments, the % FXa in the presence of 25 nM TF antibody, as set forth in **Table 8** is selected from about 81%, about 89%, about 85%, about 109%, about 96%, about 97%, about 108%, about 104%, about 103%, about 112%, and about 89% compared to

the control conditions without the antibody. In some embodiments, such % FXa ranges from about 81% to about 112%. In some embodiments, such % FXa is about 81% or more.

[00499] In some embodiments, the % FXa in the presence of 12.5 nM TF antibody, as set forth in **Table 8** is selected from about 87%, about 89%, about 82%, about 99%, about 101%, about 98%, about 113%, about 106%, about 115%, about 110%, about 120%, about 85%, and about 108% compared to the control conditions without the antibody. In some embodiments, such % FXa ranges from about 82% to about 120%. In some embodiments, such % FXa is about 82% or more.

2.3.4. FVIIa Binding in the Presence of TF Antibodies

[00500] In some embodiments, the antibodies provided herein bind human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa. In certain embodiments, the antibodies provided herein do not compete for binding to human TF with human FVIIa.

[00501] In some embodiments, the percentage of FVIIa binding (% FVIIa) is at least 75% in the presence of no less than 250 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 80% in the presence of no less than 250 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 85% in the presence of no less than 250 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 90% in the presence of no less than 250 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 95% in the presence of no less than 250 nM TF antibody compared to the control conditions without the antibody.

[00502] In some embodiments, the % FVIIa is at least 75% in the presence of no less than 83 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 80% in the presence of no less than 83 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 85% in the presence of no less than 83 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 90% in the presence of no less than 83 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 95% in the presence of no less than 83 nM TF antibody compared to the control conditions without the antibody.

[00503] In some embodiments, the % FVIIa is at least 75% in the presence of no less than 28 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 80% in the presence of no less than 28 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 85% in the presence of no less than 28 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 90% in the presence of no less than 28 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 95% in the presence of no less than 28 nM TF antibody compared to the control conditions without the antibody.

[00504] In some embodiments, the % FVIIa is at least 75% in the presence of no less than 9.25 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 80% in the presence of no less than 9.25 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 85% in the presence of no less than 9.25 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 90% in the presence of no less than 9.25 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the % FVIIa is at least 95% in the presence of no less than 9.25 nM TF antibody compared to the control conditions without the antibody.

[00505] In some embodiments, the % FVIIa in the presence of 250 nM TF antibody, as set forth in **Table 9** is selected from about 98%, about 87%, about 80%, about 92%, about 95%, about 89%, about 91%, about 97%, about 94%, about 101%, and about 96% compared to the control conditions without the antibody. In some embodiments, such % FVIIa ranges from about 80% to about 101%. In some embodiments, such % FVIIa is about 80% or more.

[00506] In some embodiments, the % FVIIa in the presence of 83 nM TF antibody, as set forth in **Table 9** is selected from about 97%, about 88%, about 77%, about 93%, about 94%, about 91%, about 98%, about 100%, and about 92% compared to the control conditions without the antibody. In some embodiments, such % FVIIa ranges from about 77% to about 100%. In some embodiments, such % FVIIa is about 77% or more.

[00507] In some embodiments, the % FVIIa in the presence of 28 nM TF antibody, as set forth in **Table 9** is selected from about 101%, about 87%, about 79%, about 96%, about 93%, about 95%, about 98%, about 100%, about 102%, about 99%, about 92%, and about 91% compared to the control conditions without the antibody. In some embodiments, such % FVIIa ranges from about 79% to about 102%. In some embodiments, such % FVIIa is about 79% or more.

[00508] In some embodiments, the % FVIIa in the presence of 9.25 nM TF antibody, as set forth in **Table 9** is selected from about 100%, about 90%, about 76%, about 97%, about 93%, about 99%, about 98%, about 102%, about 101%, and about 95% compared to the control conditions without the antibody. In some embodiments, such % FVIIa ranges from about 76% to about 102%. In some embodiments, such % FVIIa is about 76% or more.

2.3.5. FVIIa-dependent TF Signaling in the Presence of TF Antibodies

[00509] In some embodiments, the antibodies provided herein inhibit FVIIa-dependent TF signaling. In some embodiments, the inhibition of FVIIa-dependent TF signaling is measured by the reduction of IL8. In some embodiments, the inhibition of FVIIa-dependent TF signaling is measured by the reduction of GM-CSF.

[00510] In some embodiments, the Interleukin 8 concentration (IL8 conc) is reduced by at least 70% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 80% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 90% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody.

[00511] In some embodiments, the IL8 conc is reduced by at least 70% in the presence of no less than 40 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 80% in the presence of no less than 40 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 90% in the presence of no less than 40 nM TF antibody compared to the control conditions without the antibody.

[00512] In some embodiments, the IL8 conc is reduced by at least 60% in the presence of no less than 16 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 70% in the presence of no less than 16 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 80% in the presence of no less than 16 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 90% in the presence of no less than 16 nM TF antibody compared to the control conditions without the antibody.

[00513] In some embodiments, the IL8 conc is reduced by at least 50% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody. In

some embodiments, the IL8 conc is reduced by at least 60% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 70% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 80% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the IL8 conc is reduced by at least 90% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody.

[00514] In some embodiments, the Granulocyte-Macrophage Colony-Stimulating Factor concentration (GM-CSF conc) is reduced by at least 70% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 80% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 90% in the presence of no less than 100 nM TF antibody compared to the control conditions without the antibody.

[00515] In some embodiments, the GM-CSF conc is reduced by at least 70% in the presence of no less than 40 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 80% in the presence of no less than 40 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 90% in the presence of no less than 40 nM TF antibody compared to the control conditions without the antibody.

[00516] In some embodiments, the GM-CSF conc is reduced by at least 60% in the presence of no less than 16 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 70% in the presence of no less than 16 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 80% in the presence of no less than 16 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 90% in the presence of no less than 16 nM TF antibody compared to the control conditions without the antibody.

[00517] In some embodiments, the GM-CSF conc is reduced by at least 50% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 60% in the

presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 70% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 80% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody. In some embodiments, the GM-CSF conc is reduced by at least 90% in the presence of no less than 6.4 nM TF antibody compared to the control conditions without the antibody.

[00518] In some embodiments, the percentage of Interleukin 8 (% IL8) in the presence of 100 nM TF antibody, as set forth in **Table 10** is selected from about 2%, about 9%, about 8%, about 6%, about 13%, about 1%, about 3%, about 4%, and about 5% compared to the control conditions without the antibody. In some embodiments, such % IL8 ranges from about 1% to about 13%. In some embodiments, such % IL8 is about 13% or less.

[00519] In some embodiments, the % IL8 in the presence of 40 nM TF antibody, as set forth in **Table 10** is selected from about 2%, about 8%, about 7%, about 10%, about 14%, about 4%, about 5%, and about 6% compared to the control conditions without the antibody. In some embodiments, such % IL8 ranges from about 2% to about 14%. In some embodiments, such % IL8 is about 14% or less.

[00520] In some embodiments, the % IL8 in the presence of 16 nM TF antibody, as set forth in **Table 10** is selected from about 2%, about 3%, about 10%, about 8%, about 7%, about 16%, about 9%, about 15%, about 5%, and about 6% compared to the control conditions without the antibody. In some embodiments, such % IL8 ranges from about 2% to about 16%. In some embodiments, such % IL8 is about 16% or less.

[00521] In some embodiments, the % IL8 in the presence of 6.4 nM TF antibody, as set forth in **Table 10** is selected from about 3%, about 4%, about 11%, about 9%, about 14%, about 22%, about 12%, about 6%, about 5%, about 15%, about 21%, and about 8% compared to the control conditions without the antibody. In some embodiments, such % IL8 ranges from about 3% to about 22%. In some embodiments, such % IL8 is about 22% or less.

[00522] In some embodiments, the percentage of Granulocyte-Macrophage Colony-Stimulating Factor (% GM-CSF) in the presence of 100 nM TF antibody, as set forth in **Table 11** is selected from about 6%, about 7%, about 22%, about 20%, about 12%, about 19%, about 17%, about 25%, about 5%, about 14%, about 11%, and about 10% compared to the control conditions without the antibody. In some embodiments, such % GM-CSF ranges from about 5% to about 25%. In some embodiments, such % GM-CSF is about 25% or less.

[00523] In some embodiments, the % GM-CSF in the presence of 40 nM TF antibody, as set forth in **Table 11** is selected from about 6%, about 7%, about 19%, about 15%, about 18%, about 16%, about 26%, about 5%, about 13%, about 11%, and about 10% compared to the control conditions without the antibody. In some embodiments, such % GM-CSF ranges from about 5% to about 26%. In some embodiments, such % GM-CSF is about 26% or less.

[00524] In some embodiments, the % GM-CSF in the presence of 16 nM TF antibody, as set forth in **Table 11** is selected from about 6%, about 7%, about 22%, about 19%, about 14%, about 32%, about 17%, about 26%, about 5%, about 12%, about 13%, about 9%, about 11%, and about 15% compared to the control conditions without the antibody. In some embodiments, such % GM-CSF ranges from about 5% to about 32%. In some embodiments, such % GM-CSF is about 32% or less.

[00525] In some embodiments, the % GM-CSF in the presence of 6.4 nM TF antibody, as set forth in **Table 11** is selected from about 8%, about 9%, about 24%, about 20%, about 18%, about 39%, about 34%, about 15%, about 21%, about 16%, about 17%, and about 10% compared to the control conditions without the antibody. In some embodiments, such % GM-CSF ranges from about 8% to about 39%. In some embodiments, such % GM-CSF is about 39% or less.

2.3.6. Lesion Size Reduction in Swine Choroidal Neovascularization (CNV) Model

[00526] In some embodiments, the antibodies provided herein reduce lesion size in a swine choroidal neovascularization (CNV) model. In some embodiments, the reduction in lesion size is measured by Fluorescein Angiography (FA).

[00527] In some embodiments, the lesion size in a swine CNV model is reduced by at least 5% 7 days after administration of the anti-TF antibody. In some embodiments, the lesion size in a swine CNV model is reduced by at least 10% 7 days after administration of the anti-TF antibody. In some embodiments, the lesion size in a swine CNV model is reduced by at least 20% 7 days after administration of the anti-TF antibody. In some embodiments, the lesion size in a swine CNV model is reduced by at least 40% 7 days after administration of the anti-TF antibody. In some embodiments, the lesion size in a swine CNV model is reduced by at least 60% 7 days after administration of the anti-TF antibody.

[00528] In some embodiments, the lesion size in a swine CNV model is reduced by at least 10% 21 days after administration of the anti-TF antibody. In some embodiments, the lesion size in a swine CNV model is reduced by at least 20% 21 days after administration of the anti-TF antibody. In some embodiments, the lesion size in a swine CNV model is reduced by

at least 40% 21 days after administration of the anti-TF antibody. In some embodiments, the lesion size in a swine CNV model is reduced by at least 60% 21 days after administration of the anti-TF antibody. In some embodiments, the lesion size in a swine CNV model is reduced by at least 80% 21 days after administration of the anti-TF antibody.

2.4. Germlines

[00529] The antibodies provided herein may comprise any suitable V_H and V_L germline sequences.

[00530] In some embodiments, the V_H region of an antibody provided herein is from the VH3 germline. In some embodiments, the V_H region of an antibody provided herein is from the VH1 germline. In some embodiments, the V_H region of an antibody provided herein is from the VH4 germline.

[00531] In some embodiments, the V_H region of an antibody provided herein is from the VH3-23 germline. In some embodiments, the V_H region of an antibody provided herein is from the VH1-18 germline. In some embodiments, the V_H region of an antibody provided herein is from the VH3-30 germline. In some embodiments, the V_H region of an antibody provided herein is from the VH1-69 germline. In some embodiments, the V_H region of an antibody provided herein is from the VH4-31 germline. In some embodiments, the V_H region of an antibody provided herein is from the VH4-34 germline. In some embodiments, the V_H region of an antibody provided herein is from the VH1-46 germline.

[00532] In some embodiments, the V_L region of an antibody provided herein is from the VK1 germline. In some embodiments, the V_L region of an antibody provided herein is from the VK4 germline. In some embodiments, the V_L region of an antibody provided herein is from the VK3 germline

[00533] In some embodiments, the V_L region of an antibody provided herein is from the VK1-05 germline. In some embodiments, the V_L region of an antibody provided herein is from the VK4-01 germline. In some embodiments, the V_L region of an antibody provided herein is from the VK3-15 germline. In some embodiments, the V_L region of an antibody provided herein is from the VK3-20 germline. In some embodiments, the V_L region of an antibody provided herein is from the VK1-33 germline.

2.5. Monospecific and Multispecific TF Antibodies

[00534] In some embodiments, the antibodies provided herein are monospecific antibodies.

[00535] In some embodiments, the antibodies provided herein are multispecific antibodies.

[00536] In some embodiments, a multispecific antibody provided herein binds more than one antigen. In some embodiments, a multispecific antibody binds two antigens. In some embodiments, a multispecific antibody binds three antigens. In some embodiments, a multispecific antibody binds four antigens. In some embodiments, a multispecific antibody binds five antigens.

[00537] In some embodiments, a multispecific antibody provided herein binds more than one epitope on a TF antigen. In some embodiments, a multispecific antibody binds two epitopes on a TF antigen. In some embodiments, a multispecific antibody binds three epitopes on a TF antigen.

[00538] Many multispecific antibody constructs are known in the art, and the antibodies provided herein may be provided in the form of any suitable multispecific suitable construct.

[00539] In some embodiments, the multispecific antibody comprises an immunoglobulin comprising at least two different heavy chain variable regions each paired with a common light chain variable region (*i.e.*, a "common light chain antibody"). The common light chain variable region forms a distinct antigen-binding domain with each of the two different heavy chain variable regions. *See* Merchant et al., *Nature Biotechnol.*, 1998, 16:677-681, incorporated by reference in its entirety.

[00540] In some embodiments, the multispecific antibody comprises an immunoglobulin comprising an antibody or fragment thereof attached to one or more of the N- or C-termini of the heavy or light chains of such immunoglobulin. *See* Coloma and Morrison, *Nature Biotechnol.*, 1997, 15:159-163, incorporated by reference in its entirety. In some aspects, such antibody comprises a tetravalent bispecific antibody.

[00541] In some embodiments, the multispecific antibody comprises a hybrid immunoglobulin comprising at least two different heavy chain variable regions and at least two different light chain variable regions. *See* Milstein and Cuello, *Nature*, 1983, 305:537-540; and Staerz and Bevan, *Proc. Natl. Acad. Sci. USA*, 1986, 83:1453-1457; each of which is incorporated by reference in its entirety.

[00542] In some embodiments, the multispecific antibody comprises immunoglobulin chains with alterations to reduce the formation of side products that do not have multispecificity. In some aspects, the antibodies comprise one or more "knobs-into-holes" modifications as described in U.S. Pat. No. 5,731,168, incorporated by reference in its entirety.

[00543] In some embodiments, the multispecific antibody comprises immunoglobulin chains with one or more electrostatic modifications to promote the assembly of Fc hetero-multimers. *See* WO 2009/089004, incorporated by reference in its entirety.

[00544] In some embodiments, the multispecific antibody comprises a bispecific single chain molecule. *See* Traunecker et al., *EMBO J.*, 1991, 10:3655-3659; and Gruber et al., *J. Immunol.*, 1994, 152:5368-5374; each of which is incorporated by reference in its entirety.

[00545] In some embodiments, the multispecific antibody comprises a heavy chain variable domain and a light chain variable domain connected by a polypeptide linker, where the length of the linker is selected to promote assembly of multispecific antibodies with the desired multispecificity. For example, monospecific scFvs generally form when a heavy chain variable domain and light chain variable domain are connected by a polypeptide linker of more than 12 amino acid residues. *See* U.S. Pat. Nos. 4,946,778 and 5,132,405, each of which is incorporated by reference in its entirety. In some embodiments, reduction of the polypeptide linker length to less than 12 amino acid residues prevents pairing of heavy and light chain variable domains on the same polypeptide chain, thereby allowing pairing of heavy and light chain variable domains from one chain with the complementary domains on another chain. The resulting antibodies therefore have multispecificity, with the specificity of each binding site contributed by more than one polypeptide chain. Polypeptide chains comprising heavy and light chain variable domains that are joined by linkers between 3 and 12 amino acid residues form predominantly dimers (termed diabodies). With linkers between 0 and 2 amino acid residues, trimers (termed triabodies) and tetramers (termed tetrabodies) are favored. However, the exact type of oligomerization appears to depend on the amino acid residue composition and the order of the variable domain in each polypeptide chain (*e.g.*, V_H-linker-V_L vs. V_L-linker-V_H), in addition to the linker length. A skilled person can select the appropriate linker length based on the desired multispecificity.

[00546] In some embodiments, the multispecific antibody comprises a diabody. *See* Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 1993, 90:6444-6448, incorporated by reference in its entirety. In some embodiments, the multispecific antibody comprises a triabody. *See* Todorovska et al., *J. Immunol. Methods*, 2001, 248:47-66, incorporated by reference in its entirety. In some embodiments, the multispecific antibody comprises a tetrabody. *See id.*, incorporated by reference in its entirety.

[00547] In some embodiments, the multispecific antibody comprises a trispecific F(ab')3 derivative. *See* Tutt et al. *J. Immunol.*, 1991, 147:60-69, incorporated by reference in its entirety.

[00548] In some embodiments, the multispecific antibody comprises a cross-linked antibody. *See* U.S. Patent No. 4,676,980; Brennan et al., *Science*, 1985, 229:81-83; Staerz, et al. *Nature*, 1985, 314:628-631; and EP 0453082; each of which is incorporated by reference in its entirety.

[00549] In some embodiments, the multispecific antibody comprises antigen-binding domains assembled by leucine zippers. *See* Kostelny et al., *J. Immunol.*, 1992, 148:1547-1553, incorporated by reference in its entirety.

[00550] In some embodiments, the multispecific antibody comprises complementary protein domains. In some aspects, the complementary protein domains comprise an anchoring domain (AD) and a dimerization and docking domain (DDD). In some embodiments, the AD and DDD bind to each other and thereby enable assembly of multispecific antibody structures via the "dock and lock" (DNL) approach. Antibodies of many specificities may be assembled, including bispecific antibodies, trispecific antibodies, tetraspecific antibodies, quintspecific antibodies, and hexaspecific antibodies. Multispecific antibodies comprising complementary protein domains are described, for example, in U.S. Pat. Nos. 7,521,056; 7,550,143; 7,534,866; and 7,527,787; each of which is incorporated by reference in its entirety.

[00551] In some embodiments, the multispecific antibody comprises a dual action Fab (DAF) antibody as described in U.S. Pat. Pub. No. 2008/0069820, incorporated by reference in its entirety.

[00552] In some embodiments, the multispecific antibody comprises an antibody formed by reduction of two parental molecules followed by mixing of the two parental molecules and reoxidation to assembly a hybrid structure. *See* Carlring et al., *PLoS One*, 2011, 6:e22533, incorporated by reference in its entirety.

[00553] In some embodiments, the multispecific antibody comprises a DVD-Ig™. A DVD-Ig™ is a dual variable domain immunoglobulin that can bind to two or more antigens. DVD-Igs™ are described in U.S. Pat. No. 7,612,181, incorporated by reference in its entirety.

[00554] In some embodiments, the multispecific antibody comprises a DART™. DARTs™ are described in Moore et al., *Blood*, 2011, 117:454-451, incorporated by reference in its entirety.

[00555] In some embodiments, the multispecific antibody comprises a DuoBody®. DuoBodies® are described in Labrijn et al., *Proc. Natl. Acad. Sci. USA*, 2013, 110:5145-5150; Gramer et al., *mAbs*, 2013, 5:962-972; and Labrijn et al., *Nature Protocols*, 2014, 9:2450-2463; each of which is incorporated by reference in its entirety.

[00556] In some embodiments, the multispecific antibody comprises an antibody fragment attached to another antibody or fragment. The attachment can be covalent or non-covalent. When the attachment is covalent, it may be in the form of a fusion protein or via a chemical linker. Illustrative examples of multispecific antibodies comprising antibody fragments attached to other antibodies include tetravalent bispecific antibodies, where an scFv is fused to the C-terminus of the C_{H3} from an IgG. *See* Coloma and Morrison, *Nature Biotechnol.*, 1997, 15:159-163. Other examples include antibodies in which a Fab molecule is attached to the constant region of an immunoglobulin. *See* Miler et al., *J. Immunol.*, 2003, 170:4854-4861, incorporated by reference in its entirety. Any suitable fragment may be used, including any of the fragments described herein or known in the art.

[00557] In some embodiments, the multispecific antibody comprises a CovX-Body. CovX-Bodies are described, for example, in Doppalapudi et al., *Proc. Natl. Acad. Sci. USA*, 2010, 107:22611-22616, incorporated by reference in its entirety.

[00558] In some embodiments, the multispecific antibody comprises an Fcab antibody, where one or more antigen-binding domains are introduced into an Fc region. Fcab antibodies are described in Wozniak-Knopp et al., *Protein Eng. Des. Sel.*, 2010, 23:289-297, incorporated by reference in its entirety.

[00559] In some embodiments, the multispecific antibody comprises a TandAb® antibody. TandAb® antibodies are described in Kipriyanov et al., *J. Mol. Biol.*, 1999, 293:41-56 and Zhukovsky et al., *Blood*, 2013, 122:5116, each of which is incorporated by reference in its entirety.

[00560] In some embodiments, the multispecific antibody comprises a tandem Fab. Tandem Fabs are described in WO 2015/103072, incorporated by reference in its entirety.

[00561] In some embodiments, the multispecific antibody comprises a Zybody™. Zybodies™ are described in LaFleur et al., *mAbs*, 2013, 5:208-218, incorporated by reference in its entirety.

2.6. Glycosylation Variants

[00562] In certain embodiments, an antibody provided herein may be altered to increase, decrease or eliminate the extent to which it is glycosylated. Glycosylation of polypeptides is typically either "N-linked" or "O-linked."

[00563] "N-linked" glycosylation refers to the attachment of a carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition

sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site.

[00564] "O-linked" glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[00565] Addition or deletion of N-linked glycosylation sites to or from an antibody provided herein may be accomplished by altering the amino acid sequence such that one or more of the above-described tripeptide sequences is created or removed. Addition or deletion of O-linked glycosylation sites may be accomplished by addition, deletion, or substitution of one or more serine or threonine residues in or to (as the case may be) the sequence of an antibody.

[00566] In some embodiments, an antibody provided herein comprises a glycosylation motif that is different from a naturally occurring antibody. Any suitable naturally occurring glycosylation motif can be modified in the antibodies provided herein. The structural and glycosylation properties of immunoglobulins, for example, are known in the art and summarized, for example, in Schroeder and Cavacini, *J. Allergy Clin. Immunol.*, 2010, 125:S41-52, incorporated by reference in its entirety.

[00567] In some embodiments, an antibody provided herein comprises an IgG1 Fc region with modification to the oligosaccharide attached to asparagine 297 (Asn 297). Naturally occurring IgG1 antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn 297 of the C_{H2} domain of the Fc region. *See* Wright et al., *TIBTECH*, 1997, 15:26-32, incorporated by reference in its entirety. The oligosaccharide attached to Asn 297 may include various carbohydrates such as mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure.

[00568] In some embodiments, the oligosaccharide attached to Asn 297 is modified to create antibodies having altered ADCC. In some embodiments, the oligosaccharide is altered to improve ADCC. In some embodiments, the oligosaccharide is altered to reduce ADCC.

[00569] In some aspects, an antibody provided herein comprises an IgG1 domain with reduced fucose content at position Asn 297 compared to a naturally occurring IgG1 domain. Such Fc domains are known to have improved ADCC. *See* Shields et al., *J. Biol. Chem.*, 2002, 277:26733-26740, incorporated by reference in its entirety. In some aspects, such

antibodies do not comprise any fucose at position Asn 297. The amount of fucose may be determined using any suitable method, for example as described in WO 2008/077546, incorporated by reference in its entirety.

[00570] In some embodiments, an antibody provided herein comprises a bisected oligosaccharide, such as a biantennary oligosaccharide attached to the Fc region of the antibody that is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, for example, in WO 2003/011878; U.S. Pat. No. 6,602,684; and U.S. Pat. Pub. No. 2005/0123546; each of which is incorporated by reference in its entirety.

[00571] Other illustrative glycosylation variants which may be incorporated into the antibodies provided herein are described, for example, in U.S. Pat. Pub. Nos. 2003/0157108, 2004/0093621, 2003/0157108, 2003/0115614, 2002/0164328, 2004/0093621, 2004/0132140, 2004/0110704, 2004/0110282, 2004/0109865; International Pat. Pub. Nos. 2000/61739, 2001/29246, 2003/085119, 2003/084570, 2005/035586, 2005/035778; 2005/053742, 2002/031140; Okazaki et al., *J. Mol. Biol.*, 2004, 336:1239-1249; and Yamane-Ohnuki et al., *Biotech. Bioeng.*, 2004, 87: 614-622; each of which is incorporated by reference in its entirety.

[00572] In some embodiments, an antibody provided herein comprises an Fc region with at least one galactose residue in the oligosaccharide attached to the Fc region. Such antibody variants may have improved CDC function. Examples of such antibody variants are described, for example, in WO 1997/30087; WO 1998/58964; and WO 1999/22764; each of which is incorporated by reference in its entirety.

[00573] Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells, which are deficient in protein fucosylation (*see* Ripka et al., *Arch. Biochem. Biophys.*, 1986, 249:533-545; U.S. Pat. Pub. No. 2003/0157108; WO 2004/056312; 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).

[00574] 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.

[00575] 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. Fc Region Amino Acid Sequence Variants

[00576] 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.

[00577] 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.

[00578] 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.

[00579] 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, from amino acid position 233 to 236 of IgG1 or EFLG of IgG4, is replaced by PVA. *See* U.S. Pat. No. 9,150,641, incorporated by reference in its entirety.

[00580] 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.

[00581] In some embodiments, the Fc region of an antibody provided herein is a human IgG2 Fc region comprising one or more of mutations A330S and P331S.

[00582] In some embodiments, the Fc region of an antibody provided herein has an amino acid substitution at one or more positions selected from 238, 265, 269, 270, 297, 327 and 329. *See* U.S. Pat. No. 6,737,056, incorporated by reference in its entirety. Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 with alanine. *See* U.S. Pat. No. 7,332,581, incorporated by reference in its entirety. In some embodiments, the antibody comprises an alanine at amino acid position 265. In some embodiments, the antibody comprises an alanine at amino acid position 297.

[00583] In certain embodiments, an antibody provided herein comprises an Fc region with one or more amino acid substitutions which improve ADCC, such as a substitution at one or more of positions 298, 333, and 334 of the Fc region. In some embodiments, an antibody provided herein comprises an Fc region with one or more amino acid substitutions at positions 239, 332, and 330, as described in Lazar et al., *Proc. Natl. Acad. Sci. USA*, 2006,103:4005-4010, incorporated by reference in its entirety.

[00584] In some embodiments, an antibody provided herein comprises one or more alterations that improves or diminishes C1q binding and/or CDC. *See* U.S. Pat. No. 6,194,551; WO 99/51642; and Idusogie et al., *J. Immunol.*, 2000, 164:4178-4184; each of which is incorporated by reference in its entirety.

[00585] In some embodiments, an antibody provided herein comprises one or more alterations to increase half-life. Antibodies with increased half-lives and improved binding to the neonatal Fc receptor (FcRn) are described, for example, in Hinton et al., *J. Immunol.*, 2006, 176:346-356; and U.S. Pat. Pub. No. 2005/0014934; each of which is incorporated by reference in its entirety. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 250, 256, 265, 272, 286, 303, 305, 307, 311, 312, 314, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424, 428, and 434 of an IgG.

[00586] In some embodiments, an antibody provided herein comprises one or more Fc region variants as described in U.S. Pat. Nos. 7,371,826, 5,648,260, and 5,624,821; Duncan and Winter, *Nature*, 1988, 322:738-740; and WO 94/29351; each of which is incorporated by reference in its entirety.

2.8. Pyroglutamate

[00587] As is known in the art, both glutamate (E) and glutamine (Q) at the N-termini of recombinant proteins can cyclize spontaneously to form pyroglutamate (pE) *in vitro* and *in vivo*. *See* Liu et al., *J. Biol. Chem.*, 2011, 286:11211-11217, incorporated by reference in its entirety.

[00588] In some embodiments, provided herein are antibodies comprising a polypeptide sequence having a pE residue at the N-terminal position. In some embodiments, provided herein are antibodies comprising a polypeptide sequence in which the N-terminal residue has been converted from Q to pE. In some embodiments, provided herein are antibodies comprising a polypeptide sequence in which the N-terminal residue has been converted from E to pE.

2.9. Cysteine Engineered Antibody Variants

[00589] In certain embodiments, provided herein are cysteine engineered antibodies, also known as "thioMAbs," in which one or more residues of the antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at solvent accessible sites of the antibody. By substituting such residues with cysteine, reactive thiol groups are introduced at solvent accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, for example, to create an immunoconjugate.

[00590] In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 of the light chain; A118 of the heavy chain Fc region; and S400 of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, for example, in U.S. Pat. No. 7,521,541, which is incorporated by reference in its entirety.

3. Anti-TF Antibody-Drug Conjugates

[00591] Provided herein are antibody-drug conjugates (ADCs) comprising an antibody that binds specifically to TF and a cytotoxic agent. In some embodiments, the cytotoxic agent is linked directly to the anti-TF antibody. In some embodiments, the cytotoxic agent is linked indirectly to the anti-TF antibody.

[00592] In some embodiments, the ADCs further comprise a linker. In some embodiments, the linker links the anti-TF antibody to the cytotoxic agent.

[00593] In some embodiments, the ADCs provided herein have a drug-antibody ratio (DAR) of 1. In some embodiments, the ADCs provided herein have a DAR of 2. In some embodiments, the ADCs provided herein have a DAR of 3. In some embodiments, the ADCs provided herein have a DAR of 4. In some embodiments, the ADCs provided herein have a DAR of 5. In some embodiments, the ADCs provided herein have a DAR of 1-2, 1-3, 1-4, 1-5, 2-3, 2-4, 2-5, 3-4, 3-5, 4-5, 1, 2, 3, 4, or 5. In some embodiments, the ADCs provided herein have a DAR greater than 5. In some embodiments, the DAR is measured by UV/vis spectroscopy, hydrophobic interaction chromatography (HIC), and/or reverse phase liquid chromatography separation with time-of-flight detection and mass characterization (RP-UPLC/Mass spectrometry).

4. Methods for Making TF Antibodies

4.1. TF Antigen Preparation

[00594] The TF antigen used for isolation of the antibodies provided herein may be intact TF or a fragment of TF. The TF antigen may be, for example, in the form of an isolated protein or a protein expressed on the surface of a cell.

[00595] In some embodiments, the TF antigen is a non-naturally occurring variant of TF, such as a TF protein having an amino acid sequence or post-translational modification that does not occur in nature.

[00596] In some embodiments, the TF antigen is truncated by removal of, for example, intracellular or membrane-spanning sequences, or signal sequences. In some embodiments, the TF antigen is fused at its C-terminus to a human IgG1 Fc domain or a polyhistidine tag.

4.2. Methods of Making Monoclonal Antibodies

[00597] Monoclonal antibodies may be obtained, for example, using the hybridoma method first described by Kohler et al., *Nature*, 1975, 256:495-497 (incorporated by reference in its entirety), and/or by recombinant DNA methods (*see e.g.,* U.S. Patent No. 4,816,567, incorporated by reference in its entirety). Monoclonal antibodies may also be obtained, for example, using phage-display libraries (*see e.g.*, U.S. Patent No. 8,258,082, which is incorporated by reference in its entirety) or, alternatively, using yeast-based libraries (see *e.g.,* U.S. Patent No. 8,691,730, which is incorporated by reference in its entirety).

[00598] In the hybridoma method, a mouse or other appropriate host animal is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be

immunized *in vitro*. Lymphocytes are then fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. *See* Goding J.W., *Monoclonal Antibodies: Principles and Practice* 3rd ed. (1986) Academic Press, San Diego, CA, incorporated by reference in its entirety.

[00599] The hybridoma cells are seeded and grown in a suitable culture medium that contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[00600] Useful myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive media conditions, such as the presence or absence of HAT medium. Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOP-21 and MC-11 mouse tumors (available from the Salk Institute Cell Distribution Center, San Diego, CA), and SP-2 or X63-Ag8-653 cells (available from the American Type Culture Collection, Rockville, MD). Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. *See e.g.,* Kozbor, *J. Immunol.*, 1984, 133:3001, incorporated by reference in its entirety.

[00601] After the identification of hybridoma cells that produce antibodies of the desired specificity, affinity, and/or biological activity, selected clones may be subcloned by limiting dilution procedures and grown by standard methods. *See* Goding, *supra*. Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

[00602] DNA encoding the monoclonal antibodies may be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). Thus, the hybridoma cells can serve as a useful source of DNA encoding antibodies with the desired properties. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as bacteria (*e.g.*, *E. coli*), yeast (*e.g.*, *Saccharomyces* or *Pichia sp.*), COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody, to produce the monoclonal antibodies.

4.3. Methods of Making Chimeric Antibodies

[00603] Illustrative methods of making chimeric antibodies are described, for example, in U.S. Pat. No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA*, 1984, 81:6851-6855; each of which is incorporated by reference in its entirety. In some embodiments, a chimeric antibody is made by using recombinant techniques to combine a non-human variable region (*e.g.*, a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) with a human constant region.

4.4. Methods of Making Humanized Antibodies

[00604] Humanized antibodies may be generated by replacing most, or all, of the structural portions of a non-human monoclonal antibody with corresponding human antibody sequences. Consequently, a hybrid molecule is generated in which only the antigen-specific variable, or CDR, is composed of non-human sequence. Methods to obtain humanized antibodies include those described in, for example, Winter and Milstein, *Nature*, 1991, 349:293-299; Rader et al., *Proc. Nat. Acad. Sci. U.S.A.*, 1998, 95:8910-8915; Steinberger et al., *J. Biol. Chem.*, 2000, 275:36073-36078; Queen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1989, 86:10029-10033; and U.S. Patent Nos. 5,585,089, 5,693,761, 5,693,762, and 6,180,370; each of which is incorporated by reference in its entirety.

4.5. Methods of Making Human Antibodies

[00605] Human antibodies can be generated by a variety of techniques known in the art, for example by using transgenic animals (*e.g.*, humanized mice). *See, e.g.,* Jakobovits et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1993, 90:2551; Jakobovits et al., *Nature*, 1993, 362:255-258; Bruggermann et al., *Year in Immuno.*, 1993, 7:33; and U.S. Patent Nos. 5,591,669, 5,589,369 and 5,545,807; each of which is incorporated by reference in its entirety. Human antibodies can also be derived from phage-display libraries (*see e.g.,* Hoogenboom et al., *J. Mol. Biol.*, 1991, 227:381-388; Marks et al., *J. Mol. Biol.*, 1991, 222:581-597; and U.S. Pat. Nos. 5,565,332 and 5,573,905; each of which is incorporated by reference in its entirety). Human antibodies may also be generated by *in vitro* activated B cells (*see e.g.,* U.S. Patent. Nos. 5,567,610 and 5,229,275, each of which is incorporated by reference in its entirety). Human antibodies may also be derived from yeast-based libraries (*see e.g.,* U.S. Patent No. 8,691,730, incorporated by reference in its entirety).

4.6. Methods of Making Antibody Fragments

[00606] The antibody fragments provided herein may be made by any suitable method, including the illustrative methods described herein or those known in the art. Suitable methods include recombinant techniques and proteolytic digestion of whole antibodies.

Illustrative methods of making antibody fragments are described, for example, in Hudson et al., *Nat. Med.*, 2003, 9:129-134, incorporated by reference in its entirety. Methods of making scFv antibodies are described, for example, in Plückthun, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); WO 93/16185; and U.S. Pat. Nos. 5,571,894 and 5,587,458; each of which is incorporated by reference in its entirety.

4.7. Methods of Making Alternative Scaffolds

[00607] The alternative scaffolds provided herein may be made by any suitable method, including the illustrative methods described herein or those known in the art. For example, methods of preparing Adnectins™ are described in Emanuel et al., *mAbs*, 2011, 3:38-48, incorporated by reference in its entirety. Methods of preparing iMabs are described in U.S. Pat. Pub. No. 2003/0215914, incorporated by reference in its entirety. Methods of preparing Anticalins® are described in Vogt and Skerra, *Chem. Biochem.*, 2004, 5:191-199, incorporated by reference in its entirety. Methods of preparing Kunitz domains are described in Wagner et al., *Biochem. & Biophys. Res. Comm.*, 1992, 186:118-1145, incorporated by reference in its entirety. Methods of preparing thioredoxin peptide aptamers are provided in Geyer and Brent, *Meth. Enzymol.*, 2000, 328:171-208, incorporated by reference in its entirety. Methods of preparing Affibodies are provided in Fernandez, *Curr. Opinion in Biotech.*, 2004, 15:364-373, incorporated by reference in its entirety. Methods of preparing DARPins are provided in Zahnd et al., *J. Mol. Biol.*, 2007, 369:1015-1028, incorporated by reference in its entirety. Methods of preparing Affilins are provided in Ebersbach et al., *J. Mol. Biol.*, 2007, 372:172-185, incorporated by reference in its entirety. Methods of preparing Tetranectins are provided in Graversen et al., *J. Biol. Chem.*, 2000, 275:37390-37396, incorporated by reference in its entirety. Methods of preparing Avimers are provided in Silverman et al., *Nature Biotech.*, 2005, 23:1556-1561, incorporated by reference in its entirety. Methods of preparing Fynomers are provided in Silacci et al., *J. Biol. Chem.*, 2014, 289:14392-14398, incorporated by reference in its entirety.

[00608] Further information on alternative scaffolds is provided in Binz et al., *Nat. Biotechnol.*, 2005 23:1257-1268; and Skerra, *Current Opin. in Biotech.*, 2007 18:295-304, each of which is incorporated by reference in its entirety.

4.8. Methods of Making Multispecific Antibodies

[00609] The multispecific antibodies provided herein may be made by any suitable method, including the illustrative methods described herein or those known in the art. Methods of making common light chain antibodies are described in Merchant et al., *Nature Biotechnol.*, 1998, 16:677-681, incorporated by reference in its entirety. Methods of making tetravalent bispecific antibodies are described in Coloma and Morrison, *Nature Biotechnol.*, 1997, 15:159-163, incorporated by reference in its entirety. Methods of making hybrid immunoglobulins are described in Milstein and Cuello, *Nature*, 1983, 305:537-540; and Staerz and Bevan, *Proc. Natl. Acad. Sci. USA*, 1986, 83:1453-1457; each of which is incorporated by reference in its entirety. Methods of making immunoglobulins with knobs-into-holes modification are described in U.S. Pat. No. 5,731,168, incorporated by reference in its entirety. Methods of making immunoglobulins with electrostatic modifications are provided in WO 2009/089004, incorporated by reference in its entirety. Methods of making bispecific single chain antibodies are described in Traunecker et al., *EMBO J.*, 1991, 10:3655-3659; and Gruber et al., *J. Immunol.*, 1994, 152:5368-5374; each of which is incorporated by reference in its entirety. Methods of making single-chain antibodies, whose linker length may be varied, are described in U.S. Pat. Nos. 4,946,778 and 5,132,405, each of which is incorporated by reference in its entirety. Methods of making diabodies are described in Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 1993, 90:6444-6448, incorporated by reference in its entirety. Methods of making triabodies and tetrabodies are described in Todorovska et al., *J. Immunol. Methods*, 2001, 248:47-66, incorporated by reference in its entirety. Methods of making trispecific F(ab')3 derivatives are described in Tutt et al. *J. Immunol.*, 1991, 147:60-69, incorporated by reference in its entirety. Methods of making cross-linked antibodies are described in U.S. Patent No. 4,676,980; Brennan et al., *Science*, 1985, 229:81-83; Staerz, et al. *Nature*, 1985, 314:628-631; and EP 0453082; each of which is incorporated by reference in its entirety. Methods of making antigen-binding domains assembled by leucine zippers are described in Kostelny et al., *J. Immunol.*, 1992, 148:1547-1553, incorporated by reference in its entirety. Methods of making antibodies via the DNL approach are described in U.S. Pat. Nos. 7,521,056; 7,550,143; 7,534,866; and 7,527,787; each of which is incorporated by reference in its entirety. Methods of making hybrids of antibody and non-antibody molecules are described in WO 93/08829, incorporated by reference in its entirety, for examples of such antibodies. Methods of making DAF antibodies are described in U.S. Pat. Pub. No. 2008/0069820, incorporated by reference in its entirety.

Methods of making antibodies via reduction and oxidation are described in Carlring et al., *PLoS One*, 2011, 6:e22533, incorporated by reference in its entirety. Methods of making DVD-Igs™ are described in U.S. Pat. No. 7,612,181, incorporated by reference in its entirety. Methods of making DARTs™ are described in Moore et al., *Blood*, 2011, 117:454-451, incorporated by reference in its entirety. Methods of making DuoBodies® are described in Labrijn et al., *Proc. Natl. Acad. Sci. USA*, 2013, 110:5145-5150; Gramer et al., *mAbs*, 2013, 5:962-972; and Labrijn et al., *Nature Protocols*, 2014, 9:2450-2463; each of which is incorporated by reference in its entirety. Methods of making antibodies comprising scFvs fused to the C-terminus of the C_{H3} from an IgG are described in Coloma and Morrison, *Nature Biotechnol.*, 1997, 15:159-163, incorporated by reference in its entirety. Methods of making antibodies in which a Fab molecule is attached to the constant region of an immunoglobulin are described in Miler et al., *J. Immunol.*, 2003, 170:4854-4861, incorporated by reference in its entirety. Methods of making CovX-Bodies are described in Doppalapudi et al., *Proc. Natl. Acad. Sci. USA*, 2010, 107:22611-22616, incorporated by reference in its entirety. Methods of making Fcab antibodies are described in Wozniak-Knopp et al., *Protein Eng. Des. Sel.*, 2010, 23:289-297, incorporated by reference in its entirety. Methods of making TandAb® antibodies are described in Kipriyanov et al., *J. Mol. Biol.*, 1999, 293:41-56 and Zhukovsky et al., *Blood*, 2013, 122:5116, each of which is incorporated by reference in its entirety. Methods of making tandem Fabs are described in WO 2015/103072, incorporated by reference in its entirety. Methods of making Zybodies™ are described in LaFleur et al., *mAbs*, 2013, 5:208-218, incorporated by reference in its entirety.

4.9. Methods of Making Variants

[00610] In some embodiments, an antibody provided herein is an affinity matured variant of a parent antibody, which may be generated, for example, using phage display-based affinity maturation techniques. Briefly, one or more CDR residues may be mutated and the variant antibodies, or portions thereof, displayed on phage and screened for affinity. Such alterations may be made in CDR "hotspots," or residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (*see* Chowdhury, *Methods Mol. Biol.*, 2008, 207:179-196, incorporated by reference in its entirety), and/or residues that contact the antigen.

[00611] Any suitable method can be used to introduce variability into a polynucleotide sequence(s) encoding an antibody, including error-prone PCR, chain shuffling, and

oligonucleotide-directed mutagenesis such as trinucleotide-directed mutagenesis (TRIM). In some aspects, several CDR residues (*e.g.*, 4-6 residues at a time) are randomized. CDR residues involved in antigen binding may be specifically identified, for example, using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted for mutation.

[00612] The introduction of diversity into the variable regions and/or CDRs can be used to produce a secondary library. The secondary library is then screened to identify antibody variants with improved affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, for example, in Hoogenboom et al., *Methods in Molecular Biology*, 2001, 178:1-37, incorporated by reference in its entirety.

4.10. Vectors, Host Cells, and Recombinant Methods

[00613] Also provided are isolated nucleic acids encoding TF antibodies, vectors comprising the nucleic acids, and host cells comprising the vectors and nucleic acids, as well as recombinant techniques for the production of the antibodies.

[00614] For recombinant production of an antibody, the nucleic acid(s) encoding it may be isolated and inserted into a replicable vector for further cloning (*i.e.*, amplification of the DNA) or expression. In some aspects, the nucleic acid may be produced by homologous recombination, for example as described in U.S. Patent No. 5,204,244, incorporated by reference in its entirety.

[00615] Many different vectors are known in the art. The vector components generally include one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence, for example as described in U.S. Patent No. 5,534,615, incorporated by reference in its entirety.

[00616] Illustrative examples of suitable host cells are provided below. These host cells are not meant to be limiting, and any suitable host cell may be used to produce the antibodies provided herein.

[00617] Suitable host cells include any prokaryotic (*e.g.*, bacterial), lower eukaryotic (*e.g.*, yeast), or higher eukaryotic (*e.g.*, mammalian) cells. Suitable prokaryotes include eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *Escherichia* (*E. coli*), *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella* (*S. typhimurium*), *Serratia* (*S. marcescans*), *Shigella*, *Bacilli* (*B. subtilis* and *B. licheniformis*), *Pseudomonas* (*P. aeruginosa*), and *Streptomyces*. One useful *E. coli* cloning host is *E. coli*

294, although other strains such as *E. coli* B, *E. coli* X1776, and *E. coli* W3110 are also suitable.

[00618] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are also suitable cloning or expression hosts for TF antibody-encoding vectors. *Saccharomyces cerevisiae*, or common baker's yeast, is a commonly used lower eukaryotic host microorganism. However, a number of other genera, species, and strains are available and useful, such as *Schizosaccharomyces pombe*, *Kluyveromyces* (*K. lactis*, *K. fragilis, K. bulgaricus K. wickeramii*, *K. waltii*, *K. drosophilarum*, *K. thermotolerans*, and *K. marxianus*), *Yarrowia*, *Pichia pastoris*, *Candida* (*C. albicans*), *Trichoderma reesia*, *Neurospora crassa*, *Schwanniomyces* (*S. occidentalis*), and filamentous fungi such as, for example *Penicillium*, *Tolypocladium*, and *Aspergillus* (*A. nidulans* and *A. niger*).

[00619] Useful mammalian host cells include COS-7 cells, HEK293 cells, baby hamster kidney (BHK) cells, Chinese hamster ovary (CHO), mouse sertoli cells, African green monkey kidney cells (VERO-76), and the like.

[00620] The host cells used to produce the TF antibody of this invention may be cultured in a variety of media. Commercially available media such as, for example, Ham's F10, Minimal Essential Medium (MEM), RPMI-1640, and Dulbecco's Modified Eagle's Medium (DMEM) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., *Meth. Enz.*, 1979, 58:44; Barnes et al., *Anal. Biochem.*, 1980, 102:255; and U.S. Patent Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655, and 5,122,469; or WO 90/03430 and WO 87/00195 may be used. Each of the foregoing references is incorporated by reference in its entirety.

[00621] Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics, trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art.

[00622] The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

[00623] When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced

intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration. For example, Carter et al. (*Bio/Technology*, 1992, 10:163-167, incorporated by reference in its entirety) describes a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation.

[00624] In some embodiments, the antibody is produced in a cell-free system. In some aspects, the cell-free system is an *in vitro* transcription and translation system as described in Yin et al., *mAbs*, 2012, 4:217-225, incorporated by reference in its entirety. In some aspects, the cell-free system utilizes a cell-free extract from a eukaryotic cell or from a prokaryotic cell. In some aspects, the prokaryotic cell is *E. coli*. Cell-free expression of the antibody may be useful, for example, where the antibody accumulates in a cell as an insoluble aggregate, or where yields from periplasmic expression are low.

[00625] Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon® or Millipore® Pellcon® ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

[00626] The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being a particularly useful purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that comprise human γ1, γ2, or γ4 heavy chains (Lindmark et al., *J. Immunol. Meth.*, 1983, 62:1-13, incorporated by reference in its entirety). Protein G is useful for all mouse isotypes and for human γ3 (Guss et al., *EMBO J.*, 1986, 5:1567-1575, incorporated by reference in its entirety).

[00627] The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_{H3} domain, the BakerBond ABX® resin is useful for purification.

[00628] Other techniques for protein purification, such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin Sepharose®, chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available, and can be applied by one of skill in the art.

[00629] Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5 to about 4.5, generally performed at low salt concentrations (*e.g.*, from about 0 to about 0.25 M salt).

5. Cytotoxic Agents

[00630] In some embodiments, ADCs provided herein comprise a cytotoxic agent. The cytotoxic agents provided herein include various anti-tumor or anti-cancer agents known in the art. In some embodiments, the cytotoxic agents cause destruction of cancer cells. In some embodiments, the cytotoxic agents inhibit the growth or proliferation of cancer cells.

[00631] Suitable cytotoxic agents include anti-angiogenic agents, pro-apoptotic agents, anti-mitotic agents, anti-kinase agents, alkylating agents, hormones, hormone agonists, hormone antagonists, chemokines, drugs, prodrugs, toxins, enzymes, antimetabolites, antibiotics, alkaloids, and radioactive isotopes.

[00632] In some embodiments, the cytotoxic agent comprises at least one of: calicheamycin, camptothecin, carboplatin, irinotecan, SN-38, carboplatin, camptothecan, cyclophosphamide, cytarabine, dacarbazine, docetaxel, dactinomycin, daunorubicin, doxorubicin, doxorubicin, etoposide, idarubicin, topotecan, vinca alkaloid, maytansinoid, maytansinoid analog, pyrrolobenzodiazepine, taxoid, duocarmycin, dolastatin, auristatin and derivatives thereof. In certain embodiments, the cytotoxic agent is monomethyl auristatin E (MMAE).

[00633] In some embodiments, the cytotoxic agent is a diagnostic agent, such as a radioactive isotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound, or a chemiluminescent compound.

[00634] In some embodiments, the cytotoxic agent is a cytotoxic payload improved safety profile, for example XMT-1267 and other cytotoxic payloads described in Trail et al., *Pharmacol Ther*, 2018, 181:126-142.

6. Linkers

[00635] In some embodiments, ADCs provided herein comprise a linker. In some embodiments, an unbound linker comprises two reactive termini: an antibody conjugation reactive termini and an cytotoxic agent conjugation reactive termini. The antibody conjugation reactive terminus of the linker can be conjugated to the antibody through a cysteine thiol or lysine amine group on the antibody, typically a thiol-reactive group such as a double bond, a leaving group such as a chloro, bromo or iodo, an R-sulfanyl group or sulfonyl group, or an amine-reactive group such as a carboxyl group. The cytotoxic agent conjugation reactive terminus of the linker can be conjugated to the cytotoxic agent through formation of an amide bond with a basic amine or carboxyl group on the cytotoxin, typically a carboxyl or basic amine group.

[00636] In some embodiments, the linker is a non-cleavable linker. In some embodiments, the linker is a cleavable linker. In some embodiments, the cytotoxic agent is released from the ADC in a cell.

[00637] Suitable linkers of ADCs include labile linkers, acid labile linkers (*e.g.*, hydrazone linkers), photolabile linkers, charged linkers, disulfide-containing linkers, peptidase-sensitive linkers (*e.g.*, peptide linkers comprising amino acids, for example, valine and/or citrulline such as citrulline-valine or phenylalanine-lysine), β-glucuronide-linkers (*See e.g.*, Graaf et al., *Curr Pharm Des*, 2002, 8:1391-1403), dimethyl linkers (*See e.g.*, Chari et al., *Cancer Research*, 1992, 52:127-131; U.S. Pat. No. 5,208,020), thio-ether linkers, or hydrophilic linkers (*See e.g.*, Kovtun et al., *Cancer Res.*, 2010, 70:2528-2537). In certain embodiments, the cytotoxic agent is conjugated to the antibody using a valine-citrulline (vc) linker.

7. Methods for Making Antibody-Drug Conjugates

[00638] The antibody-drug conjugates (ADCs) provided herein can be made using a variety of bifunctional protein coupling agents such as BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfoSIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate)). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science*, 1987, 238:1098. Addtionally, the ADCs can be prepared using any suitable methods as disclosed in the art, *e.g.*, in *Bioconjugate Techniques,* 2nd Ed., G. T. Hermanson, ed., Elsevier, San Francisco, 2008.

[00639] In some embodiments, the ADCs are made with site-specific conjugation techniques, resulting in homogeneous drug loading and avoiding ADC subpopulations with altered antigen-binding or pharmacokinetics. In some embodiments, "thiomabs" comprising

cysteine substitutions at positions on the heavy and light chains are engineered to provide reactive thiol groups that do not disrupt immunoglobulin folding and assembly or alter antigen binding (Junutula et al., *J. Immunol. Meth.*, 2008, 332: 41-52; Junutula et al., *Nat. Biotechnol.*, 2008, 26: 925-932,). In some embodiments, selenocysteine is co-translationally inserted into an antibody sequence by recoding the stop codon UGA from termination to selenocysteine insertion, allowing site specific covalent conjugation at the nucleophilic selenol group of selenocysteine in the presence of the other natural amino acids (*See e.g.*, Hofer et al., *Proc. Natl. Acad. Sci. USA*, 2008, 105:12451-12456; Hofer et al., *Biochemistry*, 2009, 48(50):12047-12057). In certain embodiments, ADCs were synthesized as described in Behrens et al., *Mol Pharm*, 2015, 12:3986-98.

8. Assays

[00640] A variety of assays known in the art may be used to identify and characterize anti-TF antibodies and anti-TF ADCs provided herein.

8.1. Binding, Competition, and Epitope Mapping Assays

[00641] Specific antigen-binding activity of the antibodies provided herein may be evaluated by any suitable method, including using SPR, BLI, RIA and MSD-SET, as described elsewhere in this disclosure. Additionally, antigen-binding activity may be evaluated by ELISA assays and Western blot assays.

[00642] Assays for measuring competition between two antibodies, or an antibody and another molecule (*e.g.*, one or more ligands of TF) are described elsewhere in this disclosure and, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual* ch.14, 1988, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y, incorporated by reference in its entirety.

[00643] Assays for mapping the epitopes to which the antibodies provided herein bind are described, for example, in Morris "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66, 1996, Humana Press, Totowa, N.J., incorporated by reference in its entirety. In some embodiments, the epitope is determined by peptide competition. In some embodiments, the epitope is determined by mass spectrometry. In some embodiments, the epitope is determined by crystallography.

8.2. Thrombin Generation, FXa Conversion, and TF Signaling Assays

[00644] Thrombin generation in the presence of the antibodies provided herein can be determined by the Thrombin Generation Assay (TGA), as described elsewhere in this disclosure.

[00645] Assays for measuring FXa conversion in the presence of the antibodies provided herein are described elsewhere in this disclosure.

[00646] Inhibition of TF signaling can be determined by measuring the production of a cytokine regulated by the TF signaling, such as IL8 and GM-CSF. Assays for determining the IL8 and/or GM-CSF level are provided elsewhere in this disclosure and, for example, in Hjortoe et al., *Blood*, 2004, 103:3029-3037.

8.3. Assays for Effector Functions

[00647] Effector function following treatment with the antibodies provided herein may be evaluated using a variety of *in vitro* and *in vivo* assays known in the art, including those described in Ravetch and Kinet, *Annu. Rev. Immunol.*, 1991, 9:457-492; U.S. Pat. Nos. 5,500,362, 5,821,337; Hellstrom et al., *Proc. Nat'l Acad. Sci. USA*, 1986, 83:7059-7063; Hellstrom et al., *Proc. Nat'l Acad. Sci. USA*, 1985, 82:1499-1502; Bruggemann et al., *J. Exp. Med.*, 1987, 166:1351-1361; Clynes et al., *Proc. Nat'l Acad. Sci. USA*, 1998, 95:652-656; WO 2006/029879; WO 2005/100402; Gazzano-Santoro et al., *J. Immunol. Methods*, 1996, 202:163-171; Cragg et al., *Blood*, 2003, 101:1045-1052; Cragg et al. *Blood*, 2004, 103:2738-2743; and Petkova et al., *Int'l. Immunol.*, 2006, 18:1759-1769; each of which is incorporated by reference in its entirety.

8.4. Cytotoxicity Assays and *In Vivo* Studies

[00648] Assays for evaluating cytotoxicity of the antibody-drug conjugates (ADCs) provided herein are described elsewhere in this disclosure.

[00649] Xenograft studies in immune compromised mice for evaluating the *in vivo* efficacy of the ADCs provided herein are described elsewhere in this disclosure.

[00650] Syngeneic studies in immune competent mice for evaluating the in *vivo* efficacy of the ADCs are included in this disclosure.

8.5. Immunohistochemistry (IHC) Assays

[00651] Immunohistochemistry (IHC) assays for evaluating the TF expression in patient samples are described elsewhere in this disclosure.

8.6. Chimeric Construct Mapping and Epitope Binning Assays

[00652] Epitope binding differences between the anti-human TF antibodies provided herein can be determined by the chimeric TF construct mapping experiments and the epitope binning assays, as described elsewhere in this disclosure.

9. Pharmaceutical Compositions

[00653] The antibodies or ADCs provided herein can be formulated in any appropriate pharmaceutical composition and administered by any suitable route of administration. Suitable routes of administration include, but are not limited to, the intravitreal, intraarterial, intradermal, intramuscular, intraperitoneal, intravenous, nasal, parenteral, pulmonary, and subcutaneous routes.

[00654] The pharmaceutical composition may comprise one or more pharmaceutical excipients. Any suitable pharmaceutical excipient may be used, and one of ordinary skill in the art is capable of selecting suitable pharmaceutical excipients. Accordingly, the pharmaceutical excipients provided below are intended to be illustrative, and not limiting. Additional pharmaceutical excipients include, for example, those described in the *Handbook of Pharmaceutical Excipients*, Rowe et al. (Eds.) 6th Ed. (2009), incorporated by reference in its entirety.

9.1. Parenteral Dosage Forms

[00655] In certain embodiments, the antibodies or ADCs provided herein are formulated as parenteral dosage forms. Parenteral dosage forms can be administered to subjects by various routes including, but not limited to, subcutaneous, intravenous (including infusions and bolus injections), intramuscular, and intraarterial. Because their administration typically bypasses subjects' natural defenses against contaminants, parenteral dosage forms are typically, sterile or capable of being sterilized prior to administration to a subject. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry (*e.g.*, lyophilized) products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

10. Dosage and Unit Dosage Forms

[00656] In human therapeutics, the doctor will determine the posology which he considers most appropriate according to a preventive or curative treatment and according to the age, weight, condition and other factors specific to the subject to be treated.

[00657] In certain embodiments, a composition provided herein is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and single unit

dosage forms provided herein comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic antibodies or ADCs.

[00658] The amount of the antibody/ADC or composition which will be effective in the prevention or treatment of a disorder or one or more symptoms thereof can vary with the nature and severity of the disease or condition, and the route by which the antibody/ADC is administered. The frequency and dosage can also vary according to factors specific for each subject depending on the specific therapy (*e.g.*, therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the subject. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[00659] Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the antibodies or ADCs provided herein are also encompassed by the dosage amounts and dose frequency schedules provided herein. Further, when a subject is administered multiple dosages of a composition provided herein, not all of the dosages need be the same. For example, the dosage administered to the subject may be increased to improve the prophylactic or therapeutic effect of the composition or it may be decreased to reduce one or more side effects that a particular subject is experiencing.

[00660] As discussed in more detail elsewhere in this disclosure, an antibody or ADC provided herein may optionally be administered with one or more additional agents useful to prevent or treat a disease or disorder. The effective amount of such additional agents may depend on the amount of ADC present in the formulation, the type of disorder or treatment, and the other factors known in the art or described herein.

11. Therapeutic Applications

[00661] For therapeutic applications, the antibodies or ADCs of the invention are administered to a mammal, generally a human, in a pharmaceutically acceptable dosage form such as those known in the art and those discussed above. For example, the antibodies or ADCs of the invention may be administered to a human intravenously as a bolus or by continuous infusion over a period of time, by intravitreal, intramuscular, intraperitoneal, intra-cerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, or intratumoral

routes. The antibodies or ADCs also are suitably administered by peritumoral, intralesional, or perilesional routes, to exert local as well as systemic therapeutic effects. The intraperitoneal route may be particularly useful, for example, in the treatment of ovarian tumors.

[00662] The antibodies or ADCs provided herein may be useful for the treatment of any disease or condition involving TF. In some embodiments, the disease or condition is a disease or condition that can benefit from treatment with an anti-TF antibody or ADC.

[00663] In some embodiments, the antibodies or ADCs provided herein are provided for use as a medicament. In some embodiments, the antibodies or ADCs provided herein are provided for use in the manufacture or preparation of a medicament. In some embodiments, the medicament is for the treatment of a disease or condition that can benefit from an anti-TF antibody or ADC.

[00664] In some embodiments, provided herein is a method of treating a disease or condition in a subject in need thereof by administering an effective amount of an anti-TF antibody or ADC provided herein to the subject.

[00665] In some embodiments, the disease or condition that can benefit from treatment with an anti-TF antibody or ADC is cancer. In some embodiments, the anti-TF antibodies or ADCs provided herein are provided for use as a medicament for the treatment of cancer. In some embodiments, the anti-TF antibodies or ADCs provided herein are provided for use in the manufacture or preparation of a medicament for the treatment of cancer. In some embodiments, provided herein is a method of treating cancer in a subject in need thereof by administering an effective amount of an anti-TF antibody or ADC provided herein to the subject.

[00666] TF is involved in thrombosis, metastasis, tumor growth, and/or tumor angiogenesis of various types of cancers, such as ovarian cancer (*See* Sakurai et al., *Int J Gynecol Cancer*, 2017, 27:37-43; Koizume et al., *Biomark Cancer*, 2015, 7:1-13; each of which is incorporated by reference in its entirety), cervical cancer (*See* Cocco et al., *BMC Cancer*, 2011, 11:263, incorporated by reference in its entirety), head and neck cancer (*See* Christensen et al., *BMC Cancer*, 2017, 17:572, incorporated by reference in its entirety), prostate cancer (*See* Yao et al., *Cancer Invest.*, 2009, 27:430-434; Abdulkadir et al., *Hum Pathol.*, 2009, 31:443-447; each of which is incorporated by reference in its entirety), pancreatic cancer (*See* Zhang et al., *Oncotarget*, 2017, 8:59086-59102, incorporated by reference in its entirety), triple negative breast cancer (*See* Zhang et al., *Oncotarget*, 2017, 8:59086-59102, incorporated by reference in its entirety), glioblastoma (*See* Guan et al., *Clin*

Biochem., 2002, 35:321-325; Carneiro-Lobo et al., *J Thromb Haemost*, 2009, 7:1855-1864; each of which is incorporated by reference in its entirety), lung cancer (*See* Yeh et al., *PLoS One*, 2013, 8:e75287; Regina et al., *Clin Chem.*, 2009, 55:1834-42; each of which is incorporated by reference in its entirety), gastric cancer (*See* Lo et al., *Br J Cancer.*, 2012, 107:1125-1130, incorporated by reference in its entirety), esophageal cancer (*See* Chen et al., *Acta Histochem.*, 2010, 3:233-239, incorporated by reference in its entirety), bladder cancer (*See* Patry et al., *Int J Cancer.*, 2008, 122:1592-1597, incorporated by reference in its entirety), melanoma (*See* Bromberg et al., *Proc Natl Acad Sci U S A.*, 1995, 92:8205-8209, incorporated by reference in its entirety), and kidney cancer (*See* Silva et al., *Int Braz J Urol.*, 2014, 40:499-506, incorporated by reference in its entirety).

[00667] Any suitable cancer may be treated with the antibodies or ADCs provided herein. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is cervical cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is kidney cancer. Additional information on the types of cancers that can be treated with anti-TF antibodies or ADCs is provided in van den Berg et al., *Blood*, 2012, 119:924-932, which is incorporated by reference in its entirety.

[00668] In some embodiments, provided herein is a method of delaying the onset of a cancer in a subject in need thereof by administering an effective amount of an antibody or ADC provided herein to the subject.

[00669] In some embodiments, provided herein is a method of preventing the onset of a cancer in a subject in need thereof by administering an effective amount of an antibody or ADC provided herein to the subject.

[00670] In some embodiments, provided herein is a method of reducing the size of a tumor in a subject in need thereof by administering an effective amount of an antibody or ADC provided herein to the subject.

[00671] In some embodiments, provided herein is a method of reducing the number of metastases in a subject in need thereof by administering an effective amount of an antibody or ADC provided herein to the subject.

[00672] In some embodiments, provided herein is a method for extending the period of overall survival, median survival time, or progression-free survival in a subject in need thereof by administering an effective amount of an antibody or ADC provided herein to the subject.

[00673] In some embodiments, provided herein is a method for treating a subject who has become resistant to a standard of care therapeutic by administering an effective amount of an antibody or ADC provided herein to the subject.

[00674] In some embodiments, the disease or condition that can benefit from treatment with an anti-TF antibody is a disease or condition involving neovascularization. In certain embodiments, the disease or condition involving neovascularization is age-related macular degeneration (AMD). In certain embodiments, the disease or condition involving neovascularization is diabetic retinopathy. In certain embodiments, the disease or condition involving neovascularization is cancer. In some embodiments, the disease or condition that can benefit from treatment with an anti-TF antibody is a disease or condition involving vascular inflammation.

[00675] In some embodiments, the anti-TF antibodies provided herein are provided for use as a medicament for the treatment of a disease or condition involving neovascularization. In some embodiments, the anti-TF antibodies provided herein are provided for use in the manufacture or preparation of a medicament for the treatment of a disease or condition involving neovascularization. In certain embodiments, the disease or condition involving neovascularization is age-related macular degeneration (AMD). In certain embodiments, the disease or condition involving neovascularization is diabetic retinopathy. In certain embodiments, the disease or condition involving neovascularization is cancer. In some embodiments, the anti-TF antibodies provided herein are provided for use as a medicament for the treatment of a disease or condition involving vascular inflammation. In some embodiments, the anti-TF antibodies provided herein are provided for use in the manufacture or preparation of a medicament for the treatment of a disease or condition involving vascular inflammation.

[00676] In some embodiments, provided herein is a method of treating a disease or condition involving neovascularization in a subject in need thereof by administering an effective amount of an anti-TF antibody provided herein to the subject. In certain embodiments, the disease or condition involving neovascularization is age-related macular degeneration (AMD). In certain embodiments, the disease or condition involving neovascularization is diabetic retinopathy. In certain embodiments, the disease or condition

involving neovascularization is cancer. In some embodiments, provided herein is a method of treating a disease or condition involving vascular inflammation in a subject in need thereof by administering an effective amount of an anti-TF antibody provided herein to the subject.

[00677] In some embodiments, provided herein is a method of delaying the onset of a disease or condition involving neovascularization in a subject in need thereof by administering an effective amount of an antibody provided herein to the subject.

[00678] In some embodiments, provided herein is a method of preventing the onset of a disease or condition involving neovascularization in a subject in need thereof by administering an effective amount of an antibody provided herein to the subject.

[00679] In some embodiments, provided herein is a method of delaying the onset of age-related macular degeneration (AMD) in a subject in need thereof by administering an effective amount of an antibody provided herein to the subject.

[00680] In some embodiments, provided herein is a method of preventing the onset of age-related macular degeneration (AMD) in a subject in need thereof by administering an effective amount of an antibody provided herein to the subject.

[00681] In some embodiments, provided herein is a method of delaying the onset of diabetic retinopathy in a subject in need thereof by administering an effective amount of an antibody provided herein to the subject.

[00682] In some embodiments, provided herein is a method of preventing the onset of diabetic retinopathy in a subject in need thereof by administering an effective amount of an antibody provided herein to the subject.

[00683] In some embodiments, provided herein is a method of delaying the onset of a disease or condition involving vascular inflammation in a subject in need thereof by administering an effective amount of an antibody provided herein to the subject.

[00684] In some embodiments, provided herein is a method of preventing the onset of a disease or condition involving vascular inflammation in a subject in need thereof by administering an effective amount of an antibody provided herein to the subject.

12. Combination Therapies

[00685] In some embodiments, an antibody or ADC provided herein is administered with at least one additional therapeutic agent. Any suitable additional therapeutic agent may be administered with an antibody or ADC provided herein. In some aspects, the additional therapeutic agent is selected from radiation, a cytotoxic agent, a chemotherapeutic agent, a

cytostatic agent, an anti-hormonal agent, an immunostimulatory agent, an anti-angiogenic agent, and combinations thereof.

[00686] The additional therapeutic agent may be administered by any suitable means. In some embodiments, an antibody or ADC provided herein and the additional therapeutic agent are included in the same pharmaceutical composition. In some embodiments, an antibody or ADC provided herein and the additional therapeutic agent are included in different pharmaceutical compositions.

[00687] In embodiments where an antibody or ADC provided herein and the additional therapeutic agent are included in different pharmaceutical compositions, administration of the antibody or ADC can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent.

13. Diagnostic Methods

[00688] Also provided are methods for detecting the presence of TF on cells from a subject. Such methods may be used, for example, to predict and evaluate responsiveness to treatment with an antibody or ADC provided herein.

[00689] In some embodiments, the method can be used to detect TF in a subject having or suspected of having a disease or condition. In some embodiments, the methods comprise (a) receiving a sample from the subject; and (b) detecting the presence or the level of TF in the sample by contacting the sample with the antibody provided herein. In some embodiments, the methods comprise (a) administering to the subject the antibody provided herein; and (b) detecting the presence or the level of TF in the subject. In some embodiments, the disease or condition is a cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is cervical cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is kidney cancer. In some embodiments, the disease or condition involves neovascularization. In certain embodiments, the disease or condition involving neovascularization is age-related macular degeneration (AMD). In certain embodiments, the disease or condition involving

neovascularization is diabetic retinopathy. In certain embodiments, the disease or condition involving neovascularization is cancer. In some embodiments, the disease or condition involves vascular inflammation.

[00690] In some embodiments, the methods comprise (a) administering to the subject the ADC provided herein; and (b) detecting the presence or the level of TF in the subject. In some embodiments, the disease or condition is a cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is cervical cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is bladder cancer. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is kidney cancer.

[00691] In some embodiments, the antibody provided herein is conjugated with a fluorescent label. In some embodiments, the antibody provided herein is conjugated with a radioactive label. In some embodiments, the antibody provided herein is conjugated with an enzyme label.

[00692] In some embodiments, the ADC provided herein comprises a fluorescent label. In some embodiments, the ADC provided herein comprises a radioactive label. In some embodiments, the ADC provided herein comprises an enzyme label.

[00693] In some embodiments, the relative amount of TF expressed by such cells is determined. The fraction of cells expressing TF and the relative amount of TF expressed by such cells can be determined by any suitable method. In some embodiments, flow cytometry is used to make such measurements. In some embodiments, fluorescence assisted cell sorting (FACS) is used to make such measurement.

14. Kits

[00694] Also provided are kits comprising the antibodies or ADCs provided herein. The kits may be used for the treatment, prevention, and/or diagnosis of a disease or disorder, as described herein.

[00695] In some embodiments, the kit comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials,

syringes, and IV solution bags. The containers may be formed from a variety of materials, such as glass or plastic. The container holds a composition that is by itself, or when combined with another composition, effective for treating, preventing and/or diagnosing a disease or disorder. The container may have a sterile access port. For example, if the container is an intravenous solution bag or a vial, it may have a port that can be pierced by a needle. At least one active agent in the composition is an antibody or ADC provided herein. The label or package insert indicates that the composition is used for treating the selected condition.

[00696] In some embodiments, the kit comprises (a) a first container with a first composition contained therein, wherein the first composition comprises an antibody or ADC provided herein; and (b) a second container with a second composition contained therein, wherein the second composition comprises a further therapeutic agent. The kit in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition.

[00697] Alternatively, or additionally, the kit may further comprise a second (or third) container comprising a pharmaceutically-acceptable excipient. In some aspects, the excipient is a buffer. The kit may further include other materials desirable from a commercial and user standpoint, including filters, needles, and syringes.

EXAMPLES

[00698] The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided herein.

[00699] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

[00700] The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. *See, e.g.*, T.E. Creighton, *Proteins: Structures and Molecular Properties* (W.H. Freeman and Company, 1993); A.L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition); Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989); *Methods In Enzymology* (S. Colowick and N. Kaplan eds., Academic Press, Inc.);

Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990); Carey and Sundberg *Advanced Organic Chemistry 3rd Ed.* (Plenum Press) Vols A and B(1992).

Example 1: Generation of TF Antibodies

[00701] Human, cynomolgus monkey, and mouse TF extracellular domain (ECD) fragments were expressed as C-terminal His or Fcγ fragment fusions. Expi293 cells (ThermoFisher Scientific, Waltham, MA, USA) were transiently transfected as recommended by the manufacturer with pcDNA3.1V5-HisA (ThermoFisher Scientific) encoding human, cynomolgus, or mouse TF ECD–His6 (TF-His; SEQ ID NOs:811, 815, and 819, respectively) or pFUSE-hIgG1-Fc (Invivogen, San Diego, CA, USA) encoding human, cynomolgus or mouse TF ECD–Fc (TF-Fc; SEQ ID NOs:812, 816, and 820, respectively). For the His-tagged proteins, cell culture supernatants cleared from cells by centrifugation were preconditioned with 330 mM sodium chloride and 13.3 mM imidazole. Using recommended procedures, the TF-His6 and TF-Fc proteins were purified by affinity chromatography with a HisTrap HP and MabSelect SuRe column (GE Healthcare Bio-Sciences, Marlborough, MA, USA), respectively. FVII-Fc expressed in Expi293 was purified by affinity chromatography with a MabSelect SuRe column, followed by size exclusion chromatography. The TF-His6 and TF-Fc proteins were biotinylated with a 15x molar excess of Sulfo-NHS-SS-biotin as recommended (ThermoFisher Scientific). The non-labeled and biotinylated proteins were further purified by size exclusion chromatography using a Superdex 200 Increase 10/300 column (GE Healthcare Bio-Sciences).

[00702] Human antibodies against human TF were generated by Adimab™ yeast-based antibody presentation using the biotinylated recombinant TF proteins as screening antigens, as described below. All antibodies against human TF were evaluated for cross-reactivity with cynomolgus monkey and mouse TF. The binding activity of the antibodies to human, cynomolgus monkey, and mouse TF is shown in **Table 5**.

[00703] I. Library interrogation and selection methodology for isolation of anti-TF antibodies

[00704] *Naive library selections*

[00705] Eight naïve human synthetic yeast libraries each of ~10^9 diversity were designed, generated, and propagated as described previously (*see, e.g.*, WO2009036379; WO2010105256; WO2012009568; Xu et al., *Protein Eng Des Sel.*, 2013, 26(10):663-70).

Eight parallel selections were performed, using the eight naïve libraries for monomeric human TF selections.

[00706] For the first two rounds of selection, a magnetic bead sorting technique utilizing the Miltenyi MACS system was performed, essentially as described (Siegel et al., *J Immunol Methods,* 2004, 286(1-2):141-53). Briefly, yeast cells (~10^{10} cells/library) were incubated with 10 nM of biotinylated human TF Fc-fusion antigen for 15 min at room temperature in FACS wash buffer PBS with 0.1% BSA. After washing once with 50 mL ice-cold wash buffer, the cell pellet was resuspended in 40 mL wash buffer, and 500 µl Streptavidin MicroBeads (Miltenyi Biotec, Bergisch Gladbach, Germany; Cat # 130-048-101) were added to the yeast and incubated for 15 min at 4°C. Next, the yeast were pelleted, resuspended in 5 mL wash buffer, and loaded onto a MACS LS column (Miltenyi Biotec, Bergisch Gladbach, Germany; Cat.# 130-042-401). After the 5 mL was loaded, the column was washed 3 times with 3 mL FACS wash buffer. The column was then removed from the magnetic field, and the yeast were eluted with 5 mL of growth media and then grown overnight.

[00707] Subsequent to the two rounds of MACS, the following four rounds of sorting were performed using flow cytometry (FACS). For the first round of FACS, approximately 5×10^7 yeast were pelleted, washed three times with wash buffer, and incubated with 10 nM of each the biotinylated Fc-fusion proteins of mouse and/or cynomolgus TF antigen for 10-15 min at room temperature. Yeast were then washed twice and stained with LC-FITC diluted 1:100 (Southern Biotech, Birmingham, Alabama; Cat# 2062-02) and either SA-633 (Life Technologies, Grand Island, NY; Cat # S21375) diluted 1:500, or EA-PE (Sigma-Aldrich, St Louis; Cat # E4011) diluted 1:50, secondary reagents for 15 min at 4°C. After washing twice with ice-cold wash buffer, the cell pellets were resuspended in 0.4 mL wash buffer and transferred to strainer-capped sort tubes. Sorting was performed using a FACS ARIA sorter (BD Biosciences), and sort gates were determined to select for TF binding. The mouse- and cyno-selected populations from the first round of FACS were grown out and expanded through sub-culturing in selective media. The second, third, and fourth rounds of FACS involved positive sorts to enrich for TF binders and/or negative sorts to decrease the number of non-specific binders using soluble membrane proteins from CHO cells (*see, e.g.*, WO2014179363 and Xu et al., *PEDS*, 2013, 26(10):663-70). After the final round of sorting, yeast were plated and sequenced.

[00708] *Affinity maturation of clones identified in naïve selections*

[00709] Heavy chains from the naïve outputs (described above) were used to prepare light chain diversification libraries, which were then used for additional selection rounds. In

particular, heavy chain variable regions were extracted from the fourth naïve selection round outputs and transformed into a light chain library with a diversity of 1 x 10^6.

[00710] The first of selection round utilized Miltenyi MACS beads and 10 nM biotinylated human TF Fc-fusion as antigen. Subsequent to the MACS bead selections, three rounds of FACS sorting were performed as described above using cynomolgus and mouse Fc-fusion TF at 10 nM oreither biotinylated Fc-fusion TF antigens or biotinylated monomeric HIS-forms of human, mouse or cynomolgus TF. Individual colonies from each FACS selection round were sequenced.

[00711] *Optimization of leads identified from naïve or light chain diversification selections*

[00712] Optimization of lead clones was carried out utilizing three maturation strategies: diversification of CDR-H1 and CDR-H2; diversification of CDR-H3 following CDR-H1 and CDR-H2 diversity pool optimization; and diversification of CDR-L3 within selected CDR-L1 and CDR-L2 diversity pools.

[00713] CDR-H1 and CDR-H2 selection: The CDR-H3s from clones selected from either naïve or light chain diversification procedure were recombined into a premade library with CDR-H1 and CDR-H2 variants of a diversity of 1 x 10^8 and selections were performed using biotinylated Fc-fusion cynomolgus TF antigen, biotinylated cynomolgus HIS-TF antigen, and/or biotinylated human HIS-TF. Affinity pressures were applied by using decreasing concentrations of biotinylated HIS-TF antigens (down to 1 nM) under equilibrium conditions at room temperature.

[00714] CDR-H3/CDR-H1/CDR-H2 selections: Oligos were ordered from IDT which comprised the CDR-H3 as well as a homologous flanking region on either side of the CDR-H3. Amino acid positions in the CDR-H3 were variegated via NNK diversity at two positions per oligo across the entire CDR-H3. The CDR-H3 oligos were double-stranded using primers which annealed to the flanking region of the CDR-H3. The remaining FR1 to FR3 of the heavy chain variable region was amplified from pools of antibodies with improved affinity that were isolated from the CDR-H1 and CDR-H2 diversities selected above. The library was then created by transforming the double stranded CDR-H3 oligo, the FR1 to FR3 pooled fragments, and the heavy chain expression vector into yeast already containing the light chain of the parent. Selections were performed as during previous cycles using FACS sorting. FACS rounds assessed non-specific binding, species cross-reactivity, and affinity pressure, and sorting was performed to obtain populations with the desired characteristics. Affinity pressures for these selections were performed as described above in the CDR-H1 and CDR-H2 selection.

[00715] CDR-L3/CDR-L1/CDR-L2 selections: Oligos were ordered from IDT which comprised the CDR-L3 as well as a homologous flanking region on either side of the CDR-L3. Amino acid positions in the CDR-L3 were variegated via NNK diversity at one position per oligo across the entire CDR-L3. The CDR-L3 oligos were double-stranded using primers which annealed to the flanking region of the CDR-L3. The remaining FR1 to FR3 of the light chain variable region was amplified from pools of antibodies with improved affinity that were isolated from the CDR-L1 and CDR-L2 diversities selected above. The library was then created by transforming the double stranded CDR-L3 oligo, the FR1 to FR3 pooled fragments, and the light chain expression vector into yeast already containing the heavy chain of the parent. Selections were performed as during previous cycles using FACS sorting. FACS rounds assessed non-specific binding, species cross-reactivity, and affinity pressure, and sorting was performed to obtain populations with the desired characteristics. Affinity pressures included titrations as well as incorporation of the parental Fab in antigen pre-complexation.

[00716] II. IgG and Fab production and purification

[00717] In order to produce sufficient amounts of selected antibodies for further characterization, the yeast clones were grown to saturation and then induced for 48 h at 30°C with shaking. After induction, yeast cells were pelleted and the supernatants were harvested for purification. IgGs were purified using a Protein A column and eluted with acetic acid, pH 2.0. Fab fragments were generated by papain digestion and purified over CaptureSelect IgG-CH1 affinity matrix (LifeTechnologies, Cat # 1943200250).

Example 2: Binding Affinity Assay

[00718] Kinetic measurements for the anti-TF antibodies were conducted on an Octet QK384 (Pall ForteBio, Fremont, CA, USA) or a Biacore (GE Healthcare Bio-Sciences).

[00719] ForteBio affinity measurements were performed generally as previously described (Estep *et al.*, MAbs. 2013 Mar-Apr;5(2):270-8). Briefly, ForteBio affinity measurements were performed by loading IgGs on-line onto AHC sensors. Sensors were equilibrated off-line in assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded IgGs were exposed to 100 nM antigen (human, cynomolgus, or mouse TF) for 3 min, afterwards they were transferred to assay buffer for 3 min for off-rate measurement. Alternatively, binding measurements were obtained by loading biotinylated TF monomer on SA sensors followed by exposure to 100 nM antibody Fab in solution. Kinetic data was analyzed and fitted using a 1:1 Langmuir binding model and the

K_D was calculated by dividing the k_{off} by the k_{on}. The K_D values of the TF antibodies measured by the Octet-based experiments are shown in **Table 5**.

[00720] For the Biacore-based measurements, the antibody was covalently coupled to a CM5 or C1 chip using an amine-coupling kit (GE Healthcare Bio-Sciences). Association between the anti-TF antibodies and a five-point three-fold titration of TF-His starting at 25 to 500 nM was measured for 300 sec. Subsequently, dissociation between the anti-TF antibody and TF-His was measured for up to 1800 sec. Kinetic data was analyzed and fitted globally using a 1:1 binding model. The K_D values of the TF antibodies measured by the Biacore-based experiments are shown in **Table 5**.

[00721] As shown in **Table 5**, the affinity of the antibodies for hTF, as indicated by K_D, is between 10^{-7} M and 10^{-11} M. All anti-hTF antibodies are cross-reactive with cTF. In addition, all anti-hTF antibodies from groups 25 and 43 exhibit binding activity to mTF. The anti-hTF antibodies 25G, 25G1, 25G9, and 43D8 are cross-reactive with mTF. There are no other known human or humanized anti-hTF monoclonal antibodies that exhibit binding activity and cross-reactivity to mouse TF, indicating that the antibodies from groups 25 and 43 bind to a novel TF epitope.

Table 5: Antibody Kinetics

Ab	Human K_D (nM) [Biacore]	Cynomolgus K_D (nM) [Biacore]	Mouse K_D (nM) [Biacore]	Human K_D (nM) [ForteBio]	Cynomolgus K_D (nM) [ForteBio]	Mouse K_D (nM) [ForteBio]
1F	0.31	0.26	nd*	1.28	1.43	no binding*
1G	nd*	nd*	nd*	2.20	2.70	nd*
25A	6.20	5.42	nd*	8.45	7.65	263
25A3	0.36	0.21	nd*	1.67	1.36	131
25A5	0.08	0.04	nd*	0.64	0.76	188
25G	23.0	18.0	nd*	21.9	17.5	114
25G1	0.94	0.78	5.4	3.97	4.99	34.2
25G9	13.3	16.4	2.9	35.8	42.9	9.16
29D	nd*	nd*	nd*	3.30	12.0	nd
29E	0.47	5.06	nd*	2.32	15.0	no binding*
39A	0.09	0.08	nd*	0.83	0.57	no binding*
43B	1.75	5.64	nd*	2.40	3.40	161
43B1	0.07	0.12	nd*	0.96	1.05	72.1
43B7	0.14	0.24	nd*	0.86	0.94	360
43D	2.09	5.66	nd*	3.84	4.12	281
43D7	0.06	0.12	21	1.02	1.11	41.4

Ab	Human K_D (nM) [Biacore]	Cynomolgus K_D (nM) [Biacore]	Mouse K_D (nM) [Biacore]	Human K_D (nM) [ForteBio]	Cynomolgus K_D (nM) [ForteBio]	Mouse K_D (nM) [ForteBio]
43D8	0.15	0.39	2.4	1.61	1.96	6.12
43E	1.46	5.69	nd*	2.52	4.07	121
43Ea	1.60	6.42	nd*	2.28	2.71	140
54E	0.42	1.83	nd*	1.59	4.16	no binding*

no binding*: no to weak binding, with no reportable K_D

nd*: not determined

Example 3: Cell-Based Binding Assay

[00722] HCT116 cells with endogenous expression of human TF were obtained from the American Tissue Culture Collection (ATCC, Manassas, VA, USA) and were maintained as recommended. Flp-In-CHO cells expressing mouse TF were generated by transfection of Flp-In-CHO cells as recommended with a pcDNA5/FRT vector (ThermoFisher Scientific) encoding full-length mouse TF with a C-terminal FLAG tag. A mouse TF-positive CHO clone was isolated by limiting dilution in tissue culture-treated 96-well plates.

[00723] Cell-based antibody binding was assessed as previously described in Liao-Chan et al., *PLoS One*, 2015, 10:e0124708, which is incorporated by reference in its entirety. $1.2x10^5$ cells collected with Cellstripper (Mediatech, Manassas, VA, USA) were incubated with a twelve-point 1:3 dilution titration of anti-human TF IgG1 or Fab antibody starting at 250 nM or 100 nM for 2 hr on ice. After 2 washes, cells labeled with IgG1 or Fab were incubated for 30 min on ice with 150 nM of Goat Phycoerythrin (PE) $F(ab')_2$ fragment goat anti-human IgG, Fcγ fragment specific (Jackson ImmunoResearch, West Grove, PA, USA) or FITC-labeled $F(ab')_2$ fragment goat anti–human kappa (SouthernBiotech, Birmingham, AL, USA), respectively. After 2 washes, dead cells were labeled with TO-PRO-3 Iodide (ThermoFisher Scientific) and samples were analyzed on a CytoFLEX flow cytometer (Beckman Coulter, Brea, CA, USA) or Novocyte flow cytometer (ACEA Biosciences, San Diego, CA, USA). The median fluorescence intensities (MFIs) at each dilution were plotted and cell EC_{50}'s were derived using a 4-parameter binding model in Prism (GraphPad, La Jolla, CA, USA). The results of binding of anti-TF antibodies to human TF-positive HCT-116 cells are shown in **Figures 1A and 1B**. The results of binding of anti-TF antibodies to CHO cells expressing mouse TF are shown in **Figures 2A and 2B**.

[00724] All anti-hTF antibodies in **Figures 1A and 1B** exhibit high affinity to human TF-positive HCT-116 cells with an EC_{50} ranging from about 687 pM to about 39 pM. Antibodies

from groups 25 and 43 exhibit binding to CHO cells expressing mouse TF with an EC_{50} ranging from about 455 nM to about 2.9 nM, as shown in **Figures 2A and 2B**. The binding activity to mouse TF is a unique property of the anti-hTF antibodies from groups 25 and 43. This is advantageous for pre-clinical studies of these antibodies with mouse models.

Example 4: Thrombin Generation Assay (TGA)

[00725] The TGA assay was performed using the calibrated-automated-thrombogram (CAT) instrument manufactured and distributed by STAGO. The test method design was equivalent to a standard CAT assay measurement, except that the plasma source was NPP in citrate/CTI. The anti-TF antibodies were titrated at 0, 10, 50 and 100 nM and mixed with normal pooled plasma (NPP) collected in 11 mM citrate supplemented with 100 microgram/mL of corn trypsin inhibitor (citrate/CTI). Relipidated TF was added to a 96-well assay plate, followed by addition of the antibody/NPP mixture. After a 10-min incubation or directly after combining the relipidated TF with antibody/NPP, thrombin generation was initiated by the addition of calcium and the thrombin substrate. The STAGO software was used to report the following parameters: Peak IIa (highest thrombin concentration generated [nM]); Lag Time (time to IIa generation [min]); ETP (endogenous thrombin potential, area under the curve [nM x min]); and ttPeak (time to Peak IIa [min]). Percent peak thrombin generation (% Peak IIa) and percent endogenous thrombin potential (% ETP) in the presence of each antibody relative to a no antibody plasma control on the same plate were also reported.

[00726] The Peak IIa, Lag Time, ETP, ttPeak, % Peak IIa, and % ETP in the presence of each antibody selected from 1F, 25A, 25A3, 25G1, 29E, 39A, 43B1, 43D7, 43Ea, and 54E without antibody incubation prior to addition of calcium and thrombin substrate are shown in **Table 6**. The Peak IIa, Lag Time, ETP, ttPeak, % Peak IIa, and % ETP in the presence of each antibody selected from 1F, 25A, 25A3, 25G1, 29E, 39A, 43B1, 43D7, 43Ea, and 54E with 10 min antibody incubation prior to addition of calcium and thrombin substrate are shown in **Table** 7. The % Peak IIa in the presence of titrations of anti-TF antibodies without antibody incubation prior to addition of calcium and thrombin substrate is plotted in **Figure 3A**. The % Peak IIa in the presence of titrations of anti-TF antibodies with 10 min antibody incubation prior to addition of calcium and thrombin substrate is plotted in **Figure 3B**.

[00727] The % Peak IIa is greater than 90% in the presence of antibodies from group 25, including 25A, 25A3, and 25G1. The % ETP is greater than 100% in the presence of antibodies from group 25, including 25A, 25A3, and 25G1. The % Peak IIa is greater than

40% in the presence of antibodies from group 43, including 43B1, 43D7, and 43Ea. The % ETP is greater than 90% in the presence of antibodies from group 43, including 43B1, 43D7, and 43Ea.

[00728] This data indicates that antibodies from groups 25 and 43 allow normal thrombin generation, and therefore are not inhibitors of thrombin generation.

Table 6: Thrombin Generation Assay without Antibody Pre-Incubation

Plate	Antibody	Ab conc. (nM)	Peak IIa (nM)	Lag Time (min)	ETP (nM•min)	ttPeak (min)	% Peak IIa	% ETP
1	1F	100	29	25.9	*	37.9	7	*
		50	32	27.2	*	36.8	8	*
		10	83	12.1	1395	19.8	21	58
1	25A	100	398	4.4	2610	7.1	99	108
		50	399	4.2	2621	7.1	99	108
		10	403	4.1	2555	6.8	100	106
1	25A3	100	405	3.9	2493	6.5	100	103
		50	404	3.9	2495	6.6	100	103
		10	401	4.2	2550	7.3	99	106
1	25G1	100	416	4.5	2626	7.1	103	109
		50	416	4.5	2680	7.1	103	111
		10	417	4.5	2635	7.0	103	109
1	29E	100	99	17.3	*	26.4	25	*
		50	107	14.4	1747	22.7	26	72
		10	266	5.7	2189	10.0	66	91
1	39A	100	26	28.9	*	40.1	6	*
		50	30	30.5	*	40.0	7	*
		10	82	12.1	1330	19.6	20	55
1	Plasma ctrl.	NA	403	4.1	2417	6.8	100	100
2	43B1	100	221	5.2	2167	10.6	64	100
		50	232	5.2	2195	10.3	67	101
		10	299	4.9	2288	8.9	87	105
2	43D7	100	179	5.4	2094	11.8	52	96
		50	202	5.3	2116	11.1	58	97
		10	287	5.0	2263	9.0	83	104
2	43Ea	100	300	4.6	2219	8.1	87	102
		50	307	4.6	2234	8.1	89	103
		10	328	5.0	2329	8.3	95	107
2	54E	100	68	14.8	1175	23.9	20	54
		50	154	8.9	2019	15.9	44	93
		10	307	5.7	2307	9.6	89	106
2	Isotype	100	348	5.0	2415	8.3	101	111
		50	347	5.0	2360	8.0	101	109
		10	346	4.3	2260	7.6	100	104
2	Plasma ctrl.	NA	345	4.7	2171	7.8	100	100

* Groups with "No Tail Found" Errors when the software cannot calculate the ETP.

Table 7: Thrombin Generation Assay with 10 min Antibody Pre-Incubation

Plate	Antibody	Ab conc. (nM)	Peak IIa (nM)	Lag Time (min)	ETP (nM•min)	ttPeak (min)	% Peak IIa	% ETP
1	1F	100	17	30.3	*	42.0	7	*
		50	20	27.6	*	38.9	7	*
		10	27	18.8	540	28.6	10	31
1	25A	100	285	3.3	1898	6.7	108	110
		50	284	3.3	1887	6.6	107	110
		10	277	3.3	1842	6.7	105	107
1	25A3	100	277	3.1	1785	6.3	105	104
		50	275	3.2	1824	6.4	104	106
		10	278	3.2	1827	6.6	105	106
1	25G1	100	293	3.3	1827	6.4	111	106
		50	301	3.3	1853	6.3	114	108
		10	302	3.3	1891	6.3	114	110
1	29E	100	68	15.1	1098	25.3	26	64
		50	70	14.2	1168	24.3	27	68
		10	78	10.4	1254	20.2	30	73
1	39A	100	17	28.0	*	40.2	7	*
		50	17	28.4	346	38.9	7	20
		10	25	20.8	482	30.7	9	28
1	Plasma ctrl.	NA	264	3.3	1720	6.8	100	100
2	43B1	100	152	3.2	1712	9.3	58	98
		50	163	3.2	1797	9.0	62	103
		10	200	3.2	1788	8.1	76	103
2	43D7	100	124	3.6	1656	10.3	47	95
		50	128	3.6	1677	10.3	49	96
		10	178	3.6	1745	8.8	68	100
2	43Ea	100	239	2.9	1820	6.9	91	104
		50	227	2.9	1791	7.1	87	103
		10	247	3.2	1825	7.0	94	105
2	54E	100	29	22.1	580	32.3	11	33
		50	35	18.3	680	28.4	13	39
		10	112	6.1	1530	13.4	43	88
2	Isotype	100	288	3.2	1888	6.6	110	108
		50	285	3.2	1879	6.6	109	108
		10	273	3.2	1804	6.6	104	104
2	Plasma ctrl.	NA	262	3.2	1742	6.9	100	100

* Groups with "No Tail Found" Errors when the software cannot calculate the ETP.

Example 5: FXa Conversion Assay

[00729] To evaluate the ability of TF:FVIIa to convert FX into FXa in the presence of human antibodies against TF, $5x10^4$ MDA-MB-231 cells (ATCC, Manassas, VA, USA) were plated into tissue culture-treated black 96-well plates (Greiner Bio-One, Monroe, NC, USA). After removal of the cell culture media and addition of a final concentration of 200 nM of FX

in a HEPES buffer with 1.5 mM $CaCl_2$, cells were incubated with a titration of the antibodies for 15 min at 37°C. Upon reconstitution of the binary TF:FVIIa complex with a final concentration of 20 nM of FVIIa, cells were incubated for 5 min at 37°C. After quenching the reaction with ethylenediaminetetraacetic acid (EDTA), generated FXa was measured with 50 µM of SN-7 6-amino-1-naphthalenesulfonamide-based fluorogenic substrate (Haematologic Technologies, Essex Junction, VT, USA) on an Envision plate reader equipped with an Umbelliferone 355 excitation filter, an Umbelliferone 460 emission filter, and a LANCE/DELFIA top mirror (Perkin Elmer, Waltham, MA, USA). FXa conversion percentages (% FXa) in the presence of an anti-TF antibody titration relative to a no-antibody control are summarized in **Table 8** and plotted in **Figures 4A and 4B**.

[00730] The FXa conversion percentage ranges from about 78% to about 120% in presence of different concentrations of antibodies from groups 25 and 43, including 25A, 25A3, 25G, 25G1, 25G5, 25G9, 43B, 43B1, 43B7, 43D, 43D7, 43D8, 43E, and 43Ea.

[00731] This data indicates that anti-TF antibodies from groups 25 and 43 do not inhibit TF:FVIIa mediated FXa conversion from FX. This data also indicates that anti-TF antibodies from groups 25 and 43 have a human TF binding site that is distinct from the human TF binding site bound by FX.

Table 8: % FXa conversion

Antibody	% FXa			
	12.5 nM	**25 nM**	**50 nM**	**100 nM**
1F	49	40	37	38
1G	55	48	41	41
25A	87	81	94	89
25A3	89	89	93	96
25A5	82	85	78	89
25G	99	109	102	116
25G1	101	96	99	108
25G9	98	97	104	117
29D	85	77	75	75
29E	81	68	63	66
39A	39	38	37	39
43B	113	109	105	105
43B1	106	108	108	112
43B7	113	104	108	112
43D	115	109	104	106
43D7	110	103	102	103
43D8	120	112	107	111

Antibody	% FXa			
	12.5 nM	25 nM	50 nM	100 nM
43E	85	89	97	98
43Ea	108	103	106	101
54E	53	44	41	42
5G9	37	33	30	30
Isotype ctrl	93	95	89	97

Example 6: FVIIa Competition Assay

[00732] FVII-Fc conjugates were generated using Alexa Fluor 488 5-sulfo-dichlorophenol esters (ThermoFisher Scientific). Excess Alexa Fluor dye was removed from the conjugate preparations by gel filtration (ThermoFisher Scientific).

[00733] To evaluate competition between FVIIa and the human antibodies against TF, TF-positive MDA-MB-231 cells (ATCC, Manassas, VA, USA) were first incubated for 1 hr on ice with a titration of the human antibodies against TF. Subsequently, a final concentration of 20 nM of FVII-Fc conjugated to Alexa488 was added to the antibody cell mixture. After another 1 hr incubation on ice, cells were washed, stained with a viability dye, and analyzed by flow cytometry. The Alexa488 fluorescence data from viable cells was summarized using median fluorescence intensity. FVII-Fc binding was summarized with % FVII-Fc binding = $[MFI_{\text{antibody labeled cells}} - MFI_{\text{unstained cells}}] / [MFI_{\text{IgG1 control labeled cells}} - MFI_{\text{unstained cells}}]$. Percentage of FVIIa binding (% FVIIa) in the presence of an anti-TF antibody titration relative to a no-antibody control is summarized in **Table 9** and plotted in **Figures 5A and 5B**.

[00734] The FVIIa binding percentage ranges from about 76% to about 102% in the presence of antibodies of different concentrations from groups 25 and 43, including 25A, 25A3, 25G, 25G1, 25G5, 25G9, 43B, 43B1, 43B7, 43D, 43D7, 43D8, 43E, and 43Ea.

[00735] This data indicates that anti-TF antibodies from groups 25 and 43 do not compete for binding to human TF with FVIIa. This data also indicates that anti-TF antibodies from groups 25 and 43 have a human TF binding site that is distinct from the human TF binding site bound by FVIIa.

Table 9: Competition of Anti-TF Antibody with FVIIa

Antibody	% FVIIa			
	9.25 nM	28 nM	83 nM	250 nM
1F	7	7	7	6
1G	7	7	7	6
25A	100	101	97	98

Antibody	% FVIIa			
	9.25 nM	28 nM	83 nM	250 nM
25A3	90	87	88	87
25A5	76	79	77	80
25G	97	96	93	92
25G1	97	93	94	95
25G9	93	93	91	89
29D	6	4	3	3
29E	5	3	2	2
39A	2	2	2	2
43B	99	95	93	91
43B1	97	95	93	91
43B7	98	98	97	97
43D	102	100	98	94
43D7	101	102	100	101
43D8	100	99	98	96
43E	95	92	91	89
43Ea	93	91	92	89
54E	11	3	3	2
Isotype	99	98	97	99

Example 7: TF Signaling Assay

[00736] IL-8 and GM-CSF protein levels were measured as described previously in Hjortoe et al., *Blood*, 2004, 103:3029-3037. TF-positive MDA-MB-231 cells (ATCC, Manassas, VA, USA) that underwent a 2 hr serum starvation with Leibovitz's L-15 medium were incubated with an 8-point 1:2.5 titration starting at 100 nM of anti-TF antibody. After 30 min at 37°C, FVIIa (NovoSeven RT, Novo Nordisk, Bagsvaerd, Denmark) was added to the cells at a final concentration of 20 nM. 5 hr later cell culture supernatants were harvested and analyzed by ELISA for IL8 or GM-CSF as recommended (R&D Biosystems, Minneapolis, MN, USA). A standard curve using recombinant IL8 or GM-CSF (R&D Biosystems, Minneapolis, MN, USA) was used in Prism to calculate cytokine concentration in the cell culture supernatants. Percent IL8 and GM-CSF (% IL8 and % GM-CSF) at reported antibody concentration were calculated relative to a no antibody control. The concentration of IL8 with the anti-TF antibody titration is plotted in **Figures 6A and 6B** and the % IL8 at different antibodies concentrations are shown in **Table 10**. The concentration of GM-CSF with the anti-TF antibody titration is plotted in **Figures 6C and 6D** and the % IL8 at different antibodies concentrations are shown in **Table 11**.

[00737] IL8 concentrations were reduced by more than 75% in the presence of the anti-TF antibodies at concentrations greater than or equal to 6.4 nM. GM-CSF concentrations were

reduced by more than 60% in the presence of the anti-TF antibodies at concentrations greater than or equal to 6.4 nM.

[00738] This data indicates that all tested anti-TF antibodies inhibit FVIIa-dependent TF signaling.

Table 10: Inhibition of IL8

Antibody	% IL8				
	100 nM	**40 nM**	**16 nM**	**6.4 nM**	**2.56 nM**
1F	2	2	2	3	18
1G	2	2	3	4	26
25A	9	8	10	11	43
25A3	8	8	8	9	47
25A5	6	7	7	14	70
25G	9	10	16	22	60
25G1	9	8	9	12	46
25G9	13	14	15	22	51
29D	1	2	2	6	27
29E	2	2	2	5	33
39A	3	2	2	6	52
43B	4	4	5	11	50
43B1	5	5	6	12	56
43B7	4	4	8	15	55
43D	5	5	7	21	58
43D7	5	4	5	11	48
43D8	5	5	5	21	67
43E	5	5	6	15	49
43Ea	6	6	6	14	52
54E	2	2	3	8	48
Control	106	108	84	88	90

Table 11: Inhibition of GM-CSF

Antibody	% GM-CSF				
	100 nM	**40 nM**	**16 nM**	**6.4 nM**	**2.56 nM**
1F	6	6	6	8	27
1G	7	7	7	9	34
25A	22	19	22	24	57
25A3	20	19	19	20	59
25A5	12	15	14	18	72
25G	19	18	32	39	77
25G1	17	16	17	18	48
25G9	25	26	26	34	60
29D	5	6	7	15	38
29E	6	6	5	9	33
39A	7	5	5	8	42
43B	14	13	12	21	59
43B1	11	11	13	16	50
43B7	11	11	13	17	50
43D	12	11	13	24	56
43D7	10	10	9	15	45

Antibody	% GM-CSF				
	100 nM	40 nM	16 nM	6.4 nM	2.56 nM
43D8	12	11	11	24	57
43E	14	15	15	21	61
43Ea	14	15	14	21	65
54E	5	5	5	10	38
Control	105	111	94	86	88

Example 8: Antibody Competition Assay

[00739] Alexa Fluor antibodies were generated using Alexa Fluor 488 5-sulfo-dichlorophenol esters (ThermoFisher Scientific). Excess Alexa Fluor dye was removed from the antibody dye conjugate preparations by gel filtration (ThermoFisher Scientific).

[00740] To evaluate competition between a first human antibody against TF and 25A, TF-positive A431 cells (ATCC, Manassas, VA, USA) were first incubated for 1 hr on ice with a titration of the first human antibody against TF. Subsequently, a final concentration of 20 nM of 25A conjugated to Alexa488 was added to the antibody cell mixture. After another 1 hr incubation on ice, cells were washed, stained with a viability dye, and analyzed by flow cytometry. The Alexa488 fluorescence data from viable cells was summarized using median fluorescence intensity. 25A binding was summarized with % 25A binding = [$MFI_{\text{antibody labeled cells}} - MFI_{\text{unstained cells}}$] / [$MFI_{\text{IgG1 control labeled cells}} - MFI_{\text{unstained cells}}$].

[00741] To evaluate competition between a first human antibody against TF and 43Ea, TF-positive A431 cells (ATCC, Manassas, VA, USA) were first incubated for 1 hr on ice with a titration of the first human antibody against TF. Subsequently, a final concentration of 20 nM of 43Ea conjugated to Alexa488 was added to the antibody cell mixture. After another 1 hr incubation on ice, cells were washed, stained with a viability dye, and analyzed by flow cytometry. The Alexa488 fluorescence data from viable cells was summarized using median fluorescence intensity. 43Ea binding was summarized with % 43Ea binding = [$MFI_{\text{antibody labeled cells}} - MFI_{\text{unstained cells}}$] / [$MFI_{\text{IgG1 control labeled cells}} - MFI_{\text{unstained cells}}$].

[00742] % 25A binding and % 43Ea binding are shown in **Table 12**. Antibodies from group 25 and group 43 reduced the % 25A binding and % 43Ea binding to less than 10%.

[00743] This data indicates that antibodies of group 25 and antibodies of group 43 compete with each other for binding to human TF, and may bind the same or an overlapping epitope of human TF.

Table 12: Competition of Anti-TF Antibody with Antibody Clone 25A or 43Ea

Antibody (100 nM)	% 25A binding	% 43Ea binding
1F	95	77
1G	75	58
25A	3	1

Antibody (100 nM)	% 25A binding	% 43Ea binding
25G	7	3
29D	70	64
29E	96	85
39A	99	96
43B	0	0
43D	0	0
43E	0	0
54E	99	96
Isotype	100	100

Example 9: Cell Viability Assay

[00744] To evaluate internalization of the anti-TF antibodies, a cytotoxicity assay was conducted. Briefly, cells were plated in 384-well plates (Greiner Bio-One, Monroe, NC, USA) at $4x10^3$ cells per well in 40 µl of media. Antibodies and secondary anti-human Fc antibodies conjugated to the tubulin inhibitor mono-methyl auristatin F (MMAF) (Moradec, San Diego, CA, USA) were serially diluted starting at 5 and 30 nM, respectively. Plates were incubated for 3 days, followed by lysis in CellTiter-Glo (CTG) assay reagent (Promega, Madison, WI, USA). CTG luminescence was measured on an Envision plate reader and the mean and standard deviation of 4 replicates graphed in Prism. For each anti-TF antibody, the IC_{50} and its associated 95% confidence interval were calculated in Prism using a 4-parameter binding model.

[00745] **Figures 7A and 7B** show the cell viability as indicated by the level of luminescence and the calculated IC_{50}.

[00746] This data indicates that all anti-TF antibodies tested from groups 1, 25, 29, 39, 43, and 54 were effective in reducing the viability of TF-positive A431 cells.

Example 10: Thrombin Generation Assay (TGA)

[00747] The TGA assay was performed using the calibrated-automated-thrombogram (CAT) instrument manufactured and distributed by STAGO. The test method design was equivalent to a standard CAT assay measurement, except that the plasma source was normal pooled plasma (NPP) in citrate supplemented with corn trypsin inhibitor (citrate/CTI). The anti-TF antibodies were titrated at 0, 10, 50 and 100 nM and mixed with normal pooled plasma (NPP) collected in 11 mM citrate supplemented with 100 microgram/mL of corn trypsin inhibitor (citrate/CTI). Relipidated TF was added to a 96-well assay plate, followed by addition of the antibody/NPP mixture. After a 10-min incubation or directly after combining the relipidated TF with antibody/NPP, thrombin generation was initiated by the addition of calcium and the thrombin substrate. The STAGO software was used to report the following parameters: Peak IIa (highest thrombin concentration generated [nM]); Lag Time

(time to IIa generation [min]); ETP (endogenous thrombin potential, area under the curve [nM x min]); and ttPeak (time to Peak IIa [min]). Percent peak thrombin generation (% Peak IIa) and percent endogenous thrombin potential (% ETP) in the presence of each antibody relative to a no antibody plasma control on the same plate were also reported.

[00748] The Peak IIa, Lag Time, ETP, ttPeak, % Peak IIa, and % ETP in the presence of each antibody selected from 25A, 25A3, 25A5, 39A, 43B1, 43D7, 43Ea, and M1593 without antibody incubation prior to addition of calcium and thrombin substrate are shown in **Table 37**. The Peak IIa, Lag Time, ETP, ttPeak, % Peak IIa, and % ETP in the presence of each antibody selected from 25A, 25A3, 25A5, 39A, 43B1, 43D7, 43Ea, and M1593 with 10 min antibody incubation prior to addition of calcium and thrombin substrate are shown in **Table 38**. The % Peak IIa in the presence of titrations of anti-TF antibodies without antibody incubation prior to addition of calcium and thrombin substrate is plotted in **Figure 8A**. The % Peak IIa in the presence of titrations of anti-TF antibodies with 10 min antibody incubation prior to addition of calcium and thrombin substrate is plotted in **Figure 8B**. The M1593 antibody has a VH sequence of SEQ ID NO:821 and VL sequence of SEQ ID NO:822.

[00749] The % Peak IIa is 95% or greater in the presence of antibodies from group 25, including 25A, 25A3, and 25A5 without antibody pre-incubation. The % Peak IIa is 100% or greater in the presence of antibodies from group 25, including 25A, 25A3, and 25A5 with 10 min antibody pre-incubation. The % ETP is 99% or greater in the presence of the tested antibodies from group 25.

[00750] The % Peak IIa is greater than 50% but equal to or less than 96% in the presence of antibodies from group 43, including 43B1, 43D7, and 43Ea and anti-TF antibody M1593 without antibody pre-incubation. The % Peak IIa is greater than 40% but equal to or less than 93% in the presence of antibodies from group 43, including 43B1, 43D7, and 43Ea and anti-TF antibody M1593 with 10 min antibody pre-incubation. The % ETP is 92% or greater in the presence of the tested antibodies from group 43 and M1593 antibody.

[00751] This data indicates that antibodies from groups 25 and 43 allow normal thrombin generation, and therefore are not inhibitors of thrombin generation. The percent peak thrombin generation (% Peak IIa) is greater in the presence of antibodies of group 25 compared to antibodies of group 43 and M1593 antibody.

Table 37: Thrombin Generation Assay without Antibody Pre-Incubation

Plate	Antibody	Ab conc. (nM)	Peak IIa (nM)	Lag Time (min)	ETP (nM•min)	ttPeak (min)	% Peak IIa	% ETP
3	25A	100	334	5.0	2390	8.7	96	105

Plate	Antibody	Ab conc. (nM)	Peak IIa (nM)	Lag Time (min)	ETP (nM•min)	ttPeak (min)	% Peak IIa	% ETP
		50	335	5.0	2380	8.7	96	104
		10	333	5.0	2387	8.6	95	104
3	25A3	100	343	5.0	2405	8.4	98	105
		50	349	5.0	2433	8.4	100	106
		10	350	5.0	2426	8.0	100	106
3	25A5	100	342	5.1	2393	8.5	98	105
		50	344	4.8	2317	8.1	98	101
		10	343	4.7	2270	8.0	98	99
3	39A	100	22	38.1	*	48.3	6	*
		50	29	33.1	*	43.2	8	*
		10	84	12.4	1332	20.7	24	58
3	43B1	100	223	4.8	2111	10.0	64	92
		50	239	4.9	2134	9.9	68	93
		10	303	5.1	2318	9.1	87	101
3	43D7	100	186	5.6	2105	12.2	53	92
		50	216	5.5	2183	11.3	62	96
		10	301	5.4	2338	9.3	86	102
3	43Ea	100	302	5.1	2347	9.1	87	103
		50	308	5.1	2392	8.8	88	105
		10	336	4.5	2305	7.8	96	101
3	M1593	100	242	5.1	2235	10.4	69	98
		50	270	5.1	2282	9.8	77	100
		10	322	5.1	2368	8.8	92	104
3	Isotype	100	347	5.0	2319	8.1	99	101
		50	348	5.0	2324	8.1	100	102
		10	348	5.0	2326	8.3	100	102
3	Plasma ctrl.	NA	349	4.7	2285	7.7	100	100

* Groups with "No Tail Found" Errors when the software cannot calculate the ETP.

Table 38: Thrombin Generation Assay with 10 min Antibody Pre-Incubation

Plate	Antibody	Ab conc. (nM)	Peak IIa (nM)	Lag Time (min)	ETP (nM•min)	ttPeak (min)	% Peak IIa	% ETP
3	25A	100	274	3.3	1879	7.0	103	106
		50	279	3.3	1876	7.0	105	106
		10	280	3.6	1872	7.0	105	106
3	25A3	100	290	3.4	1906	6.8	109	108
		50	291	3.6	1925	6.8	109	109
		10	287	3.3	1886	6.8	108	107
3	25A5	100	286	3.7	1883	7.0	107	107
		50	277	3.7	1803	7.0	104	102
		10	278	3.7	1808	7.0	104	102
3	39A	100	17	32.1	*	43.2	6	*
		50	21	29.0	*	39.7	8	*
		10	30	20.9	*	30.8	11	*
3	43B1	100	156	3.6	1701	9.3	58	96
		50	148	3.3	1667	9.6	55	94
		10	203	3.7	1776	8.2	76	101
3	43D7	100	120	3.7	1633	10.8	45	92

		50	131	3.7	1724	10.4	49	98
		10	197	3.7	1784	8.8	74	101
3	43Ea	100	244	3.3	1817	7.3	91	103
		50	246	3.3	1833	7.3	92	104
		10	247	3.3	1779	7.1	93	101
3	M1593	100	160	3.7	1737	9.4	60	98
		50	165	3.7	1739	9.3	62	99
		10	224	3.7	1807	8.0	84	102
3	Isotype	100	279	3.7	1829	7.2	105	104
		50	283	3.7	1839	7.0	106	104
		10	279	3.7	1814	7.1	105	103
3	Plasma ctrl.	NA	267	3.7	1766	7.2	100	100

* Groups with "No Tail Found" Errors when the software cannot calculate the ETP.

Example 11: Synthesis of Antibody-Drug Conjugates (ADCs)

[00752] Antibody-Drug Conjugates (ADCs) were synthesized as described in Behrens et al., *Mol Pharm*, 2015, 12:3986-98. 5 mg/mL of antibody in phosphate-buffered saline (PBS), pH 7.4 was reduced with 2.5 molar equivalents of Tris(2-carboxyehtyl)phosphine. After 2 hr at 37ºC, the partially reduced antibody was cooled to room temperature and conjugated for 1 hr to 3 to 5 molar equivalents of MC-vc-PAB-MMAE (maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl-monomethyl auristatin E). The reaction was buffer exchanged into PBS to remove small molecular weight reagents. The drug-antibody ratio (DAR) of the resulting ADCs was 3-4. The DAR was determined with the following formula: Absorbance (248 nm) / Absorbance (280 nm) = (n x $Ex_{PAB[248\ nm]}$ + $Ex_{antibody[248\ nm]}$) / (n x $Ex_{PAB[280\ nm]}$ + $Ex_{antibody[280\ nm]}$) with n as a variable for the DAR and Ex as the extinction coefficients of PAB and the antibody. Hydrophobic interaction chromatography and size exclusion chromatography were used to corroborate the absorbance-based DAR estimation and to ensure the ADC preparation was at least 95% monomeric, respectively.

Example 12: Cytotoxicity Assays of Antibody-Drug Conjugates (ADCs)

[00753] To evaluate cytotoxicity of ADCs, TF-positive A431 and HPAF-II cells were plated in 384-well plates (Greiner Bio-One, Monroe, NC, USA) at $4x10^3$ cells per well in 40 µL of media. Anti-TF antibodies conjugated to MC-vc-PAB-MMAE were serially diluted starting at 5 nM. Plates were incubated for 3 to 4 days, followed by lysis in CellTiter-Glo (CTG) assay reagent (Promega, Madison, WI, USA). CTG luminescence was measured on an Envision plate reader and the mean and standard deviation of 4 replicates were graphed in Prism. For each ADC, the IC_{50} and its associated 95% confidence interval were calculated in Prism using a 4-parameter binding model.

[00754] **Figures 9A and 9B** show the cell viability as indicated by CTG luminescence and the calculated IC_{50} in TF-positive A431 and HPAF-II cells, respectively. ADCs comprising anti-TF antibodies from groups 25, 43, and 39 conjugated to MC-vc-PAB-MMAE resulted in cytotoxicity in TF-positive A431 and HPAF-II cells.

[00755] This data indicates that anti-TF antibody-drug conjugates reduced the viability of TF-positive cells *in vitro*.

Example 13: Xenograft Cell Line Studies

[00756] Xenograft studies in immune compromised mice were performed to evaluate the efficacy of the ADCs *in vivo*. The TF-positive A431 epidermoid carcinoma and the HPAF-II pancreatic carcinoma xenografts were implanted subcutaneously in the flank of athymic nude mice (Charles River Laboratories, Wilmington, MA). Animals were randomized when tumors reached an average size of 150-200 mm^3 and treated with 5 mg/kg of the indicated ADC or vehicle (PBS) intraperitoneally (i.p.) once weekly for 3 weeks. Body weight and tumor size assessments were performed bi-weekly. Animals were removed from study and euthanized once tumor size reached 1200 mm^3 or skin ulceration was evident.

[00757] **Figures 10A and 10B** show the tumor size of vehicle-treated, IgG1 ADC-treated, and anti-TF ADC-treated groups in the TF-positive A431 epidermoid carcinoma and the HPAF-II pancreatic carcinoma xenograft models, respectively. ADCs comprising anti-TF antibodies 25A and 43Ea conjugated to MC-vc-PAB-MMAE decreased the tumor size in both xenograft models compared to the vehicle-treated or IgG1 ADC-treated groups.

[00758] This data indicates that anti-TF antibody-drug conjugates 25A-vc-MMAE and 43Ea-vc-MMAE were effective in reducing the tumor size *in vivo*.

Example 14: Studies of Patient-Derived Xenograft (PDX) Model

[00759] A TF-positive head and neck cancer patient-derived xenograft model was generated in athymic nude mice (Envigo, Indianapolis, IN) to further evaluate the efficacy of the ADCs *in vivo*. Tumors were passaged in stock animals and harvested for re-implantation. Study animals were implanted unilaterally on the left flank with tumor fragments and were randomized to treatment group when tumors reached an average size of 150-200 mm^3. Animals were treated with 5 mg/kg of the indicated ADC intraperitoneally (i.p.) once weekly for 2 weeks. Body weight and tumor size assessments were performed bi-weekly. Animals were removed from study and euthanized once tumor size reached 1200 mm^3 or skin ulceration was evident.

[00760] **Figure 11** shows the tumor size of IgG1 ADC-treated and anti-TF ADC-treated groups in the head and neck cancer patient-derived xenograft model. ADCs comprising anti-TF antibodies 25A and 43Ea conjugated to MC-vc-PAB-MMAE decreased the tumor size in the cancer patient-derived xenograft model compared to the IgG1 ADC-treated group.

[00761] This data indicates that anti-TF antibody-drug conjugates 25A-vc-MMAE and 43Ea-vc-MMAE were effective in reducing the tumor size in a cancer patient-derived xenograft model *in vivo*.

Example 15: Binding Affinity Assay For Pig TF

[00762] The ability of certain antibodies was tested for binding to pig TF. For pig TF Biacore-based measurements, a given anti-TF antibody was captured by an anti-human IgG antibody covalently coupled to a CM5 chip (GE Healthcare Bio-Sciences). Association between the anti-TF antibodies and a five-point three-fold titration of pig TF-His starting at 100 nM was measured for 180 to 240 sec. Subsequently, dissociation between the anti-TF antibody and TF-His was measured for 1800 sec. Kinetic data was analyzed and fitted globally using a 1:1 binding model. The K_D values of the indicated TF antibodies measured by the Biacore-based experiments are shown in **Table 40**.

[00763] As shown in **Table 40**, anti-hTF antibodies from groups 25 and 43, 25G9 and 43D8, exhibit binding activity and cross-reactivity to pig TF.

Table 40: Antibody kinetics for pig TF

Ab	Pig K_D (nM) [standard deviation]
1G	no binding*
29D	no binding*
25G9	3.31 [0.08]
43D8	12.9 [0.03]

no binding*: no binding to weak binding, with no reportable K_D

Example 16: Cell-Based Binding Assay

[00764] Human TF-positive cancer cell lines A431 and MDA-MB-231 and *Macaca mulatta* TF-positive cell line RF/6A were obtained from the American Tissue Culture Collection (ATCC, Manassas, VA, USA) and were maintained as recommended.

[00765] Cell-based antibody binding was assessed as previously described in Liao-Chan et al., *PLoS One*, 2015, 10:e0124708, which is incorporated by reference in its entirety. $1.2x10^5$ cells collected with Cellstripper (Mediatech, Manassas, VA, USA) were incubated with a twelve-point 1:3 dilution titration of anti-human TF IgG1 antibody starting at 250 nM or 100

nM for 2 hr on ice. After 2 washes, cells labeled with IgG1 antibody were incubated for 30 min on ice with 150 nM of Goat Phycoerythrin (PE) $F(ab')_2$ fragment goat anti-human IgG, Fcγ fragment specific (Jackson ImmunoResearch, West Grove, PA, USA) or FITC-labeled $F(ab')_2$ fragment goat anti–human kappa (SouthernBiotech, Birmingham, AL, USA), respectively. After 2 washes, dead cells were labeled with TO-PRO-3 Iodide (ThermoFisher Scientific) and samples were analyzed on a CytoFLEX flow cytometer (Beckman Coulter, Brea, CA, USA) or Novocyte flow cytometer (ACEA Biosciences, San Diego, CA, USA). The median fluorescence intensities (MFIs) at each dilution were plotted and cell EC_{50}'s were derived using a 4-parameter binding model in Prism (GraphPad, La Jolla, CA, USA). Antibodies that does not substantially affect FX conversion (i.e. 25A, 25A3, 25G1, 43B1, 43D7 and 43Ea) and antibodies that inhibited FX conversion by more than 50 % (i.e. 1F, 29E, 39A and 54E) were included in the assay. The results of binding of anti-TF antibodies to human TF-positive A431 cells are shown in **Figure 12A**. The results of binding of anti-TF antibodies to human TF-positive MDA-MB-231 cells are shown in **Figure 12B**.

[00766] All tested anti-hTF antibodies in **Figures 12A** exhibit high affinity to human TF-positive A431 cells with an EC_{50} ranging from about 1.50 nM to about 0.34 nM. An IgG1 isotype control did not bind A431 cells (no binding, nb). All tested anti-hTF antibodies in **Figures 12B** exhibit high affinity to human TF-positive MDA-MB-231 cells with an EC_{50} ranging from about 1.50 nM to about 0.06 nM. An IgG1 isotype control did not bind MDA-MB-231 cells (no binding, nb).

[00767] As described in **Example 2** and shown in **Table 5**, the binding affinity of anti-hTF antibodies was evaluated on TF from cynomolgus monkey (*Macaca fascicularis*). The protein sequences of *Macaca fascicularis* TF and *Macaca mulatta* TF are identical. The binding of the TF-specific antibodies to cynomolgus monkey was confirmed using the *Macaca mulatta* RF/6A cell line as shown in **Table 42**. All tested anti-hTF antibodies exhibit high affinity to TF-positive *Macaca mulatta* RF/6A cells with an EC_{50} ranging from about 1.28 nM to about 0.17 nM. The ability of the anti-TF antibodies to bind to cynomolgus monkey is advantageous for toxicology studies of these antibodies with nonhuman primate models.

Table 42: Binding of anti-TF antibodies to *Macaca mulatta* RF/6A cells

Ab	RF/6A EC50 (nM)	RF/6A 95% CI
1F	0.17	0.14 to 0.21
25A	0.43	0.37 to 0.50

Ab	RF/6A EC50 (nM)	RF/6A 95% CI
25A3	0.27	0.24 to 0.30
25G1	0.27	0.23 to 0.32
29E	0.53	0.46 to 0.61
39A	0.27	0.23 to 0.32
43B1	0.47	0.40 to 0.55
43D7	0.41	0.35 to 0.49
43Ea	0.92	0.83 to 1.01
54E	1.28	1.16 to 1.41

Example 17: Binding Assay to *E. Coli*-Derived TF

[00768] *E. coli*-derived TF was expressed as a fusion between the OmpA signal sequence and TF ECD-His6, and purified by affinity and anion exchange chromatography. The binding of anti-TF antibodies 1F, 25A, 25A3, 25G1, 29E, 39A, 43B1, 43D7, 43Ea, and 54E to Expi293- or *E. coli*-derived TF was determined by protein ELISA studies. Plates coated with Expi293- or *E. coli*-derived TF-His were incubated with increasing concentrations of antibodies. After incubation with an HRP-conjugated secondary antibody (Jackson Immunoresearch), luminescence data were obtained and used to calculate an EC_{50} with 95 % confidence intervals using Prism. The EC_{50}'s and 95% confidence intervals of the antibodies are listed in **Table 43**.

Table 43: Binding of anti-TF antibodies to Expi293- or *E. coli*-derived TF

Ab	Expi293-derived TF protein EC50 (nM)	Expi293-derived TF protein 95% CI	*E.coli*-derived TF protein EC50 (nM)	*E.coli*-derived TF protein 95% CI
1F	0.41	0.37 to 0.46	0.32	0.30 to 0.34
25A	0.54	0.49 to 0.60	0.35	0.30 to 0.41
25A3	0.47	0.39 to 0.56	0.36	0.31 to 0.42
25G1	0.42	0.36 to 0.47	0.31	0.29 to 0.33
29E	0.98	0.78 to 1.24	0.68	0.39 to 1.26
39A	0.45	0.39 to 0.53	0.34	0.28 to 0.40
43B1	0.57	0.53 to 0.61	0.39	0.34 to 0.44
43D7	0.71	0.62 to 0.80	0.43	0.35 to 0.53
43Ea	0.74	0.68 to 0.81	0.46	0.40 to 0.53
54E	0.96	0.73 to 1.29	0.38	0.22 to 0.62

[00769] All tested anti-hTF antibodies exhibit high affinity to *E. coli*-derived TF with an EC_{50} ranging from about 0.68 nM to about 0.31 nM, which is comparable to the binding affinity of the antibodies to Expi293-derived TF (about 0.98 nM to 0.41 nM). These results indicate that although the anti-TF antibodies were selected against glycosylated TF from a human cell line, the antibodies can bind to *E. coli*-derived TF with similar affinity when measured by protein ELISA.

Example 18: Thrombin Generation Assay (TGA)

[00770] TGA assay was performed using the calibrated-automated-thrombogram (CAT) instrument manufactured and distributed by STAGO (Diagnostica Stago SAS, Asnières sur Seine, France). *See* Samama et al., *Thromb Res*, 2012, 129:e77-82, which is incorporated by reference in its entirety. The test method design was equivalent to a standard CAT assay measurement, except that the plasma source was normal pooled plasma (NPP) collected in 11 mM citrate supplemented with 100 µg/mL of corn trypsin inhibitor (citrate/CTI). The anti-TF antibodies were titrated at 0, 10, 50 and 100 nM and mixed with NPP in citrate/CTI. Relipidated TF was added to a 96-well assay plate, followed by addition of the antibody/NPP mixture. After a 10-min incubation or directly after combining the relipidated TF with antibody/NPP, thrombin generation was initiated by the addition of calcium and the thrombin substrate. The STAGO software was used to report the following parameters: Peak IIa (highest thrombin concentration generated on the thrombin generation curve [nM]); Lag Time (time from assay start to the moment 10 nM of thrombin is formed [min]); ETP (endogenous thrombin potential, area under the curve [nM x min]); and ttPeak (time from assay start to Peak IIa [min]). Percent peak thrombin generation (% Peak IIa), percent endogenous thrombin potential (% ETP), and percent ttPeak (% ttPeak) in the presence of each antibody relative to a no-antibody plasma control on the same plate were also reported. As used herein, the term "thrombin generation assay" (TGA) refers to the TGA used in this example.

[00771] The Peak IIa, Lag Time, ETP, ttPeak, % Peak IIa, % ETP, and % ttPeak in the presence of each antibody selected from 1F, 25A, 25A3, 25G1, 29E, 39A, 43B1, 43D7, 43Ea, 54E, TF-011, 5G9, and 10H10 without antibody incubation prior to addition of calcium and thrombin substrate are shown in **Table 44**. The Peak IIa, Lag Time, ETP, ttPeak, % Peak IIa, % ETP, and % ttPeak in the presence of each antibody selected from 1F, 25A, 25A3, 25G1, 29E, 39A, 43B1, 43D7, 43Ea, 54E, TF-011, 5G9, and 10H10 with 10 min antibody incubation prior to addition of calcium and thrombin substrate are shown in **Table 45**. The

thrombin generation curve in the presence of 100 nM anti-TF antibody without antibody pre-incubation is plotted in **Figures 13A and 13B**. The Peak thrombin concentration in the presence of titrations of anti-TF antibodies without antibody pre-incubation is plotted in **Figure 13C**.

[00772] As shown in **Figures 13A, 13B, and 13C** and **Table 44**, under the conditions without antibody pre-incubation, at the 100 nM antibody concentration, 1F, 29E, 39A, 54E diminished the peak IIa concentration by 92, 76, 91 and 70 %, respectively. Similarly, 100 nM of 5G9 and TF-011 inhibited peak IIa concentration by 92 % and 91 %, respectively. Severely reduced thrombin generation in the presence of the two highest concentrations of 1F, 39A, 5G9 and TF-011 hampered endogenous thrombin generation (ETP) calculations and increased time to Peak IIa/thrombin generation (ttPeak) by at least 284 % and 353 % at 50 nM and 100 nM respectively. In contrast, antibodies from group 25 did not impact the peak IIa concentration or ttPeak by more than 9 %. Group 43 antibodies and 10H10 exhibited mild interference with the peak IIa concentration: 100 nM of 43B1, 43D7, 43Ea and 10H10 reduced the peak IIa concentration by 33, 44, 13 and 34 %, respectively. In addition, 100 nM of 43B1, 43D7 and 10H10 showed at least a 29 % increase in ttPeak. However, the observed decline in peak IIa concentration and delayed ttPeak for group 43 antibodies and 10H10 did not result in more than a 10 % decline in the ETP.

[00773] Similar results are shown in **Table 45** under the conditions with 10 min antibody pre-incubation. At the 100 nM antibody concentration, 1F, 29E, 39A, 54E diminished the peak IIa concentration by 93, 72, 93 and 87 %, respectively. Similarly, 100 nM of 5G9 and TF-011 inhibited peak IIa concentration by 92 % and 91 %, respectively. Severely reduced thrombin generation in the presence of the two highest concentrations of 1F, 39A, 54E and TF-011 and all tested concentrations of 5G9 hampered endogenous thrombin generation (ETP) calculations and increased time to Peak IIa/thrombin generation (ttPeak) by at least 303 % and 371 % at 50 nM and 100 nM respectively. In contrast, antibodies from group 25 did not decrease the peak IIa concentration or increase ttPeak. Group 43 antibodies and 10H10 exhibited mild interference with the peak IIa concentration: 100 nM of 43B1, 43D7, 43Ea and 10H10 reduced the peak IIa concentration by 41, 56, 13 and 48 %, respectively. In addition, 100 nM of 43B1, 43D7 and 10H10 showed at least a 33 % increase in ttPeak. However, the observed decline in peak IIa concentration and delayed ttPeak for group 43 antibodies and 10H10 did not result in more than an 11 % decline in the ETP.

[00774] Overall, these results indicate that group 25 antibodies are completely inert in the penultimate step of the coagulation cascade when all three TGA parameters (ETP, Peak IIa concentration and ttPeak) are taken into consideration.

Table 44: Thrombin Generation Assay without Antibody Pre-Incubation

Plate	Sample	Ab conc. (nM)	Peak IIa [nM] (SD)	Lag Time [min] (SD)	ETP [nM•min] (SD)	ttPeak [min] (SD)	% Peak IIa	% ETP	% ttPeak
1	1F	100	25 (1)	31 (1)	*	41 (0.7)	8	*	419
		50	31 (0)	25.6 (0.3)	*	35.3 (0.3)	9	*	347
		10	155 (1)	8.2 (0.2)	1738 (25)	14.9 (0.2)	47	86	89
1	25A	100	317 (6)	5.2 (0.2)	2134 (28)	8.6 (0.2)	95	105	9
		50	317 (2)	5.2 (0.2)	2122 (30)	8.6 (0.2)	95	105	9
		10	322 (2)	5 (0)	2108 (29)	8.2 (0.2)	97	104	4
1	25A3	100	323 (1)	4.6 (0.2)	2031 (19)	7.9 (0.2)	97	100	0
		50	328 (2)	4.7 (0)	2080 (23)	8 (0)	98	103	1
		10	326 (4)	5.3 (0)	2152 (14)	8.4 (0.2)	98	106	6
1	25G1	100	340 (3)	5.3 (0)	2160 (27)	8.3 (0)	102	107	5
		50	346 (6)	5.1 (0.2)	2221 (40)	8.2 (0.2)	104	110	4
		10	337 (1)	4.7 (0)	2061 (34)	7.8 (0.2)	101	102	-1
1	29E	100	81 (0)	17.1 (0.2)	1257 (18)	26.2 (0.2)	24	62	232
		50	95 (1)	14.1 (0.2)	1365 (26)	22.6 (0.4)	29	67	186
		10	235 (3)	7 (0)	1926 (9)	11.7 (0)	71	95	48
1	Isotype	100	326 (3)	5.3 (0)	2132 (13)	8.6 (0.2)	98	105	9
		50	331 (3)	5.3 (0)	2177 (19)	8.3 (0)	99	108	5
		10	328 (4)	5.3 (0)	2129 (26)	8.4 (0.2)	98	105	6
1	TF-011	100	30 (1)	26 (0.3)	*	35.8 (0.2)	9	*	353
		50	39 (3)	21.3 (0.5)	*	30.3 (1.1)	12	*	284
		10	156 (7)	8 (0)	1714 (41)	14.7 (0.5)	47	85	86
1	5G9	100	27 (1)	29.9 (0.4)	*	39.6 (0.4)	8	*	401
		50	28 (0)	25.1 (0.4)	*	34.6 (0.2)	8	*	338
		10	79 (1)	10.4 (0.2)	1176 (16)	18.6 (0.2)	24	58	135
1	10H10	100	221 (4)	5.2 (0.2)	1945 (37)	10.2 (0.2)	66	96	29
		50	248 (3)	5.2 (0.2)	1978 (32)	9.8 (0.3)	74	98	24
		10	310 (2)	5.2 (0.2)	2036 (33)	8.6 (0.2)	93	101	9
1	Plasma ctrl.	NA	333 (0)	4.7 (0)	2023 (30)	7.9 (0.2)	100	100	0
2	39A	100	29 (0)	34.7 (0)	*	44.6 (0.2)	9	*	465
		50	36 (1)	29.8 (0.7)	*	39.3 (0.7)	11	*	397

		10	122 (3)	10.8 (0.3)	1694 (57)	18.6 (0.2)	37	84	135
2	43B1	100	238 (4)	5.3 (0)	2300 (32)	10.8 (0.2)	67	99	37
		50	258 (5)	5.2 (0.2)	2301 (29)	10.2 (0.2)	72	99	29
		10	317 (1)	5 (0)	2341 (34)	8.6 (0.2)	89	101	9
2	43D7	100	199 (6)	5.1 (0.2)	2124 (27)	11.2 (0.2)	56	91	42
		50	234 (1)	5 (0)	2190 (15)	10.3 (0)	66	94	30
		10	312 (3)	5 (0)	2343 (49)	8.9 (0.2)	88	101	13
2	43Ea	100	308 (2)	5 (0)	2349 (9)	9 (0)	87	101	14
		50	316 (3)	5 (0)	2430 (69)	8.7 (0)	89	105	10
		10	337 (4)	5 (0)	2416 (82)	8.3 (0)	95	104	5
2	54E	100	108 (3)	12.2 (0.2)	1589 (13)	20.2 (0.2)	30	68	156
		50	191 (2)	8 (0)	2109 (51)	14.3 (0)	54	91	81
		10	311 (5)	5 (0)	2275 (41)	8.8 (0.2)	87	98	11
2	Isotype	100	351 (2)	4.7 (0)	2304 (14)	7.9 (0.2)	99	99	0
		50	353 (1)	5 (0)	2391 (29)	8.2 (0.2)	99	103	4
		10	348 (1)	5 (0)	2367 (9)	8.3 (0)	98	102	5
2	Plasma ctrl.	NA	356 (1)	4.9 (0.2)	2323 (76)	8.11 (0.3)	100	100	3

* Groups with "No Tail Found" Errors when the software cannot calculate the ETP.

Table 45: Thrombin Generation Assay with 10 min Antibody Pre-Incubation

Plate	Sample	Ab conc. (nM)	Peak IIa [nM] (SD)	Lag Time [min] (SD)	ETP [nM•min] (SD)	ttPeak [min] (SD)	% Peak IIa	% ETP	% ttPeak
1	1F	100	20 (1)	29.5 (0.2)	*	40.8 (0.6)	7	*	483
		50	23 (0)	26.5 (0.7)	*	37.3 (0.4)	8	*	433
		10	44 (2)	13.8 (0.5)	742 (23)	22.4 (0.4)	16	41	220
1	25A	100	291 (3)	3.3 (0.1)	1964 (36)	6.7 (0.1)	106	108	-4
		50	290 (0)	3.3 (0.1)	1972 (22)	6.8 (0)	106	108	-3
		10	284 (1)	3.3 (0.1)	1899 (21)	6.8 (0)	104	104	-3
1	25A3	100	290 (3)	3.1 (0)	1893 (28)	6.4 (0)	106	104	-9
		50	284 (4)	3.1 (0)	1875 (16)	6.4 (0)	104	103	-9
		10	288 (3)	3.1 (0)	1901 (26)	6.4 (0)	105	105	-9
1	25G1	100	311 (3)	3.1 (0)	1954 (20)	6.3 (0.1)	114	107	-10
		50	311 (1)	3.1 (0)	1951 (22)	6.1 (0)	114	107	-13
		10	302 (3)	3.1 (0)	1877 (33)	6.1 (0)	110	103	-13
1	29E	100	76 (1)	14.7 (0.1)	1201 (24)	24.3 (0.3)	28	66	247
		50	83 (1)	14.1 (0)	1300 (17)	23.6 (0.1)	30	72	237
		10	98 (1)	9.4 (0)	1408 (11)	18.1 (0)	36	77	159
1	Isotype	100	288 (2)	3.4 (0)	1922 (28)	6.8 (0)	105	106	-3
		50	292 (2)	3.4 (0)	1921 (25)	6.8 (0)	107	106	-3
		10	290 (3)	3.4 (0)	1926 (38)	6.8 (0)	106	106	-3
1	TF-011	100	26 (0)	23.8 (1.1)	*	34.2 (0.9)	9	*	389

		50	27 (1)	22.4 (0.1)	*	33 (0.1)	10	*	371
		10	46 (3)	13.5 (0.5)	792 (55)	22.5 (0.2)	17	44	221
1	5G9	100	22 (0)	26.7 (0.3)	*	37.5 (0.5)	8	*	436
		50	23 (3)	23.6 (2.2)	*	34 (2.4)	8	*	386
		10	30 (1)	19.3 (0.4)	*	29 (0.8)	11	*	314
1	10H10	100	169 (3)	3.4 (0)	1795 (36)	9.3 (0.1)	62	99	33
		50	175 (4)	3.4 (0)	1754 (20)	9.2 (0.1)	64	96	31
		10	235 (8)	3.4 (0)	1807 (42)	7.8 (0)	86	99	11
1	Plasma ctrl.	NA	274 (1)	3.4 (0)	1818 (24)	7 (0.1)	100	100	0
2	39A	100	19 (1)	33.6 (0.7)	*	44.6 (0.9)	7	*	537
		50	22 (0)	30.7 (0.1)	*	41.4 (0.1)	8	*	491
		10	36 (1)	19.6 (0.7)	*	29.3 (0.8)	13	0	319
2	43B1	100	167 (0)	4 (0)	1806 (15)	9.8 (0.1)	59	98	40
		50	174 (1)	3.8 (0.1)	1831 (22)	9.6 (0)	62	99	37
		10	222 (5)	3.7 (0.1)	1841 (37)	8.3 (0)	79	100	19
2	43D7	100	123 (2)	4 (0)	1673 (27)	11.5 (0.1)	44	91	64
		50	122 (1)	3.7 (0.1)	1639 (29)	11.3 (0)	43	89	61
		10	194 (5)	4 (0)	1796 (35)	8.8 (0.1)	69	97	26
2	43Ea	100	244 (2)	3.5 (0.1)	1857 (42)	7.5 (0.1)	87	101	7
		50	245 (0)	3.6 (0)	1851 (29)	7.6 (0)	87	100	9
		10	262 (1)	3.6 (0)	1877 (15)	7.3 (0)	93	102	4
2	54E	100	37 (1)	22.3 (0.2)	*	33 (0.5)	13	*	371
		50	44 (1)	18.3 (0.4)	*	28.2 (1)	16	*	303
		10	121 (4)	6.5 (0.1)	1523 (20)	13.7 (0.3)	43	83	96
2	Isotype	100	275 (2)	3.6 (0)	1862 (23)	7.3 (0)	98	101	4
		50	284 (0)	3.6 (0)	1899 (15)	7.2 (0.1)	101	103	3
		10	281 (3)	3.6 (0)	1877 (13)	7.3 (0)	100	102	4
2	Plasma ctrl.	NA	282 (2)	3.8 (0.1)	1845 (22)	7.3 (0)	100	100	4

* Groups with "No Tail Found" Errors when the software cannot calculate the ETP.

Example 19: FXa Conversion Assay and FVIIa Competition Assay with Previously Described Anti-TF Antibodies

[00775] The previously described TF-specific antibodies TF-011, 5G9 and 10H10 (Breij et al., *Cancer Res*, 2014, 74:1214-1226; Versteeg et al., *Blood*, 2008,111:190-199; each of which is incorporated by reference in its entirety) were tested in FXa conversion assay and FVIIa competition assay.

[00776] To evaluate the ability of TF:FVIIa to convert FX into FXa in the presence of human antibodies against TF, a cell-based FX conversion assay was conducted as described in Larsen et al., *J Biol Chem*, 2010, 285:19959-19966, which is incorporated by reference in

its entirety. Briefly, $5x10^4$ MDA-MB-231 cells (ATCC, Manassas, VA, USA) were plated into tissue culture-treated black 96-well plates (Greiner Bio-One, Monroe, NC, USA) and cultured overnight. After removal of the cell culture media and addition of a final concentration of 200 nM of FX in a HEPES buffer with 1.5 mM $CaCl_2$, cells were incubated with a titration of the antibodies for 15 min at 37°C. Upon reconstitution of the binary TF:FVIIa complex with a final concentration of 20 nM of FVIIa, cells were incubated for 5 min at 37°C. After quenching the reaction with ethylenediaminetetraacetic acid (EDTA) in a black 94-well plate, generated FXa was measured with 50 μM of SN-7 6-amino-1-naphthalenesulfonamide-based fluorogenic substrate (Haematologic Technologies, Essex Junction, VT, USA) on an Envision plate reader equipped with an Umbelliferone 355 excitation filter, an Umbelliferone 460 emission filter, and a LANCE/DELFIA top mirror (Perkin Elmer, Waltham, MA, USA). FXa conversion percentages (% FXa) in the presence of an anti-TF antibody titration relative to a no antibody control are plotted in **Figure 14A**.

[00777] To evaluate competition between FVIIa and the human antibodies against TF, TF-positive MDA-MB-231 cells (ATCC, Manassas, VA, USA) were first incubated for 1 hr on ice with a titration of the human antibodies against TF or an isotype control. Subsequently, FVII-Fc conjugated to Alexa488 was added to the antibody-cell mixture at a final concentration of 20 nM. After another 1 hr incubation on ice, cells were washed, stained with a viability dye, and analyzed by flow cytometry. The Alexa488 fluorescence data from viable cells was summarized using median fluorescence intensity (MFI). FVII-Fc binding was summarized with % FVII-Fc binding = $[MFI_{\text{antibody labeled cells}} - MFI_{\text{unstained cells}}] / [MFI_{\text{IgG1 control labeled cells}} - MFI_{\text{unstained cells}}]$. Percentage of FVIIa binding (% FVIIa) in the presence of an anti-TF antibody titration relative to an isotype control is plotted in **Figure 14B**.

[00778] As presented in **Figure 14A**, TF-011 and 5G9 inhibited FX conversion by 57-59 % and 67-70 % at concentrations of 25, 50, and 100 nM. 10H10 did not significantly inhibit FX conversion at these three concentraions.

[00779] As presented in **Figure 14B**, TF-011 effectively competed with FVII, whereas 5G9 and 10H10 showed less than 25 % and 10 % competition at the highest concentration of antibody, respectively.

[00780] These results indicate that 5G9 predominantly competes with substrate FX binding, resulting in the observed inhibition of FX conversion and thrombin generation. TF-011 inhibits thrombin generation by competing with FVIIa for binding to TF. However, 10H10 inhibits TF-FVIIa mediated signaling without substantially affecting binding of FVIIa

to TF. These findings are consistent with previous observations described in Huang et al., *J Mol Biol*, 1998, 275:873-894; Ruf et al., *Biochem J*, 1991, 278:729-733; and Teplyakov et al., *Cell Signal*, 2017, 36:139-144; each of which is incorporated by reference in its entirety.

Example 20: Antibody Competition Assay

[00781] Alexa Fluor antibodies were generated using Alexa Fluor 488 5-sulfo-dichlorophenol esters (ThermoFisher Scientific) following manufacturer's protocol. Excess Alexa Fluor dye was removed from the antibody dye conjugate preparations by gel filtration (ThermoFisher Scientific).

[00782] To evaluate competition between a first human antibody against TF and 25A3, TF-positive MDA-MB-231 cells (ATCC, Manassas, VA, USA) were first incubated for 1 hr on ice with a titration of the first human antibody against TF. Subsequently, a final concentration of 20 nM of 25A3 conjugated to Alexa488 was added to the antibody cell mixture. After another 1 hr incubation on ice, cells were washed, stained with a viability dye, and analyzed by flow cytometry. The Alexa488 fluorescence data from viable cells was summarized using median fluorescence intensity. 25A3 binding was summarized with % 25A3 binding = $[MFI_{\text{antibody labeled cells}} - MFI_{\text{unstained cells}}] / [MFI_{\text{IgG1 control labeled cells}} - MFI_{\text{unstained cells}}]$.

[00783] To evaluate competition between a first human antibody against TF and 43D7, TF-positive MDA-MB-231 cells (ATCC, Manassas, VA, USA) were first incubated for 1 hr on ice with a titration of the first human antibody against TF. Subsequently, a final concentration of 20 nM of 43D7 conjugated to Alexa488 was added to the antibody cell mixture. After another 1 hr incubation on ice, cells were washed, stained with a viability dye, and analyzed by flow cytometry. The Alexa488 fluorescence data from viable cells was summarized using median fluorescence intensity. 43D7 binding was summarized with % 43D7 binding = $[MFI_{\text{antibody labeled cells}} - MFI_{\text{unstained cells}}] / [MFI_{\text{IgG1 control labeled cells}} - MFI_{\text{unstained cells}}]$.

[00784] To evaluate competition between a first human antibody against TF and 39A, TF-positive MDA-MB-231 cells (ATCC, Manassas, VA, USA) were first incubated for 1 hr on ice with a titration of the first human antibody against TF. Subsequently, a final concentration of 20 nM of 39A conjugated to Alexa488 was added to the antibody cell mixture. After another 1 hr incubation on ice, cells were washed, stained with a viability dye, and analyzed by flow cytometry. The Alexa488 fluorescence data from viable cells was summarized using

median fluorescence intensity. 39A binding was summarized with % 39A binding = [$MFI_{antibody\ labeled\ cells} - MFI_{unstained\ cells}$] / [$MFI_{IgG1\ control\ labeled\ cells} - MFI_{unstained\ cells}$].

[00785] % 25A3 binding, % 43D7 binding, and % 39A binding are shown in **Figures 15A and 15B**, **Figures 16A and 16B**, and **Figures 17A and 17B**, respectively. Antibodies from groups 25 and 43, 5G9, and 10H10 reduced % 25A3 binding and % 43D7 binding and did not reduce % 39A binding. Antibodies from groups 1, 29, 39, and 54, and TF-011 reduced % 39A binding and did not reduce % 25A3 binding and % 43D7 binding.

[00786] While the antibody competition assay results indicate that groups 25 and 43 antibodies, 5G9, and 10H10 may bind to the same or an overlapping epitope of human TF or may affect the TF binding of each other through an allosteric mechanism, the chimeric TF construct mapping experiments as described elsewhere in this disclosure demonstrate that group 25 antibodies, group 43 antibodies, 5G9 and 10H10 bind distinct epitopes. In addition, while the antibody competition assay results indicate that antibodies of groups 1, 29, 39, and 54, and TF-011 may bind to the same or an overlapping epitope of human TF or may affect the TF binding of each other through an allosteric mechanism, the chimeric TF construct mapping experiments as described elsewhere in this disclosure demonstrate that the antibodies of groups 29, 39 and 54 bind epitopes distinct from TF-011's epitope.

Example 21: Anti-TF Antibody Internalization

[00787] To evaluate internalization of the anti-TF antibodies, a cytotoxicity assay was conducted as described in Liao-Chan et al., *PLoS One*, 2015, 10:e0124708, which is incorporated by reference in its entirety. Briefly, cells were plated in 384-well plates (Greiner Bio-One, Monroe, NC, USA) at $4x10^3$ cells per well in 40 µl of media. Antibodies and an anti-human Fc Fab conjugated to the tubulin inhibitor mono-methyl auristatin F (MMAF) (Moradec, San Diego, CA, USA) were serially diluted starting at 5 and 30 nM, respectively. The anti-human Fc Fab conjugated to MMAF consisted of a polyclonal antibody specific to the Fc region of human IgGs with a DAR of 1.2 to 1.5. Plates were incubated for 3 days, followed by lysis in CellTiter-Glo (CTG) assay reagent (Promega, Madison, WI, USA). CTG luminescence was measured on an Envision plate reader and the mean and standard deviation of 4 replicates graphed in Prism (GraphPad, La Jolla, CA, USA). For each anti-TF antibody, the IC_{50} and its associated 95% confidence interval were calculated in Prism using a 4-parameter binding model. The cell viability results after incubation with anti-TF antibodies and anti-TF antibody Fab:MMAF complexes are shown in **Figures 18A and 18B**. The 95% confidence intervals for the IC_{50} values are shown in **Table 46**.

[00788] Internalization of the anti-TF antibodies was also evaluated by a quantitative assay based on internalized fluorescence and quenched surface-fluorescence. Cell surface fluorescence quenching was assessed as described in Liao-Chan et al., *PLoS One*, 2015,10:e0124708. Briefly, $1.2x10^5$ MDA-MB-231 cells were pre-incubated with 100 nM of A488-conjugated antibodies in media for 2 hr on ice. After 2 washes, cells were resuspended in cold media and pulsed for up to 4 hr at 37°C. Cells were rapidly chilled and incubated with or without 300 nM of anti-A488 antibody (clone 19A) for 30 min on ice. After 2 washes, dead cells were labeled with DAPI and samples were analyzed on a Novocyte flow cytometer (ACEA Biosciences). The median fluorescence intensities (MFIs) at each anti-A488 mAb concentration were normalized against the isotype control to obtain a normalized MFI percentage. Internalized fluorescence was calculated from quenched and non-quenched sample data by correcting for incomplete surface quenching: $1–(N_1–Q_1)/(N_1– (N_1Q_0/N_0))$ with N_1 = unquenched MFI at each time point (t_1); Q_1 = Quenched MFI at t_1; Q_0 = Quenched MFI for the sample kept on ice (t_0); N_0 = Unquenched MFI at t_0. Percent internalization of anti-TF antibodies conjugated to A488 is shown in **Figure 18C**.

[00789] Because Fab:MMAF binds the Fc region of the TF-specific antibodies, cellular uptake of these complexes can trigger cell death. While the TF-specific antibodies alone had no impact on cell viability in three-day cultures of TF-positive A431 cells (**Figure 18A**), the TF-specific antibodies in complex with Fab:MMAF showed dose-dependent cell killing with IC_{50} values ranging between 0.07 and 0.14 nM (**Figure 18B**).

[00790] Cellular uptake was corroborated with fluorescently labeled TF-specific antibodies. In a quantitative assay based on internalized fluorescence and quenched surface-fluorescence, the TF-specific antibodies showed between 28 and 37 % internalization after a 4 h incubation (**Figure 18C**).

[00791] These results indicate that the tested anti-TF antibodies can medicate internalization and toxin delivery into TF-positive cells.

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Table 46: ADC Data With Ranking (Continuous Incubation)

	Cell line:	A431			A431			MDA-MB-231			HPAF-II			**Continuous Primary ADC RANK**
	ADC format:	Secondary ADC			Primary ADC			Primary ADC			Primary ADC			
	Treatment:	Continuous			Continuous			Continuous			Continuous			
	Figure:	**Figure 18B**			**Figure 20A**			**Figure 22D**			**Figure 22E**			
	Binding data:	IC_{50} (nM)	95% CI	rank	IC_{50} (nM)	95% CI	rank	IC_{50} (nM)	95% CI	rank	IC_{50} (nM)	95% CI	rank	
Antibody:	1F	0.07	0.06 to 0.07	Not included	Not tested			Not tested			Not tested			Not included
	25A	0.11	0.10 to 0.11	6	0.09	0.08 to 0.09	7	0.14	0.12 to 0.16	7	0.06	0.05 to 0.07	8	7
	25A3	0.09	0.08 to 0.09	3	0.07	0.07 to 0.08	5	0.11	0.10 to 0.12	4	0.05	0.04 to 0.05	5	4
	25G1	0.08	0.07 to 0.08	1	0.06	0.06 to 0.06	3	0.09	0.08 to 0.10	3	0.04	0.04 to 0.05	3	3
	29E	0.10	0.09 to 0.10	4	0.06	0.05 to 0.06	2	0.07	0.07 to 0.08	2	0.04	0.04 to 0.05	2	2
	39A	0.08	0.08 to 0.09	2	0.05	0.05 to 0.05	1	0.05	0.05 to 0.05	1	0.04	0.03 to 0.05	1	1
	43B1	0.12	0.11 to 0.13	7	0.08	0.08 to 0.08	6	0.14	0.13 to 0.15	5	0.05	0.04 to 0.06	4	5
	43D7	0.10	0.10 to 0.10	5	0.06	0.06 to 0.07	4	0.14	0.12 to 0.16	6	0.05	0.05 to 0.06	6	6
	43Ea	0.13	0.13 to 0.14	8	0.09	0.09 to 0.10	8	0.15	0.13 to 0.17	8	0.06	0.05 to 0.06	7	8
	54E	0.11	0.11 to 0.12	Not included	0.07	0.07 to 0.07	Not included	Not tested			Not tested			Not included
	Isotype	Not applicable			Not applicable			Not applicable			Not applicable			Not included
	TF-011	Not tested			0.05	0.05 to 0.05		Not tested			Not tested			Not included

Table 47: ADC Data With Ranking (4 h Incubation)

	Cell line:	A431			A431			**4 hr Primary ADC RANK**
	ADC format:	Primary ADC			Primary ADC			
	Treatment:	4 hr, followed by washout			4 hr, followed by washout			
	Figure:	**Figure 20B**			**Figure 21A**			
	Measurement:	IC_{50} (nM)	95% CI	rank	IC_{50} (nM)	95% CI	rank	
Antibody:	1F	Not tested			Not tested			Not included
	25A	0.35	0.32 to 0.39	6	0.18	0.17 to 0.19	6	6
	25A3	0.19	0.17 to 0.21	3	0.12	0.11 to 0.12	3	3
	25G1	0.19	0.17 to 0.20	2	0.10	0.09 to 0.10	2	2
	29E	0.20	0.18 to 0.21	4	0.13	0.12 to 0.14	4	4
	39A	0.12	0.11 to 0.13	1	0.09	0.09 to 0.10	1	1
	43B1	0.36	0.32 to 0.41	7	0.19	0.17 to 0.20	7	7
	43D7	0.28	0.25 to 0.30	5	0.14	0.13 to 0.15	5	5
	43Ea	0.43	0.39 to 0.48	8	0.24	0.22 to 0.25	8	8
	54E	0.26	0.24 to 0.29		0.20	0.18 to 0.22		Not included
	Isotype	Not applicable			Not applicable			Not included
	TF-011	0.17	0.16 to 0.18		0.09	0.09 to 0.10		Not included

Example 22: Cell-Based Binding Assay of Antibody-Drug Conjugates (ADCs)

[00792] To evaluate the cell binding properties of ADCs, binding of anti-TF antibodies and anti-TF ADCs to endogenous human TF expressing HCT116 cells was was assessed as previously described in Liao-Chan et al., *PLoS One*, 2015, 10:e0124708, which is incorporated by reference in its entirety. Briefly, $1.2x10^5$ cells collected with Cellstripper (Mediatech, Manassas, VA, USA) were incubated with a twelve-point 1:3 dilution titration of anti-human TF antibody or ADC starting at 100 nM for 2 hr on ice. After 2 washes, cells labeled with antibody or ADC were incubated for 30 min on ice with 150 nM of Goat Phycoerythrin (PE) $F(ab')_2$ fragment goat anti-human IgG, Fcγ fragment specific (Jackson ImmunoResearch, West Grove, PA, USA) or FITC-labeled $F(ab')_2$ fragment goat anti–human kappa (SouthernBiotech, Birmingham, AL, USA), respectively. After 2 washes, dead cells were labeled with TO-PRO-3 Iodide (ThermoFisher Scientific) and samples were analyzed on a CytoFLEX flow cytometer (Beckman Coulter, Brea, CA, USA) or Novocyte flow cytometer (ACEA Biosciences, San Diego, CA, USA). The median fluorescence intensities (MFIs) at each dilution were plotted and cell EC_{50}'s were derived using a 4-parameter binding model in Prism (GraphPad, La Jolla, CA, USA). **Figures 19A and 19B** exhibit the binding curves of anti-TF antibodies and anti-TF ADCs, respectively. **Figure 19C** lists the reportable cell EC_{50}'s and their 95% confidence intervals of the anti-TF antibodies and ADCs.

[00793] As shown in **Figures 19A, 19B, and 19C**, the cell binding properties of TF-specific ADCs are comparable to the cell binding properties of TF-specific antibodies, which indicates that the conjugation process of ADC did not alter the cell-binding properties of the TF-specific antibody moiety of the ADC.

Example 23: Cytotoxicity Assays of Antibody-Drug Conjugates (ADCs)

[00794] To evaluate ADC cytotoxicity, A431cells were plated in 384-well plates (Greiner Bio-One). Anti-TF antibodies conjugated to MC-vc-PAB-MMAE were serially diluted as shown. The TF-specific ADCs were added to A431 cells, with either a 72 h incubation or a 4 h incubation followed by removal of excess ADC and culture for another 68 h. A431cells were lysed in CTG assay reagent after treatment. CTG luminescence was measured and the mean and standard deviation of 4 replicates graphed in Prism. For each ADC, the IC_{50} and its associated 95% confidence interval were calculated in Prism using a 4-parameter binding model.

[00795] **Figure 20A** shows the cell viability after titrations of anti-TF ADCs with a continuous 72 h incubation. **Figure 20B** shows the cell viability after titrations of anti-TF ADCs with a 4 h incubation followed by removal of excess ADC and culture for another 68 h. **Figure 20C** shows the reportable IC_{50} values of ADCs under both the continuous treatment and the pulse treatment. The 95 % confidence intervals for the IC_{50}'s of the continuous treatment and the pulse treatment are listed in **Table 46** and **Table 47** respectively.

[00796] Both treatments resulted in efficacious cell killing, with a 2.4 to 4.7-fold increase in IC_{50} when excess ADC was removed from the culture after the 4 h incubation compared to the 72 h incubation. Removal of excess 25A3 and 39A ADC had the smallest impact on IC_{50}, with a 2.7 and 2.4-fold increase from 0.07 and 0.05 nM, respectively.

[00797] These results indicate that similar to the TF-specific antibodies, the TF-specific ADCs undergo substantial cellular internalization.

Example 24: Cytotoxicity Assays in the Presence of FVIIa

[00798] To understand whether FVIIa interfered with the activity of the TF-specific ADC, we treated A431 cells for 4 h with the TF-specific ADCs (anti-TF antibodies conjugated to MC-vc-PAB-MMAE) in the absence or presence of FVIIa and measured cell viability 68 h later. A431 cells were pre-incubated for 30 min without or with 50 nM of FVIIa prior to the addition of an anti-TF ADC titration. Cell viability was determined by CTG assay. The mean and standard deviation of 4 replicates were graphed in Prism. For each ADC, the IC_{50} were calculated in Prism using a 4-parameter binding model.

[00799] The cell viability after titrations of anti-TF ADCs in the absence or presence of FVIIa is shown in **Figures 21A and 21B** respectively. The reportable IC_{50} values of ADCs in the absence or presence of FVIIa are listed in **Figure 21C**.

[00800] While the ADCs that competed with FVIIa (29E, 39A, 54E and TF-011) were negatively affected by the presence of FVIIa by at least 2.3-fold, the ADCs that did not compete with FVIIa (group 25 and 43 antibodies) were equally efficacious in the absence or presence of FVIIa.

[00801] These results indicate that FVIIa does not interfere with the activity of anti-TF ADCs from groups 25 and 43.

Example 25: Cytotoxicity Assays on Additional Cancer Cell Lines

[00802] To evaluate TF copy number on the cell surface of different cell lines, $1.2x10^5$ cells were harvested and incubated with 133 nM of anti-human TF antibody 5G9 on a mouse IgG2a backbone for 2 hr on ice. After 2 washes, QIFIKIT beads (Agilent) and cells labeled

with anti-TF antibody were incubated for 30 min on ice with 150 nM of Goat Phycoerythrin (PE) $F(ab')_2$ fragment goat anti-mouse IgG, Fc-gamma fragment specific (Jackson ImmunoResearch). After 2 washes, dead cells were labeled with TO-PRO-3 Iodide (ThermoFisher Scientific) and samples were analyzed on a CytoFLEX flow cytometer (Beckman Coulter). After gating for single live cells, the MFI's were determined using FlowJo (Flowjo, Ashland, OR, USA). A standard curve using QIFIKIT beads was generated in Prism using a 5-parameter binding model to determine copy number. The lower limit of quantitation was $1.9x10^3$ antibody binding sites (also referred to as copy number) and the upper limit of quantitation was $8.0x10^5$ antibody binding sites.

[00803] The TF copy number on A431, CHO, HCT-116, HPAF-II, MDA-MB-231, and RF/6A is listed in **Figure 22A**. The level of surface TF ranged from $1.9x10^5$ to $5.7x10^5$ copies in A431, MDA-MB-231 and HPAF-II cells. HCT-116 cells expressed $2.2x10^4$ copies of surface TF and TF expression in CHO cells was below limit of quantitation (BLOQ). As 5G9 cross-reacts with *Macaca fascicularis* TF and the TF protein sequence between *M. fascicularis* and *mulatta* is identical, the level of surface TF in the *M. mulatta* cell line RF/6A was also qualtified ($1.7x10^4$ copies).

[00804] Cell viability of HCT-116, CHO, MDA-MB-231, and HPAF-II cells in the presence of titrations of anti-TF MMAE ADCs was shown in **Figures 22B, 22C, 22D, and 22E** respectively.

[00805] The TF-specific ADCs effectively reduced the viability of MDA-MB-231 and HPAF-II cancer cell lines (**Figures 22D and 22E**). Compared to the activity on MDA-MB-231 and HPAF-II cells, the ADCs were less efficacious on HCT-116 cells, with some activity at the highest concentration and no reportable IC_{50} value (**Figures 22B**). The TF-specific ADCs did not affect the viability of the CHO cultures (**Figures 22C**).

[00806] These results indicate that the cytotoxicity of anti-TF ADCs is specific for TF positive cells.

[00807] When ranking the cell-killing efficacy of the ADCs on A431, HPAF-II and MDA-MB-231 cells, the top four ADCs in descending order were 39A, 29E, 25G1 and 25A3 (**Table 46**). When A431 cells were incubated for 4 h with the TF-specific ADCs followed by a washout, the top four ADCs in descending order were 39A, 25G1, 25A3 and 29E (**Table 47**). Thus, the top 2 ranking ADCs with no impact on coagulation were 25G1 and 25A3.

Example 26: Intracellular Microtubule Network in the Presence of Antibody-Drug Conjugates (ADCs)

[00808] Immunofluorescence of the intracellular microtubule network of cells was conducted to illustrate the mechanism of action of the ADC. *See* Theunissen et al., *Methods Enzymol*, 2006, 409:251-284. Briefly, A431 or HPAF-II cells were seeded onto 8-well poly-D-lysine treated slides (Corning Inc, Corning, NY, USA). One day later, the culture medium was replaced with medium containing ADC at 5 nM. After twenty hours of ADC exposure, the cells were fixed for 15 min at room temperature with 4 % paraformaldehyde (ThermoFisher Scientific). After three washes with PBS, the cells were permeabilized for 1 h with PBS containing 0.3 % Triton X-100 and 5 % normal goat serum. Next, the microtubule networks were stained for 3 h with anti-tubulin (11H10) rabbit mAb (Alexa Fluor 488 conjugate) (Cell Signaling Technology, Danvers, MA, USA) in PBS containing 1 % BSA and 0.3 % Triton X-100. After three washes, ProLong Gold Antifade reagent with DAPI (ThermoFisher Scientific) was added to the cells and the slide was mounted for microscopy by using a 0.17 mm coverslip. Image acquisition was conducted on a DMi8 fluorescence microscope (Leica Microsystems, Buffalo Grove, IL, USA) equipped with a sCMOS camera. The Leica LAS X software was used to acquire a system-optimized Z-stack of 6 to 7 microns. A sharp two-dimensional image from this Z-stack was created automatically with the extended depth of field (EDF) image feature. Representative images of tubulin staining of A431 or HPAF-II cells are shown in **Figures 23A and 23B** respectively.

[00809] While the isotype control ADC did not affect the microtubule network, the 25A3 ADC disrupted the microtubule network effectively in both A431 and HPAF-II cells.

[00810] These results indicate the MMAE-based anti-TF ADCs induce cytotoxicity in TF-positive cancer cells through disruption of the intracellular microtubule network.

Example 27: Cytotoxicity Assays and G_2/M arrest in HUVECs

[00811] To evaluate TF copy number on the cell surface of human umbilical vein endothelial cells (HUVECs), $1.2x10^5$ HUVECs were harvested and incubated with 133 nM of anti-human TF antibody 5G9 on a mouse IgG2a backbone for 2 hr on ice. After 2 washes, QIFIKIT beads (Agilent) and cells labeled with anti-TF antibody were incubated for 30 min on ice with 150 nM of Goat Phycoerythrin (PE) $F(ab')_2$ fragment goat anti-mouse IgG, Fc-gamma fragment specific (Jackson ImmunoResearch). After 2 washes, dead cells were labeled with TO-PRO-3 Iodide (ThermoFisher Scientific) and samples were analyzed on a CytoFLEX flow cytometer (Beckman Coulter). After gating for single live cells, the MFI's were determined using FlowJo (Flowjo, Ashland, OR, USA). A standard curve using

QIFIKIT beads was generated in Prism using a 5-parameter binding model to determine copy number. The lower limit of quantitation was $1.9x10^3$ antibody binding sites (also referred to as copy number) and the upper limit of quantitation was $8.0x10^5$ antibody binding sites.

[00812] In response to injury, inflammatory and angiogenic factors transiently increase expression of surface TF in the vasculature. *See* Holy et al., *Adv Pharmacol*, 2010, 59:259-592, which is incorporated by reference in its entirety. The transient upregulation of TF in cell culture was mimicked by treating HUVECs with a combination of inflammatory cytokines (5 ng/mL IL1-beta, 25 ng/mL TNF-alpha and 50 ng/mL VEGF). As shown in **Figure 24A**, surface TF levels increased from $2.4x10^3$ copies in the absence of inflammatory cytokines to $1.2x10^4$ copies after 6 h of cytokine treatment. The surface TF was ~3-fold lower after 20 h of cytokine treatment relative to 6 h of treatment, which indicates that the cytokine-induced TF upregulation was transient.

[00813] For the ADC cytotoxicity assay, HUVEC cultures were seeded on half-area 96-well plates. The next day, the combination of inflammatory cytokines and a titration of ADCs was added to the cultures. Four days later viability of the cultures was assessed by lysis in CellTiter-Glo (CTG) assay reagent. As shown in **Figure 24B**, the cell viability of inflammatory cytokine-treated HUVEC cultures was unaffected by the anti-TF ADCs, 25A-vc-MMAE and 43Ea-vc-MMAE. The results indicates that the inflammatory cytokine-treated endothelial cells are resistant to anti-TF ADCs.

[00814] To further understand the resistance of endothelial cells to anti-TF ADCs, cell cycle progression was evaluated 24 h after addition of the cytokines and TF-specific ADCs. Arrest at the the G_2/M phase of the cell cycle was analyzed as previously described in Theunissen et al, *Methods Enzymol*, 2006, 409:251-284. Briefly, low-passage HUVECs (Lifeline Cell Technologies, Frederick, MD, USA), propagated in VascuLife VEGF-Mv Endothelial media (Lifeline Cell Technologies), and HCT-116 cells were seeded on 12-well plates. The next day, media was removed and replaced with fresh media (no cytokines) or media containing 5 ng/mL IL1-beta, 25 ng/mL TNF-alpha and 50 ng/mL VEGF (with cytokines). A titration of MMAE-linked ADCs or free MMAE was added to the cells. After 24 h of treatment, cells were fixed in ice-cold 70 % ethanol. Subsequently, the cells were washed with flow cytometry buffer (PBS, 1 % FBS, 0.1 % Triton) and stained for 1 h with a 1:100 dilution of phospho-Histone H3 (Ser10) (D2C8 PE Conjugate, Cell Signaling Technology). After 2 washes, the cells were treated for 20 min with 100 µg/mL PureLink RNAse A (ThermoFisher Scientific), followed by the addition of the viability dye TO-PRO-3 Iodide (ThermoFisher Scientific). 40,000 events were collected on a Novocyte flow

cytometer. In the Flowjo data analysis software cell doublets and aneuploid cells were excluded. The pH3 signal was plotted against DNA content to determine the percentage of pH3-positive cells.

[00815] The percentage of pH3-positive cells (% pH3) with titrations of anti-TF ADCs on HUVECs in the absence or presence of inflammatory cytokines is shown in **Figures 25A and 25B** respectively. The percentage of pH3-positive cells (% pH3) with titrations of anti-TF ADCs on HCT-116 cells is shown in **Figure 25C**.

[00816] While the TF-specific ADCs induced an arrest at the G_2/M phase of the cell cycle in HCT-116 cells, the ADCs did not impact cell cycle progression in HUVECs with or without inflammatory cytokine treatment. As shown in **Figures 26A and 26B**, the percentage of pH3-positive HCT-116 cells increased 5 times after treatment of 25A-vc-MMAE as compared to treatment of Isotype-vc-MMAE.

[00817] **Figures 27A and 27B** show that unconjugated MMAE increase the phosphorylation of histone H3 to a similar extent in both HCT-116 cells and HUVECs, indicating that the resistance in endothelial cells is specific for the MMAE-based ADC.

[00818] Taken together, these results indicate that the anti-TF ADCs do not affect the viability of HUVECs in the absence or presence of inflammatory cytokines.

Example 28: Erk Phosphorylation Assay

[00819] For assessment of Erk phosphorylation, A431 cells were plated in 6-well plates (Corning) in media overnight. The following day, cells were washed once and serum starved in serum-free media. After starvation, cells were preincubated with 100 nM of anti-TF antibodies for 30 min at 37 °C. FVIIa was spiked into the wells at 50 nM and incubated for 20 min at 37 °C for p-ERK induction. After induction, cells were lysed with RIPA Lysis and Extraction Buffer with Halt™ Protease and Phosphatase Inhibitor Cocktail (ThermoFisher Scientific). Western blot was performed with 20 µg of cell lysate using Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) and p44/42 MAPK (Erk1/2) (137F5) (Cell Signaling Technology) as primary antibodies and Peroxidase AffiniPure Donkey Anti-Rabbit IgG (H+L) (Jackson ImmunoResearch) as a secondary antibody. Non-saturating band intensities for pErk and Erk were measured on an Amersham AI600 (GE Healthcare). Each pErk intensity was normalized against its respective Erk intensity and the no-antibody no-FVIIa sample intensity.

[00820] The Western blot results of pErk and Erk are shown in **Figure 28**. Treatment with FVIIa induced Erk phosphorylation by 5.2 fold in cell cultures without pretreatment of anti-

TF antibodies. The inducation of Erk phosphorylation was ablated by pretreatment with 1F, 39A and 54E (fold induction between 0.8 and 1.2) and attenuated by 29E and the members of groups 25 and 43 (fold induction between 2.0 and 3.4).

[00821] This data indicates that anti-TF antibodies inhibit FVIIa-dependent TF signaling when assessing Erk phosphorylation.

Example 29: Antibody-Dependent Cellular Cytotoxicity (ADCC) Assay

[00822] To evaluate ADCC activity, an ADCC Reporter Bioassay Core Kit (Promega) was used following the manufacturer's protocol. Briefly, A431 cells were plated on a microtiter plate (Corning). The following day, the cells were incubated with a ten-point 1:3 dilution titration of anti-TF antibodies or the ADCs starting at 50 nM. An ADCC effector-to-target cell ratio of 8:1 was added to each well and incubated for 6 h at 37 ºC. Bio-Glo™ Luciferase Assay Reagent was added to each well to measure luminescence on an Envision plate reader (PerkinElmer, Waltham, MA, USA). The mean and standard deviation of 4 replicates were graphed in Prism. For each antibody and ADC, the EC_{50} and its associated 95 % confidence interval were calculated in Prism using a 4-parameter binding model.

[00823] ADCC reporter luminescence after incubation with the reporter Jurkat cell line in the represece titrations of anti-TF antibodies or anti-TF ADCs is shown in **Figures 29A and 29B** respectively. The ADCC reporter luminescence EC_{50} values for each anti-TF antibody or ADC are listed in **Figure 29C**.

[00824] All the tested TF-specific antibodies and ADCs exerted induction of luciferase-dependent luminescence with EC_{50} values ranging between 0.18 and 0.43 nM.

[00825] These data indicate that both the TF-specific antibodies and ADCs can induce antibody-dependent cellular cytotoxicity (ADCC) via the IgG1 Fc domain of the antibody.

Example 30: Studies in Cell Line-Derived Xenograft (CDX) Models

[00826] To evaluate the efficacy of the ADCs *in vivo,* xenograft studies in immune compromised mice were performed as described in Kim et al., *Blood Cancer J*, 2015, 5:e316, which is incorporated by reference in its entirety. Briefly, the A431 epidermoid carcinoma and the HPAF-II pancreatic carcinoma cell lines were implanted subcutaneously in the flank of athymic nude mice (Charles River Laboratories, Wilmington, MA). Animals were randomized and treated as indicated in the figures. Body weight and tumor size assessments were performed bi-weekly. Animals were removed from study and euthanized once tumor size reached 1200mm^3 or skin ulceration was evident. In addition, the MTV curve for the treatment group in question was no longer shown once an animal was removed from study

due to size. The animals' care was in accordance with institutional guidelines. Mean tumor volume (MTV) with the standard error of the mean (SEM) was plotted over time. Treatment efficacy was determined by calculating tumor growth inhibition (% TGI = 100 % x [1-(final MTV – initial MTV of a treated group) / (final MTV – initial MTV of the control group)]) before any of the animals in the vehicle arm were euthanized due to a tumor size ≥ 1200mm^3. Statistical comparisons between the MTVs were conducted using one-way ANOVA followed by Tukey's multiple comparisons test comparing all groups. The *P*-values for each ADC compared to the vehicle control arm are reported. At the end of the study, efficacy was also determined in each treatment arm by counting the number of animals with a partial regression (PR) or a complete regression (CR) of the tumor. In a PR response, the tumor volume was 50 % or less of its day 1 volume for 3 consecutive measurements during the course of study, and equal to or greater than 14mm^3 for 1 or more of these measurements. In a CR response, the tumor volume was less than 14mm^3 for 3 consecutive measurements. When an animal exhibited a CR response at the end of the study, it was classified as a tumor-free survivor (TFS) instead of a CR. Throughout the ADC studies no significant body weight changes due to ADC treatment were observed.

[00827] As shown in **Figure 30A**, HPAF-II tumor-bearing mice were treated with 5 mg/kg of ADC on day 1, 8 and 15 after randomization. The effect of TF-011 ADC was compared with two representative clones from the two groups that did not impact coagulation (i.e. 25A and 43Ea). Twenty-one days after randomization the efficacy of the 25A, 43Ea and TF-011 ADCs was equivalent, with tumor growth inhibition ranging between 131 and 136 %.

[00828] In the second HPAF-II study as shown in **Figure 30B**, the highest affinity antibody that affected coagulation (i.e. 39A) and six antibodies with varying affinities from groups 25 and 43 (i.e. 25A, 25A3, 25G1, 43Ea, 43B1 and 43D7) were equally efficacious when dosed twice at 2 mg/kg. Tumor growth inhibition for the TF-specific ADCs ranged between 129 and 139 % on day 21, and 6 to 9 out of 10 animals per treatment arm were classified as tumor-free survivors at the end of the study.

[00829] In the MDA-MB-231 xenograft model, the ADCs were administered on day 1 and 8 post-randomization at 4 or 2 mg/kg. As shown in **Figure 31A**, all the TF-specific ADCs were active at 4 mg/kg, with tumor growth inhibition ranging between 69 and 100 %, and a significant difference in mean tumor volume for each TF-specific ADC compared to the vehicle control arm. While a notable difference was observed in mean tumor volume between 25G1 and the other TF-specific ADCs, it was not statistically significant ($P > 0.05$).

[00830] At 2 mg/kg of ADC as shown in **Figure 31B**, all the TF-specific antibodies showed suboptimal activity with varying degrees of significance in mean tumor volume compared to the vehicle control arm. 25A3, 39A and 43B1 showed the greatest degree of significance in mean tumor volume compared to the vehicle control arm ($P < 1x10^{-4}$). The difference in mean tumor volume between 39A and the other antibodies was only significant for the comparison between 39A and 43Ea ($P < 0.05$).

[00831] In contrast, the unconjugated antibodies of 25A, 25A3 and 43Ea lacked substantial anticancer activity when dosed twice at 10 mg/kg in the HPAF-II xenograft model (**Figure 32**).

[00832] There results indicate that the TF-specific ADCs are efficacious in the HPAF-II and MDA-MB-231 xenograft model under various dosing regimens. The activity of the ADCs are caused by the toxin delivery of the anti-TF antibodies.

Example 31: Studies in Patient-Derived Xenograft (PDX) Models

[00833] TF-positive PDX models were performed in athymic nude mice (Envigo, Indianapolis, IN) to evaluate the efficacy of the ADCs *in vivo*. The animals' care was in accordance with institutional guidelines. Study animals were implanted unilaterally on the left flank with tumor fragments.

[00834] For immunohistochemistry (IHC) analysis, tissues underwent pretreatment using Rip Tide (Mosaic Laboratories, Lake Forest, CA) for 40 min at 95-97 °C in a water bath, cooled for 10 min on the bench, rinsed 3 times with distilled water, and rinsed for 5 min with Splash-T Buffer (Mosaic Laboratories). Tissue sections were blocked in EnVision Peroxidase-Blocking Reagent (EnVision+ Mouse HRP Detection Kit, Agilent, Carpinteria, CA) for 5 min, followed by 2 rinses in Splash-T Buffer for 5 min each. Next, the tissue sections were stained with an anti-TF antibody (mouse clone HTF-1) or a mouse negative control reagent for 30 min, followed by 2 rinses in Splash-T Buffer for 5 min each. The second staining step of the tissue sections was carried out for 30 min with EnVision+ Mouse HRP (EnVision+ Mouse HRP Detection Kit), followed by 2 rinses in Splash-T Buffer for 5 min each. To visualize the anti-TF staining, tissue sections were developed with DAB chromogen (EnVision+ Mouse HRP Detection Kit) for 5 min, followed by 10 dips and a 5 min rinse in distilled water. Tissue sections were counterstained with Hematoxylin for 5 min followed by 3 rinses in distilled water.

[00835] Animals were randomized and treated as indicated in the figures. Animals were removed from study and euthanized once tumor size reached 1200mm^3 or skin ulceration was

evident. In addition, the MTV curve for the treatment group in question was no longer shown once an animal was removed from study due to size. TGI and statistical analyses were conducted in the same manner as for the CDX studies. The CR and PR response definitions were as follows for the PDX studies: a PR responder had a MTV $\leq$ 30 % of MTV at day 1 for 2 consecutive measurements; a CR responder had an undetectable MTV for 2 consecutive measurements. When an animal exhibited a CR response at the end of the study, it was classified as a TFS instead of a CR.

[00836] While the squamous cell carcinoma of the head and neck (SCCHN) and ovarian adenocarcinoma PDX had H-scores of 250 and 220, respectively, the gastric adenocarcinoma PDX had an H-score of 155 (data not shown). Upon randomization of tumor-bearing mice, treatment occurred on a weekly basis either twice or three times with the dose ranging between 2.5 and 5 mg/kg. As shown in **Figures 33A, 33B, and 33C** in all the PDX models a significant reduction in mean tumor volume was observed for each TF-specific ADC compared to the isotype control arm ($P < 1x10^{-4}$), with no significant difference between the various TF-specific ADCs ($P > 0.05$). In the head and neck and ovarian PDX model, the number of complete responders and tumor-free survivors did not exceed 2 out of 10 animals at the end of the study in any of the treatment groups (**Figures 33A and 33B**). However, in the gastric PDX the 25A treatment arm had 2 partial responders, 2 complete responders and 3 tumor-free survivors, and the TF-011 arm contained 1 complete responder and 5 tumor-free survivors at the end of the study (**Figure 33C**).

[00837] These data indicate that the anti-TF ADCs from groups 25 and 43 (i.e. 25A and 43Ea) were equally efficacious as tisotumab vedotin (TF-011) ADC.

Example 32: Efficacy Study in Swine CNV Model

[00838] An efficacy study in a swine choroidal neovascularization (CNV) model was performed to determine the effect 4 different anti-TF antibodies in reducing lesion size.

[00839] 10-12 week old animals (Swine/Hampshire Cross) underwent bilateral laser using an 810 nm Diode laser delivered through an indirect ophthalmoscope to create approximately 6 single laser spots between retinal veins in each eye of each animal. For efficacy assessments, 2mg of each anti-TF antibody, 25G9, 43D8, 1G, and 29D respectively, were administered intravitreally on day 7 post-laser treatment. A vehicle control group was also included in the study. Fluorescein Angiography (FA) to determine total lesion fluorescence was performed on day 7 (baseline), day 14 and day 28. FA was evaluated using a Corrected Total Lesion Fluorescence (CTLF) measurement for each individual lesion. The perimeter of

the lesion was traced, and an integrated density value was obtained. CTLF was then calculated by subtracting the mean fluorescence background adjacent to the lesion from the integrated density measurement. Percent change in lesion size from day 7 to day 14 and from day 7 to day 28 are shown in **Figure 34A** and **Figure 34B**, respectively.

[00840] From day 7 to day 14, anti-hTF antibodies from groups 25 and 43, 25G9 and 43D8, reduced lesion size by greater than 20%. From day 7 to day 28, anti-hTF antibody 25G9 reduced lesion size by greater than 40%. Anti-hTF antibodies 1G and 29D did not reduce lesion size significantly as compared to the vehicle control group.

[00841] This data indicates that antibodies from groups 25 and 43, 25G9 and 43D8, were effective in reducing lesion size in a swine CNV model.

Example 33: Efficacy of 25G9 in Swine CNV Model

[00842] An efficacy study in a swine choroidal neovascularization (CNV) model was performed to compare different doses of anti-TF antibody 25G9 for their ability to reduce lesion size.

[00843] 10-12 week old animals (Swine/Hampshire Cross) underwent bilateral laser using an 810 nm Diode laser delivered through an indirect ophthalmoscope to create approximately 6 single laser spots between retinal veins in each eye. For efficacy assessments 600ug, 2mg and 4mg of anti-TF antibody 25G9 were administered intravitreally on Day 7 post-laser treatment. Fluorescein Angiography (FA) to determine total lesion fluorescence was performed on day 7 (baseline) and day 28. FA was evaluated using a Corrected Total Lesion Fluorescence (CTLF) measurement for each individual lesion. The perimeter of the lesion was traced, and an integrated density value was obtained. CTLF was then calculated by subtracting the mean fluorescence background adjacent to the lesion from the integrated density measurement. Percent changes in lesion size from day 7 to day 28 are shown in **Figure 35**.

[00844] From day 7 to day 28, anti-hTF antibody 25G9 reduced lesion size in a dose-depenent matter. 25G9 reduced lesion size by greater than 50% at 4mg. This data indicates that antibody 25G9 was effective in reducing lesion size in the swine CNV model in a dose-dependent matter.

Example 34: Binding Affinity Assay For Pig TF and Rabbit TF

[00845] The ability of certain antibodies was tested for binding to pig TF. For pig TF Biacore-based measurements, a given anti-TF antibody was captured by an anti-human IgG antibody covalently coupled to a CM5 chip (GE Healthcare Bio-Sciences). Association

between the anti-TF antibodies and a five-point three-fold titration of pig TF-His starting at 100 nM was measured for 180 to 240 sec. Subsequently, dissociation between the anti-TF antibody and TF-His was measured for 1800 sec. Kinetic data was analyzed and fitted globally using a 1:1 binding model. The K_D values of the indicated TF antibodies measured by the Biacore-based experiments are shown in **Table 48**.

[00846] The ability of certain antibodies was tested for binding to rabbit TF. For rabbit TF Biacore-based measurements, a given anti-TF antibody was captured by an anti-human IgG antibody covalently coupled to a CM5 chip (GE Healthcare Bio-Sciences). Association between the anti-TF antibodies and a five-point three-fold titration of rabbit TF-His starting at 100 nM was measured for 180 to 240 sec. Subsequently, dissociation between the anti-TF antibody and TF-His was measured for 1800 sec. Kinetic data was analyzed and fitted globally using a 1:1 binding model. The K_D values of the indicated TF antibodies measured by the Biacore-based experiments are shown in **Table 48**.

[00847] As shown in **Table 48**, anti-hTF antibodies from groups 25 and 43 exhibit binding activity and cross-reactivity to pig TF and rabbit TF. In contrast, antibodies from groups 1 and 29 show no binding activity to pig TF or rabbit TF.

Table 48: Antibody kinetics for pig and rabbit TF

Antibody	**Pig K_D, nM**	**Rabbit K_D, nM**
1G	no binding	no binding
25A	18.7	50.5
25A3	5.5	12.4
25A5	5.2	5.4
25A5-T	4.5	5.4
25G	26.0	75.5
25G1	2.6	3.6
25G9	3.3	4.2
29D	no binding	no binding
43D7	8.8	6.8
43D8	19.2	7.7

no binding*: no binding to weak binding, with no reportable K_D

Example 35: Immunohistochemistry (IHC) Assay

[00848] Tissues underwent pretreatment using Rip Tide (Mosaic Laboratories, Lake Forest, CA) for 40 min at 95-97 °C in a water bath, cooled for 10 min on the bench, rinsed 3

times with distilled water, and rinsed for 5 min with Splash-T Buffer (Mosaic Laboratories). Tissue sections were blocked in EnVision Peroxidase-Blocking Reagent (EnVision+ Mouse HRP Detection Kit, Agilent, Carpinteria, CA) for 5 min, followed by 2 rinses in Splash-T Buffer for 5 min each. The tissue sections were then stained with an anti-TF antibody (mouse clone HTF-1) or a mouse negative control reagent for 30 min, followed by 2 rinses in Splash-T Buffer for 5 min each. The second staining step of the tissue sections was carried out for 30 min with EnVision+ Mouse HRP (EnVision+ Mouse HRP Detection Kit), followed by 2 rinses in Splash-T Buffer for 5 min each. To visualize the anti-TF staining, tissue sections were developed with DAB chromogen (EnVision+ Mouse HRP Detection Kit) for 5 min, followed by 10 dips and a 5 min rinse in distilled water. Tissue sections were counterstained with Hematoxylin for 5 min followed by 3 rinses in distilled water.

[00849] Staining intensity was scored on a semi-quantitative integer scale from 0 (negative) to 3 (or "3+") by a certified anatomic pathologist. The percentage of cells staining positively at each intensity level was recorded. Scoring was based on localization of TF to the cell membrane. The H score combines components of staining intensity with the percentage of positive cells. It has a value between 0 and 300 and is defined as: 1 × (percentage of cells staining at 1+ intensity) + 2 × (percentage of cells staining at 2+ intensity) + 3 × (percentage of cells staining at 3+ intensity) = H score.

[00850] Tissue sections from patients with kidney cancer, head & neck cancer, ovarian cancer, gastric cancer, prostate cancer, gastroesophageal junction cancer, cervical cancer, and glioblastoma were stained. The number of patients with scores within each H score range and the total number of patient for each cancer are shown in **Table 50**. These results indicate that TF is expressed in kidney cancer, head & neck cancer, ovarian cancer, gastric cancer, prostate cancer, gastroesophageal junction cancer, cervical cancer, and glioblastoma.

Table 50: Results of IHC assay

Indication	**H score 0**	**H score 1-100**	**H score 101-200**	**H score 201-300**
Kidney	19/28	6/28	1/28	2/28
Head & Neck	4/74	31/74	19/74	20/74
Ovarian	13/26	11/26	0/26	2/26
Gastric	1/20	9/20	4/20	6/20
Prostrate	1/24	8/24	7/24	8/24
Pancreatic	14/37	18/37	5/37	0/37
Gastroesophageal junction	28/59	23/59	6/59	2/59
Cervical	31/60	21/60	7/60	1/60
Glioblastoma	2/41	7/41	23/41	9/41

Example 36: Epitope Binning of Anti-TF Antibodies

[00851] To establish epitope binding differences between the anti-human TF antibodies, chimeric TF construct mapping experiments were conducted. This mapping technique enables discrimination of antibody epitopes.

[00852] Because all the anti-human TF antibodies evaluated do not bind rat TF, the rat TF sequence was used for the construction of chimeric human-rat TF constructs. Chimeric human-rat construct design was guided by the N- and C-terminal domain of TF extracellular domain (amino acids 1 – 107 and 108 – 219 of the extracellular domain, respectively), with an alignment shown in **Figure 36**. Based on the chimera mapping results using the constructs from **Figure 36**, rat amino acid segment 141 – 194 was replaced by the human sequence (amino acid 136 – 189 of hTF extracelluar domain), with an alignment shown in **Figure 37**. Design of three human TF constructs with either 1 or 2 human–rat substitutions (hTF_K68N, hTF_K149N and hTF_N171H_T197K) was based on reported contact residues K68, K149 and N171 and T197 for the 10H10 antibody (Teplyakov et al., *Cell Signal.*, 2017, 36:139-144), with an alignment shown in **Figure 38**.

[00853] To establish binding of the anti-human TF antibodies to the various TF constructs, HEK293 cells were transfected with a DNA plasmid that co-expresses the TF construct and a green fluorescent protein marker. For a subset of the antibodies, an antibody titration (a 12-point 1:3 dilution series starting at 250 nM) was evaluated on select TF constructs (**Figures 39A-F**). These antibody titrations demonstrated that the antibody concentration of 15 µg /ml (100 nM) used in **Tables 51 and 52** was appropriate to establish "Percentage antibody binding to TF construct relative to hTF". Two days after transfection, cells were collected from the tissue culture plate, stained with 15 µg/ml of the indicated anti-TF antibody, washed, stained with anti-human IgG-Fc Alexa Fluor 647 polyclonal antibody, washed, and stained with the viability dye 4',6-Diamidino-2-Phenylindole, Dihydrochloride. Upon acquisition of 80,000 live events on a flow cytometer, live cells marked with the fluorescent marker were analyzed for the degree of staining by the anti-TF antibody. The median fluorescence intensity values relative to an isotype control for each TF expression construct were divided by the median fluorescence intensity value relative to an isotype control for the hTF expression construct, and the resulting percentage listed as "Percentage antibody binding to TF construct relative to hTF" in **Tables 51 and 52**. As used herein, the term "live cell staining assay" refers to the antibody binding assay used in this example.

[00854] The assumption that all chimeric TF constructs were expressed on the cell surface at levels between 50% and 150% of the hTF control construct was met for all TF constructs

for at least one anti-human TF antibody in the antibody collection, with the exception of the h1-107_r construct (human amino acid segment 1–107 replaced by rat sequence). Lack of binding of the anti-human TF antibodies to cell surface-expressed rat TF was expected. When "Percentage antibody binding to TF construct relative to hTF" in **Tables 51 and 52** was less than 50%, the antibody was considered a non-binder (0) in **Tables 53 and 54**. When "Percentage antibody binding to TF construct relative to hTF" in **Tables 51 and 52** was between 50% and 150%, the antibody was considered a binder (1) in **Tables 53 and 54**.

[00855] Each antibody was assigned to an epitope bin in **Table 55** based on the combination of unbound constructs from **Table 53**. The antibodies from Lineage 25 (25A, 25A3, 25A5-T, 25G1 and 25G9) bind a unique epitope, referred to as Epitope Bin 6 in **Table 55**. The antibodies from Lineage 43 (43B1, 43D7, 43D8 and 43Ea) also bind a unique epitope, referred to as Epitope Bin 7 in **Table 55**. The antibody from Lineage 29 (29E) binds a unique epitope, referred to as Epitope Bin 2 in **Table 55**. The antibodies from Lineage 39 and 54 (39A and 54E) bind a unique epitope, referred to as Epitope Bin 3 in **Table 55**.

[00856] Lineage 25 and 43 antibodies are the only antibodies in the antibody panel that bind r141-194_h, the chimeric construct in which rat amino acids 141–194 were replaced by human sequence (**Figure 39F**; **Table 54**). Furthermore, while M1593 cannot bind hTF_K68N, all the other antibodies in the antibody panel bind hTF_K68N (**Figure 39C**; **Table 54**). Only Lineage 25 and 43 antibodies cannot bind hTF_K149N (**Figure 39D**; **Table 54**). Only Lineage 25 antibodies cannot bind hTF_N171H_T197K (**Figure 39E**; **Table 54**).

[00857] In summary, these results indicate that lineage 25 antibodies bind a unique epitope on human TF compared to all other antibodies tested. Lineage 43 antibodies bind a unique epitope on human TF compared to all other antibodies tested. Lineage 25 and lineage 43 antibodies bind a different epitope on human TF from M1593.

Table 51: Percent antibody binding to TF construct relative to hTF

		Antibody														
	Construct	**1F**	**29E**	**39A**	**54E**	**TF-011**	**5G9**	**M1593**	**25A**	**25A3**	**25A5-T**	**25G1**	**25G9**	**43B1**	**43D7**	**43D8**	**43Ea**
	hTF	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	rTF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Human amino acid segment replaced by rat segment (in parentheses: number of amino acid changes relative to human TF)	**h1-107_r** (52)	0	0	0	0	0	41	0	32	36	36	37	28	33	35	31	37
	h1-77_r (25)	0	0	0	0	0	94	0	86	95	84	88	64	64	75	69	69
	h1-38_r (14)	91	87	100	102	104	100	104	101	104	93	101	88	97	106	104	103
	h39-77_r (11)	0	0	0	0	0	88	2	82	88	80	87	71	59	75	71	69
	h78-107_r (21)	0	8	81	68	32	114	74	108	116	103	113	108	113	114	117	114
	h78-107_r.v2 (27)	0	0	76	62	23	101	59	95	96	91	94	93	97	100	101	101
	h78-93_r (18)	102	0	77	91	110	102	104	106	105	92	101	98	101	104	102	103
	h94-107_r (9)	1	82	85	89	27	91	46	82	86	78	83	77	84	92	89	91
	h108-219_r (46)	119	118	118	122	128	0	0	0	0	0	0	0	0	0	0	0
	h108-158_r (19)	98	101	107	108	108	63	4	1	0	0	11	22	0	1	0	0
	h108-132_r (10)	105	108	109	107	124	125	124	112	112	106	111	118	122	126	122	124
	h133-158_r (9)	113	122	119	130	134	91	0	0	0	0	2	3	0	4	1	0
	h133-145_r (4)	84	95	96	104	104	108	100	77	80	80	87	100	99	104	103	106
	h133-139_r (2)	82	90	95	103	102	104	103	88	89	88	91	86	94	101	97	101
	h140-145_r (2)	89	100	101	110	109	113	97	80	87	86	89	105	101	104	104	109
	h146-158_r (5)	115	122	125	134	134	91	133	2	17	18	17	0	3	20	10	0
	h146-151_r (1)	122	133	139	142	143	141	118	3	14	17	7	0	11	39	23	2
	h152-158_r (4)	110	121	128	127	136	82	132	110	116	112	116	111	119	134	129	134
	h159-219_r (27)	132	134	141	142	155	0	137	0	0	0	0	0	132	130	130	76
	h159-189_r (11)	94	101	104	110	112	0	105	0	0	0	0	0	100	106	104	94
	h159-174_r (6)	96	98	101	118	120	0	98	0	0	0	0	0	103	115	112	101
	h159-166_r (3)	89	93	96	100	98	104	100	93	95	87	91	88	99	106	105	110
	h167-174_r (3)	96	112	96	122	128	0	118	0	0	0	0	0	109	121	112	104
	h175-189_r (5)	97	113	112	118	123	119	114	86	95	99	100	86	109	118	114	122
	h190-219_r (16)	111	138	149	141	145	12	143	125	124	119	127	144	133	140	136	147

Table 52: Percent antibody binding to TF construct relative to hTF

	Antibody															
Construct	**1F**	**29E**	**39A**	**54E**	**TF-011**	**5G9**	**M1593**	**25A**	**25A3**	**25A5-T**	**25G1**	**25G9**	**43B1**	**43D7**	**43D8**	**43Ea**
hTF	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
rTF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
r141-194_h*	0	0	0	0	0	32	0	65	89	88	83	108	90	102	95	81
hTF_K68N	105	115	119	118	111	132	0	93	124	126	115	103	107	116	119	118
hTF_K149N	115	117	131	127	132	145	111	2	12	13	7	0	10	29	20	1
hTF_N171H_T197K	83	98	94	89	109	102	113	1	4	7	1	0	98	101	103	118

*rat amino acid segment replaced by human segment, resulting in 20 amino acid changes

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Table 53: Antibody binding to TF construct

Human amino acid segment replaced by rat segment (in parentheses: number of amino acid changes relative to human TF)	Construct	Antibody														
		1F	29E	39A	54E	TF-011	5G9	M1593	25A	25A3	25A5-T	25G1	25G9	43B1	43D7	43D8	43Ea
	hTF	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	rTF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h1-107_r (52)		0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
h1-77_r (25)		0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1
h1-38_r (14)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h39-77_r (11)		0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1
h78-107_r (21)		0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1
h78-107_r.v2 (27)		0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1
h78-93_r (18)		1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h94-107_r (9)		0	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1
h108-219_r (46)		1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0
h108-158_r (19)		1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
h108-132_r (10)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h133-158_r (9)		1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
h133-145_r (4)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h133-139_r (2)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h140-145_r (2)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h146-158_r (5)		1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
h146-151_r (1)		1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
h152-158_r (4)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h159-219_r (27)		1	1	1	1	1	0	1	0	0	0	0	0	1	1	1	1
h159-189_r (11)		1	1	1	1	1	0	1	0	0	0	0	0	1	1	1	1
h159-174_r (6)		1	1	1	1	1	0	1	0	0	0	0	0	1	1	1	1
h159-166_r (3)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h167-174_r (3)		1	1	1	1	1	0	1	0	0	0	0	0	1	1	1	1
h175-189_r (5)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
h190-219_r (16)		1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1

Table 54: Antibody binding to TF construct

	Antibody															
Construct	**1F**	**29E**	**39A**	**54E**	**TF-011**	**5G9**	**M1593**	**25A**	**25A3**	**25A5-T**	**25G1**	**25G9**	**43B1**	**43D7**	**43D8**	**43Ea**
hTF	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
rTF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
r141-194_h*	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1
hTF_K68N	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
hTF_K149N	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
hTF_N171H_T197K	1	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1

*rat amino acid segment replaced by human segment, resulting in 20 amino acid changes

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Table 55: Epitope Bin assignment based on unbound chimeric constructs

Antibody	Constructs not bound by antibody	Epitope Bin
1F	rTF, h1-107_r, h1-77_r, h39-77_r, h78-107_r, h78-107_r.v2, h94-107_r	1
29E	rTF, h1-107_r, h1-77_r, h39-77_r, h78-107_r, h78-107_r.v2, h78-93_r	2
39A	rTF, h1-107_r, h1-77_r, h39-77_r	3
54E	rTF, h1-107_r, h1-77_r, h39-77_r	3
TF-011	rTF, h1-107_r, h1-77_r, h39-77_r, h78-107_r, h78-107_r.v2, h94-107_r	1
5G9	rTF, h1-107_r, h108-219_r, h159-219_r, h159-189_r, h159-174_r, h167-174_r, h190-219_r	4
M1593	rTF, h1-107_r, h1-77_r, h39-77_r, h94-107_r, h108-219_r, h108-158_r, h133-158_r	5
25A	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r, h159-219_r, h159-189_r, h159-174_r, h167-174_r	6
25A3	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r, h159-219_r, h159-189_r, h159-174_r, h167-174_r	6
25A5-T	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r, h159-219_r, h159-189_r, h159-174_r, h167-174_r	6
25G1	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r, h159-219_r, h159-189_r, h159-174_r, h167-174_r	6
25G9	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r, h159-219_r, h159-189_r, h159-174_r, h167-174_r	6
43B1	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r	7
43D7	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r	7
43D8	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r	7
43Ea	rTF, h1-107_r, h108-219_r, h108-158_r, h133-158_r, h146-158_r, h146-151_r	7

[00858] While the invention has been particularly shown and described with reference to a preferred embodiment and various alternate embodiments, it will be understood by persons skilled in the relevant art that various changes in form and details can be made therein without departing from the spirit and scope of the invention.

[00859] All references, issued patents and patent applications cited within the body of the instant specification are hereby incorporated by reference in their entirety, for all purposes.

SEQUENCES

Table 13: Variable region sequences

Clone	VH Domains (SEQ ID NO)	VL Domains (SEQ ID NO)
1F	EVQLLESGGGLVQPGGSLRLSCAASGF TFSDYAMGWVRQAPGKGLEWVSTISG SGGLTYYADSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCAKAPYGYYM DVWGKGTTVTVSS (SEQ ID NO:37)	DIQMTQSPSTLSASVGDRVTITCRASQS ISSWLAWYQQKPGKAPKLLIYKASSLE SGVPSRFSGSGSGTEFTLTISSLQPDDF ATYYCQQYKSYITFGGGTKVEIK (SEQ ID NO:38)
1G	EVQLLESGGGLVQPGGSLRLSCAASGF TFSSYAMAWVRQAPGKGLEWVSAISG SGGLTYYADSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCAKAPYGYYM DVWGKGTTVTVSS (SEQ ID NO:75)	DIQMTQSPSTLSASVGDRVTITCRASQS ISSWLAWYQQKPGKAPKLLIYKASSLE SGVPSRFSGSGSGTEFTLTISSLQPDDF ATYYCQQYKSYITFGGGTKVEIK (SEQ ID NO:76)
25A	QVQLVQSGAEVKKPGASVKVSCKASG YTFDVYGISWVRQAPGQGLEWMGWI APYNGNTNYAQKLQGRVTMTTDTSTS TAYMELRSLRSDDTAVYYCARDAGTY SPFGYGMDVWGQGTTVTVSS (SEQ ID NO:113)	DIQMTQSPSTLSASVGDRVTITCRASQS ISSWLAWYQQKPGKAPKLLIYKASSLE SGVPSRFSGSGSGTEFTLTISSLQPDDF ATYYCQQFQSLPPFTFGGGTKVEIK (SEQ ID NO:114)
25A3	QVQLVQSGAEVKKPGASVKVSCKASG YTFDVYGISWVRQAPGQGLEWMGWI APYSGNTNYAQKLQGRVTMTTDTSTS TAYMELRSLRSDDTAVYYCARDAGTY SPFGYGMDVWGQGTTVTVSS (SEQ ID NO:151)	DIQMTQSPSTLSASVGDRVTITCQASQS INNWLAWYQQKPGKAPKLLIYKAYNL ESGVPSRFSGSGSGTEFTLTISSLQPDDF ATYYCQLFQSLPPFTFGGGTKVEIK (SEQ ID NO:152)
25A5	QVQLVQSGAEVKKPGASVKVSCKASG YTFDVYGISWVRQAPGQGLEWMGWI APYSGNTNYAQKLQGRVTMTTDTSTS TAYMELRSLRSDDTAVYYCARDAGTY SPFGYGMDVWGQGTTVTVSS (SEQ ID NO:189)	DIQMTQSPSTLSASVGDRVTITCRASES ISNWLAWYQQKPGKAPKLLIYKAYSL EYGVPSRFSGSGSGTEFTLTISSLQPDD FATYYCQQFQKLPPFTFGGGTKVEIK (SEQ ID NO:190)
25A5-T	QVQLVQSGAEVKKPGASVKVSCKASG YTFDAYGISWVRQAPGQGLEWMGWI APYSGNTNYAQKLQGRVTMTTDTSTS TAYMELRSLRSDDTAVYYCARDAGTY SPFGYGMDVWGQGTTVTVSS (SEQ ID NO:836)	DIQMTQSPSTLSASVGDRVTITCRASES ISNWLAWYQQKPGKAPKLLIYKAYSL EYGVPSRFSGSGSGTEFTLTISSLQPDD FATYYCQQFQKLPPFTFGGGTKVEIK (SEQ ID NO:837)
25G	QVQLVQSGAEVKKPGASVKVSCKASG YTFRSYGISWVRQAPGQGLEWMGWV APYNGNTNYAQKLQGRVTMTTDTSTS TAYMELRSLRSDDTAVYYCARDAGTY SPYGYGMDVWGQGTTVTVSS (SEQ ID NO:227)	DIQMTQSPSTLSASVGDRVTITCRASQS ISSWLAWYQQKPGKAPKLLIYKASSLE SGVPSRFSGSGSGTEFTLTISSLQPDDF ATYYCQQFQSLPPFTFGGGTKVEIK (SEQ ID NO:228)
25G1	QVQLVQSGAEVKKPGASVKVSCKASG YTFRSYGISWVRQAPGQGLEWMGWV APYSGNTNYAQKLQGRVTMTTDTSTS TAYMELRSLRSDDTAVYYCARDAGTY SPYGYGMDVWGQGTTVTVSS (SEQ ID NO:265)	DIQMTQSPSTLSASVGDRVTITCRASHS IDSWLAWYQQKPGKAPKLLIYKASYL ESGVPSRFSGSGSGTEFTLTISSLQPDDF ATYYCQLFQSLPPFTFGGGTKVEIK (SEQ ID NO:266)
25G9	QVQLVQSGAEVKKPGASVKVSCKASG YTFRSYGISWVRQAPGQGLEWMGWV APYSGNTNYAQKLQGRVTMTTDTSTS TAYMELRSLRSDDTAVYYCARDAGTY	DIQMTQSPSTLSASVGDRVTITCQASQS IDSWLAWYQQKPGKAPKLLIYSASYLE SGVPSRFSGSGSGTEFTLTISSLQPDDF

Clone	VH Domains (SEQ ID NO)	VL Domains (SEQ ID NO)
	SPYGYGMDVWGQGTTVTVSS (SEQ ID NO:303)	ATYYCQRFQSLPPFTFGGGTKVEIK (SEQ ID NO:304)
29D	QVQLVESGGGVVQPGRSLRLSCAASG FTFHSRGMHWVRQAPGKGLEWVAVIT YDGINKYYADSVEGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARDGVYYG VYDYWGQGTLVTVSS (SEQ ID NO:341)	DIVMTQSPDSLAVSLGERATINCKSSQS VLFSSNNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTIS SLQAEDVAVYYCQQFHSYPLTFGGGT KVEIK (SEQ ID NO:342)
29E	QVQLVESGGGVVQPGRSLRLSCAASG FTFRSYGMHWVRQAPGKGLEWVAVIT YDGINKYYADSVEGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCARDGVYYG VYDYWGQGTLVTVSS (SEQ ID NO:379)	DIVMTQSPDSLAVSLGERATINCKSSQS VLFSSNNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTIS SLQAEDVAVYYCQQFHSYPLTFGGGT KVEIK (SEQ ID NO:380)
39A	QVQLVQSGAEVKKPGSSVKVSCKASG GTFSSNAIGWVRQAPGQGLEWMGSIIP IIGFANYAQKFQGRVTITADESTSTAY MELSSLRSEDTAVYYCARDSGYYYGA SSFGMDVWGQGTTVTVSS (SEQ ID NO:417)	EIVMTQSPATLSVSPGERATLSCRASQS VSSNLAWYQQKPGQAPRLLIYGASTR ATGIPARFSGSGSGTEFTLTISSLQSEDF AVYYCEQYNNLPLTFGGGTKVEIK (SEQ ID NO:418)
43B	QVQLQESGPGLVKPSQTLSLTCTVSGG SISSGQYWSWIRQHPGKGLEWIGEIYY SGSTRYNPSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYCARDAPYYYGGGY YYYMDVWGKGTTVTVSS (SEQ ID NO:455)	EIVLTQSPGTLSLSPGERATLSCRASQS VSSSYLAWYQQKPGQAPRLLIYGASSR ATGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQVGVVPYTFGGGTKVEIK (SEQ ID NO:456)
43B1	QVQLQESGPGLVKPSQTLSLTCTVSGG SISSGQYWSWIRQHPGKGLEWIGEIYY SGSTRYNPSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYCARDAPYYYGGGY YYYMDVWGKGTTVTVSS (SEQ ID NO:493)	EIVLTQSPGTLSLSPGERATLSCRASES VDSSYLAWYQQKPGQAPRLLIYGAST RQTGIPDRFSGSGSGTDFTLTISRLEPED FAVYYCQQAGVVPYTFGGGTKVEIK (SEQ ID NO:494)
43B7	QVQLQESGPGLVKPSQTLSLTCTVSGG SISSGQYWSWIRQHPGKGLEWIGEIYY SGSTRYNPSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYCARDAPYYYGGGY YYYMDVWGKGTTVTVSS (SEQ ID NO:531)	EIVLTQSPGTLSLSPGERATLSCRASES VDSSYLAWYQQKPGQAPRLLIYGADS RATGIPDRFSGSGSGTDFTLTISRLEPED FAVYYCQQDGVVPYTFGGGTKVEIK (SEQ ID NO:532)
43D	QVQLQQWGAGLLKPSETLSLTCAVYG GSLSGYYWSWIRQPPGKGLEWIGEIGA SGSTRYNPSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYCARDTPYYYEGGY YYYMDVWGKGTTVTVSS (SEQ ID NO:569)	EIVLTQSPGTLSLSPGERATLSCRASQS VSSSYLAWYQQKPGQAPRLLIYGASSR ATGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQVGVVPYTFGGGTKVEIK (SEQ ID NO:570)
43D7	QVQLQQWGAGLLKPSETLSLTCAVYG GSLSGYYWSWIRQPPGKGLEWIGEIGA SGSTRYNPSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYCARDTPYYYEGGY YYYMDVWGKGTTVTVSS (SEQ ID NO:607)	EIVLTQSPGTLSLSPGERATLSCRASDS VDSSYLAWYQQKPGQAPRLLIYGAFS RANGIPDRFSGSGSGTDFTLTISRLEPE DFAVYYCQQAGVVPYTFGGGTKVEIK (SEQ ID NO:608)
43D8	QVQLQQWGAGLLKPSETLSLTCAVYG GSLSGYYWSWIRQPPGKGLEWIGEIGA SGSTRYNPSLKSRVTISVDTSKNQFSLK	EIVLTQSPGTLSLSPGERATLSCRASQS VSSSFLAWYQQKPGQAPRLLIYGAYSR ATGIPDRFSGSGSGTDFTLTISRLEPEDF

Clone	VH Domains (SEQ ID NO)	VL Domains (SEQ ID NO)
	LSSVTAADTAVYYCARDTPYYYEGGY YYYMDVWGKGTTVTVSS (SEQ ID NO:645)	AVYYCQQAGVVPYTFGGGTKVEIK (SEQ ID NO:646)
43E	QVQLQESGPGLVKPSQTLSLTCTVSGG SISSGQYWSWIRQHPGKGLEWIGEIYY SGSTRYNPSLKSRVTISVDTSKDQFSLK LSSVTAADTAVYYCARDTPYYYDGGY YYYMDVWGKGTTVTVSS (SEQ ID NO:683)	EIVLTQSPGTLSLSPGERATLSCRASQS VSSSYLAWYQQKPGQAPRLLIYGASSR ATGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQVGVVPYTFGGGTKVEIK (SEQ ID NO:684)
43Ea	QVQLQESGPGLVKPSQTLSLTCTVSGG SISSGQYWSWIRQHPGKGLEWIGEIYY SGSTRYNPSLKSRVTISVDTSKNQFSLK LSSVTAADTAVYYCARDTPYYYDGGY YYYMDVWGKGTTVTVSS (SEQ ID NO:721)	EIVLTQSPGTLSLSPGERATLSCRASQS VSSSYLAWYQQKPGQAPRLLIYGASSR ATGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQVGVVPYTFGGGTKVEIK (SEQ ID NO:722)
54E	QVQLVQSGAEVKKPGASVKVSCKASG YTFANYYMHWVRQAPGQGLEWMGII NPSGGITVYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARGGSKVA ALAFDIWGQGTMVTVSS (SEQ ID NO:759)	DIQMTQSPSSLSASVGDRVTITCQASQ DISNSLNWYQQKPGKAPKLLIYDASNL ETGVPSRFSGSRSGTDFTFTISSLQPEDI ATYYCQQYNFHPLTFGGGTKVEIK (SEQ ID NO:760)

Table 14: Variable region sequence consensus

Group	VH Domain Consensus (SEQ ID NO)	VL Domain Consensus (SEQ ID NO)
1	EVQLLESGGGLVQPGGSLRLSCAASGF TFSx[D/S]YAMx[A/G]WVRQAPGKGLE WVSx[A/T]ISGSGGLTYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYC AKAPYGYYMDVWGKGTTVTVSS (SEQ ID NO:761)	DIQMTQSPSTLSASVGDRVTITCRASQ SISSWLAWYQQKPGKAPKLLIYKASSL ESGVPSRFSGSGSGTEFTLTISSLQPDD FATYYCQQYKSYITFGGGTKVEIK (SEQ ID NO:762)
25	QVQLVQSGAEVKKPGASVKVSCKASG YTFx[D/R]x[S/V/A]YGISWVRQAPGQG LEWMGWx[I/V]APYx[S/N]GNTNYAQK LQGRVTMTTDTSTSTAYMELRSLRSD DTAVYYCARDAGTYSPx[F/Y]GYGMD VWGQGTTVTVSS (SEQ ID NO:763)	DIQMTQSPSTLSASVGDRVTITCx[R/Q] ASx[Q/E/H]SIx[S/D/N]x[S/N]WLAWYQ QKPGKAPKLLIYx[K/S]Ax[S/Y]x[S/Y/N] LEx[S/Y]GVPSRFSGSGSGTEFTLTISSL QPDDFATYYCQx[Q/L/R]FQx[S/K]LPPF TFGGGTKVEIK (SEQ ID NO:764)
29	QVQLVESGGGVVQPGRSLRLSCAASG FTFx[H/R]Sx[R/Y]GMHWVRQAPGKGL EWVAVITYDGINKYYADSVEGRFTISR DNSKNTLYLQMNSLRAEDTAVYYCA RDGVYYGVYDYWGQGTLVTVSS (SEQ ID NO:765)	DIVMTQSPDSLAVSLGERATINCKSSQ SVLFSSNNKNYLAWYQQKPGQPPKLL IYWASTRESGVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYCQQFHSYPLTFGGG TKVEIK (SEQ ID NO:766)
39	QVQLVQSGAEVKKPGSSVKVSCKASG GTFSSNAIGWVRQAPGQGLEWMGSIIP IIGFANYAQKFQGRVTITADESTSTAY MELSSLRSEDTAVYYCARDSGYYYGA SSFGMDVWGQGTTVTVSS (SEQ ID NO:767)	EIVMTQSPATLSVSPGERATLSCRASQ SVSSNLAWYQQKPGQAPRLLIYGAST RATGIPARFSGSGSGTEFTLTISSLQSED FAVYYCEQYNNLPLTFGGGTKVEIK (SEQ ID NO:768)
43	QVQLQx[E/Q]x[S/W]Gx[P/A]GLx[V/L]K PSx[Q/E]TLSLTCx[T/A]Vx[S/Y]GGSx[I/ L]SSGx[Q/Y]YWSWIRQx[H/P]PGKGLE WIGEIx[Y/G]x[Y/A]SGSTRYNPSLKSRV	EIVLTQSPGTLSLSPGERATLSCRASx[Q /E/D]SVx[S/D]SSx[Y/F]LAWYQQKPGQ APRLLIYGAx[S/D/F/Y]x[S/T]Rx[A/Q]x[T/N]GIPDRFSGSGSGTDFTLTISRLEPE

Group	VH Domain Consensus (SEQ ID NO)	VL Domain Consensus (SEQ ID NO)
	TISVDTSKx[N/D]QFSLKLSSVTAADTAVYYCARDx[T/A]PYYYx[E/G/D]GGYYYYMDVWGKGTTVTVSS (SEQ ID NO:769)	DFAVYYCQQx[V/A/D]GVVPYTFGGGTKVEIK (SEQ ID NO:770)
54	QVQLVQSGAEVKKPGASVKVSCKASGYTFANYYMHWVRQAPGQGLEWMGIINPSGGITVYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGSKVAALAFDIWGQGTMVTVSS (SEQ ID NO:771)	DIQMTQSPSSLSASVGDRVTITCQASQDISNSLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSRSGTDFTFTISSLQPEDIATYYCQQYNFHPLTFGGGTKVEIK (SEQ ID NO:772)

Table 15: Antibody 1F-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GFTFSDYAMG (SEQ ID NO:1)	DYAMG (SEQ ID NO:7)	GFTFSDY (SEQ ID NO:13)	GFTFSDYAMG (SEQ ID NO:19)	SDYAMG (SEQ ID NO:25)	GFTFSDYA (SEQ ID NO:31)
	VH CDR2	TISGSGGLTYYA DSVKG (SEQ ID NO:2)	TISGSGGLTYYA DSVKG (SEQ ID NO:8)	GSGG (SEQ ID NO:14)	TISGSGGLTY (SEQ ID NO:20)	WVSTISGSGGLT Y (SEQ ID NO:26)	ISGSGGLT (SEQ ID NO:32)
	VH CDR3	APYGYYMDV (SEQ ID NO:3)	APYGYYMDV (SEQ ID NO:9)	PYGYYMD (SEQ ID NO:15)	APYGYYMDV (SEQ ID NO:21)	AKAPYGYYMD (SEQ ID NO:27)	AKAPYGYYMDV (SEQ ID NO:33)
VL CDR Seq.	*VL CDR1*	RASQSISSWLA (SEQ ID NO:4)	RASQSISSWLA (SEQ ID NO:10)	SQSISSW (SEQ ID NO:16)	RASQSISSWLA (SEQ ID NO:22)	SSWLAWY (SEQ ID NO:28)	QSISSW (SEQ ID NO:34)
	VL CDR2	KASSLES (SEQ ID NO:5)	KASSLES (SEQ ID NO:11)	KAS (SEQ ID NO:17)	KASSLES (SEQ ID NO:23)	LLIYKASSLE (SEQ ID NO:29)	KAS (SEQ ID NO:35)
	VL CDR3	QQYKSYIT (SEQ ID NO:6)	QQYKSYIT (SEQ ID NO:12)	YKSYI (SEQ ID NO:18)	QQYKSYIT (SEQ ID NO:24)	QQYKSYI (SEQ ID NO:30)	QQYKSYIT (SEQ ID NO:36)
VH Sequence*: EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSDYAMG**WVRQAPGKGLEWVS**TISGSGGLTYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTA VYYCAK**APYGYYMDV**WGKGTTVTVSS (SEQ ID NO:37)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**RASQSISSWLA**WYQQKPGKAPKLLIY**KASSLES**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QQYKSYIT** FGGGTKVEIK (SEQ ID NO:38)							

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

Table 16: Antibody 1G-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GFTFSSYAMA (SEQ ID NO:39)	SYAMA (SEQ ID NO:45)	GFTFSSY (SEQ ID NO:51)	GFTFSSYAMA (SEQ ID NO:57)	SSYAMA (SEQ ID NO:63)	GFTFSSYA (SEQ ID NO:69)
	VH CDR2	AISGSGGLTYYA DSVKG (SEQ ID NO:40)	AISGSGGLTYYA DSVKG (SEQ ID NO:46)	GSGG (SEQ ID NO:52)	AISGSGGLTY (SEQ ID NO:58)	WVSAISGSGGLT Y (SEQ ID NO:64)	ISGSGGLT (SEQ ID NO:70)
	VH CDR3	APYGYYMDV (SEQ ID NO:41)	APYGYYMDV (SEQ ID NO:47)	PYGYYMD (SEQ ID NO:53)	APYGYYMDV (SEQ ID NO:59)	AKAPYGYYMD (SEQ ID NO:65)	AKAPYGYYMDV (SEQ ID NO:71)
VL CDR Seq.	*VL CDR1*	RASQSISSWLA (SEQ ID NO:42)	RASQSISSWLA (SEQ ID NO:48)	SQSISSW (SEQ ID NO:54)	RASQSISSWLA (SEQ ID NO:60)	SSWLAWY (SEQ ID NO:66)	QSISSW (SEQ ID NO:72)
	VL CDR2	KASSLES (SEQ ID NO:43)	KASSLES (SEQ ID NO:49)	KAS (SEQ ID NO:55)	KASSLES (SEQ ID NO:61)	LLIYKASSLE (SEQ ID NO:67)	KAS (SEQ ID NO:73)
	VL CDR3	QQYKSYIT (SEQ ID NO:44)	QQYKSYIT (SEQ ID NO:50)	YKSYI (SEQ ID NO:56)	QQYKSYIT (SEQ ID NO:62)	QQYKSYI (SEQ ID NO:68)	QQYKSYIT (SEQ ID NO:74)
VH Sequence*: EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSYAMA**WVRQAPGKGLEWVS**AISGSGGLTYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTA VYYCAK**APYGYYMDV**WGKGTTVTVSS (SEQ ID NO:75)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**RASQSISSWLA**WYQQKPGKAPKLLIY**KASSLES**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QQYKSYIT** FGGGTKVEIK (SEQ ID NO:76)							

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

Table 17: 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)	ARDAGTYSPFGT 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 18: 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	WIAPYSGNTNYAQKLQG (SEQ ID NO:116)	WIAPYSGNTNYAQKLQG (SEQ ID NO:122)	PYSG (SEQ ID NO:128)	WIAPYSGNTN (SEQ ID NO:134)	WMGWIAPYSGNTN (SEQ ID NO:140)	IAPYSGNT (SEQ ID NO:146)
	VH CDR3	DAGTYSPFGYGMDV (SEQ ID NO:117)	DAGTYSPFGYGMDV (SEQ ID NO:123)	AGTYSPFGYGMD (SEQ ID NO:129)	DAGTYSPFGYGMDV (SEQ ID NO:135)	ARDAGTYSPFGYGMD (SEQ ID NO:141)	ARDAGTYSPFGTGMDV (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**RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR**DAGTYSPFGYGMDV**WGQGTTVTVSS (SEQ ID NO:151)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**QASQSINNWLA**WYQQKPGKAPKLLIY**KAYNLES**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QLFQSLPPFT**FGGGTKVEIK (SEQ ID NO:152)							

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

Table 19a: 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	WIAPYSGNTNYAQKLQG (SEQ ID NO:154)	WIAPYSGNTNYAQKLQG (SEQ ID NO:160)	PYSG (SEQ ID NO:166)	WIAPYSGNTN (SEQ ID NO:172)	WMGWIAPYSGNTN (SEQ ID NO:178)	IAPYSGNT (SEQ ID NO:184)
	VH CDR3	DAGTYSPFGYGMDV (SEQ ID NO:155)	DAGTYSPFGYGMDV (SEQ ID NO:161)	AGTYSPFGYGMD (SEQ ID NO:167)	DAGTYSPFGYGMDV (SEQ ID NO:173)	ARDAGTYSPFGYGMD (SEQ ID NO:179)	ARDAGTYSPFGTGMDV (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**RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR**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 19b: 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	WIAPYSGNTNYAQKLQG (SEQ ID NO:885)	WIAPYSGNTNYAQKLQG (SEQ ID NO:891)	PYSG (SEQ ID NO:897)	WIAPYSGNTN (SEQ ID NO:903)	WMGWIAPYSGNTN (SEQ ID NO:909)	IAPYSGNT (SEQ ID NO:915)
	VH CDR3	DAGTYSPFGYGMDV (SEQ ID NO:886)	DAGTYSPFGYGMDV (SEQ ID NO:892)	AGTYSPFGYGMD (SEQ ID NO:898)	DAGTYSPFGYGMDV (SEQ ID NO:904)	ARDAGTYSPFGYGMD (SEQ ID NO:910)	ARDAGTYSPFGTGMDV (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**RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR**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

Table 20: Antibody 25G-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GYTFRSYGIS (SEQ ID NO:191)	SYGIS (SEQ ID NO:197)	GYTFRSY (SEQ ID NO:203)	GYTFRSYGIS (SEQ ID NO:209)	RSYGIS (SEQ ID NO:215)	GYTFRSYG (SEQ ID NO:221)
	VH CDR2	WVAPYNGNTNY AQKLQG (SEQ ID NO:192)	WVAPYNGNTNY AQKLQG (SEQ ID NO:198)	PYNG (SEQ ID NO:204)	WVAPYNGNTN (SEQ ID NO:210)	WMGWVAPYNG NTN (SEQ ID NO:216)	VAPYNGNT (SEQ ID NO:222)
	VH CDR3	DAGTYSPYGYG MDV (SEQ ID NO:193)	DAGTYSPYGYG MDV (SEQ ID NO:199)	AGTYSPYGYGM D (SEQ ID NO:205)	DAGTYSPYGYG MDV (SEQ ID NO:211)	ARDAGTYSPYG YGMD (SEQ ID NO:217)	ARDAGTYSPYG YGMDV (SEQ ID NO:223)
VL CDR Seq.	*VL CDR1*	RASQSISSWLA (SEQ ID NO:194)	RASQSISSWLA (SEQ ID NO:200)	SQSISSW (SEQ ID NO:206)	RASQSISSWLA (SEQ ID NO:212)	SSWLAWY (SEQ ID NO:218)	QSISSW (SEQ ID NO:224)
	VL CDR2	KASSLES (SEQ ID NO:195)	KASSLES (SEQ ID NO:201)	KAS (SEQ ID NO:207)	KASSLES (SEQ ID NO:213)	LLIYKASSLE (SEQ ID NO:219)	KAS (SEQ ID NO:225)
	VL CDR3	QQFQSLPPFT (SEQ ID NO:196)	QQFQSLPPFT (SEQ ID NO:202)	FQSLPPF (SEQ ID NO:208)	QQFQSLPPFT (SEQ ID NO:214)	QQFQSLPPF (SEQ ID NO:220)	QQFQSLPPFT (SEQ ID NO:226)
VH Sequence*: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFRSYGIS**WVRQAPGQGLEWMG**WVAPYNGNTNYAQKLQG**RVTMTTDTSTSTAYMELRSLRSD DTAVYYCAR**DAGTYSPYGYGMDV**WGQGTTVTVSS (SEQ ID NO:227)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**RASQSISSWLA**WYQQKPGKAPKLLIY**KASSLES**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QQFQSLPP FT**FGGGTKVEIK (SEQ ID NO:228)							

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

Table 21: Antibody 25G1-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GYTFRSYGIS (SEQ ID NO:229)	SYGIS (SEQ ID NO:235)	GYTFRSY (SEQ ID NO:241)	GYTFRSYGIS (SEQ ID NO:247)	RSYGIS (SEQ ID NO:253)	GYTFRSYG (SEQ ID NO:259)
	VH CDR2	WVAPYSGNTNY AQKLQG (SEQ ID NO:230)	WVAPYSGNTNY AQKLQG (SEQ ID NO:236)	PYSG (SEQ ID NO:242)	WVAPYSGNT N (SEQ ID NO:248)	WMGWVAPYSG NTN (SEQ ID NO:254)	VAPYSGNT (SEQ ID NO:260)
	VH CDR3	DAGTYSPYGYG MDV (SEQ ID NO:231)	DAGTYSPYGYG MDV (SEQ ID NO:237)	AGTYSPYGYGM D (SEQ ID NO:243)	DAGTYSPYGYG MDV (SEQ ID NO:249)	ARDAGTYSPYG YGMD (SEQ ID NO:255)	ARDAGTYSPYG YGMDV (SEQ ID NO:261)
VL CDR Seq.	*VL CDR1*	RASHSIDSWLA (SEQ ID NO:232)	RASHSIDSWLA (SEQ ID NO:238)	SHSIDSW (SEQ ID NO:244)	RASHSIDSWLA (SEQ ID NO:250)	DSWLAWY (SEQ ID NO:256)	HSIDSW (SEQ ID NO:262)
	VL CDR2	KASYLES (SEQ ID NO:233)	KASYLES (SEQ ID NO:239)	KAS (SEQ ID NO:245)	KASYLES (SEQ ID NO:251)	LLIY KASYLE (SEQ ID NO:257)	KAS (SEQ ID NO:263)
	VL CDR3	QLFQSLPPFT (SEQ ID NO:234)	QLFQSLPPFT (SEQ ID NO:240)	FQSLPPF (SEQ ID NO:246)	QLFQSLPPFT (SEQ ID NO:252)	QLFQSLPPF (SEQ ID NO:258)	QLFQSLPPFT (SEQ ID NO:264)
VH Sequence*: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFRSYGIS**WVRQAPGQGLEWMG**WVAPYSGNTNYAQKLQG**RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR**DAGTYSPYGYGMDV**WGQGTTVTVSS (SEQ ID NO:265)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**RASHSIDSWLA**WYQQKPGKAPKLLIY**KASYLES**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QLFQSLPPFT**FGGGTKVEIK (SEQ ID NO:266)							

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

Table 22: Antibody 25G9-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GYTFRSYGIS (SEQ ID NO:267)	SYGIS (SEQ ID NO:273)	GYTFRSY (SEQ ID NO:279)	GYTFRSYGIS (SEQ ID NO:285)	RSYGIS (SEQ ID NO:291)	GYTFRSYG (SEQ ID NO:297)
	VH CDR2	WVAPYSGNT NYAQKLQG (SEQ ID NO:268)	WVAPYSGNTNY AQKLQG (SEQ ID NO:274)	PYSG (SEQ ID NO:280)	WVAPYSGNTN (SEQ ID NO:286)	WMGWVAPYSG NTN (SEQ ID NO:292)	VAPYSGNT (SEQ ID NO:298)
	VH CDR3	DAGTYSPYGY GMDV (SEQ ID NO:269)	DAGTYSPYGYG MDV (SEQ ID NO:275)	AGTYSPYGYGM D (SEQ ID NO:281)	DAGTYSPYGYG MDV (SEQ ID NO:287)	ARDAGTYSPYG YGMD (SEQ ID NO:293)	ARDAGTYSPYG YGMDV (SEQ ID NO:299)
VL CDR Seq.	*VL CDR1*	QASQSIDSWLA (SEQ ID NO:270)	QASQSIDSWLA (SEQ ID NO:276)	SQSIDSW (SEQ ID NO:282)	QASQSIDSWLA (SEQ ID NO:288)	DSWLAWY (SEQ ID NO:294)	QSIDSW (SEQ ID NO:300)
	VL CDR2	SASYLES (SEQ ID NO:271)	SASYLES (SEQ ID NO:277)	SAS (SEQ ID NO:283)	SASYLES (SEQ ID NO:289)	LLIYSASYLE (SEQ ID NO:295)	SAS (SEQ ID NO:301)
	VL CDR3	QRFQSLPPFT (SEQ ID NO:272)	QRFQSLPPFT (SEQ ID NO:278)	FQSLPPF (SEQ ID NO:284)	QRFQSLPPFT (SEQ ID NO:290)	QRFQSLPPF (SEQ ID NO:296)	QRFQSLPPFT (SEQ ID NO:302)
VH Sequence*: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFRSYGIS**WVRQAPGQGLEWMG**WVAPYSGNTNYAQKLQG**RVTMTTDTSTSTAYMELRSLRSDD TAVYYCAR**DAGTYSPYGYGMDV**WGQGTTVTVSS (SEQ ID NO:303)							
VL Sequence*: DIQMTQSPSTLSASVGDRVTITC**QASQSIDSWLA**WYQQKPGKAPKLLIY**SASYLES**GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC**QRFQSLPPF** **T**FGGGTKVEIK (SEQ ID NO:304)							

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

Table 23: Antibody 29D-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GFTFHSRGMH (SEQ ID NO:305)	SRGMH (SEQ ID NO:311)	GFTFHSR (SEQ ID NO:317)	GFTFHSRGMH (SEQ ID NO:323)	HSRGMH (SEQ ID NO:329)	GFTFHSRG (SEQ ID NO:335)
	VH CDR2	VITYDGINKYYA DSVEG (SEQ ID NO:306)	VITYDGINKYYA DSVEG (SEQ ID NO:312)	YDGI (SEQ ID NO:318)	VITYDGINKY (SEQ ID NO:324)	WVAVITYDGINK Y (SEQ ID NO:330)	ITYDGINK (SEQ ID NO:336)
	VH CDR3	DGVYYGVYDY (SEQ ID NO:307)	DGVYYGVYDY (SEQ ID NO:313)	GVYYGVYD (SEQ ID NO:319)	DGVYYGVYDY (SEQ ID NO:325)	ARDGVYYGVYD (SEQ ID NO:331)	ARDGVYYGVYD Y (SEQ ID NO:337)
VL CDR Seq.	*VL CDR1*	KSSQSVLFSSNN KNYLA (SEQ ID NO:308)	KSSQSVLFSSNN KNYLA (SEQ ID NO:314)	SQSVLFSSNNKN Y (SEQ ID NO:320)	KSSQSVLFSSNN KNYLA (SEQ ID NO:326)	LFSSNNKNYLA WY (SEQ ID NO:332)	QSVLFSSNNKNY (SEQ ID NO:338)
	VL CDR2	WASTRES (SEQ ID NO:309)	WASTRES (SEQ ID NO:315)	WAS (SEQ ID NO:321)	WASTRES (SEQ ID NO:327)	LLIYWASTRE (SEQ ID NO:333)	WAS (SEQ ID NO:339)
	VL CDR3	QQFHSYPLT (SEQ ID NO:310)	QQFHSYPLT (SEQ ID NO:316)	FHSYPL (SEQ ID NO:322)	QQFHSYPLT (SEQ ID NO:328)	QQFHSYPL (SEQ ID NO:334)	QQFHSYPLT (SEQ ID NO:340)
VH Sequence*: QVQLVESGGGVVQPGRSLRLSCAAS**GFTFHSRGMH**WVRQAPGKGLEWVA**VITYDGINKYYADSVEG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**DGVYYGVYDY**WGQGTLVTVSS (SEQ ID NO:341)						
VL Sequence*: DIVMTQSPDSLAVSLGERATINC**KSSQSVLFSSNNKNYLA**WYQQKPGQPPKLLIY**WASTRES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQFHSYPLT**FGGGTKVEIK (SEQ ID NO:342)						

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

Table 24: Antibody 29E-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GFTFRSYGMH (SEQ ID NO:343)	SYGMH (SEQ ID NO:349)	GFTFRSY (SEQ ID NO:355)	GFTFRSYGMH (SEQ ID NO:361)	RSYGMH (SEQ ID NO:367)	GFTFRSYG (SEQ ID NO:373)
	VH CDR2	VITYDGINKYYA DSVEG (SEQ ID NO:344)	VITYDGINKYYA DSVEG (SEQ ID NO:350)	YDGI (SEQ ID NO:356)	VITYDGINKY (SEQ ID NO:362)	WVAVITYDGINK Y (SEQ ID NO:368)	ITYDGINK (SEQ ID NO:374)
	VH CDR3	DGVYYGVYDY (SEQ ID NO:345)	DGVYYGVYDY (SEQ ID NO:351)	GVYYGVYD (SEQ ID NO:357)	DGVYYGVYDY (SEQ ID NO:363)	ARDGVYYGVYD (SEQ ID NO:369)	ARDGVYYGVYD Y (SEQ ID NO:375)
VL CDR Seq.	*VL CDR1*	KSSQSVLFSSNN KNYLA (SEQ ID NO:346)	KSSQSVLFSSNN KNYLA (SEQ ID NO:352)	SQSVLFSSNNKN Y (SEQ ID NO:358)	KSSQSVLFSSNN KNYLA (SEQ ID NO:364)	LFSSNNKNYLA WY (SEQ ID NO:370)	QSVLFSSNNKNY (SEQ ID NO:376)
	VL CDR2	WASTRES (SEQ ID NO:347)	WASTRES (SEQ ID NO:353)	WAS (SEQ ID NO:359)	WASTRES (SEQ ID NO:365)	LLIYWASTRE (SEQ ID NO:371)	WAS (SEQ ID NO:377)
	VL CDR3	QQFHSYPLT (SEQ ID NO:348)	QQFHSYPLT (SEQ ID NO:354)	FHSYPL (SEQ ID NO:360)	QQFHSYPLT (SEQ ID NO:366)	QQFHSYPL (SEQ ID NO:372)	QQFHSYPLT (SEQ ID NO:378)
VH Sequence*: QVQLVESGGGVVQPGRSLRLSCAAS**GFTFRSYGMH**WVRQAPGKGLEWVA**VITYDGINKYYADSVEG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**DGVYYGVYDY**WGQGTLVTVSS (SEQ ID NO:379)						
VL Sequence*: DIVMTQSPDSLAVSLGERATINC**KSSQSVLFSSNNKNYLA**WYQQKPGQPPKLLIY**WASTRES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQFHSYPLT**FGGGTKVEIK (SEQ ID NO:380)						

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

Table 25: Antibody 39A-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GGTFSSNAIG (SEQ ID NO:381)	SNAIG (SEQ ID NO:387)	GGTFSSN (SEQ ID NO:393)	GGTFSSNAIG (SEQ ID NO:399)	SSNAIG (SEQ ID NO:405)	GGTFSSNA (SEQ ID NO:411)
	VH CDR2	SIIPIIGFANYAQK FQG (SEQ ID NO:382)	SIIPIIGFANYAQK FQG (SEQ ID NO:388)	PIIG (SEQ ID NO:394)	SIIPIIGFAN (SEQ ID NO:400)	WMGSIIPIIGFAN (SEQ ID NO:406)	IIPIIGFA (SEQ ID NO:412)
	VH CDR3	DSGYYYGASSFG MDV (SEQ ID NO:383)	DSGYYYGASSFG MDV (SEQ ID NO:389)	SGYYYGASSFG MD (SEQ ID NO:395)	DSGYYYGASSFG MDV (SEQ ID NO:401)	ARDSGYYYGASS FGMD (SEQ ID NO:407)	ARDSGYYYGASS FGMDV (SEQ ID NO:413)
VL CDR Seq.	*VL CDR1*	RASQSVSSNLA (SEQ ID NO:384)	RASQSVSSNLA (SEQ ID NO:390)	SQSVSSN (SEQ ID NO:396)	RASQSVSSNLA (SEQ ID NO:402)	SSNLAWY (SEQ ID NO:408)	QSVSSN (SEQ ID NO:414)
	VL CDR2	GASTRAT (SEQ ID NO:385)	GASTRAT (SEQ ID NO:391)	GAS (SEQ ID NO:397)	GASTRAT (SEQ ID NO:403)	LLIYGASTRA (SEQ ID NO:409)	GAS (SEQ ID NO:415)
	VL CDR3	EQYNNLPLT (SEQ ID NO:386)	EQYNNLPLT (SEQ ID NO:392)	YNNLPL (SEQ ID NO:398)	EQYNNLPLT (SEQ ID NO:404)	EQYNNLPL (SEQ ID NO:410)	EQYNNLPLT (SEQ ID NO:416)
VH Sequence*: QVQLVQSGAEVKKPGSSVKVSCKAS**GGTFSSNAIG**WVRQAPGQGLEWMG**SIIPIIGFANYAQKFQG**RVTITADESTSTAYMELSSLRSEDTAVY YCAR**DSGYYYGASSFGMDV**WGQGTTVTVSS (SEQ ID NO:417)						
VL Sequence*: EIVMTQSPATLSVSPGERATLSC**RASQSVSSNLA**WYQQKPGQAPRLLIY**GASTRAT**GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC**EQYNNLPL** **T**FGGGTKVEIK (SEQ ID NO:418)						

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

Table 26: Antibody 43B-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GGSISSGQYWS (SEQ ID NO:419)	SGQYWS (SEQ ID NO:425)	GGSISSGQ (SEQ ID NO:431)	GGSISSGQYWS (SEQ ID NO:437)	SSGQYWS (SEQ ID NO:443)	GGSISSGQY (SEQ ID NO:449)
	VH CDR2	EIYYSGSTRYNPSLKS (SEQ ID NO:420)	EIYYSGSTRYNPSLKS (SEQ ID NO:426)	YSG (SEQ ID NO:432)	EIYYSGSTR (SEQ ID NO:438)	WIGEIYYSGSTR (SEQ ID NO:444)	IYYSGST (SEQ ID NO:450)
	VH CDR3	DAPYYYGGGYYYYMDV (SEQ ID NO:421)	DAPYYYGGGYYYYMDV (SEQ ID NO:427)	APYYYGGGYYYYMD (SEQ ID NO:433)	DAPYYYGGGYYYYMDV (SEQ ID NO:439)	ARDAPYYYGGGYYYYMD (SEQ ID NO:445)	ARDAPYYYGGGYYYYMDV (SEQ ID NO:451)
VL CDR Seq.	*VL CDR1*	RASQSVSSSYLA (SEQ ID NO:422)	RASQSVSSSYLA (SEQ ID NO:428)	SQSVSSSY (SEQ ID NO:434)	RASQSVSSSYLA (SEQ ID NO:440)	SSSYLAWY (SEQ ID NO:446)	QSVSSSY (SEQ ID NO:452)
	VL CDR2	GASSRAT (SEQ ID NO:423)	GASSRAT (SEQ ID NO:429)	GAS (SEQ ID NO:435)	GASSRAT (SEQ ID NO:441)	LLIYGASSRA (SEQ ID NO:447)	GAS (SEQ ID NO:453)
	VL CDR3	QQVGVVPYT (SEQ ID NO:424)	QQVGVVPYT (SEQ ID NO:430)	VGVVPY (SEQ ID NO:436)	QQVGVVPYT (SEQ ID NO:442)	QQVGVVPY (SEQ ID NO:448)	QQVGVVPYT (SEQ ID NO:454)
VH Sequence*: QVQLQESGPGLVKPSQTLSLTCTVS**GGSISSGQYWS**WIRQHPGKGLEWIG**EIYYSGSTRYNPSLKS**RVTISVDTSKNQFSLKLSSVTAADTAVYY CAR**DAPYYYGGGYYYYMDV**WGKGTTVTVSS (SEQ ID NO:455)						
VL Sequence*: EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQVGVVPY** **T**FGGGTKVEIK (SEQ ID NO:456)						

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

Table 27: Antibody 43B1-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GGSISSGQYWS (SEQ ID NO:457)	SGQYWS (SEQ ID NO:463)	GGSISSGQ (SEQ ID NO:469)	GGSISSGQYWS (SEQ ID NO:475)	SSGQYWS (SEQ ID NO:481)	GGSISSGQY (SEQ ID NO:487)
	VH CDR2	EIYYSGSTRYNPSLKS (SEQ ID NO:458)	EIYYSGSTRYNPSLKS (SEQ ID NO:464)	YSG (SEQ ID NO:470)	EIYYSGSTR (SEQ ID NO:476)	WIGEIYYSGSTR (SEQ ID NO:482)	IYYSGST (SEQ ID NO:488)
	VH CDR3	DAPYYYGGGYYYYMDV (SEQ ID NO:459)	DAPYYYGGGYYYYMDV (SEQ ID NO:465)	APYYYGGGYYYYMD (SEQ ID NO:471)	DAPYYYGGGYYYYMDV (SEQ ID NO:477)	ARDAPYYYGGGYYYYMD (SEQ ID NO:483)	ARDAPYYYGGGYYYYMDV (SEQ ID NO:489)
VL CDR Seq.	*VL CDR1*	RASESVDSSYLA (SEQ ID NO:460)	RASESVDSSYLA (SEQ ID NO:466)	SESVDSSY (SEQ ID NO:472)	RASESVDSSYLA (SEQ ID NO:478)	DSSYLAWY (SEQ ID NO:484)	ESVDSSY (SEQ ID NO:490)
	VL CDR2	GASTRQT (SEQ ID NO:461)	GASTRQT (SEQ ID NO:467)	GAS (SEQ ID NO:473)	GASTRQT (SEQ ID NO:479)	LLIYGASTRQ (SEQ ID NO:485)	GAS (SEQ ID NO:491)
	VL CDR3	QQAGVVPYT (SEQ ID NO:462)	QQAGVVPYT (SEQ ID NO:468)	AGVVPY (SEQ ID NO:474)	QQAGVVPYT (SEQ ID NO:480)	QQAGVVPY (SEQ ID NO:486)	QQAGVVPYT (SEQ ID NO:492)
VH Sequence*: QVQLQESGPGLVKPSQTLSLTCTVS**GGSISSGQYWS**WIRQHPGKGLEWIG**EIYYSGSTRYNPSLKS**RVTISVDTSKNQFSLKLSSVTAADTAVYY CAR**DAPYYYGGGYYYYMDV**WGKGTTVTVSS (SEQ ID NO:493)						
VL Sequence*: EIVLTQSPGTLSLSPGERATLSC**RASESVDSSYLA**WYQQKPGQAPRLLIY**GASTRQT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQAGVVP YT**FGGGTKVEIK (SEQ ID NO:494)						

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

Table 28: Antibody 43B7-CDR Sequences

		Exemplary*	**Kabat**	**Chothia**	**AbM**	**Contact**	**IMGT**
VH CDR Seq.	*VH CDR1*	GGSISSGQYWS (SEQ ID NO:495)	SGQYWS (SEQ ID NO:501)	GGSISSGQ (SEQ ID NO:507)	GGSISSGQYWS (SEQ ID NO:513)	SSGQYWS (SEQ ID NO:519)	GGSISSGQY (SEQ ID NO:525)
	VH CDR2	EIYYSGSTRYNPSLKS (SEQ ID NO:496)	EIYYSGSTRYNPSLKS (SEQ ID NO:502)	YSG (SEQ ID NO:508)	EIYYSGSTR (SEQ ID NO:514)	WIGEIYYSGSTR (SEQ ID NO:520)	IYYSGST (SEQ ID NO:526)
	VH CDR3	DAPYYYGGGYYYYMDV (SEQ ID NO:497)	DAPYYYGGGYYYYMDV (SEQ ID NO:503)	APYYYGGGYYYYMD (SEQ ID NO:509)	DAPYYYGGGYYYYMDV (SEQ ID NO:515)	ARDAPYYYGGGYYYYMD (SEQ ID NO:521)	ARDAPYYYGGGYYYYMDV (SEQ ID NO:527)
VL CDR Seq.	*VL CDR1*	RASESVDSSYLA (SEQ ID NO:498)	RASESVDSSYLA (SEQ ID NO:504)	SESVDSSY (SEQ ID NO:510)	RASESVDSSYLA (SEQ ID NO:516)	DSSYLAWY (SEQ ID NO:522)	ESVDSSY (SEQ ID NO:528)
	VL CDR2	GADSRAT (SEQ ID NO:499)	GADSRAT (SEQ ID NO:505)	GAD (SEQ ID NO:511)	GADSRAT (SEQ ID NO:517)	LLIYGADSRA (SEQ ID NO:523)	GAD (SEQ ID NO:529)
	VL CDR3	QQDGVVPYT (SEQ ID NO:500)	QQDGVVPYT (SEQ ID NO:506)	DGVVPY (SEQ ID NO:512)	QQDGVVPYT (SEQ ID NO:518)	QQDGVVPY (SEQ ID NO:524)	QQDGVVPYT (SEQ ID NO:530)
VH Sequence*: QVQLQESGPGLVKPSQTLSLTCTVS**GGSISSGQYWS**WIRQHPGKGLEWIG**EIYYSGSTRYNPSLKS**RVTISVDTSKNQFSLKLSSVTAADTAVYY CAR**DAPYYYGGGYYYYMDV**WGKGTTVTVSS (SEQ ID NO:531)						
VL Sequence*: EIVLTQSPGTLSLSPGERATLSC**RASESVDSSYLA**WYQQKPGQAPRLLIY**GADSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQDGVVP YT**FGGGTKVEIK (SEQ ID NO:532)						

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

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

1. An isolated human antibody which binds to the extracellular domain of human Tissue Factor (TF), wherein the antibody binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa.

2. The isolated human antibody of claim 0, wherein

(1) the isolated antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and wherein

(2) the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

3. The isolated human antibody of claim 0 or 2, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

4. The isolated human antibody of any one of claims 0 to 3, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

5. The isolated human antibody of any one of claims 0 to 3, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-

CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

6. The isolated human antibody of claim 0, wherein the isolated antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

7. The isolated human antibody of claim 0, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA).

8. The isolated human antibody of claim 7, wherein the antibody does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control.

9. The isolated human antibody of claim 7 or 8, wherein the antibody does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control.

10. The isolated human antibody of any one of claims 7 to 9, wherein the antibody does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control.

11. The isolated human antibody of any of the above claims, wherein the antibody allows human thrombin generation as determined by thrombin generation assay (TGA).

12. The isolated human antibody of claim 11, wherein the antibody maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control.

13. The isolated human antibody of claim 11 or 12, wherein the antibody maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control.

14. The isolated human antibody of any one of claims 11 to 13, wherein the antibody preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control.

15. The isolated human antibody of any of the above claims, wherein the antibody binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX.

16. The isolated human antibody of any of the above claims, wherein the antibody does not interfere with the ability of TF:FVIIa to convert FX into FXa.

17. The isolated human antibody of any of the above claims, wherein the antibody does not compete for binding to human TF with human FVIIa.

18. The isolated human antibody of any of the above claims, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), allows human thrombin generation as determined by thrombin generation assay (TGA), binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

19. The isolated human antibody of any of the above claims, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, allows human thrombin generation as determined by thrombin generation assay (TGA), preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

20. The isolated human antibody of any of the above claims, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control, does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control, does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, allows human thrombin generation as determined by thrombin generation assay (TGA), maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control, maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control, preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, binds human TF at a human TF

binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

21. The isolated human antibody of any of the above claims, wherein the antibody inhibits FVIIa-dependent TF signaling.

22. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

23. The isolated human antibody of claim 22, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N.

24. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

25. The isolated human antibody of claim 24, wherein the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

26. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

27. The isolated human antibody of claim 26, wherein the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

28. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the

sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

29. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

30. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

31. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

32. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in

SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

33. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

34. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

35. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

36. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

37. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid

residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and

wherein the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay

38. The isolated human antibody of claim 37, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

wherein the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

39. The isolated human antibody of any of the above claims, wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced

by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and

wherein the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ

ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

40. The isolated human antibody of claim 39, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N;

wherein the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N; and

wherein the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

41. The isolated human antibody of any of the above claims, wherein the antibody binds to cynomolgus TF.

42. The isolated human antibody of any of the above claims, wherein the antibody binds to mouse TF.

43. The isolated human antibody of any of the above claims, wherein the antibody binds to rabbit TF.

44. The isolated human antibody of any of the above claims, wherein the antibody binds to pig TF.

45. The isolated human antibody of any of the above claims, wherein the antibody reduces lesion size in a swine choroidal neovascularization (CNV) model.

46. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); and

(b) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

47. The isolated human antibody of claim 46, wherein the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

48. The isolated human antibody of any of the above claims, wherein the antibody:

(a) allows human thrombin generation as determined by thrombin generation assay (TGA); and

(b) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

49. The isolated human antibody of claim 48, wherein the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

50. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(c) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

51. The isolated human antibody of claim 50, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

52. The isolated human antibody of any of the above claims, wherein the antibody:

(a) allows human thrombin generation as determined by thrombin generation assay (TGA);

(b) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(c) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

53. The isolated human antibody of claim 52, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

54. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) binds to cynomolgus TF;

(c) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(d) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

55. The isolated human antibody of claim 54, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

56. The isolated human antibody of any of the above claims, wherein the antibody:

(a) allows human thrombin generation as determined by thrombin generation assay (TGA);

(b) binds to cynomolgus TF;

(c) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(d) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

57. The isolated human antibody of claim 56, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

58. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) allows human thrombin generation as determined by thrombin generation assay (TGA);

(c) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(d) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(e) does not compete for binding to human TF with FVIIa;

(f) inhibits FVIIa-dependent TF signaling;

(g) binds to cynomolgus TF;

(h) binds to mouse TF; and

(i) binds to rabbit TF.

59. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(c) allows human thrombin generation as determined by thrombin generation assay (TGA);

(d) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(f) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(g) does not compete for binding to human TF with FVIIa;

(h) inhibits FVIIa-dependent TF signaling;

(i) binds to cynomolgus TF;

(j) binds to mouse TF; and

(k) binds to rabbit TF.

60. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) allows human thrombin generation as determined by thrombin generation assay (TGA);

(f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(j) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(k) does not compete for binding to human TF with FVIIa;

(l) inhibits FVIIa-dependent TF signaling;

(m) binds to cynomolgus TF;

(n) binds to mouse TF; and

(o) binds to rabbit TF.

61. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) allows human thrombin generation as determined by thrombin generation assay (TGA);

(c) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(d) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(e) does not compete for binding to human TF with FVIIa;

(f) inhibits FVIIa-dependent TF signaling;

(g) binds to cynomolgus TF;

(h) binds to mouse TF;

(i) binds to rabbit TF;

(j) binds to pig TF;

and (k) reduces lesion size in a swine choroidal neovascularization (CNV) model.

62. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(c) allows human thrombin generation as determined by thrombin generation assay (TGA);

(d) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(f) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(g) does not compete for binding to human TF with FVIIa;

(h) inhibits FVIIa-dependent TF signaling;

(i) binds to cynomolgus TF;

(j) binds to mouse TF;

(k) binds to rabbit TF;

(l) binds to pig TF;

and (m) reduces lesion size in a swine choroidal neovascularization (CNV) model.

63. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) allows human thrombin generation as determined by thrombin generation assay (TGA);

(f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(j) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(k) does not compete for binding to human TF with FVIIa;

(l) inhibits FVIIa-dependent TF signaling;

(m) binds to cynomolgus TF;

(n) binds to mouse TF;

(o) binds to rabbit TF;

(p) binds to pig TF;

and (q) reduces lesion size in a swine choroidal neovascularization (CNV) model.

64. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) allows human thrombin generation as determined by thrombin generation assay (TGA);

(f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(j) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(k) does not compete for binding to human TF with FVIIa;

(l) inhibits FVIIa-dependent TF signaling;

(m) binds to cynomolgus TF;

(n) binds to mouse TF;

(o) binds to rabbit TF;

(p) binds to pig TF;

(q) reduces lesion size in a swine choroidal neovascularization (CNV) model;

(r) wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(s) wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(t) wherein the binding between the isolated antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(u) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(v) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(w) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(x) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(y) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(z) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(aa) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the

extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(bb) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; and

(cc) wherein the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

65. The isolated human antibody of any of the above claims, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) allows human thrombin generation as determined by thrombin generation assay (TGA);

(f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(j) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(k) does not compete for binding to human TF with FVIIa;

(l) inhibits FVIIa-dependent TF signaling;

(m) binds to cynomolgus TF;

(n) binds to mouse TF;

(o) binds to rabbit TF;

(p) binds to pig TF;

(q) reduces lesion size in a swine choroidal neovascularization (CNV) model;

(r) wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(s) wherein the binding between the isolated antibody and a variant TF extracellular domain comprising a mutation K68N of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(t) wherein the binding between the isolated antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(u) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(v) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(w) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(x) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(y) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the

extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(z) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(aa) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay;

(bb) wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay; and

(cc) wherein the binding between the isolated antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

66. The isolated human antibody of any of the above claims, wherein the antibody competes for binding to human TF with the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

67. The isolated human antibody of claim 64, wherein the antibody competes for binding to human TF with the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

68. The isolated human antibody of claim 64, wherein the antibody competes for binding to human TF with the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

69. The isolated human antibody of any of the above claims, wherein the antibody binds to the same human TF epitope bound by the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

70. The isolated human antibody of claim 69, wherein the antibody binds to the same human TF epitope bound by the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

71. The isolated human antibody of claim 69, wherein the antibody binds to the same human TF epitope bound by the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

72. The isolated human antibody of any of the above claims, comprising all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the

antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

73. The isolated human antibody of claim 72, wherein the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

74. The isolated human antibody of claim 72 or 73, comprising all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

75. The isolated human antibody of claim 72 or 73, comprising all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

76. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A.

77. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A3.

78. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5.

79. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5-T.

80. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G.

81. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G1.

82. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G9.

83. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B.

84. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B1.

85. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B7.

86. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D.

87. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D7.

88. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D8.

89. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43E.

90. The isolated human antibody of claim 72 or 73, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43Ea.

91. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:113 and a V_L sequence of SEQ ID NO:114.

92. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:151 and a V_L sequence of SEQ ID NO:152.

93. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:189 and a V_L sequence of SEQ ID NO:190.

94. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:836 and a V_L sequence of SEQ ID NO:837.

95. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:227 and a V_L sequence of SEQ ID NO:228.

96. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:265 and a V_L sequence of SEQ ID NO:266.

97. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:303 and a V_L sequence of SEQ ID NO:304.

98. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:455 and a V_L sequence of SEQ ID NO:456.

99. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:493 and a V_L sequence of SEQ ID NO:494.

100. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:531 and a V_L sequence of SEQ ID NO:532.

101. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:569 and a V_L sequence of SEQ ID NO:570.

102. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:607 and a V_L sequence of SEQ ID NO:608.

103. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:645 and a V_L sequence of SEQ ID NO:646.

104. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:683 and a V_L sequence of SEQ ID NO:684.

105. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:721 and a V_L sequence of SEQ ID NO:722.

106. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

107. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID

NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

108. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

109. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

110. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:763 and a V_L sequence of SEQ ID NO:764.

111. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:868 and a V_L sequence of SEQ ID NO:869.

112. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:870 and a V_L sequence of SEQ ID NO:871.

113. The isolated human antibody of any one of claims 0 to 73, wherein the antibody comprises a V_H sequence of SEQ ID NO:769 and a V_L sequence of SEQ ID NO:770.

114. The isolated human antibody of any of the above claims, wherein the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

115. The isolated human antibody of claim 114, wherein the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the

antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

116. The isolated human antibody of claim 114, wherein the antibody comprises: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

117. The isolated human antibody of any of the above claims, wherein the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

118. The isolated human antibody of claim 117, wherein the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

119. The isolated human antibody of claim 117, wherein the antibody consists of: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

120. An isolated antibody comprising all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

121. The isolated antibody of claim 120, wherein the antibody is human, humanized, or chimeric.

122. The isolated antibody of claim 120 or 121, wherein the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

123. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

124. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A.

125. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A3.

126. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5.

127. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5-T.

128. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G.

129. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G1.

130. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G9.

131. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from: the antibody

designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

132. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B.

133. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B1.

134. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B7.

135. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D.

136. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D7.

137. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D8.

138. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43E.

139. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43Ea.

140. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:113 and a V_L sequence of SEQ ID NO:114.

141. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:151 and a V_L sequence of SEQ ID NO:152.

142. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:189 and a V_L sequence of SEQ ID NO:190.

143. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:836 and a V_L sequence of SEQ ID NO:837.

144. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:227 and a V_L sequence of SEQ ID NO:228.

145. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:265 and a V_L sequence of SEQ ID NO:266.

146. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:303 and a V_L sequence of SEQ ID NO:304.

147. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:455 and a V_L sequence of SEQ ID NO:456.

148. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:493 and a V_L sequence of SEQ ID NO:494.

149. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:531 and a V_L sequence of SEQ ID NO:532.

150. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:569 and a V_L sequence of SEQ ID NO:570.

151. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:607 and a V_L sequence of SEQ ID NO:608.

152. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:645 and a V_L sequence of SEQ ID NO:646.

153. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:683 and a V_L sequence of SEQ ID NO:684.

154. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:721 and a V_L sequence of SEQ ID NO:722.

155. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID

NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

156. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

157. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

158. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

159. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:763 and a V_L sequence of SEQ ID NO:764.

160. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:868 and a V_L sequence of SEQ ID NO:869.

161. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:870 and a V_L sequence of SEQ ID NO:871.

162. The isolated antibody of any one of claims 120 to 122, wherein the antibody comprises a V_H sequence of SEQ ID NO:769 and a V_L sequence of SEQ ID NO:770.

163. The isolated antibody of any one of claims 120 to 162, wherein the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody

designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

164. The isolated antibody of any one of claim 163, wherein the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

165. The isolated antibody of any one of claim 163, wherein the antibody comprises: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

166. The isolated antibody of any one of claims 120 to 163, wherein the antibody consists: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

167. The isolated antibody of any one of claim 166, wherein the antibody consists: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

168. The isolated antibody of any one of claim 166, wherein the antibody consists: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

169. An isolated antibody that competes for binding to human TF with: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

170. The isolated antibody of claim 169, wherein the antibody is human, humanized, or chimeric.

171. The isolated antibody of claim 169 or 170, wherein the antibody inhibits FVIIa-dependent TF signaling.

172. The isolated antibody of any one of claims 169 to 171, wherein the antibody binds to cynomolgus TF.

173. The isolated antibody of any one of claims 169 to 172, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

174. The isolated antibody of any one of claims 169 to 172, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-93 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-98 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

175. The isolated antibody of any one of claims 169 to 172, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

176. The isolated antibody of any one of claims 169 to 172, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-85 and 92-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

177. The isolated antibody of any one of claims 169 to 172, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-93 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-98 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

178. The isolated antibody of any one of claims 169 to 172, wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and

wherein the binding between the isolated antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-85 and 92-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the isolated antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

as determined by the median fluorescence intensity value of the isolated antibody relative to an isotype control in a live cell staining assay.

179. The isolated antibody of any one of claims 169 to 178, comprising all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, the antibody designated 43Ea, or the antibody designated 54E.

180. The isolated antibody of claim 179, wherein the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

181. The isolated antibody of claim 179 or 180, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 1F.

182. The isolated antibody of claim 179 or 180, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 1G.

183. The isolated antibody of claim 179 or 180, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 29D.

184. The isolated antibody of claim 179 or 180, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 29E.

185. The isolated antibody of claim 179 or 180, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 39A.

186. The isolated antibody of claim 179 or 180, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 54E.

187. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:37 and a V_L sequence of SEQ ID NO:38.

188. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:75 and a V_L sequence of SEQ ID NO:76.

189. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:341 and a V_L sequence of SEQ ID NO:342.

190. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:379 and a V_L sequence of SEQ ID NO:380.

191. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:417 and a V_L sequence of SEQ ID NO:418.

192. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:759 and a V_L sequence of SEQ ID NO:760.

193. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:773; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:774; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:775; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:776; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:777; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:778.

194. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:785; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:786; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:787; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:788; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:789; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:790.

195. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:791; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:792; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:793; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:794; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:795; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:796.

196. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:803; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:804; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:805; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:806; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:807; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:808.

197. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:761 and a V_L sequence of SEQ ID NO:762.

198. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:765 and a V_L sequence of SEQ ID NO:766.

199. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:767 and a V_L sequence of SEQ ID NO:768.

200. The isolated antibody of any one of claims 169 to 180, wherein the antibody comprises a V_H sequence of SEQ ID NO:771 and a V_L sequence of SEQ ID NO:772.

201. The isolated antibody of any one of claims 169 to 200, wherein the antibody comprises: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

202. The isolated antibody of any one of claims 169 to 201, wherein the antibody consists of: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

203. An isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:773; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:774; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:775; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:776; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:777; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:778.

204. An isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

205. An isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:785; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:786; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:787; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:788; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:789; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:790.

206. An isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:791; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:792; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:793; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:794; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:795; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:796.

207. An isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the

sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

208. An isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:803; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:804; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:805; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:806; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:807; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:808.

209. An isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

210. An isolated antibody comprising: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

211. The isolated antibody of any of the above claims, wherein the antibody binds to human TF with a K_D of less than or equal to 50 nM, 10 nM, 5 nM, 1 nM, 0.5 nM or 0.1 nM, as measured by Octet QK384 or Biacore assay.

212. The isolated antibody of any of the above claims, wherein the antibody is a monoclonal antibody.

213. The isolated antibody of any of the above claims, wherein the antibody is multispecific.

214. The isolated antibody of any of the above claims, wherein the antibody 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.

215. The isolated antibody of any of the above claims, wherein the antibody comprises a scaffold, optionally wherein the scaffold is Fc, optionally human Fc.

216. The isolated antibody of claim 215, wherein the antibody comprises a heavy chain constant region of a class selected from IgG, IgA, IgD, IgE, and IgM.

217. The isolated antibody of claim 216, wherein the antibody comprises a heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4.

218. The isolated antibody of claim 217, wherein the antibody comprises a heavy chain constant region of IgG1.

219. The isolated antibody of any one of claims 215 to 218, wherein 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.

220. An isolated antibody that competes for binding to human TF with the antibody of any of the above claims.

221. An isolated antibody that binds the human TF epitope bound by the antibody of any of the above claims.

222. An isolated polynucleotide or set of polynucleotides encoding the antibody of any of the above claims, a V_H thereof, a V_L thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof.

223. A vector or set of vectors comprising the polynucleotide or set of polynucleotides of claim 222.

224. A host cell comprising the polynucleotide or set of polynucleotides of claim 222 or the vector or set of vectors of claim 223.

225. A method of producing an antibody comprising expressing the antibody with the host cell of claim 224 and isolating the expressed antibody.

226. A pharmaceutical composition comprising the antibody of any one of claims 0 to 221 and a pharmaceutically acceptable excipient.

227. 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 of any one of claims 0 to 221 or the pharmaceutical composition of claim 226.

228. The method of claim 227, wherein the disease or condition is cancer.

229. The method of claim 228, wherein the cancer is head and neck cancer.

230. The method of claim 228, wherein the cancer is ovarian cancer.

231. The method of claim 228, wherein the cancer is gastric cancer.

232. The method of claim 228, wherein the cancer is esophageal cancer.

233. The method of claim 228, wherein the cancer is cervical cancer.

234. The method of claim 228, wherein the cancer is prostate cancer.

235. The method of claim 228, wherein the cancer is pancreatic cancer.

236. The method of claim 228, wherein the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer.

237. The method of claim 228, wherein the cancer is glioblastoma.

238. The method of claim 228, wherein the cancer is lung cancer.

239. The method of claim 228, wherein the cancer is bladder cancer.

240. The method of claim 228, wherein the cancer is melanoma.

241. The method of claim 228, wherein the cancer is kidney cancer.

242. The method of claim 227, wherein the disease or condition involves neovascularization.

243. The method of claim 242, wherein the disease or condition involving neovascularization is age-related macular degeneration (AMD), diabetic retinopathy, or cancer.

244. The method of claim 227, wherein the disease or condition involves vascular inflammation.

245. The method of any one of claims 227 to 244, further comprising administering one or more additional therapeutic agents to the subject.

246. The method of claim 245, wherein the additional therapeutic agent is formulated in the same pharmaceutical composition as the antibody.

247. The method of claim 245, wherein the additional therapeutic agent is formulated in a different pharmaceutical composition from the antibody.

248. The method of claim 245, wherein the additional therapeutic agent is administered prior to administering the antibody.

249. The method of claim 245, wherein the additional therapeutic agent is administered after administering the antibody.

250. The method of claim 245, wherein the additional therapeutic agent is administered contemporaneously with the antibody.

251. A method of detecting TF in a subject having or suspected of having a disease or condition, the method comprising: (a) receiving a sample from the subject; and (b) detecting the presence or the level of TF in the sample by contacting the sample with the antibody of any one of claims 0 to 221.

252. The method of claim 251, wherein the disease or condition is cancer.

253. The method of claim 252, wherein the cancer is head and neck cancer.

254. The method of claim 252, wherein the cancer is ovarian cancer.

255. The method of claim 252, wherein the cancer is gastric cancer.

256. The method of claim 252, wherein the cancer is esophageal cancer.

257. The method of claim 252, wherein the cancer is cervical cancer.

258. The method of claim 252, wherein the cancer is prostate cancer.

259. The method of claim 252, wherein the cancer is pancreatic cancer.

260. The method of claim 252, wherein the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer.

261. The method of claim 252, wherein the cancer is glioblastoma.

262. The method of claim 252, wherein the cancer is lung cancer.

263. The method of claim 252, wherein the cancer is bladder cancer.

264. The method of claim 252, wherein the cancer is melanoma.

265. The method of claim 252, wherein the cancer is kidney cancer.

266. The method of claim 251, wherein the disease or condition involves neovascularization.

267. The method of claim 266, wherein the disease or condition involving neovascularization is age-related macular degeneration (AMD), diabetic retinopathy, or cancer.

268. The method of claim 251, wherein the disease or condition involves vascular inflammation.

269. A method of detecting TF in a subject having or suspected of having a disease or condition, the method comprising: (a) administering to the subject the antibody of any one of claims 0 to 221; and (b) detecting the presence or the level of TF in the subject.

270. The method of claim 269, wherein the disease or condition is cancer.

271. The method of claim 270, wherein the cancer is head and neck cancer.

272. The method of claim 270, wherein the cancer is ovarian cancer.

273. The method of claim 270, wherein the cancer is gastric cancer.

274. The method of claim 270, wherein the cancer is esophageal cancer.

275. The method of claim 270, wherein the cancer is cervical cancer.

276. The method of claim 270, wherein the cancer is prostate cancer.

277. The method of claim 270, wherein the cancer is pancreatic cancer.

278. The method of claim 270, wherein the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer.

279. The method of claim 270, wherein the cancer is glioblastoma.

280. The method of claim 270, wherein the cancer is lung cancer.

281. The method of claim 270, wherein the cancer is bladder cancer.

282. The method of claim 270, wherein the cancer is melanoma.

283. The method of claim 270, wherein the cancer is kidney cancer.

284. The method of claim 269, wherein the disease or condition involves neovascularization.

285. The method of claim 284, wherein the disease or condition involving neovascularization is age-related macular degeneration (AMD), diabetic retinopathy, or cancer.

286. The method of claim 269, wherein the disease or condition involves vascular inflammation.

287. A kit comprising the antibody of any one of claims 0 to 221 or the pharmaceutical composition of claim 226 and instructions for use.

288. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody binds to the extracellular domain of human Tissue Factor (TF) at a human TF binding site that is distinct from a human TF binding site bound by human FVIIa.

289. The antibody-drug conjugate of claim 288, wherein

(1) the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822, and wherein

(2) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

290. The antibody-drug conjugate of claim 288 or 289, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

291. The antibody-drug conjugate of any one of claims 288 to 290, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 HIcomprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ

ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

292. The antibody-drug conjugate of any one of claims 288 to 290, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

293. The antibody-drug conjugate of claim 288, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA) compared to a reference antibody comprising a V_H sequence of SEQ ID NO:821 and a V_L sequence of SEQ ID NO:822.

294. The antibody-drug conjugate of claim 288, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA).

295. The antibody-drug conjugate of claim 294, wherein the antibody does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control.

296. The antibody-drug conjugate of claim 294 or 295, wherein the antibody does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control.

297. The antibody-drug conjugate of any one of claims 294 to 296, wherein the antibody does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control.

298. The antibody-drug conjugate of any one of claims 288 to 297, wherein the antibody allows human thrombin generation as determined by thrombin generation assay (TGA).

299. The antibody-drug conjugate of claim 298, wherein the antibody maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control.

300. The antibody-drug conjugate of claim 298 or 299, wherein the antibody maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control.

301. The antibody-drug conjugate of any one of claims 298 to 300, wherein the antibody preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control.

302. The antibody-drug conjugate of any one of claims 288 to 301, wherein the antibody binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX.

303. The antibody-drug conjugate of any one of claims 288 to 302, wherein the antibody does not interfere with the ability of TF:FVIIa to convert FX into FXa.

304. The antibody-drug conjugate of any one of claims 288 to 303, wherein the antibody does not compete for binding to human TF with human FVIIa.

305. The antibody-drug conjugate of any one of claims 288 to 304, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), allows human thrombin generation as determined by thrombin generation assay (TGA), binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

306. The antibody-drug conjugate of any one of claims 288 to 305, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, allows human thrombin generation as determined by thrombin generation assay (TGA), preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

307. The antibody-drug conjugate of any one of claims 288 to 306, wherein the antibody does not inhibit human thrombin generation as determined by thrombin generation assay (TGA), does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control, does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control, does not decrease the endogenous thrombin potential (ETP) as determined by the area under a

thrombin generation curve compared to an isotype control, allows human thrombin generation as determined by thrombin generation assay (TGA), maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control, maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control, preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control, binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX, does not interfere with the ability of TF:FVIIa to convert FX into FXa, and does not compete for binding to human TF with FVIIa.

308. The antibody-drug conjugate of any one of claims 288 to 307, wherein the antibody inhibits FVIIa-dependent TF signaling.

309. The antibody-drug conjugate of any one of claims 288 to 308, wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

310. The antibody-drug conjugate of claim 309, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N.

311. The antibody-drug conjugate of any one of claims 288 to 310, wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

312. The antibody-drug conjugate of claim 311, wherein the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

313. The antibody-drug conjugate of any one of claims 288 to 312, wherein the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in

SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

314. The antibody-drug conjugate of claim 313, wherein the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

315. The antibody-drug conjugate of any one of claims 288 to 314, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

316. The antibody-drug conjugate of any one of claims 288 to 315, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

317. The antibody-drug conjugate of any one of claims 288 to 316, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

318. The antibody-drug conjugate of any one of claims 288 to 317, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

319. The antibody-drug conjugate of any one of claims 288 to 318, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

320. The antibody-drug conjugate of any one of claims 288 to 319, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

321. The antibody-drug conjugate of any one of claims 288 to 320, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

322. The antibody-drug conjugate of any one of claims 288 to 321, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

323. The antibody-drug conjugate of any one of claims 288 to 322, wherein the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the

binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

324. The antibody-drug conjugate of any one of claims 288 to 323, wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

325. The antibody-drug conjugate of claim 324, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

wherein the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N.

326. The antibody-drug conjugate of any one of claims 288 to 325, wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF

extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838

is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, and

wherein the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

327. The antibody-drug conjugate of claim 326, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N;

wherein the mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is K68N; and

wherein the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

328. The antibody-drug conjugate of any one of claims 288 to 327, wherein the antibody binds to cynomolgus TF.

329. The antibody-drug conjugate of any one of claims 288 to 328, wherein the antibody binds to mouse TF.

330. The antibody-drug conjugate of any one of claims 288 to 329, wherein the antibody binds to rabbit TF.

331. The antibody-drug conjugate of any one of claims 288 to 330, wherein the antibody binds to pig TF.

332. The antibody-drug conjugate of any one of claims 288 to 331, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA); and

(b) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined

by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

333. The antibody-drug conjugate of claim 332, wherein the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

334. The antibody-drug conjugate of any one of claims 288 to 333, wherein the antibody:

(a) allows human thrombin generation as determined by thrombin generation assay (TGA); and

(b) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

335. The antibody-drug conjugate of claim 334, wherein the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

336. The antibody-drug conjugate of any one of claims 288 to 335, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(c) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

337. The antibody-drug conjugate of claim 336, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

338. The antibody-drug conjugate of any one of claims 288 to 337, wherein the antibody:

(a) allows human thrombin generation as determined by thrombin generation assay (TGA);

(b) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(c) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

339. The antibody-drug conjugate of claim 338, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

340. The antibody-drug conjugate of any one of claims 288 to 339, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) binds to cynomolgus TF;

(c) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of

the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(d) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

341. The antibody-drug conjugate of claim 340, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

342. The antibody-drug conjugate of any one of claims 288 to 341, wherein the antibody:

(a) allows human thrombin generation as determined by thrombin generation assay (TGA);

(b) binds to cynomolgus TF;

(c) the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(d) the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

343. The antibody-drug conjugate of claim 342, wherein the mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is K149N; and

the mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 are N171H and T197K.

344. The antibody-drug conjugate of any one of claims 288 to 343, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) allows human thrombin generation as determined by thrombin generation assay (TGA);

(c) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(d) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(e) does not compete for binding to human TF with FVIIa;

(f) inhibits FVIIa-dependent TF signaling;

(g) binds to cynomolgus TF;

(h) binds to mouse TF; and

(i) binds to rabbit TF.

345. The antibody-drug conjugate of any one of claims 288 to 344, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(c) allows human thrombin generation as determined by thrombin generation assay (TGA);

(d) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(f) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(g) does not compete for binding to human TF with FVIIa;

(h) inhibits FVIIa-dependent TF signaling;

(i) binds to cynomolgus TF;

(j) binds to mouse TF; and

(k) binds to rabbit TF.

346. The antibody-drug conjugate of any one of claims 288 to 345, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) allows human thrombin generation as determined by thrombin generation assay (TGA);

(f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(j) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(k) does not compete for binding to human TF with FVIIa;

(l) inhibits FVIIa-dependent TF signaling;

(m) binds to cynomolgus TF;

(n) binds to mouse TF; and

(o) binds to rabbit TF.

347. The antibody-drug conjugate of any one of claims 288 to 346, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) allows human thrombin generation as determined by thrombin generation assay (TGA);

(c) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(d) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(e) does not compete for binding to human TF with FVIIa;

(f) inhibits FVIIa-dependent TF signaling;

(g) binds to cynomolgus TF;

(h) binds to mouse TF;

(i) binds to rabbit TF;

and (j) binds to pig TF.

348. The antibody-drug conjugate of any one of claims 288 to 347, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(c) allows human thrombin generation as determined by thrombin generation assay (TGA);

(d) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(f) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(g) does not compete for binding to human TF with FVIIa;

(h) inhibits FVIIa-dependent TF signaling;

(i) binds to cynomolgus TF;

(j) binds to mouse TF;

(k) binds to rabbit TF;

and (l) binds to pig TF.

349. The antibody-drug conjugate of any one of claims 288 to 348, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) allows human thrombin generation as determined by thrombin generation assay (TGA);

(f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(j) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(k) does not compete for binding to human TF with FVIIa;

(l) inhibits FVIIa-dependent TF signaling;

(m) binds to cynomolgus TF;

(n) binds to mouse TF;

(o) binds to rabbit TF;

and (p) binds to pig TF.

350. The antibody-drug conjugate of any one of claims 288 to 349, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) allows human thrombin generation as determined by thrombin generation assay (TGA);

(f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(j) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(k) does not compete for binding to human TF with FVIIa;

(l) inhibits FVIIa-dependent TF signaling;

(m) binds to cynomolgus TF;

(n) binds to mouse TF;

(o) binds to rabbit TF;

(p) binds to pig TF;

(q) wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 149 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(r) wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation at amino acid residue 68 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(s) wherein the binding between the antibody and a variant TF extracellular domain comprising mutations at amino acid residues 171 and 197 of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(t) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(u) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(v) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain

of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(w) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(x) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(y) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(z) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(aa) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(bb) wherein the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

351. The antibody-drug conjugate of any one of claims 288 to 350, wherein the antibody:

(a) does not inhibit human thrombin generation as determined by thrombin generation assay (TGA);

(b) does not reduce the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(c) does not increase the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(d) does not decrease the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(e) allows human thrombin generation as determined by thrombin generation assay (TGA);

(f) maintains the thrombin peak on a thrombin generation curve (Peak IIa) compared to an isotype control;

(g) maintains the time from the assay start to the thrombin peak on a thrombin generation curve (ttPeak) compared to an isotype control;

(h) preserves the endogenous thrombin potential (ETP) as determined by the area under a thrombin generation curve compared to an isotype control;

(i) binds human TF at a human TF binding site that is distinct from a human TF binding site bound by human FX;

(j) does not interfere with the ability of TF:FVIIa to convert FX into FXa;

(k) does not compete for binding to human TF with FVIIa;

(l) inhibits FVIIa-dependent TF signaling;

(m) binds to cynomolgus TF;

(n) binds to mouse TF;

(o) binds to rabbit TF;

(p) binds to pig TF;

(q) wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation K149N of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(r) wherein the binding between the antibody and a variant TF extracellular domain comprising a mutation K68N of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(s) wherein the binding between the antibody and a variant TF extracellular domain comprising mutations N171H and T197K of the sequence shown in SEQ ID NO:810 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(t) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 1-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 1-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(u) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 39-77 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 38-76 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(v) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(w) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 146-158 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 151-163 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(x) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-219 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-224 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(y) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-189 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-194 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

(z) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 159-174 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 164-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay;

aa) wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 167-174 of the sequence shown in SEQ ID NO:810 replaced by rat

TF extracellular domain amino acid residues 172-179 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay; and

(bb) wherein the binding between the antibody and a rat TF extracellular domain with amino acid residues 141-194 of the sequence shown in SEQ ID NO:838 replaced by human TF extracellular domain amino acid residues 136-189 of the sequence shown in SEQ ID NO:810 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

352. The antibody-drug conjugate of any one of claims 288 to 351, wherein the antibody competes for binding to human TF with the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

353. The antibody-drug conjugate of claim 352, wherein the antibody competes for binding to human TF with the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

354. The antibody-drug conjugate of claim 352, wherein the antibody competes for binding to human TF with the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

355. The antibody-drug conjugate of any one of claims 288 to 354, wherein the antibody binds to the same human TF epitope bound by the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

356. The antibody-drug conjugate of claim 355, wherein the antibody binds to the same human TF epitope bound by the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

357. The antibody-drug conjugate of claim 355, wherein the antibody binds to the same human TF epitope bound by the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

358. The antibody-drug conjugate of any one of claims 288 to 357, wherein the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

359. The antibody-drug conjugate of claim 358, wherein the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

360. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

361. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

362. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A.

363. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A3.

364. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5.

365. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25A5-T.

366. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G.

367. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G1.

368. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 25G9.

369. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B.

370. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B1.

371. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43B7.

372. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D.

373. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D7.

374. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43D8.

375. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43E.

376. The antibody-drug conjugate of claim 358 or 359, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 43Ea.

377. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:113 and a V_L sequence of SEQ ID NO:114.

378. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:151 and a V_L sequence of SEQ ID NO:152.

379. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:189 and a V_L sequence of SEQ ID NO:190.

380. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:836 and a V_L sequence of SEQ ID NO:837.

381. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:227 and a V_L sequence of SEQ ID NO:228.

382. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:265 and a V_L sequence of SEQ ID NO:266.

383. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:303 and a V_L sequence of SEQ ID NO:304.

384. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:455 and a V_L sequence of SEQ ID NO:456.

385. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:493 and a V_L sequence of SEQ ID NO:494.

386. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:531 and a V_L sequence of SEQ ID NO:532.

387. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:569 and a V_L sequence of SEQ ID NO:570.

388. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:607 and a V_L sequence of SEQ ID NO:608.

389. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:645 and a V_L sequence of SEQ ID NO:646.

390. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:683 and a V_L sequence of SEQ ID NO:684.

391. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:721 and a V_L sequence of SEQ ID NO:722.

392. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

393. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

394. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

395. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

396. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:763 and a V_L sequence of SEQ ID NO:764.

397. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:868 and a V_L sequence of SEQ ID NO:869.

398. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:870 and a V_L sequence of SEQ ID NO:871.

399. The antibody-drug conjugate of any one of claims 288 to 359, wherein the antibody comprises a V_H sequence of SEQ ID NO:769 and a V_L sequence of SEQ ID NO:770.

400. The antibody-drug conjugate of any one of claims 288 to 399, wherein the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

401. The antibody-drug conjugate of claim 400, wherein the antibody comprises: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

402. The antibody-drug conjugate of claim 400, wherein the antibody comprises: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

403. The antibody-drug conjugate of any one of claims 288 to 402, wherein the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, the antibody designated 25G9, the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

404. The antibody-drug conjugate of claim 403, wherein the antibody consists of: the antibody designated 25A, the antibody designated 25A3, the antibody designated 25A5, the antibody designated 25A5-T, the antibody designated 25G, the antibody designated 25G1, or the antibody designated 25G9.

405. The antibody-drug conjugate of claim 403, wherein the antibody consists of: the antibody designated 43B, the antibody designated 43B1, the antibody designated 43B7, the antibody designated 43D, the antibody designated 43D7, the antibody designated 43D8, the antibody designated 43E, or the antibody designated 43Ea.

406. The antibody-drug conjugate of any one of claims 288 to 405, wherein the presence of FVIIa does not interfere with the activity of the antibody-drug conjugate compared to the absence of FVIIa.

407. The antibody-drug conjugate of any one of claims 288 to 406, wherein the presence of FVIIa maintains the activity of the antibody-drug conjugate compared to the absence of FVIIa.

408. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody competes for binding to human TF with: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

409. The antibody-drug conjugate of claim 408, wherein the antibody inhibits FVIIa-dependent TF signaling.

410. The antibody-drug conjugate of claim 408 or 409, wherein the antibody binds to cynomolgus TF.

411. The antibody-drug conjugate of claim 408 or 410, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

412. The antibody-drug conjugate of claim 408 or 410, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 78-93 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-98 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

413. The antibody-drug conjugate of claim 408 or 410, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid

residues 77-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

414. The antibody-drug conjugate of claim 408 or 410, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-85 and 92-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810, as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

415. The antibody-drug conjugate of claim 408 or 410, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 78-93 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-98 of the sequence shown in SEQ ID NO:838 is less than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

416. The antibody-drug conjugate of claim 408 or 410, wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 94-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 99-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810;

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF

extracellular domain amino acid residues 77-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810; and

wherein the binding between the antibody and a human TF extracellular domain with amino acid residues 78-107 of the sequence shown in SEQ ID NO:810 replaced by rat TF extracellular domain amino acid residues 77-85 and 92-112 of the sequence shown in SEQ ID NO:838 is greater than 50% of the binding between the antibody and the extracellular domain of TF of the sequence shown in SEQ ID NO:810,

as determined by the median fluorescence intensity value of the antibody relative to an isotype control in a live cell staining assay.

417. The antibody-drug conjugate of any one of claims 408 to 416, wherein the antibody comprises all three heavy chain Complementary Determining Regions (CDRs) and all three light chain CDRs from: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, the antibody designated 43Ea, or the antibody designated 54E.

418. The antibody-drug conjugate of claim 417, wherein the three heavy chain CDRs and the three light chain CDRs are determined using Kabat, Chothia, AbM, Contact, or IMGT numbering.

419. The antibody-drug conjugate of claim 417 or 418, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 1F.

420. The antibody-drug conjugate of claim 417 or 418, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 1G.

421. The antibody-drug conjugate of claim 417 or 418, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 29D.

422. The antibody-drug conjugate of claim 417 or 418, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 29E.

423. The antibody-drug conjugate of claim 417 or 418, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 39A.

424. The antibody-drug conjugate of claim 417 or 418, wherein the antibody comprises all three heavy chain CDRs and all three light chain CDRs from the antibody designated 54E.

425. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:37 and a V_L sequence of SEQ ID NO:38.

426. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:75 and a V_L sequence of SEQ ID NO:76.

427. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:341 and a V_L sequence of SEQ ID NO:342.

428. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:379 and a V_L sequence of SEQ ID NO:380.

429. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:417 and a V_L sequence of SEQ ID NO:418.

430. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:759 and a V_L sequence of SEQ ID NO:760.

431. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:773; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:774; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:775; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:776; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:777; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:778.

432. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:785; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:786; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:787; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:788; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:789; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:790.

433. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:791; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:792; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:793; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:794; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:795; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:796.

434. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:803; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:804; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:805; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:806; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:807; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:808.

435. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:761 and a V_L sequence of SEQ ID NO:762.

436. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:765 and a V_L sequence of SEQ ID NO:766.

437. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:767 and a V_L sequence of SEQ ID NO:768.

438. The antibody-drug conjugate of any one of claims 408 to 418, wherein the antibody comprises a V_H sequence of SEQ ID NO:771 and a V_L sequence of SEQ ID NO:772.

439. The antibody-drug conjugate of any one of claims 408 to 438, wherein the antibody comprises: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

440. The antibody-drug conjugate of any one of claims 408 to 439, wherein the antibody consists of: the antibody designated 1F, the antibody designated 1G, the antibody designated 29D, the antibody designated 29E, the antibody designated 39A, or the antibody designated 54E.

441. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:773; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:774; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:775; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:776; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:777; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:778.

442. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:779; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:780; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:781; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:782; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:783; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:784.

443. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:785; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:786; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:787; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:788; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:789; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:790.

444. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:791; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:792; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:793; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:794; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:795; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:796.

445. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:797; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:798; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:799; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:800; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:801; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:802.

446. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:803; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:804; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:805; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:806; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:807; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:808.

447. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:872; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:873; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:874; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:875; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:876; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:877.

448. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody comprises: a VH-CDR1 comprising the sequence set forth in SEQ ID NO:878; a VH-CDR2 comprising the sequence set forth in SEQ ID NO:879; a VH-CDR3 comprising the sequence set forth in SEQ ID NO:880; a VL-CDR1 comprising the sequence set forth in SEQ ID NO:881; a VL-CDR2 comprising the sequence set forth in SEQ ID NO:882; and a VL-CDR3 comprising the sequence set forth in SEQ ID NO:883.

449. The antibody-drug conjugate of any one of claims 288 to 448, wherein the antibody is human, humanized, or chimeric.

450. The antibody-drug conjugate of any one of claims 288 to 449, wherein the antibody binds to human TF with a K_D of less than or equal to 50 nM, 10 nM, 5 nM, 1 nM, 0.5 nM or 0.1 nM, as measured by Octet QK384 or Biacore assay.

451. The antibody-drug conjugate of any one of claims 288 to 449, wherein the antibody is a monoclonal antibody.

452. The antibody-drug conjugate of any one of claims 288 to 451, wherein the antibody is multispecific.

453. The antibody-drug conjugate of any one of claims 288 to 452, wherein the antibody 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.

454. The antibody-drug conjugate of any one of claims 288 to 453, wherein the antibody comprises a scaffold, optionally wherein the scaffold is Fc, optionally human Fc.

455. The antibody-drug conjugate of claim 454, wherein the antibody comprises a heavy chain constant region of a class selected from IgG, IgA, IgD, IgE, and IgM.

456. The antibody-drug conjugate of claim 455, wherein the antibody comprises a heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4.

457. The antibody-drug conjugate of claim 456, wherein the antibody comprises a heavy chain constant region of IgG1.

458. The antibody-drug conjugate of any one of claims 454 to 457, wherein 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.

459. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody competes for binding to human TF with the antibody of any one of claims 288 to 458.

460. An antibody-drug conjugate comprising: an anti-human Tissue Factor (anti-hTF) antibody, a cytotoxic agent linked to the antibody, and optionally a linker that links the antibody to the cytotoxic agent, wherein the antibody binds the human TF epitope bound by the antibody of any one of claims 288 to 459.

461. The antibody-drug conjugate of any one of claims 288 to 460, wherein the cytotoxic agent comprises an anti-angiogenic agent, a pro-apoptotic agent, an anti-mitotic agent, an anti-kinase agent, an alkylating agent, a hormone, a hormone agonist, a hormone antagonist, a

chemokine, a drug, a prodrug, a toxin, an enzyme, an antimetabolite, an antibiotic, an alkaloid, or a radioactive isotope.

462. The antibody-drug conjugate of any one of claims 288 to 461, wherein the cytotoxic agent comprises at least one of: calicheamycin, camptothecin, carboplatin, irinotecan, SN-38, carboplatin, camptothecan, cyclophosphamide, cytarabine, dacarbazine, docetaxel, dactinomycin, daunorubicin, doxorubicin, doxorubicin, etoposide, idarubicin, topotecan, vinca alkaloid, maytansinoid, maytansinoid analog, pyrrolobenzodiazepine, taxoid, duocarmycin, dolastatin, and auristatin.

463. The antibody-drug conjugate of any one of claims 288 to 462, wherein the linker comprises a labile linker, an acid labile linker, a photolabile linker, a charged linker, a disulfide-containing linker, a peptidase-sensitive linker, a β-glucuronide linker, a dimethyl linker, a thio-ether linker, or a hydrophilic linker.

464. The antibody-drug conjugate of any one of claims 288 to 463, wherein the linker is a cleavable linker.

465. The antibody-drug conjugate of any one of claims 288 to 463, wherein the linker is a non-cleavable linker.

466. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 288 to 465 and a pharmaceutically acceptable excipient.

467. 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 of any one of claims 288 to 465 or the pharmaceutical composition of claim 466.

468. The method of claim 467, wherein the disease or condition is cancer.

469. The method of claim 468, wherein the cancer is head and neck cancer.

470. The method of claim 468, wherein the cancer is ovarian cancer.

471. The method of claim 468, wherein the cancer is gastric cancer.

472. The method of claim 468, wherein the cancer is esophageal cancer.

473. The method of claim 468, wherein the cancer is cervical cancer.

474. The method of claim 468, wherein the cancer is prostate cancer.

475. The method of claim 468, wherein the cancer is pancreatic cancer.

476. The method of claim 468, wherein the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer.

477. The method of claim 468, wherein the cancer is glioblastoma.

478. The method of claim 468, wherein the cancer is lung cancer.

479. The method of claim 468, wherein the cancer is bladder cancer.

480. The method of claim 468, wherein the cancer is melanoma.

481. The method of claim 468, wherein the cancer is kidney cancer.

482. The method of any one of claims 467 to 481, further comprising administering one or more additional therapeutic agents to the subject.

483. The method of claim 482, wherein the additional therapeutic agent is formulated in the same pharmaceutical composition as the antibody-drug conjugate.

484. The method of claim 482, wherein the additional therapeutic agent is formulated in a different pharmaceutical composition from the antibody-drug conjugate.

485. The method of claim 482, wherein the additional therapeutic agent is administered prior to administering the antibody-drug conjugate.

486. The method of claim 482, wherein the additional therapeutic agent is administered after administering the antibody-drug conjugate.

487. The method of claim 482, wherein the additional therapeutic agent is administered contemporaneously with the antibody-drug conjugate.

488. A method of detecting TF in a subject having or suspected of having a disease or condition, the method comprising: (a) administering to the subject the antibody-drug conjugate of any one of claims 288 to 465; and (b) detecting the presence or the level of TF in the subject.

489. The method of claim 488, wherein the disease or condition is cancer.

490. The method of claim 489, wherein the cancer is head and neck cancer.

491. The method of claim 489, wherein the cancer is ovarian cancer.

492. The method of claim 489, wherein the cancer is gastric cancer.

493. The method of claim 489, wherein the cancer is esophageal cancer.

494. The method of claim 489, wherein the cancer is cervical cancer.

495. The method of claim 489, wherein the cancer is prostate cancer.

496. The method of claim 489, wherein the cancer is pancreatic cancer.

497. The method of claim 489, wherein the cancer is estrogen receptors negative (ER-), progesterone receptors negative (PR-), and HER2 negative (HER2-) triple negative breast cancer.

498. The method of claim 489, wherein the cancer is glioblastoma.

499. The method of claim 489, wherein the cancer is lung cancer.

500. The method of claim 489, wherein the cancer is bladder cancer.

501. The method of claim 489, wherein the cancer is melanoma.

502. The method of claim 489, wherein the cancer is kidney cancer.

503. A kit comprising the antibody-drug conjugate of any one of claims 288 to 465 or the pharmaceutical composition of claim 466 and instructions for use.

Figure 1A

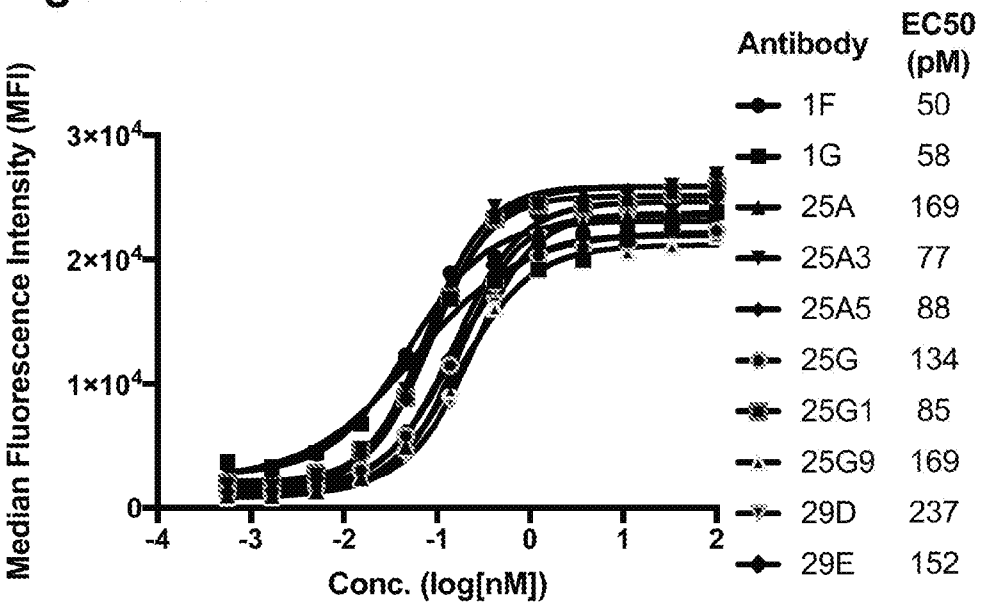


Figure 1B

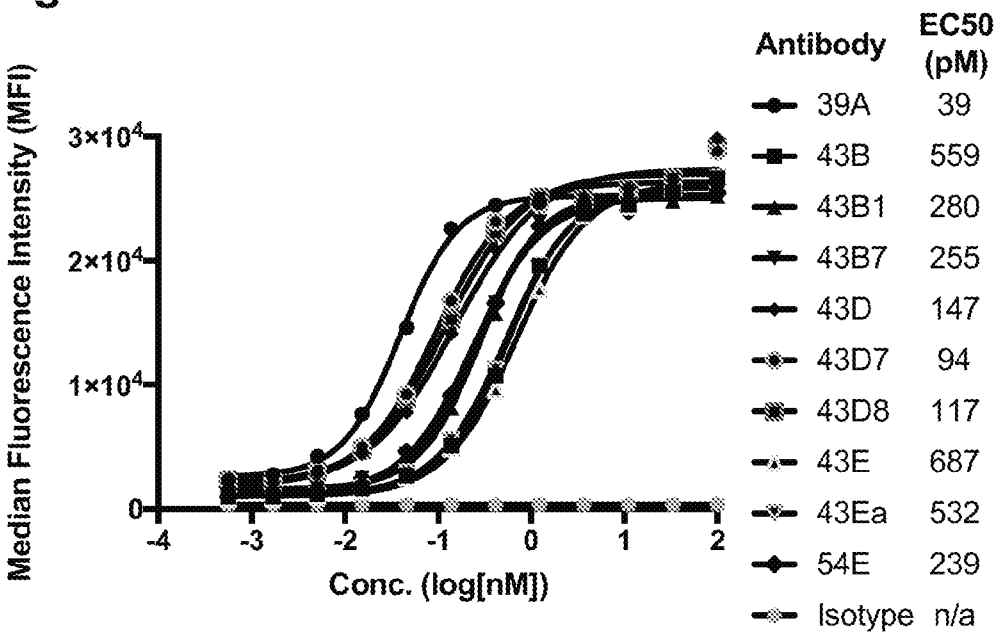
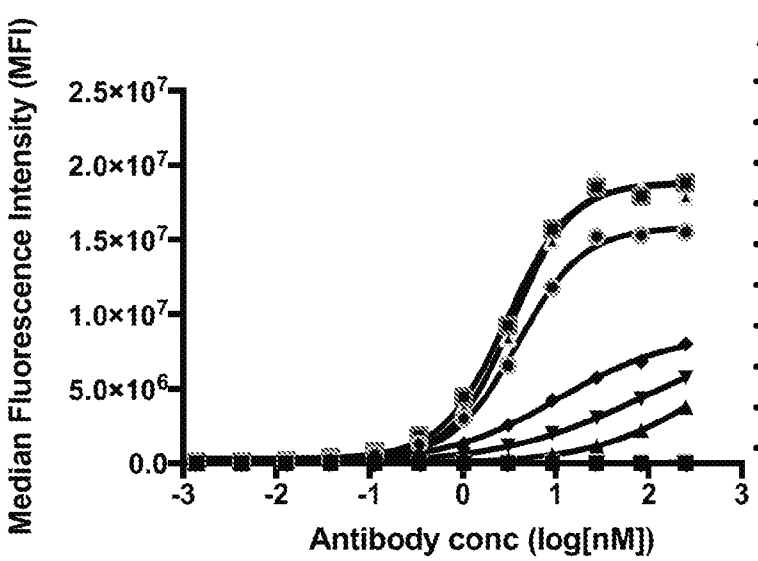
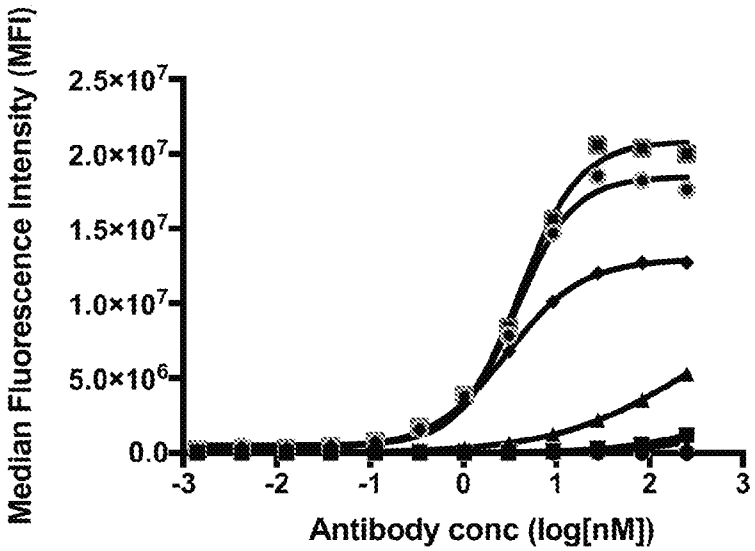


Figure 2A



Antibody	EC50 (nM)	MFI at 250 nM
1F	n/a	$4.2x10^3$
1G	n/a	$4.3x10^3$
25A	455	$3.8x10^6$
25A3	87	$5.8x10^6$
25A5	11	$8.0x10^6$
25G	3.9	$1.6x10^7$
25G1	3.0	$1.9x10^7$
25G9	3.4	$1.8x10^7$
29D	n/a	$3.0x10^4$
29E	n/a	$5.1x10^3$

Figure 2B



Antibody	EC50 (nM)	MFI at 250 nM
39A	n/a	$3.7x10^3$
43B	n/a	$1.2x10^6$
43B1	255	$5.3x10^6$
43B7	n/a	$8.0x10^5$
43D	2.9	$1.3x10^7$
43D7	3.6	$1.8x10^7$
43D8	4.0	$2.0x10^7$
43E	n/a	$7.0x10^5$
43Ea	n/a	$1.1x10^6$
54E	n/a	$2.7x10^3$
Isotype	n/a	$7.4x10^3$

Figure 3A

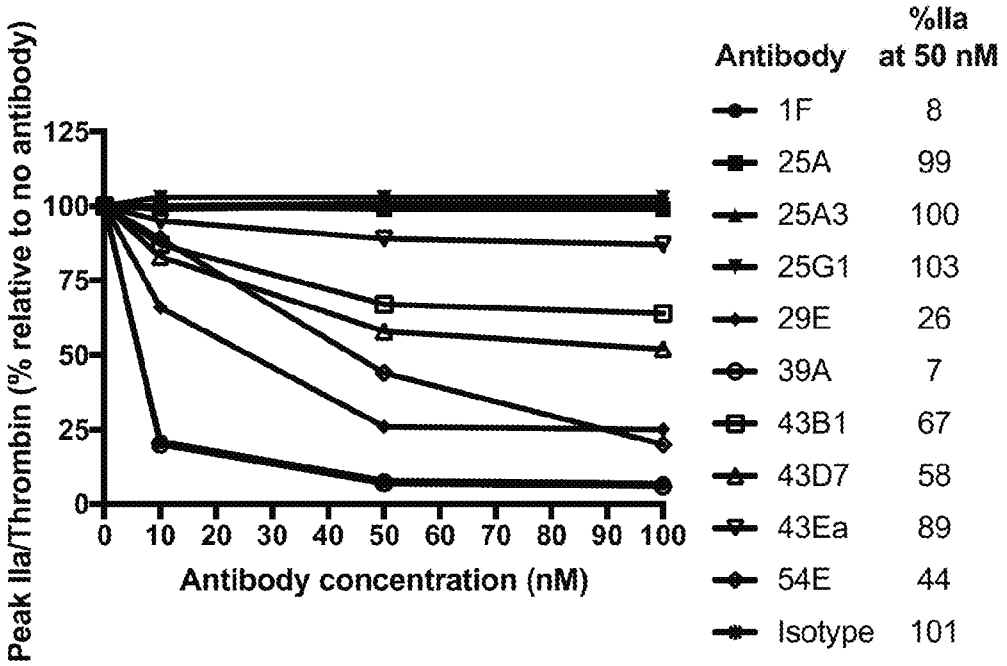


Figure 3B

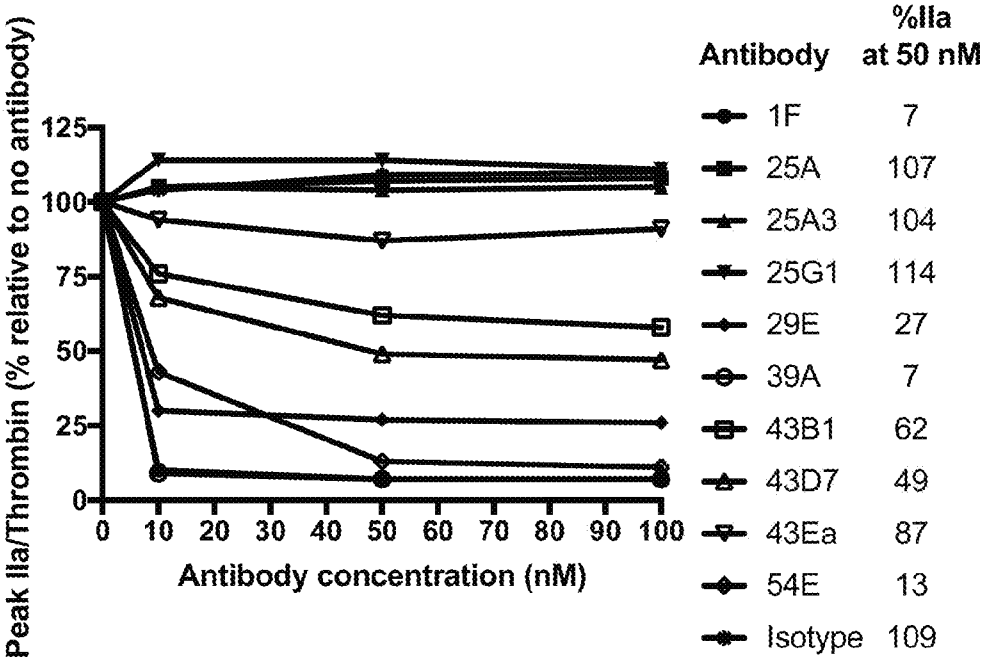


Figure 4A

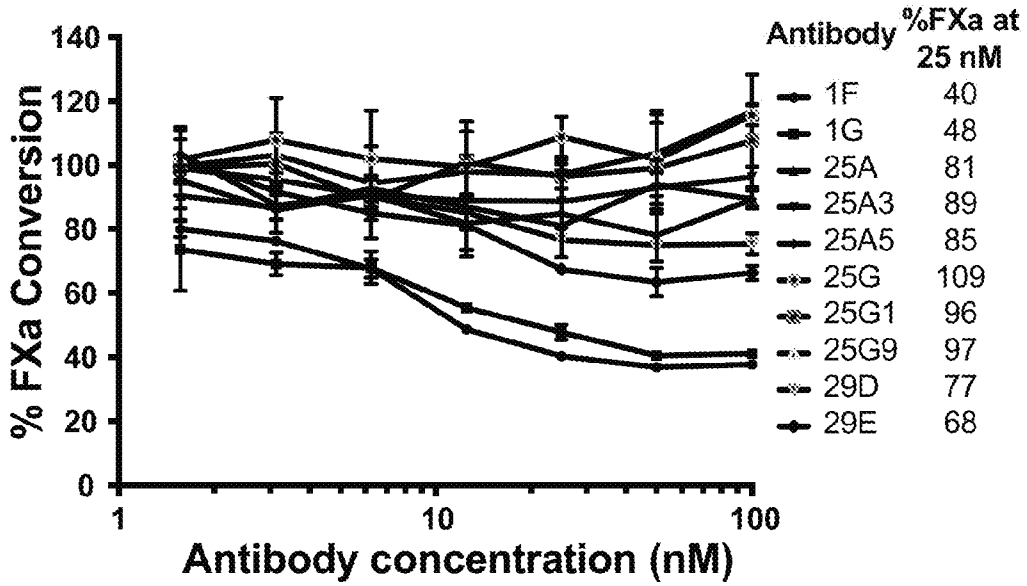


Figure 4B

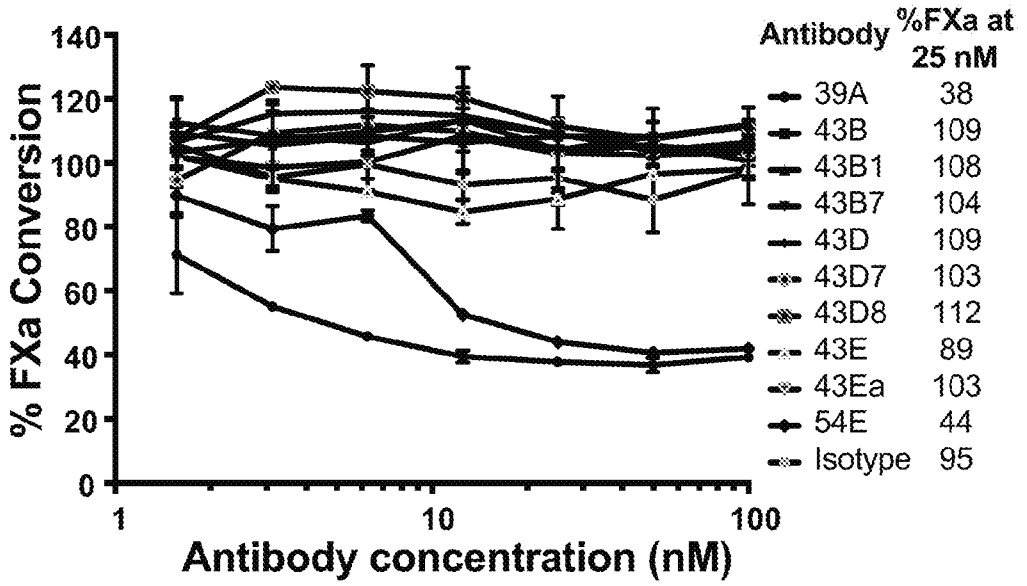


Figure 5A

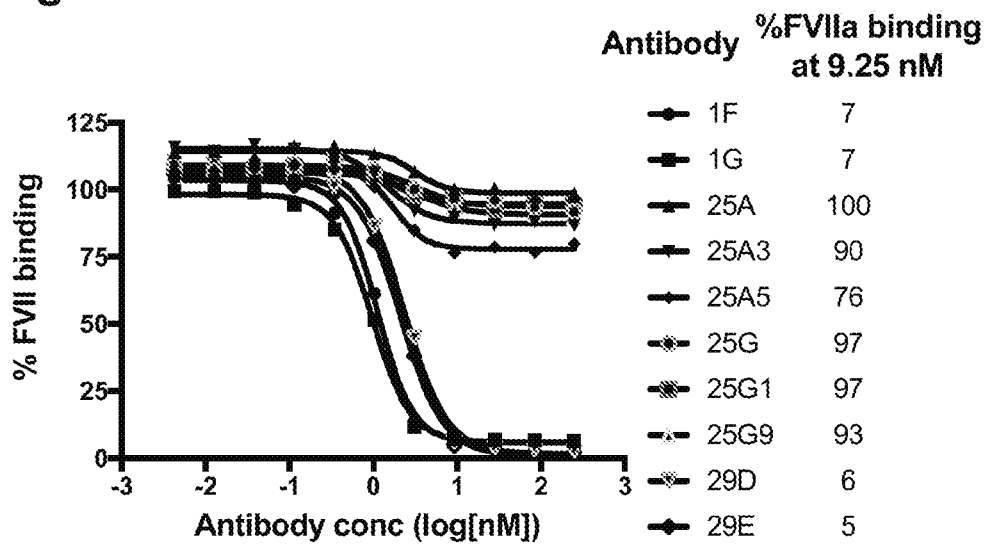


Figure 5B

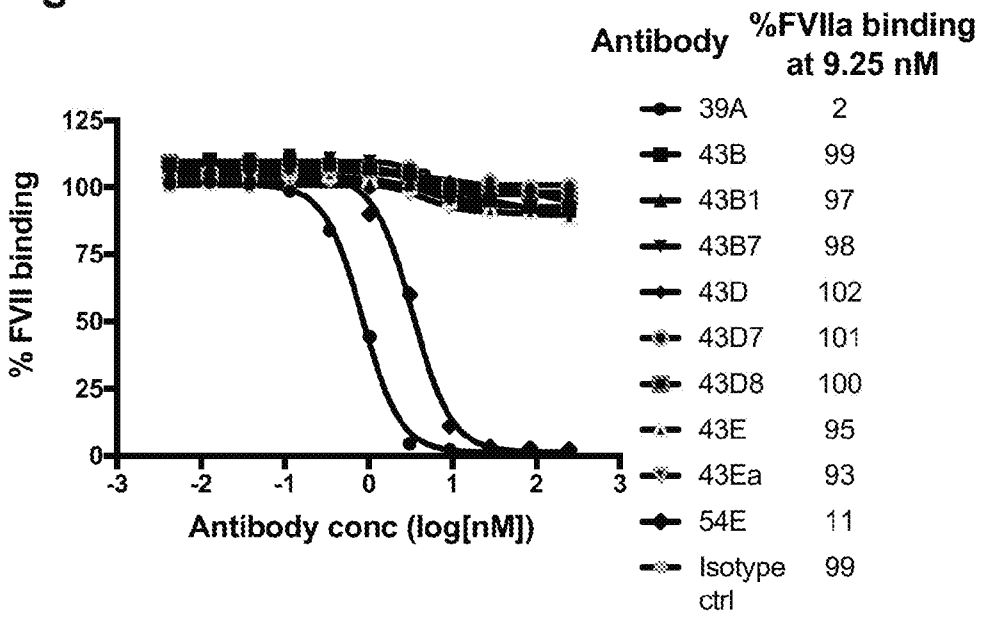


Figure 6A

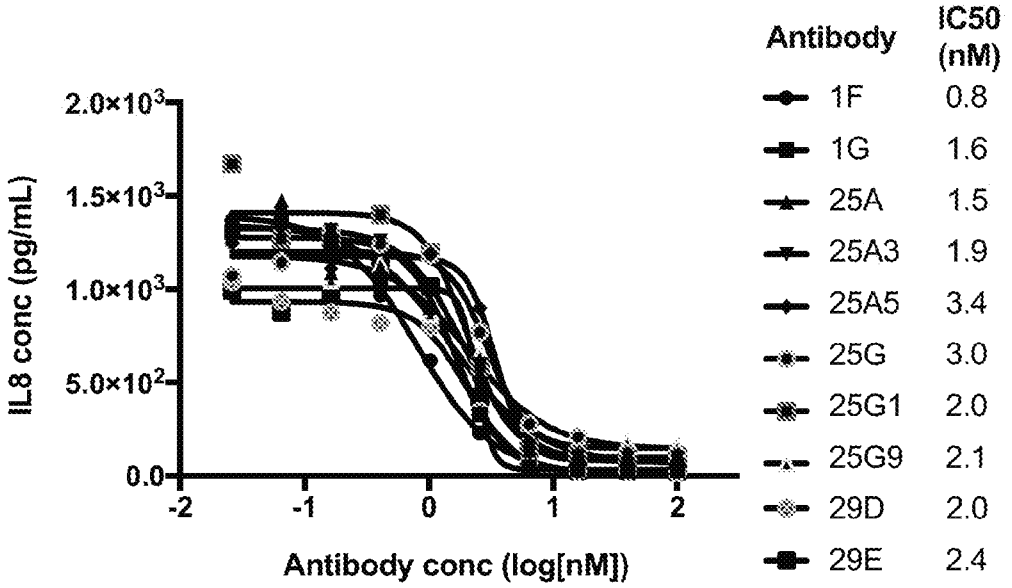


Figure 6B

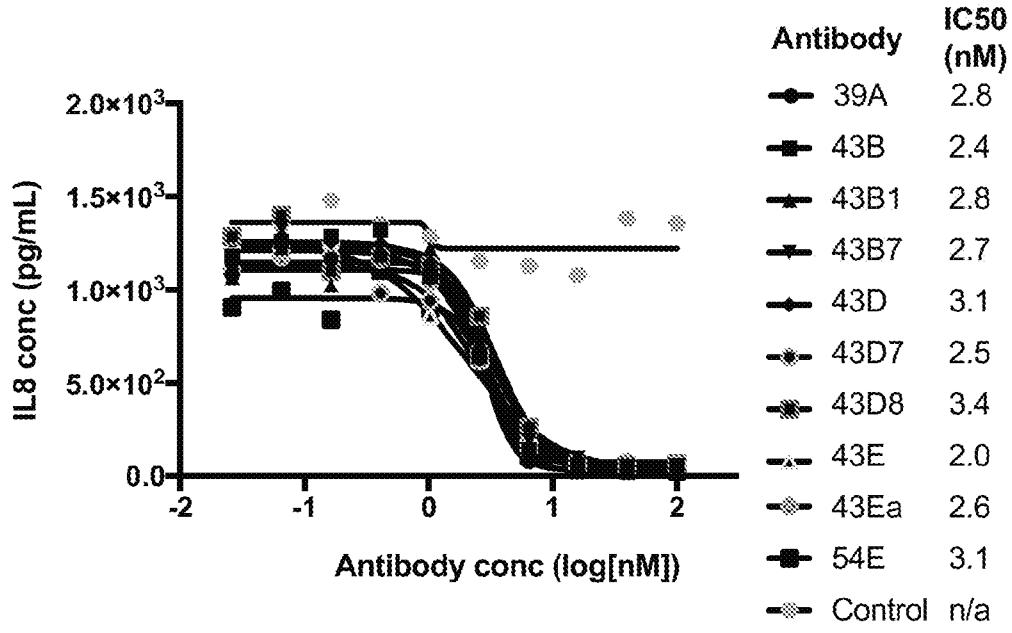
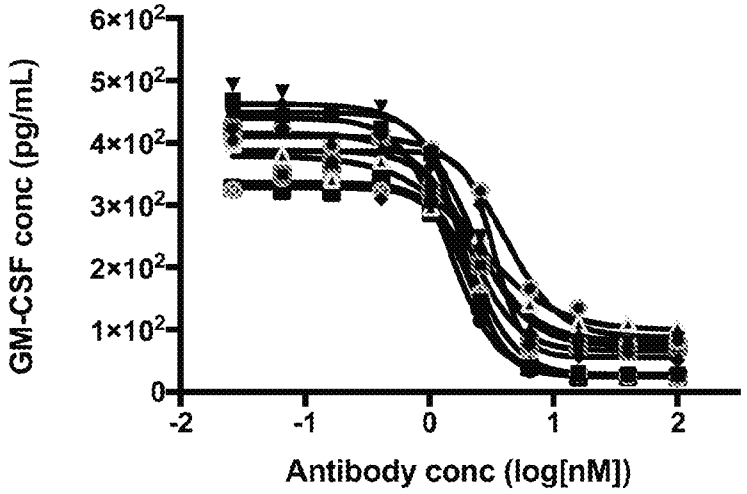
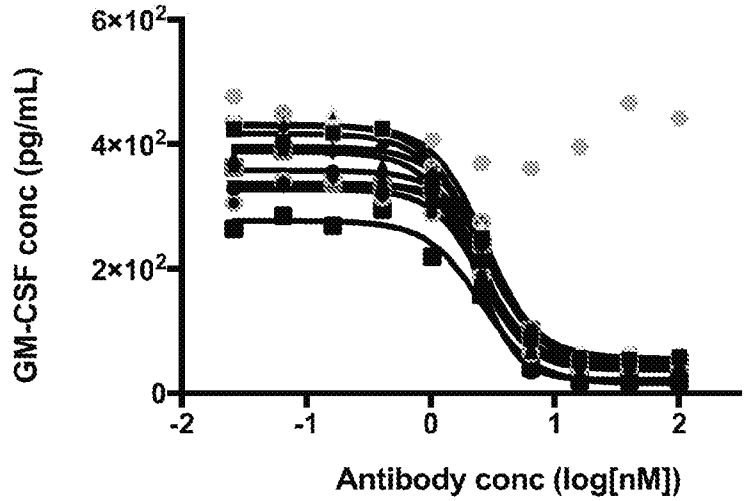


Figure 6C



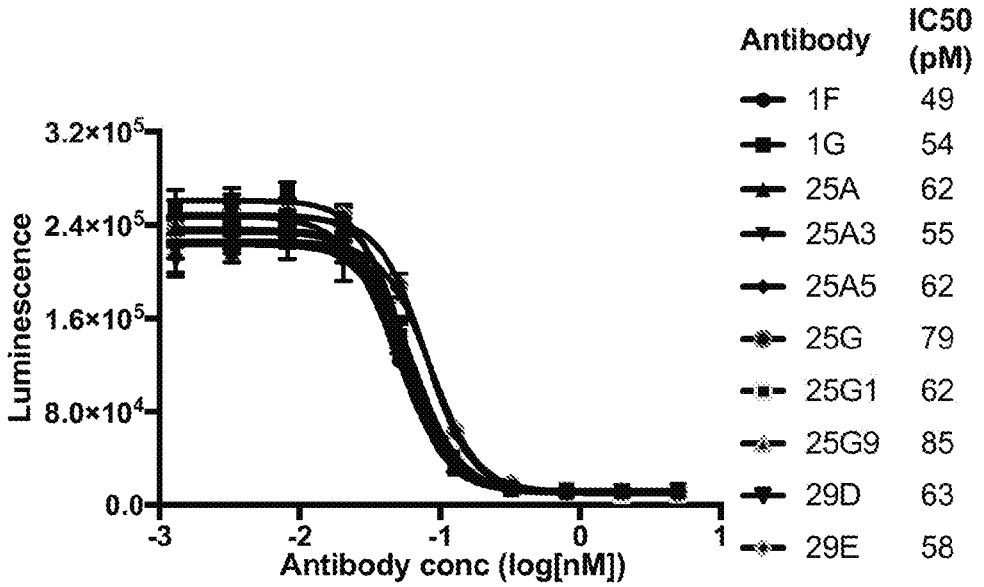
Antibody	IC50 (nM)
1F	1.4
1G	1.8
25A	2.1
25A3	2.1
25A5	3.3
25G	4.0
25G1	2.2
25G9	2.4
29D	2.3
29E	2.1

Figure 6D



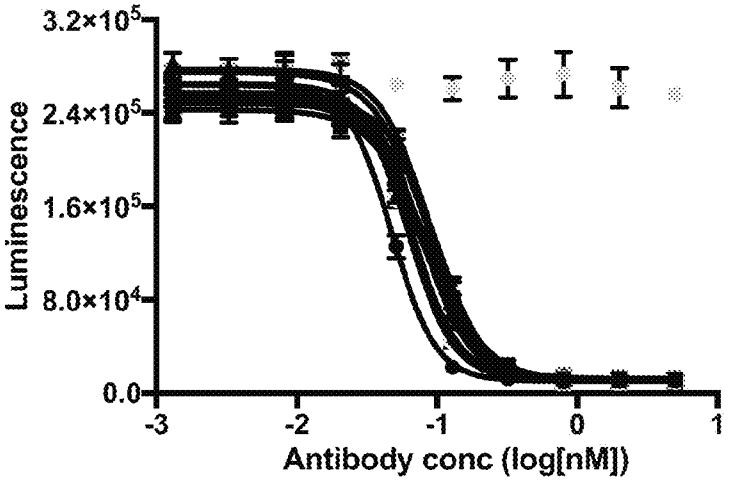
Antibody	IC50 (nM)
39A	2.5
43B	2.5
43B1	2.3
43B7	2.8
43D	2.8
43D7	2.6
43D8	3.2
43E	2.5
43Ea	2.8
54E	2.5
Control	n/a

Figure 7A



Antibody	IC50 (pM)
1F	49
1G	54
25A	62
25A3	55
25A5	62
25G	79
25G1	62
25G9	85
29D	63
29E	58

Figure 7B



Antibody	IC50 (pM)
39A	48
43B	87
43B1	77
43B7	98
43D	78
43D7	64
43D8	80
43E	85
43Ea	88
54E	66
Isotype	

Figure 8A

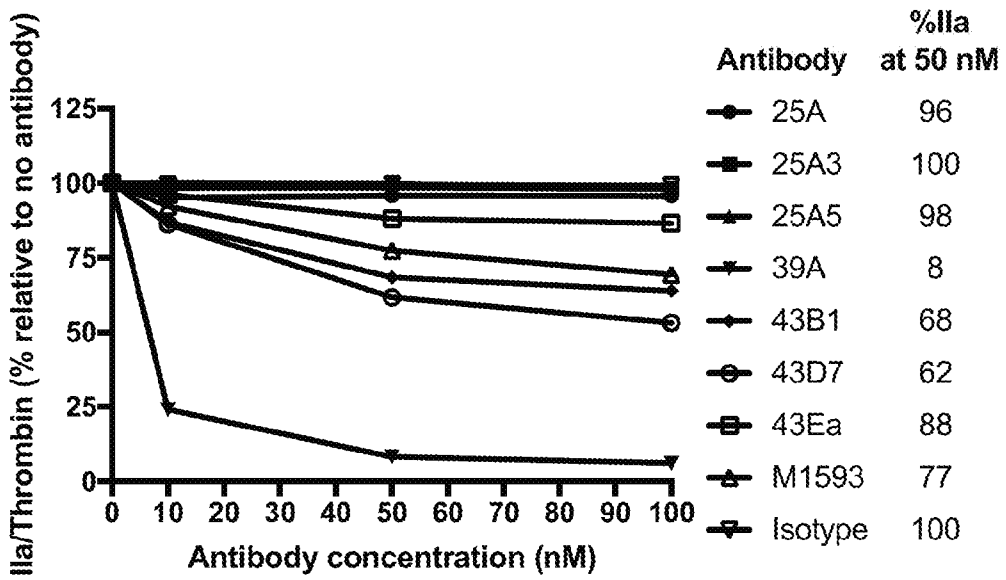


Figure 8B

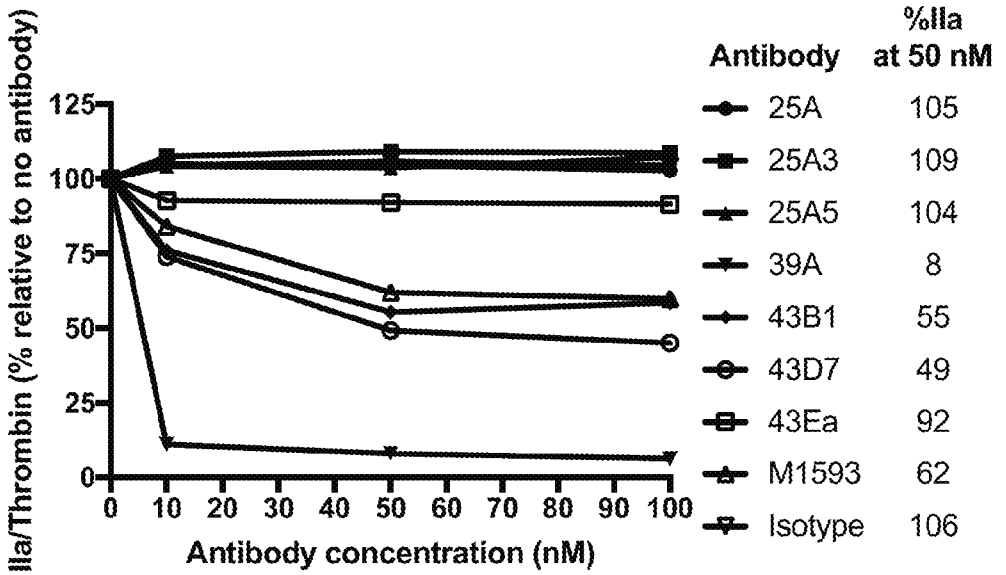
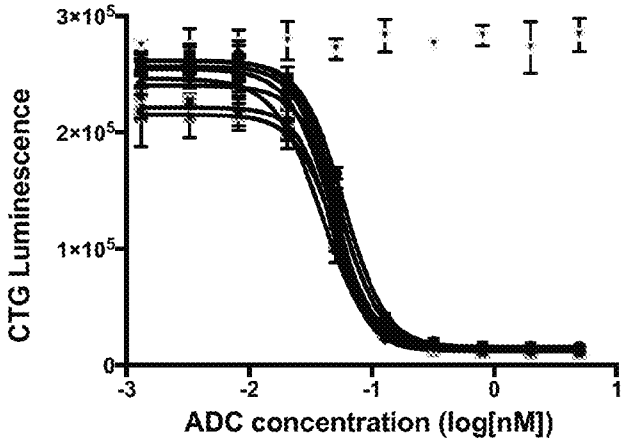
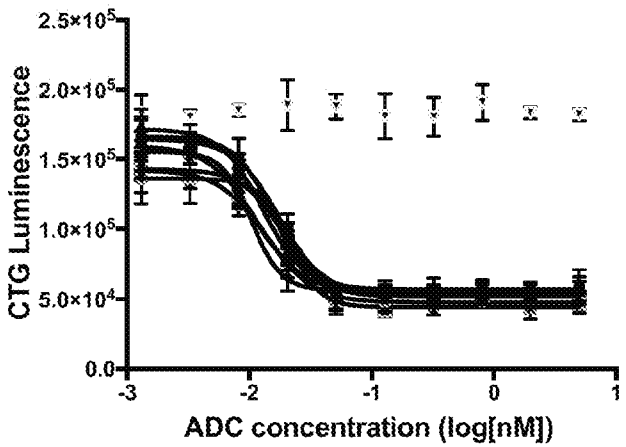


Figure 9A



ADC	IC50 (pM)
25A-vc-MMAE	59
43Ea-vc-MMAE	54
25A3-vc-MMAE	49
25G1-vc-MMAE	47
39A-vc-MMAE	39
43B1-vc-MMAE	56
43D7-vc-MMAE	48
43D8-vc-MMAE	50
Isotype-vc-MMAE	n/a

Figure 9B



ADC	IC50 (pM)
25A-vc-MMAE	15
43Ea-vc-MMAE	17
25A3-vc-MMAE	13
25G1-vc-MMAE	11
39A-vc-MMAE	10
43B1-vc-MMAE	19
43D7-vc-MMAE	14
43D8-vc-MMAE	21
Isotype-vc-MMAE	n/a

Figure 10A

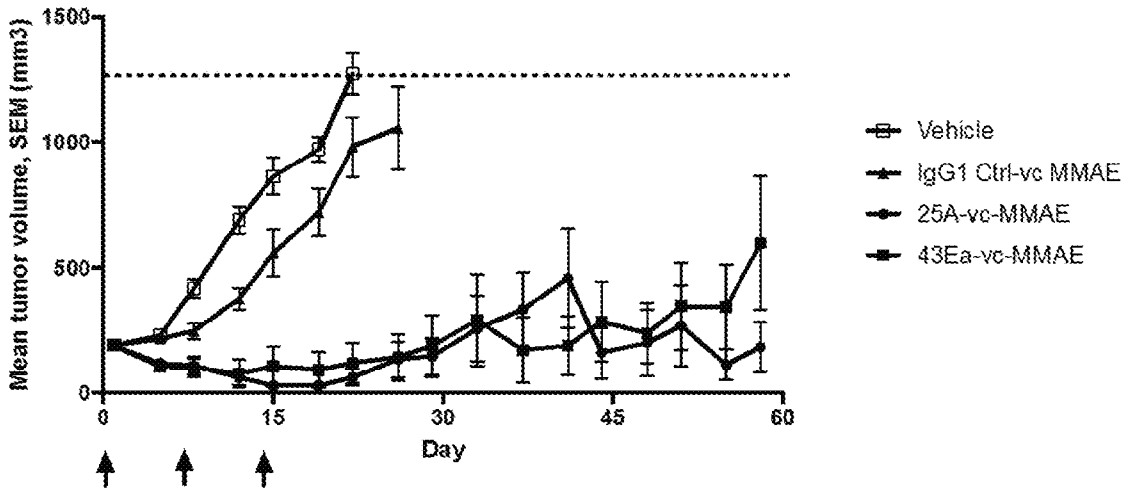


Figure 10B

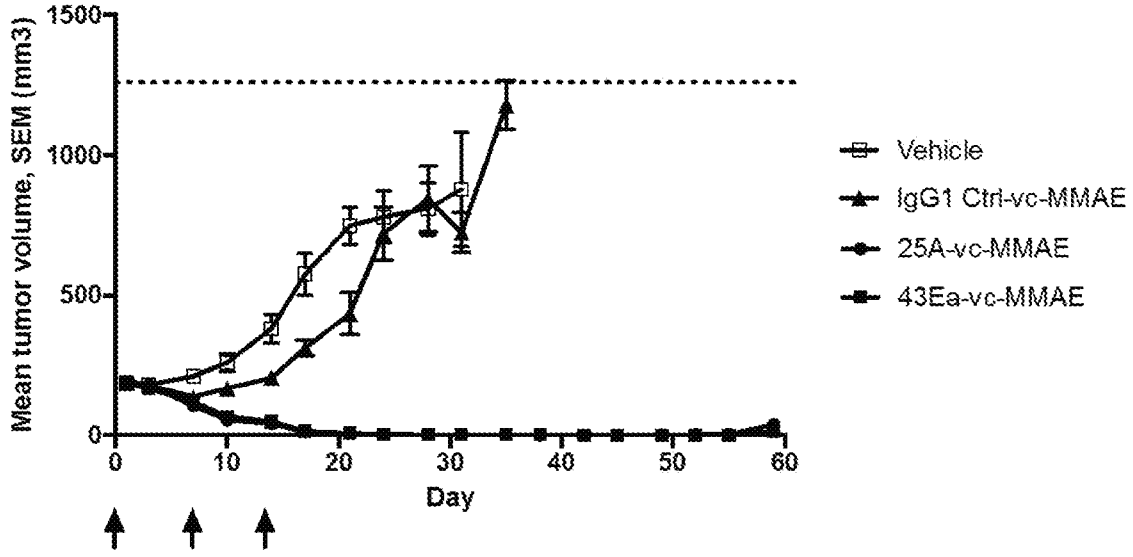


Figure 11

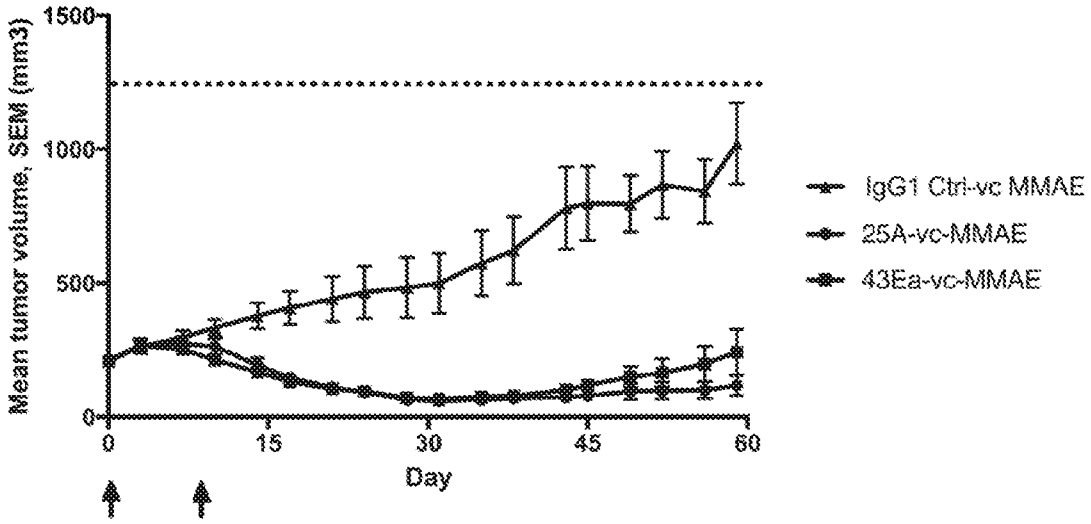
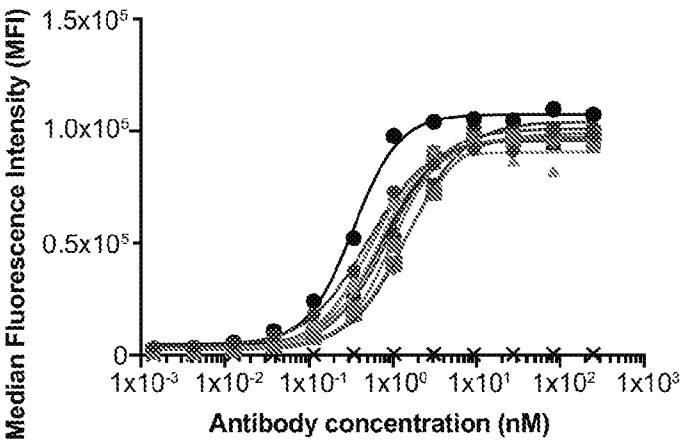
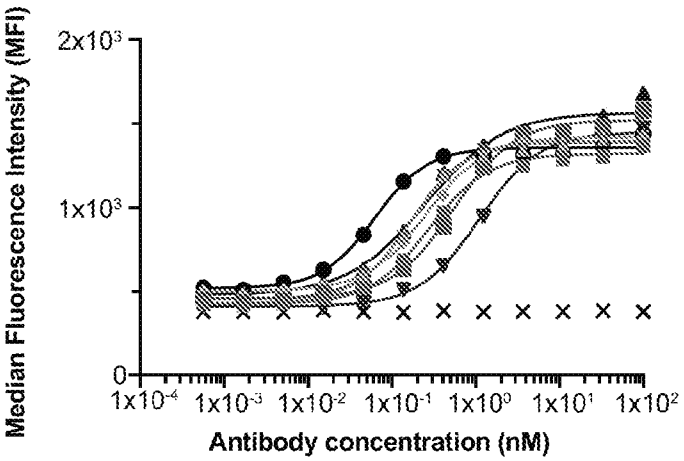

Mean tumor volume, SEM (mm3)
1500
1000
500
0
0
15
30
45
60
Day
IgG1 Ctrl-vc MMAE
25A-vc-MMAE
43Ea-vc-MMAE

Figure 12A



Antibody	EC50 (nM)	95% CI
1F	0.49	0.40 to 0.60
25A	0.97	0.83 to 1.12
25A3	0.50	0.37 to 0.67
25G1	0.56	0.50 to 0.62
29E	0.68	0.57 to 0.80
39A	0.34	0.28 to 0.41
43B1	1.37	1.18 to 1.59
43D7	0.76	0.61 to 0.94
43Ea	1.50	1.29 to 1.74
54E	0.89	0.74 to 1.07
Isotype	nb	nb

Figure 12B



Antibody	EC50 (nM)	95% CI
25A	0.27	0.22 to 0.34
25A3	0.17	0.14 to 0.20
25G1	0.17	0.14 to 0.20
29E	0.26	0.23 to 0.29
39A	0.06	0.05 to 0.08
43B1	0.54	0.44 to 0.67
43D7	0.25	0.16 to 0.42
43Ea	1.10	0.94 to 1.28
Isotype	nb	nb

Figure 13A

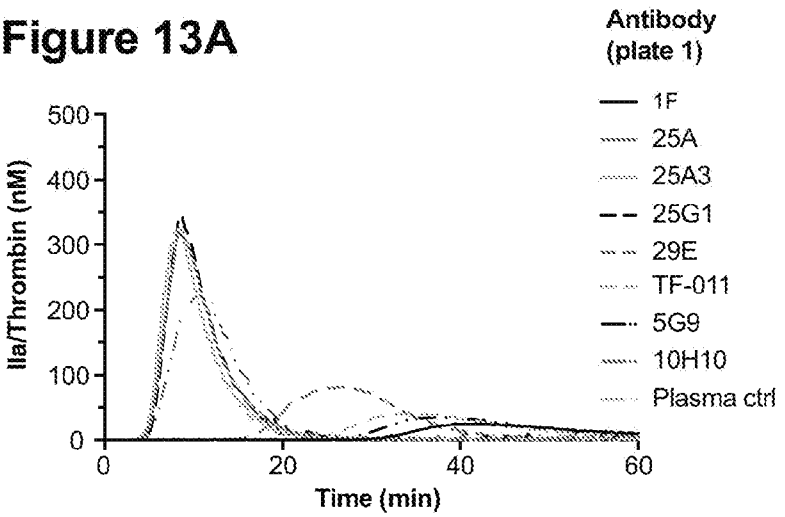


Figure 13B

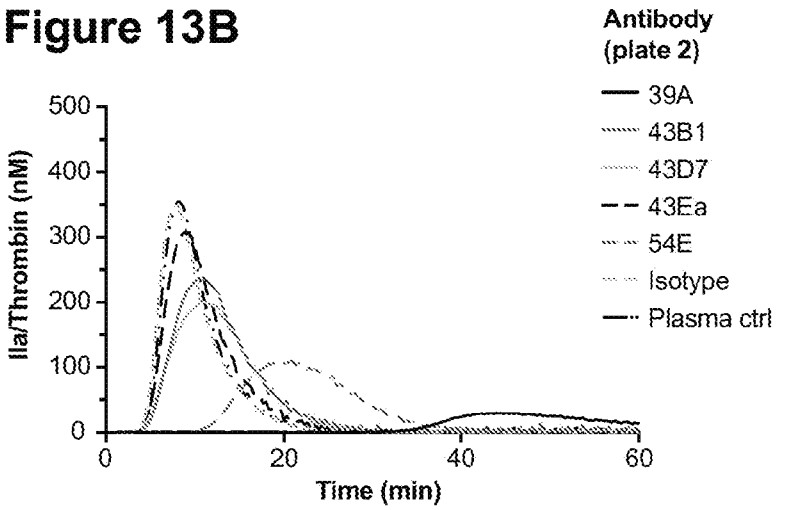


Figure 13C

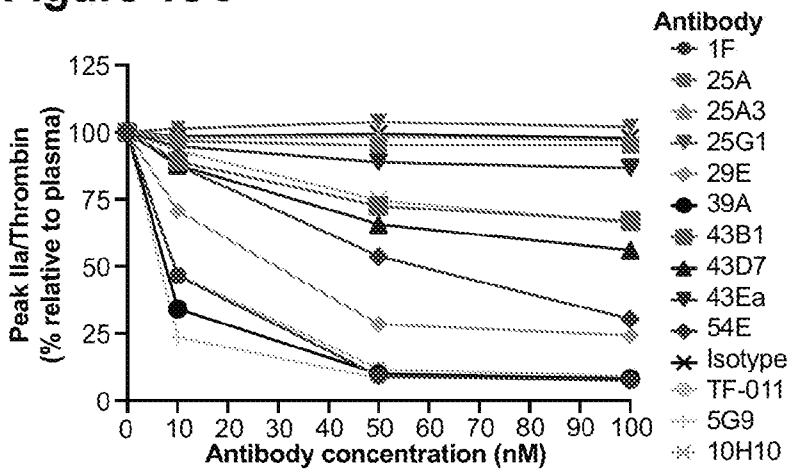


Figure 14A

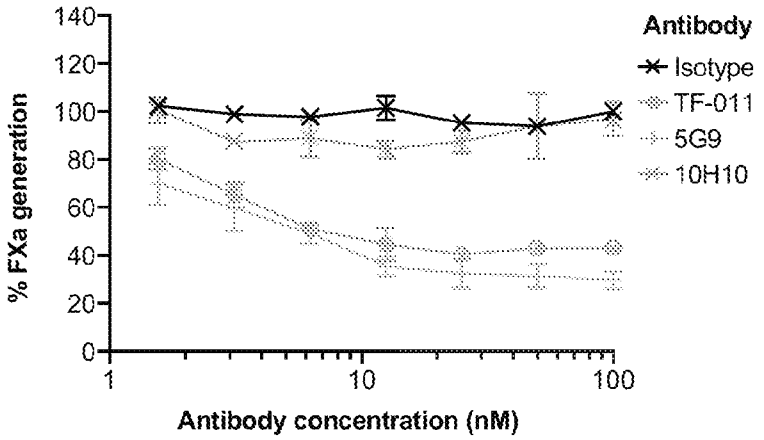


Figure 14B

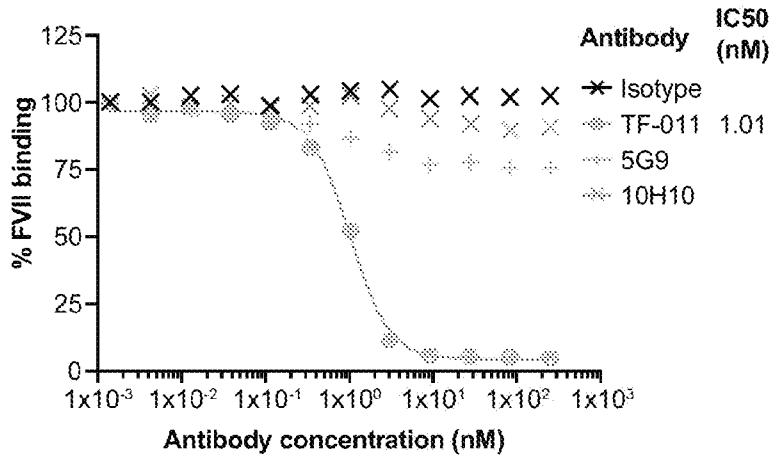


Figure 15A

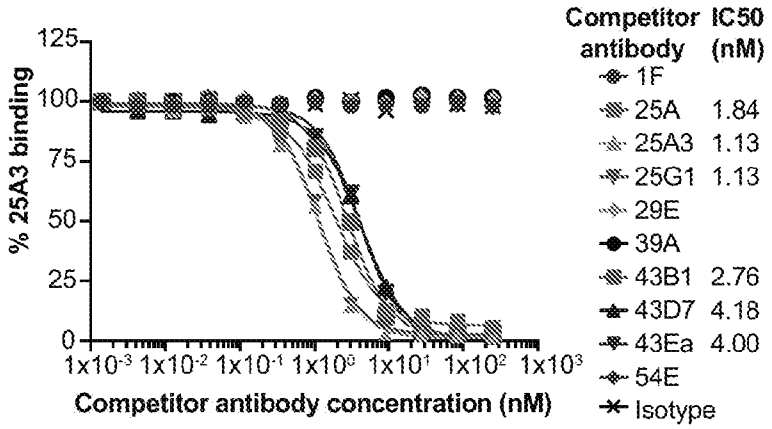


Figure 15B

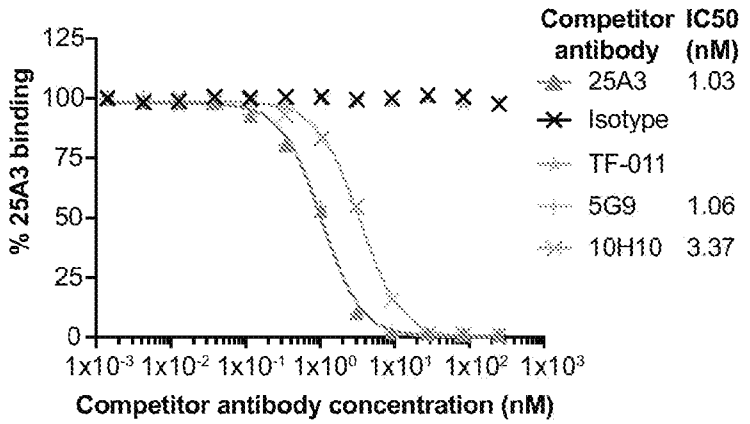


Figure 16A

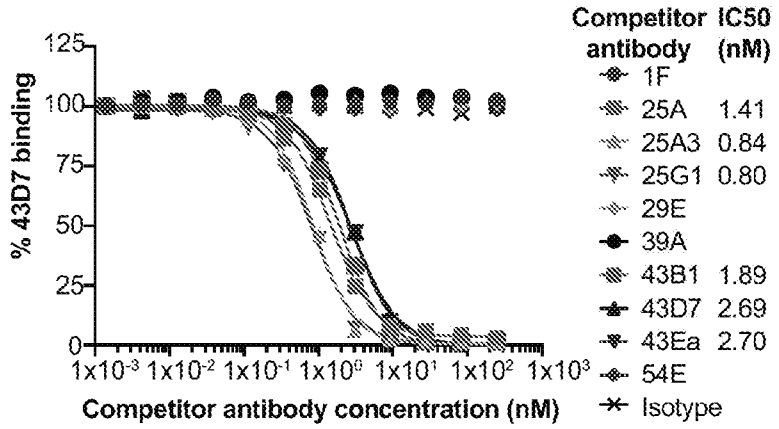


Figure 16B

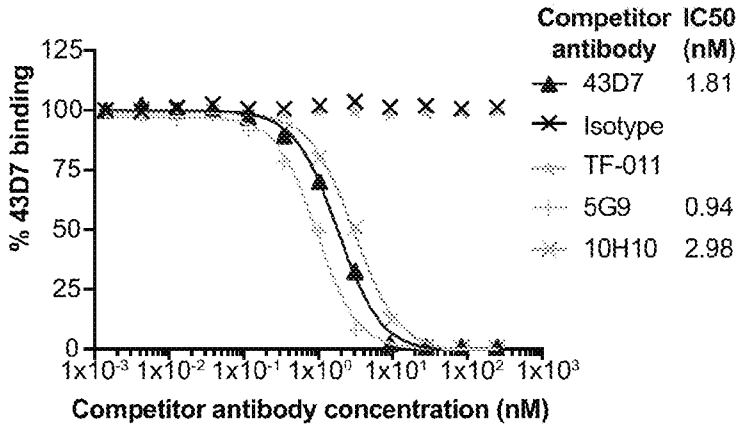


Figure 17A

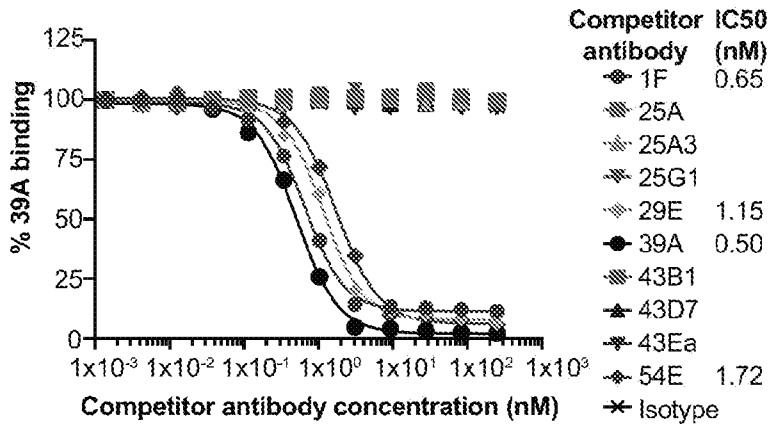


Figure 17B

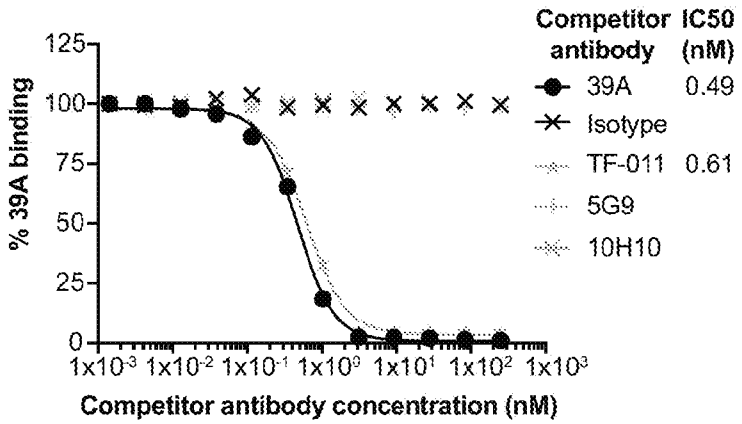


Figure 18A

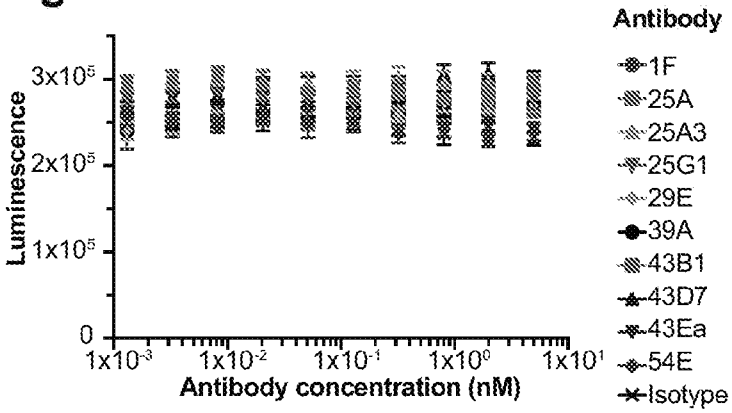


Figure 18B

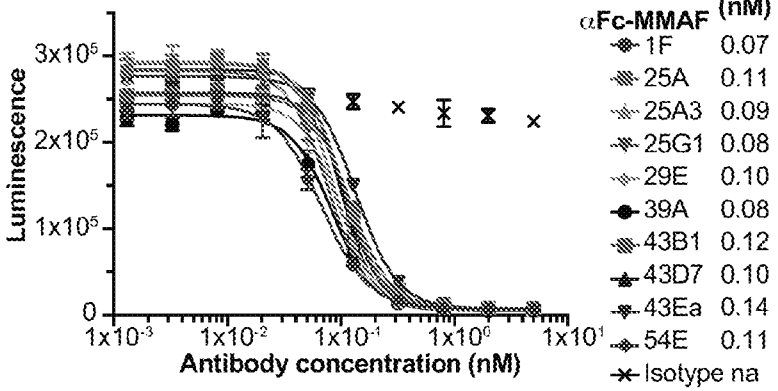


Figure 18C

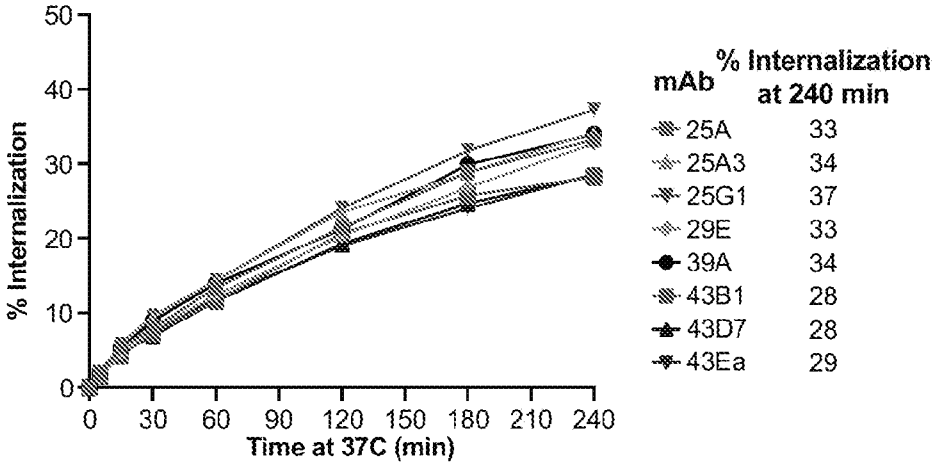


Figure 19A

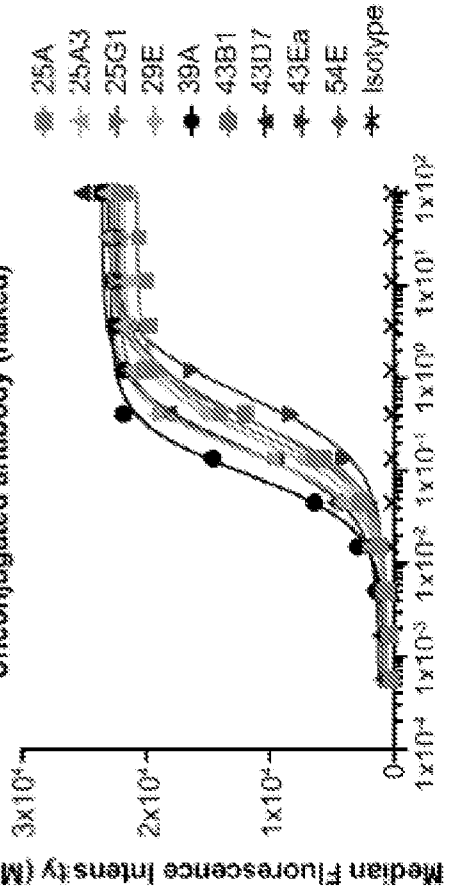


Figure 19B

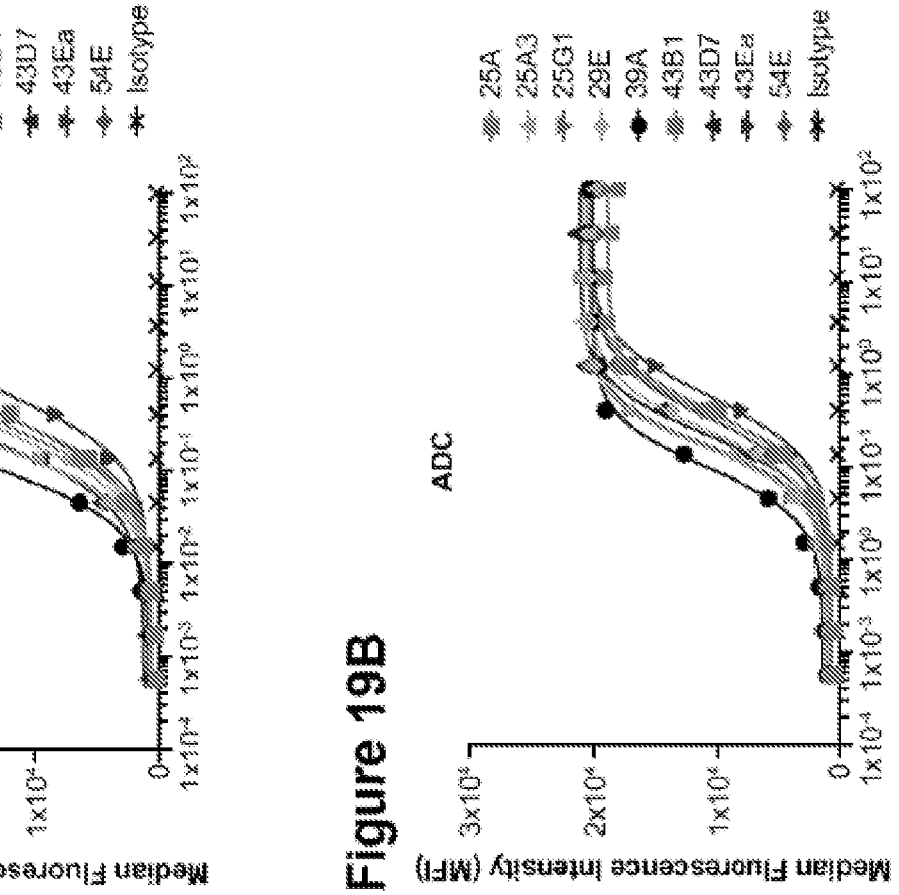


Figure 19C

Antibody	EC50 (nM)		95% CI	
	Naked	ADC	Naked	ADC
25A	0.25	0.34	0.21 to 0.29	0.29 to 0.41
25A3	0.16	0.17	0.13 to 0.19	0.14 to 0.19
25G1	0.16	0.17	0.14 to 0.18	0.13 to 0.21
29E	0.23	0.25	0.20 to 0.26	0.21 to 0.29
39A	0.09	0.10	0.08 to 0.11	0.09 to 0.11
43B1	0.36	0.40	0.31 to 0.42	0.35 to 0.47
43D7	0.19	0.23	0.15 to 0.23	0.19 to 0.27
43Ea	0.65	0.58	0.56 to 0.76	0.49 to 0.68
54E	0.36	0.33	0.31 to 0.42	0.27 to 0.39
Isotype	na	na	na	na

Figure 20A

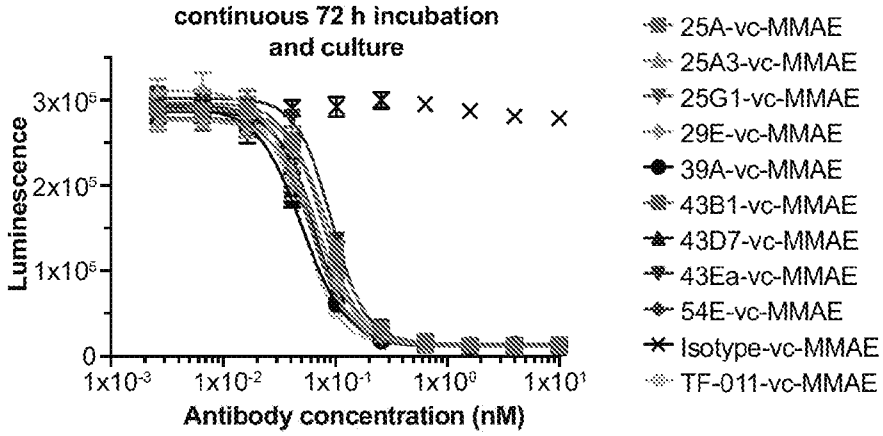


Figure 20B

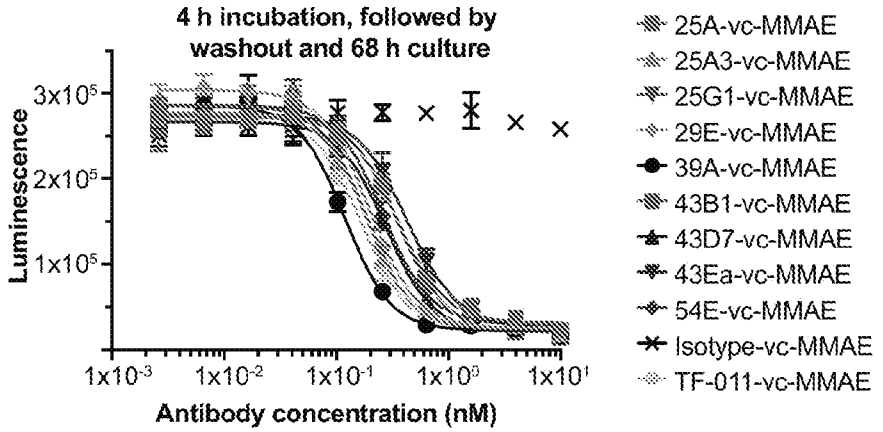


Figure 20C

	IC50 (nM)	
	Cont.	Washout
25A-vc-MMAE	0.09	0.35
25A3-vc-MMAE	0.07	0.19
25G1-vc-MMAE	0.06	0.19
29E-vc-MMAE	0.06	0.20
39A-vc-MMAE	0.05	0.12
43B1-vc-MMAE	0.08	0.36
43D7-vc-MMAE	0.06	0.28
43Ea-vc-MMAE	0.09	0.43
54E-vc-MMAE	0.07	0.26
Isotype-vc-MMAE	na	na
TF-011-vc-MMAE	0.05	0.17

Figure 21A

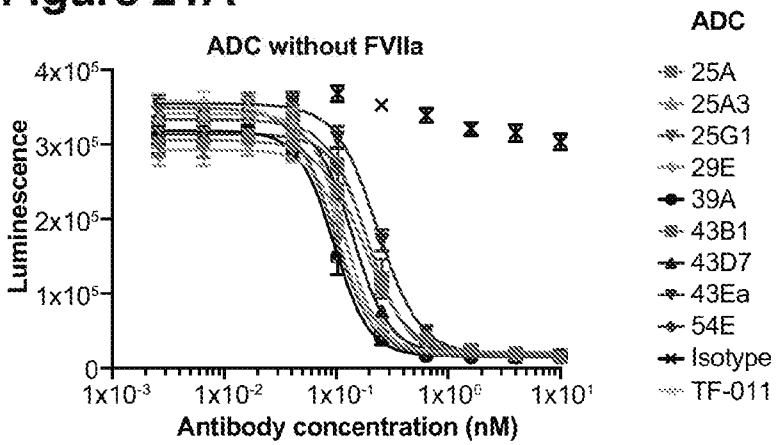


Figure 21B

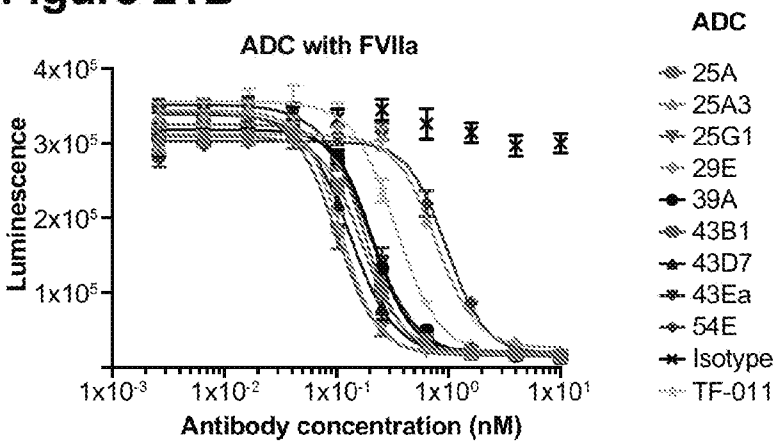


Figure 21C

ADC	IC50 (nM)	
	Without FVIIa	With FVIIa
25A	0.18	0.17
25A3	0.12	0.11
25G1	0.10	0.10
29E	0.13	0.77
39A	0.09	0.22
43B1	0.19	0.19
43D7	0.14	0.13
43Ea	0.24	0.19
54E	0.20	0.97
Isotype	na	na
TF-011	0.09	0.34

Figure 22A

Cell line	Copy number	SEM (n)
A431	$1.9x10^5$	$4.7x10^4$ (8)
CHO	BLOQ	BLOQ (2)
HCT-116	$2.2x10^4$	$6.5x10^3$ (6)
HPAF-II	$5.7x10^5$	$4.5x10^4$ (8)
MDA-MB-231	$3.2x10^5$	$2.7x10^4$ (7)
RF/6A	$7.3x10^4$	$1.7x10^4$ (4)

Figure 22B

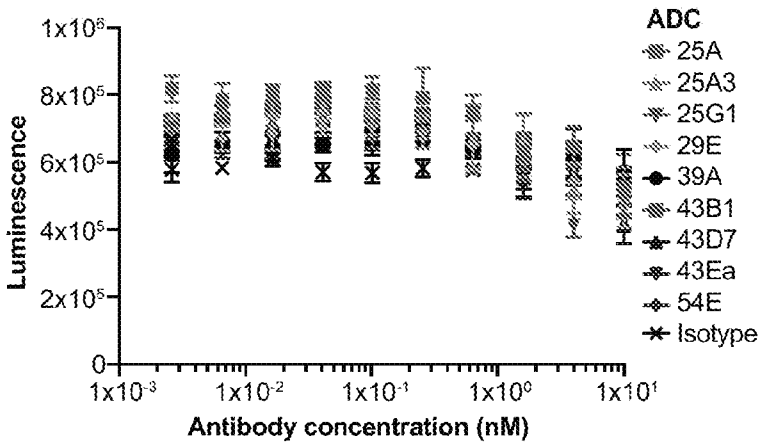


Figure 22C

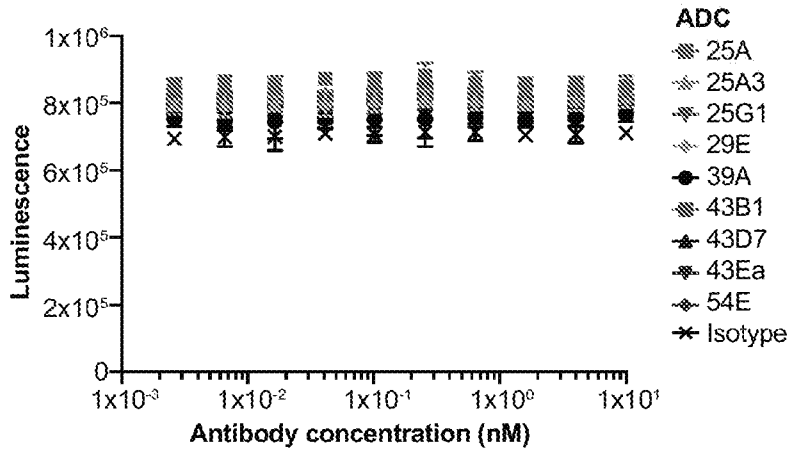


Figure 22D

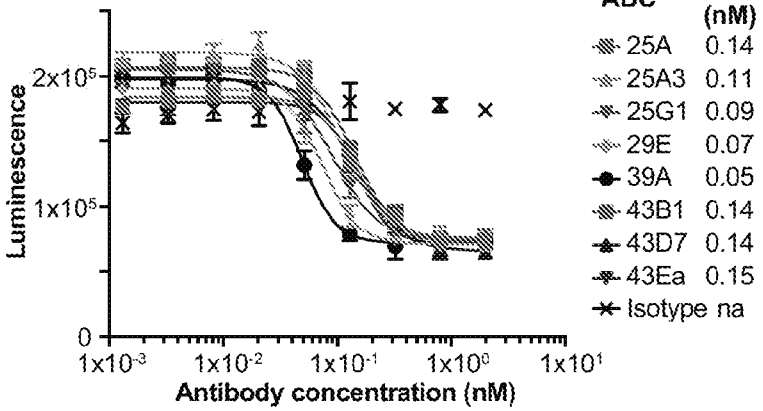


Figure 22E

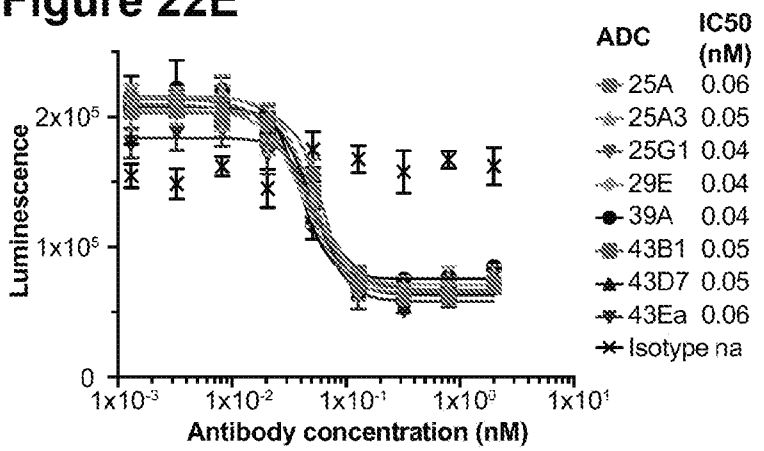


Figure 23A

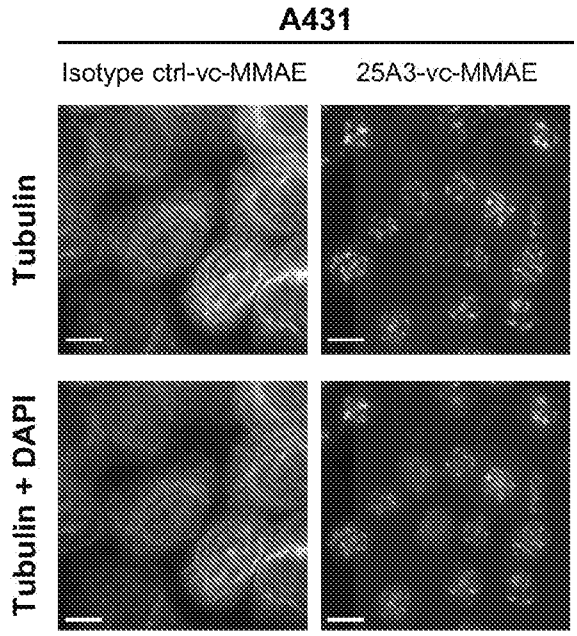


Figure 23B

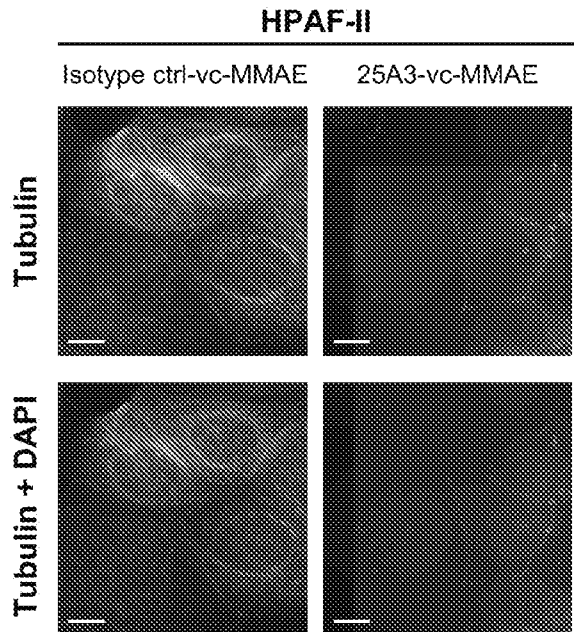


Figure 24A

Treatment	Donor number (#)	Copy #	SEM
no treatment	6	$2.4x10^3$	$4.2x10^2$
3 h of cytokines	5	$8.7x10^3$	$7.7x10^2$
6 h of cytokines	5	$1.2x10^4$	$8.5x10^2$
20 h of cytokines	2	$4.6x10^3$	$2.9x10^2$

Figure 24B

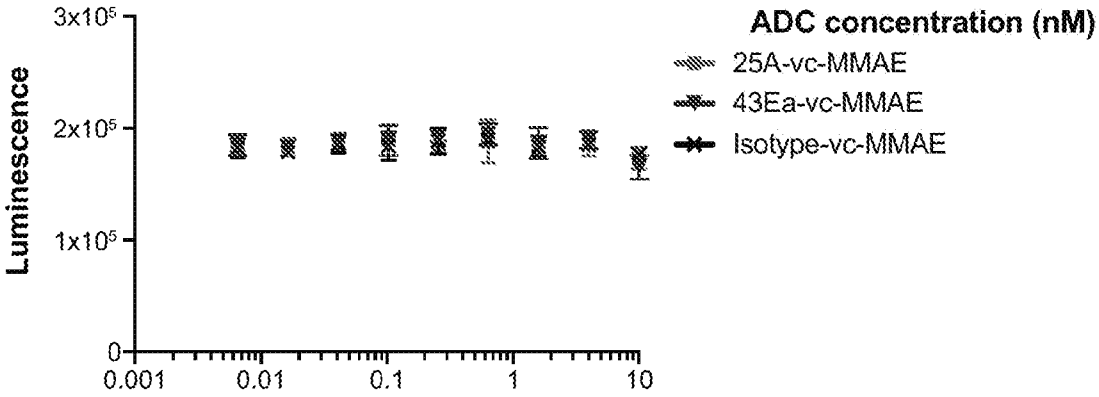


Figure 25A

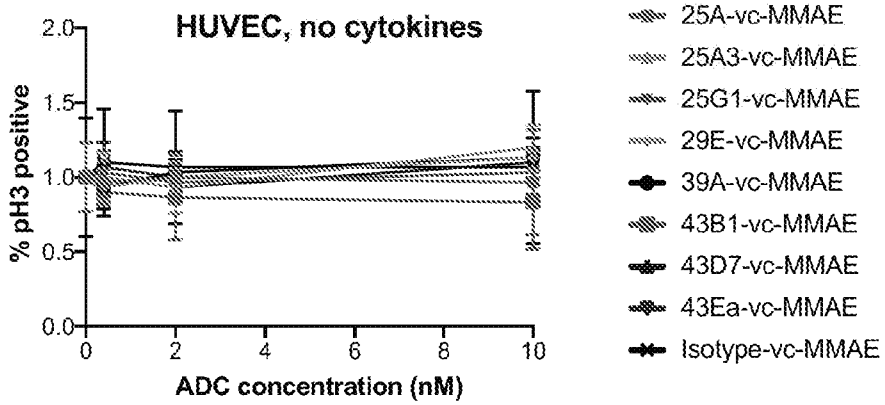


Figure 25B

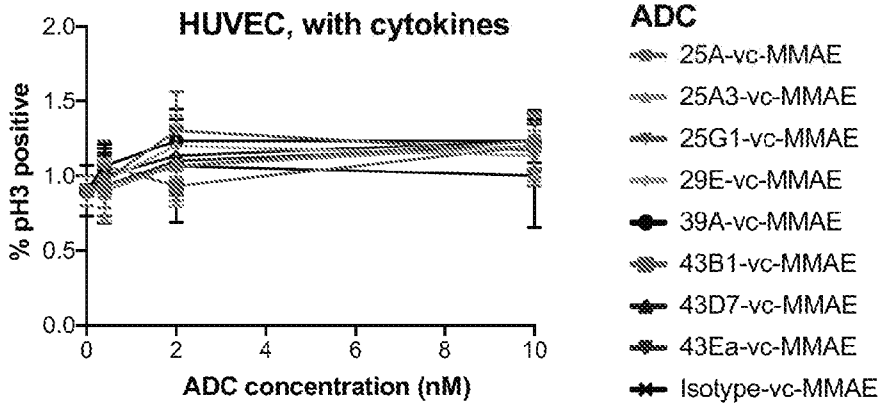


Figure 25C

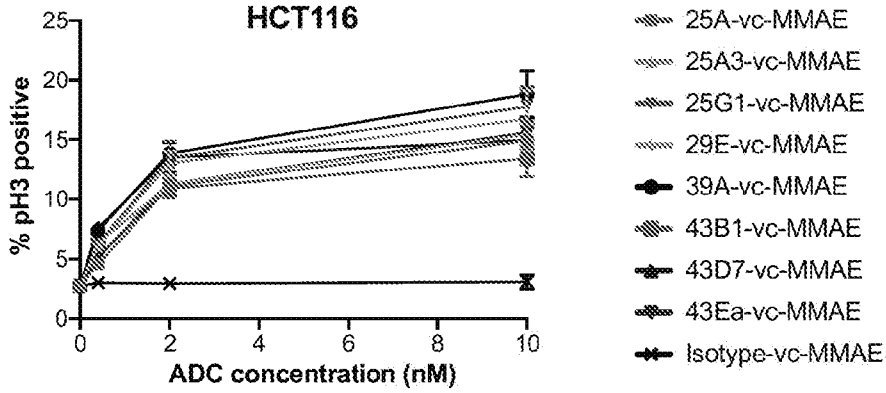


Figure 26A

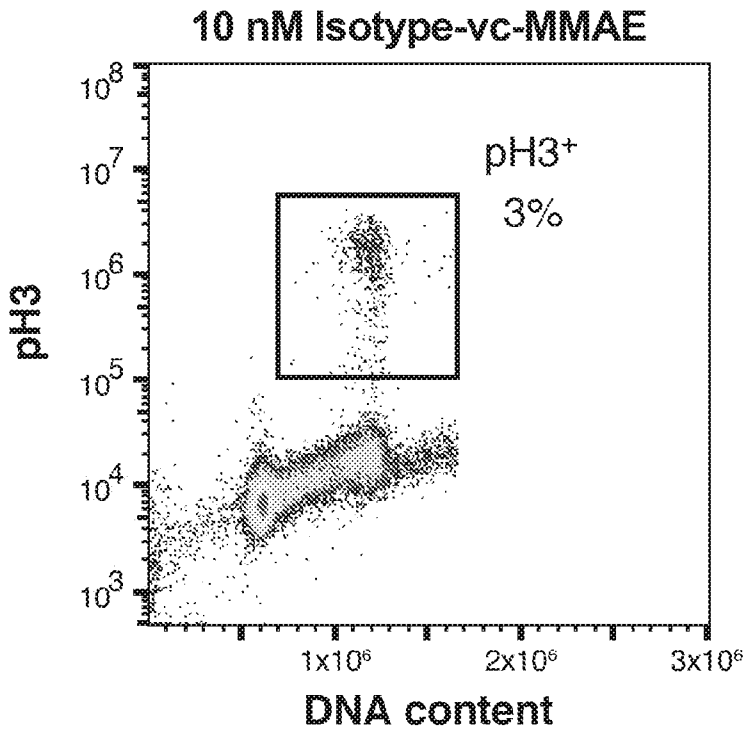


Figure 26B

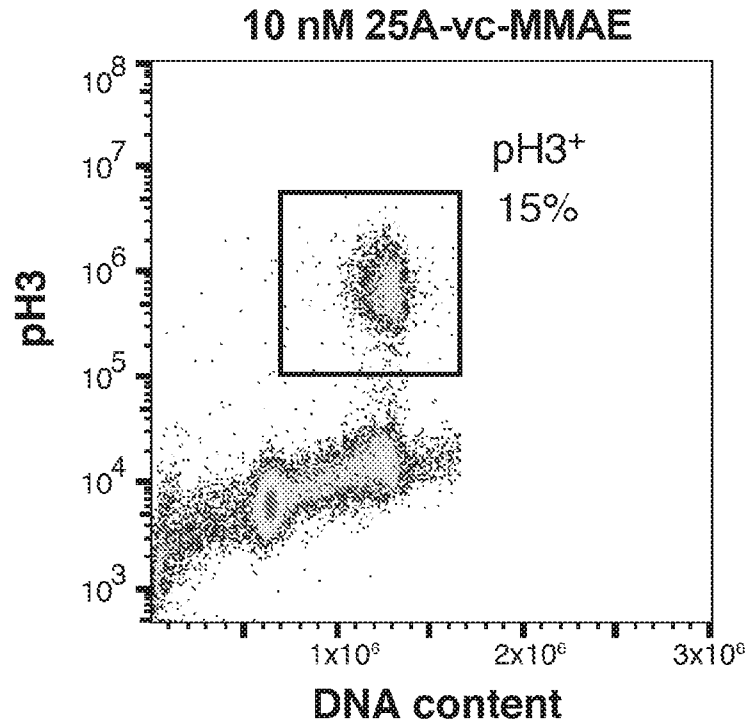


Figure 27A

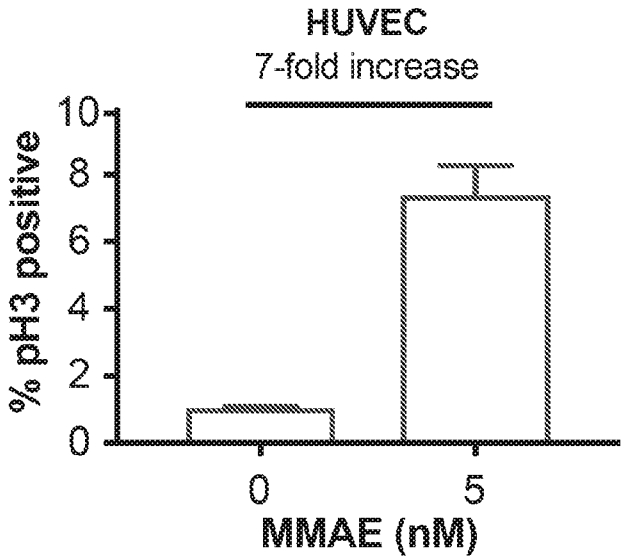


Figure 27B

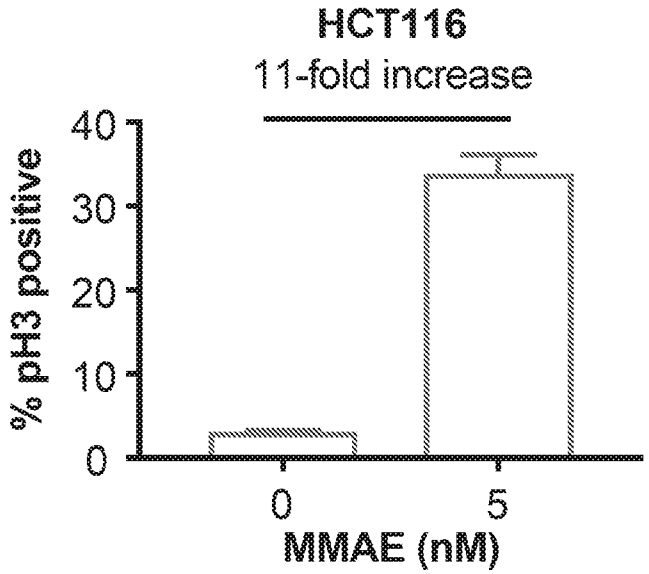


Figure 28

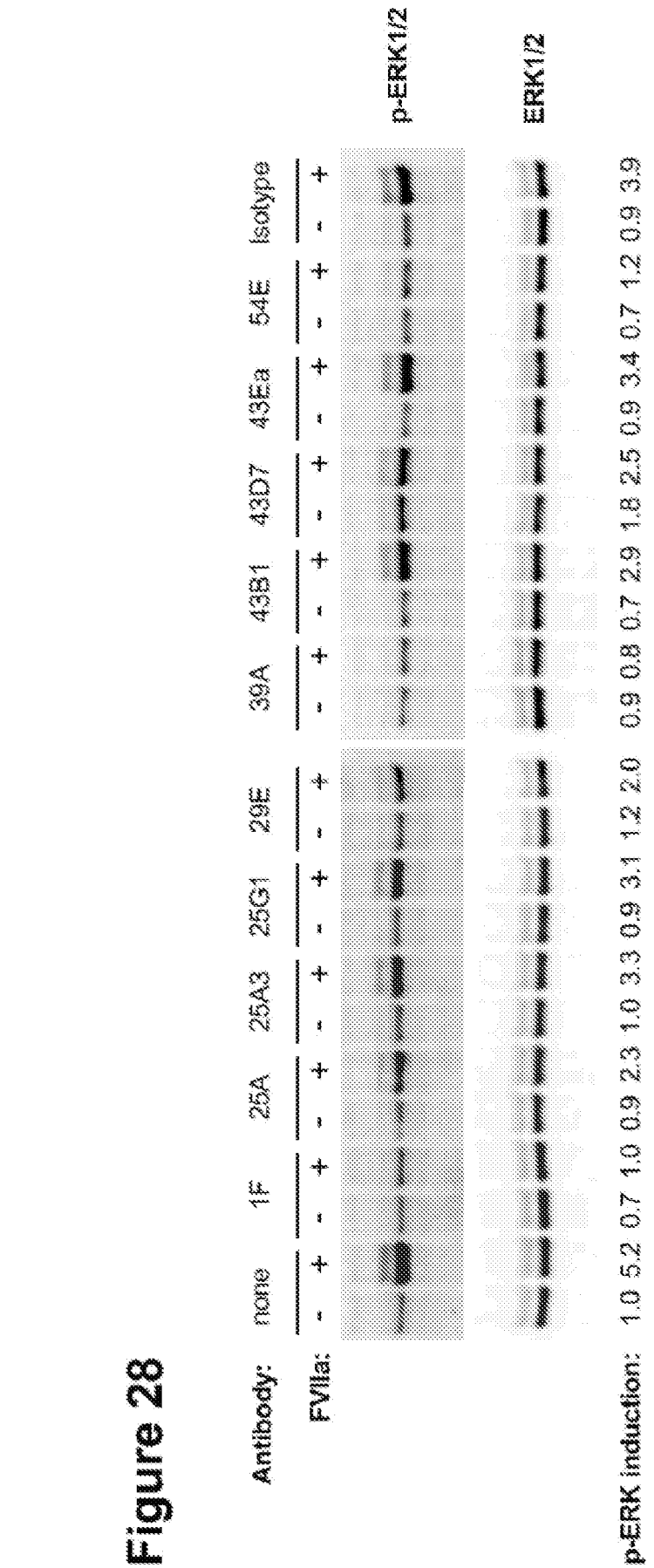

Antibody:
none
1F
25A
25A3
25G1
29E
39A
43B1
43D7
43Ea
54E
isotype
FVIIa:
p-ERK1/2
ERK1/2
p-ERK induction:
1.0 5.2 0.7 1.0 0.9 2.3 1.0 3.3 0.9 3.1 1.2 2.0 0.9 0.8 0.7 2.9 1.8 2.5 0.9 3.4 0.7 1.2 0.9 3.9

Figure 29A

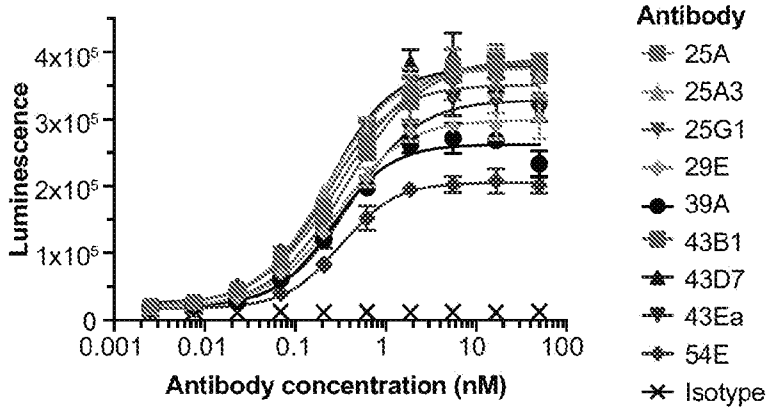


Figure 29B

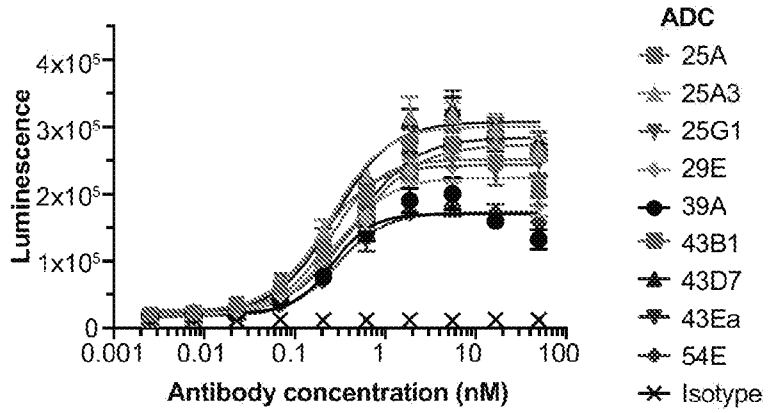


Figure 29C

	EC50 (nM)	
Antibody	Naked	ADC
25A	0.31	0.26
25A3	0.22	0.24
25G1	0.22	0.18
29E	0.29	0.28
39A	0.26	0.26
43B1	0.36	0.42
43D7	0.23	0.27
43Ea	0.40	0.43
54E	0.31	0.30
Isotype	na	na

Figure 30A

5 mg/kg, qwk x 3, IP

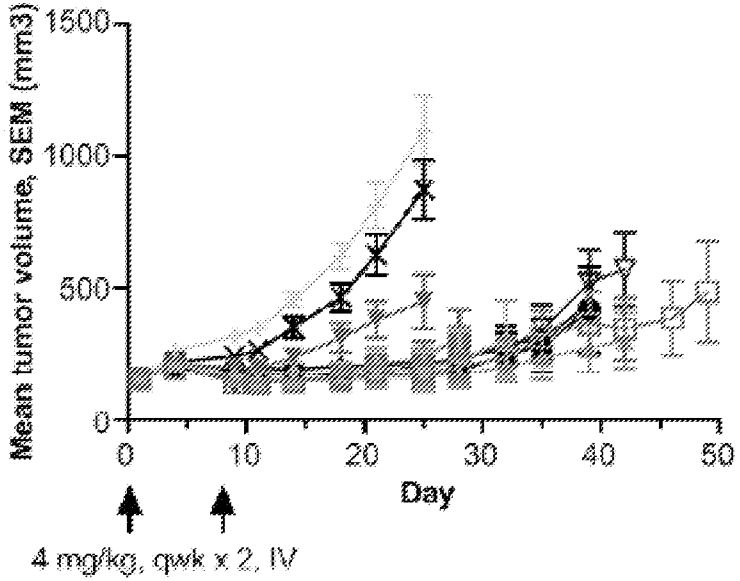
Treatment	Day 21 (n)	Mean ± [SEM] (mm³)	P	%TGI	Day 59 PR/CR/TFS
25A-vc-MMAE	10	8 [2]	<0.0001	132	0/2/2
43Ea-vc-MMAE	10	8 [3]	<0.0001	131	0/3/4
Isotype-vc-MMAE	10	434 [76]	NS	56	0/0/0
TF-011-vc-MMAE	10	7 [3]	<0.0001	132	0/5/5
Vehicle	10	749 [68]	-	0	0/0/0

Figure 30B

2 mg/kg, qwk x 2, IV

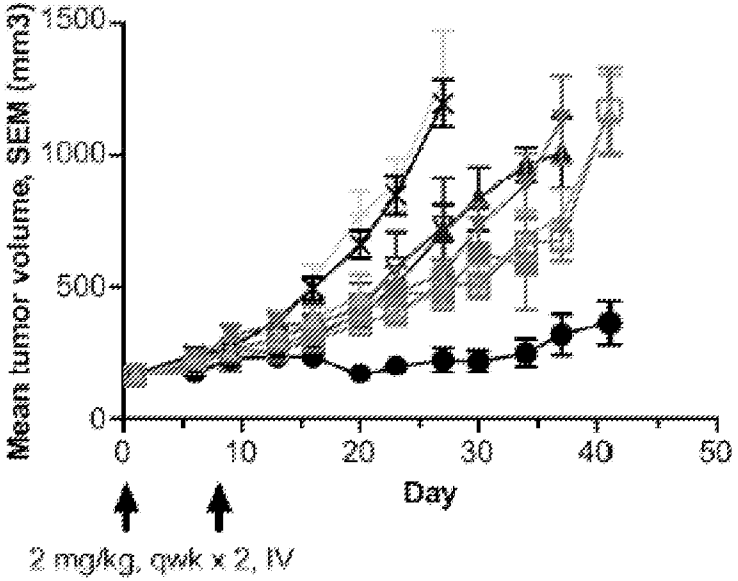
Treatment	Day 21 (n)	Mean ± [SEM] (mm³)	P	%TGI	Day 39 PR/CR/TFS
25A-vc-MMAE	10	4 [1]	<0.001	139	1/1/8
25A3-vc-MMAE	10	17 [10]	<0.001	128	2/0/7
25G1-vc-MMAE	10	4 [1]	<0.001	138	1/2/7
39A-vc-MMAE	10	8 [2]	<0.001	137	1/0/9
43B1-vc-MMAE	10	10 [3]	<0.001	137	3/1/6
43D7-vc-MMAE	10	9 [3]	<0.001	137	3/1/6
43Ea-vc-MMAE	9	23 [22]	<0.001	135	0/0/8
Isotype-vc-MMAE	10	538 [62]	NS	22	0/0/0
Vehicle	10	709 [65]	-	0	0/0/0

Figure 31A



Treatment	Day 25 (n)	Mean ± [SEM] (mm³)	P	%TGI	Day 49 PR/CR/TFS
25A-vc-MMAE	10	174 [43]	<0.0001	98	3/0/1
25A3-vc-MMAE	10	153 [43]	<0.0001	100	1/1/1
25G1-vc-MMAE	10	449 [102]	<0.0001	69	1/1/1
29E-vc-MMAE	10	180 [78]	<0.0001	97	1/0/3
39A-vc-MMAE	10	160 [45]	<0.0001	99	0/4/1
43B1-vc-MMAE	10	232 [66]	<0.0001	92	1/0/0
43D7-vc-MMAE	10	217 [49]	<0.0001	93	0/0/1
43Ea-vc-MMAE	10	203 [56]	<0.0001	95	2/0/0
Isotype-vc-MMAE	10	873 [114]	NS	24	0/0/0
Vehicle	10	1098 [133]	-	0	0/0/0

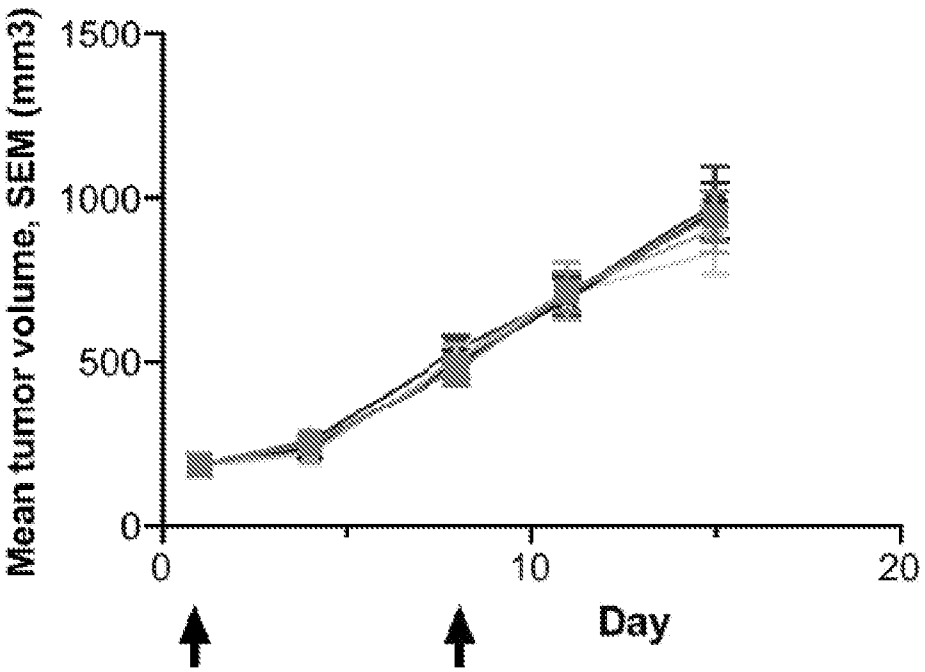
Figure 31B



Treatment	Day 27 (n)	Mean ± [SEM] (mm³)	P	%TGI	Day 41 PR/CR/TFS
25A-vc-MMAE	7	517 [52]	<0.001	67	0/0/0
25A3-vc-MMAE	7	495 [69]	<0.0001	68	0/0/0
25G1-vc-MMAE	7	550 [53]	<0.001	63	0/0/0
39A-vc-MMAE	7	223 [46]	<0.0001	92	2/0/0
43B1-vc-MMAE	7	472 [58]	<0.0001	70	0/0/0
43D7-vc-MMAE	7	708 [104]	<0.01	49	0/0/0
43Ea-vc-MMAE	7	728 [188]	<0.05	48	0/0/0
Isotype-vc-MMAE	7	1197 [88]	NS	9	0/0/0
Vehicle	7	1292 [180]	-	0	0/0/0

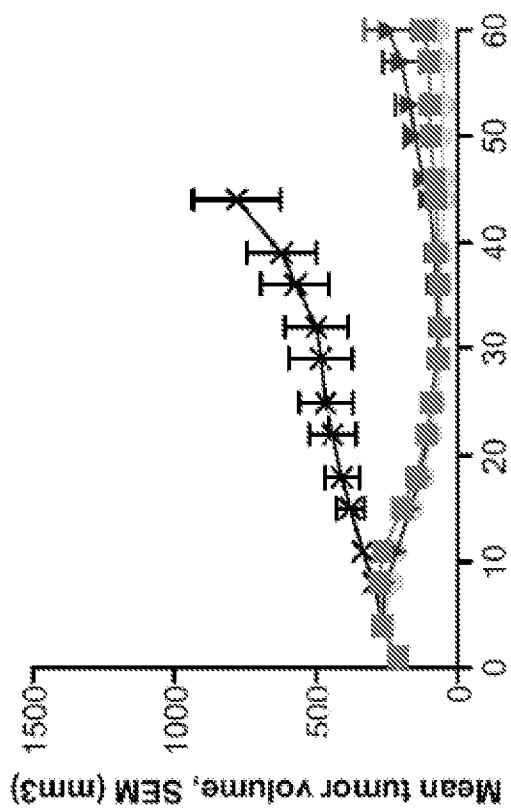
SUBSTITUTE SHEET (RULE 26)

Figure 32



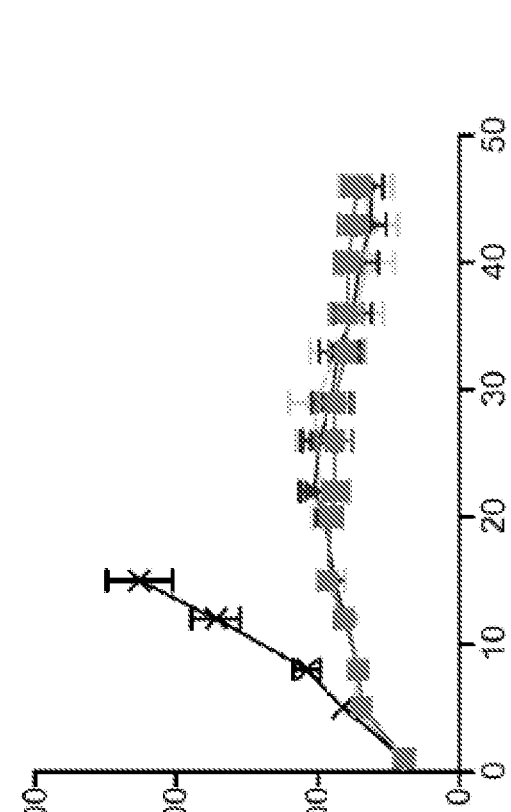
Treatment	Day 15 (n)	Mean ± [SEM] (mm³)	P
25A	9	938 [78]	NS
25A3	8	898 [73]	NS
43Ea	9	976 [114]	NS
Isotype	9	954 [86]	NS
Vehicle	8	829 [67]	-

Figure 33A



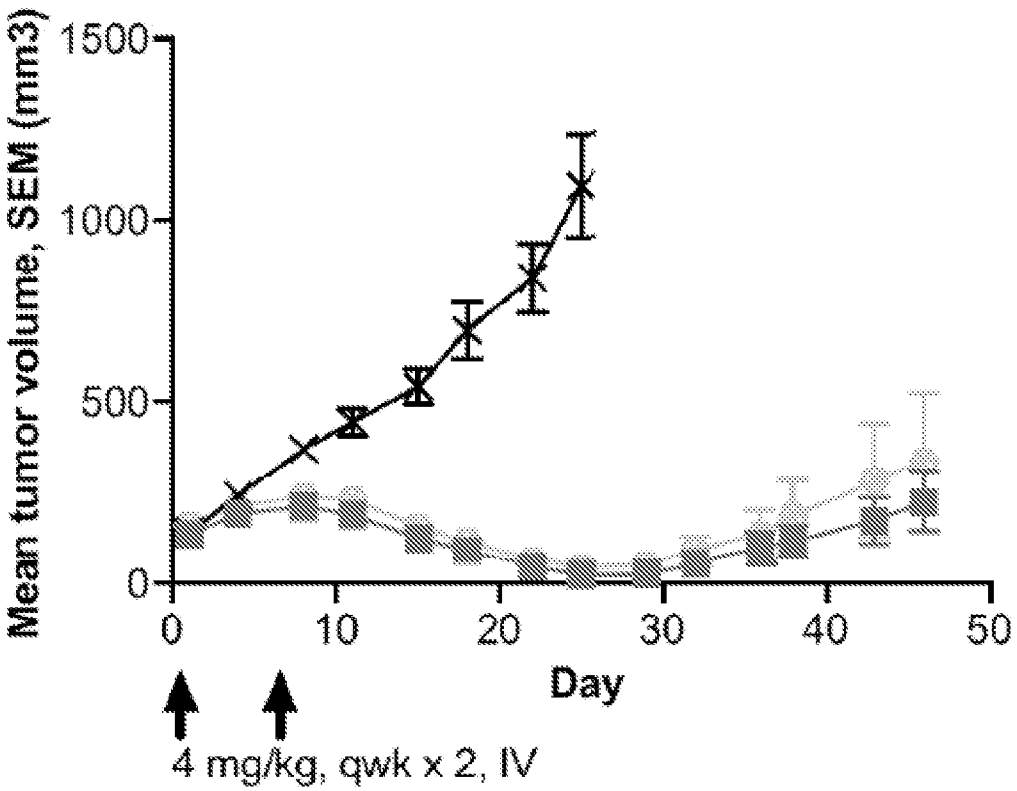
Treatment	Day 44 (n)	Mean ± [SEM] (mm³)	P	%TGI	Day 60 PR/CR/TFS
25A-vc-MMAE	10	74 [16]	<0.001	124	5/0/1
43Ea-vc-MMAE	10	100 [18]	<0.001	119	6/0/0
Isotype-vc-MMAE	10	780 [154]	-	0	0/0/0
TF-011-vc-MMAE	10	49 [8]	<0.001	128	6/0/2

Figure 33B



Treatment	Day 15 (n)	Mean ± [SEM] (mm³)	P	%TGI	Day 46 PR/CR/TFS
25A-vc-MMAE	10	464 [35]	<0.001	71	0/0/0
43Ea-vc-MMAE	10	439 [23]	<0.001	74	0/0/0
Isotype-vc-MMAE	10	1131 [118]	-	0	0/0/0
TF-011-vc-MMAE	10	452 [50]	<0.001	72	0/0/0

Figure 33C



Treatment	Day 25 (n)	Mean ± [SEM] (mm^3)	*P*	%TGI	Day 46 PR/CR/TFS
25A-vc-MMAE	9	24 [7]	<0.001	112	2/2/3
Isotype-vc-MMAE	9	1093 [143]	-	0	0/0/0
TF-011-vc-MMAE	9	46 [12]	<0.001	112	0/1/5

Figure 34A

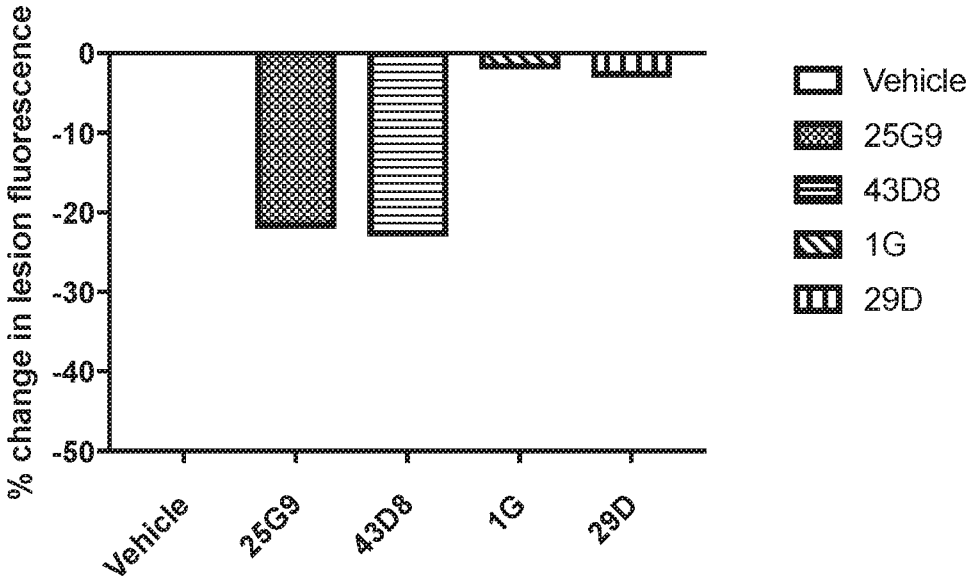


Figure 34B

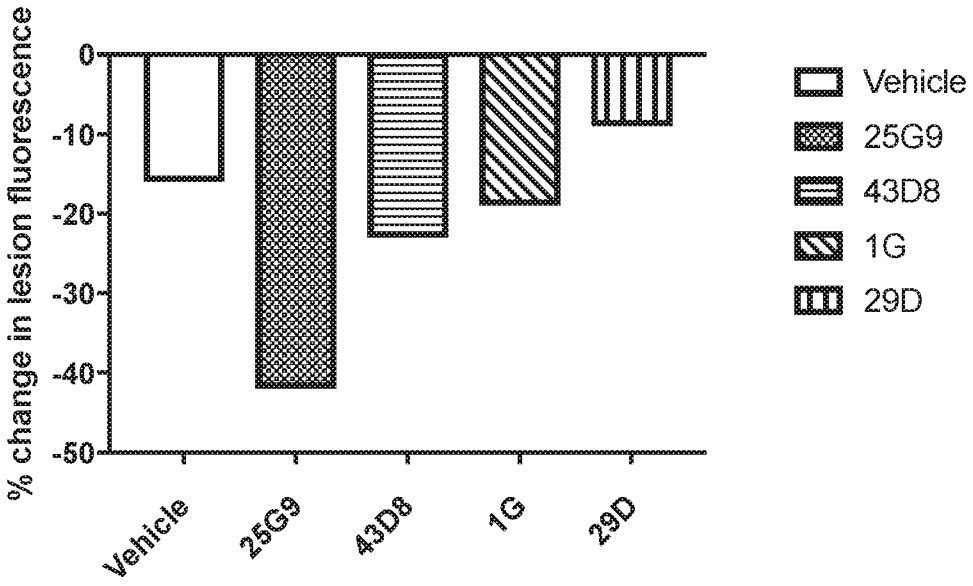


Figure 35

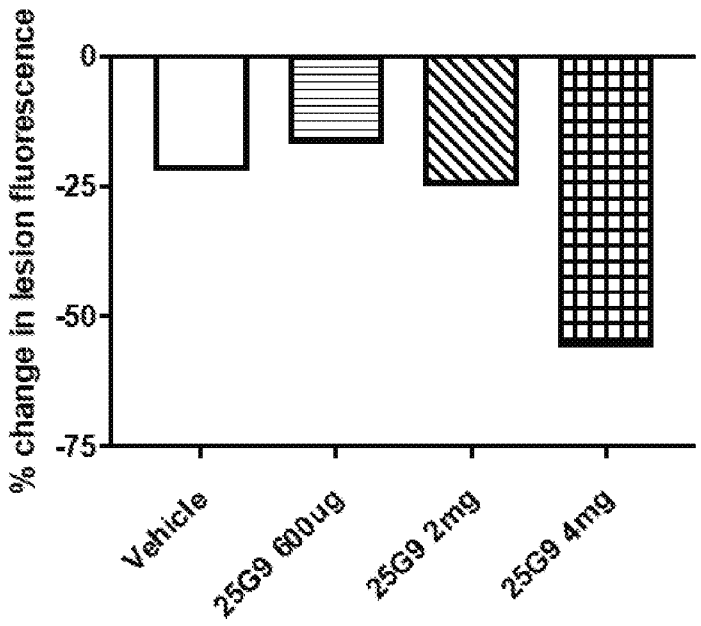

% change in lesion fluorescence
0
-25
-50
-75
Vehicle
25G9 600ug
25G9 2mg
25G9 4mg

Figure 36

```
hTF (SEQ ID NO:810)              SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
rTF (SEQ ID NO:838)              -AGTPPGKAFNLTWISTDFKTILEWQPKPTNYTYTVQISDRSRNWKYKCTGTTDTECDLT 60
h1-107_r (SEQ ID NO:839)         -AGTPPGKAFNLTWISTDFKTILEWQPKPTNYTYTVQISDRSRNWKYKCTGTTDTECDLT 60
h1-77_r (SEQ ID NO:840)          -AGTPPGKAFNLTWISTDFKTILEWQPKPTNYTYTVQISDRSRNWKYKCTGTTDTECDLT 60
h1-38_r (SEQ ID NO:841)          -AGTPPGKAFNLTWISTDFKTILEWQPKPTNYTYTVQISTKSGDWKSKCFYTTDTECDLT 60
h39-77_r (SEQ ID NO:842)         SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISDRSRNWKYKCTGTTDTECDLT 60
h78-107_r (SEQ ID NO:843)        SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h78-107_r.v2 (SEQ ID NO:844)     SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h78-93_r (SEQ ID NO:845)         SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h94-107_r (SEQ ID NO:846)        SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h108-219_r (SEQ ID NO:847)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h108-158_r (SEQ ID NO:848)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h108-132_r (SEQ ID NO:849)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h133-158_r (SEQ ID NO:850)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h133-145_r (SEQ ID NO:851)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h133-139_r (SEQ ID NO:852)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h140-145_r (SEQ ID NO:853)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h146-158_r (SEQ ID NO:854)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h146-151_r (SEQ ID NO:855)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h152-158_r (SEQ ID NO:856)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h159-219_r (SEQ ID NO:857)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h159-189_r (SEQ ID NO:858)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h159-174_r (SEQ ID NO:859)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h159-166_r (SEQ ID NO:860)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h167-174_r (SEQ ID NO:861)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h175-189_r (SEQ ID NO:862)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
h190-219_r (SEQ ID NO:863)       SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 60
                                   .  *   *:**** **:*********:***.* .******* :* :** **  **********
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Figure 36 (continued)



Figure 36 (continued)

```
hTF (SEQ ID NO:810)              SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
rTF (SEQ ID NO:838)              KYEQGGTKLKVTVKDSFTLVRKNGTFLTLRQVFGNDLGYILTYRKDSSTGRKTNTTHTNE   174
h1-107_r (SEQ ID NO:839)         SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h1-77_r (SEQ ID NO:840)          SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h1-38_r (SEQ ID NO:841)          SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h39-77_r (SEQ ID NO:842)         SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h78-107_r (SEQ ID NO:843)        SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h78-107_r.v2 (SEQ ID NO:844)     SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h78-93_r (SEQ ID NO:845)         SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h94-107_r (SEQ ID NO:846)        SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h108-219_r (SEQ ID NO:847)       KYEQGGTKLKVTVKDSFTLVRKNGTFLTLRQVFGNDLGYILTYRKDSSTGRKTNTTHTNE   174
h108-158_r (SEQ ID NO:848)       KYEQGGTKLKVTVKDSFTLVRKNGTFLTLRQVFGNDLGYILTYRKSSSSGKKTAKTNTNE   174
h108-132_r (SEQ ID NO:849)       KYEQGGTKLKVTVKDSFTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h133-158_r (SEQ ID NO:850)       SFEQVGTKVNVTVEDERTLVRKNGTFLTLRQVFGNDLGYILTYRKSSSSGKKTAKTNTNE   174
h133-145_r (SEQ ID NO:851)       SFEQVGTKVNVTVEDERTLVRKNGTFLTLRQVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h133-139_r (SEQ ID NO:852)       SFEQVGTKVNVTVEDERTLVRKNGTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h140-145_r (SEQ ID NO:853)       SFEQVGTKVNVTVEDERTLVRRNNTFLTLRQVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h146-158_r (SEQ ID NO:854)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGNDLGYILTYRKSSSSGKKTAKTNTNE   174
h146-151_r (SEQ ID NO:855)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGNDLIYTLYYWKSSSSGKKTAKTNTNE   174
h152-158_r (SEQ ID NO:856)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLGYILTYRKSSSSGKKTAKTNTNE   174
h159-219_r (SEQ ID NO:857)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKDSSTGRKTNTTHTNE   174
h159-189_r (SEQ ID NO:858)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKDSSTGRKTNTTHTNE   174
h159-174_r (SEQ ID NO:859)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKDSSTGRKTNTTHTNE   174
h159-166_r (SEQ ID NO:860)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKDSSTGRKTAKTNTNE   174
h167-174_r (SEQ ID NO:861)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTNTTHTNE   174
h175-189_r (SEQ ID NO:862)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
h190-219_r (SEQ ID NO:863)       SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
                                 .:** ***::***:*. ****:*.***:**:***:** * * * *.**:*:** .*:***
```

Figure 36 (continued)

```
hTF (SEQ ID NO:810)              FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
rTF (SEQ ID NO:838)              FLIDVEKGVSYCFFAQAVIFSRKTNHKSPESITKCTEQWKSVLGE     219
h1-107_r (SEQ ID NO:839)         FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h1-77_r (SEQ ID NO:840)          FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h1-38_r (SEQ ID NO:841)          FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h39-77_r (SEQ ID NO:842)         FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h78-107_r (SEQ ID NO:843)        FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h78-107_r.v2 (SEQ ID NO:844)     FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h78-93_r (SEQ ID NO:845)         FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h94-107_r (SEQ ID NO:846)        FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h108-219_r (SEQ ID NO:847)       FLIDVEKGVSYCFFAQAVIFSRKTNHKSPESITKCTEQWKSVLGE     219
h108-158_r (SEQ ID NO:848)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h108-132_r (SEQ ID NO:849)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h133-158_r (SEQ ID NO:850)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h133-145_r (SEQ ID NO:851)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h133-139_r (SEQ ID NO:852)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h140-145_r (SEQ ID NO:853)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h146-158_r (SEQ ID NO:854)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h146-151_r (SEQ ID NO:855)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h152-158_r (SEQ ID NO:856)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h159-219_r (SEQ ID NO:857)       FLIDVEKGVSYCFFAQAVIFSRKTNHKSPESITKCTEQWKSVLGE     219
h159-189_r (SEQ ID NO:858)       FLIDVEKGVSYCFFAQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h159-174_r (SEQ ID NO:859)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h159-166_r (SEQ ID NO:860)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h167-174_r (SEQ ID NO:861)       FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h175-189_r (SEQ ID NO:862)       FLIDVEKGVSYCFFAQAVIPSRTVNRKSTDSPVECMGQEKGEFRE     219
h190-219_r (SEQ ID NO:863)       FLIDVDKGENYCFSVQAVIFSRKTNHKSPESITKCTEQWKSVLGE     219
                                 *****:** .*** .**** **..*:** :* .:*  * *. : *
```

Figure 37

```
rTF (SEQ ID NO:838)      -AGTPPGKAFNLTWISTDFKTILEWQPKPTNYTYTVQISDRSRNWKYKCTGTTDTFECDLT 59
hTF (SEQ ID NO:810)      SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT 59
r141-194_h (SEQ ID NO:864) -AGTPPGKAFNLTWISTDFKTILEWQPKPTNYTYTVQISDRSRNWKYKCTGTTDTFECDLT 59
                           .  *    *:**** **:********;***.* .******* ;* :** **  ********** 

rTF (SEQ ID NO:838)      DEIVKDVNWTYEARVLSVPWRNSTHGKETLFGTHGEEPPFTNARKFLPYRDTKIGQPVIQ 119
hTF (SEQ ID NO:810)      DEIVKDVNWTYLARVFSYPAGNVEST------GSAGEPLYENSPEFTPYLETNLGQPTIQ 119
r141-194_h (SEQ ID NO:864) DEIVKDVNWTYEARVLSVPWRNSTHGKETLFGTHGEEPPFTNARKFLPYRDTKIGQPVIQ 119
                           ******** ** ***;* *  *                 . ** : *: :* ** ;*;:***.** 

rTF (SEQ ID NO:838)      KYEQGGTKLKVTVKDSFTLVRKNGTFLTLRQVFGNDLGYILTYRKDSSTGRKTNTTHTNE 179
hTF (SEQ ID NO:810)      SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE 179
r141-194_h (SEQ ID NO:864) KYEQGGTKLKVTVKDSFTLVPRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE 179
                            .:** ***:;:***:*. *****;*.***:**;***;** * * * * .**;*;** .*;*** 

rTF (SEQ ID NO:838)      FLIDVEKGVSYCFFAQAVIFSRKTNHKSPESITKCTEQWKSVLGE 224
hTF (SEQ ID NO:810)      FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE 225
r141-194_h (SEQ ID NO:864) FLIDVDKGENYCFSVQAVIFSRKTNHKSPESITKCTEQWKSVLGE 224
                           ******;** .*** .**** **..*;** :* .;*  * *. : * 
```

Figure 38

```
hTF (SEQ ID NO:810)                 SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT   60
rTF (SEQ ID NO:838)                 -AGTPPGKAFNLTWISTDFKTILEWQPKPTNYTYTVQISDRSRNWKYKCTGTTDTECDLT   60
hTF_K68N (SEQ ID NO:865)            SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT   60
hTF_K149N (SEQ ID NO:866)           SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT   60
hTF_N171H_T197K  (SEQ ID NO:867)    SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLT   60
                                     . *    *:**** **:*******:***.* .****** :* :** **  *********

hTF (SEQ ID NO:810)                 DEIVKDVKQTYLARVFSYPAGNVEST-------GSAGEPLYENSPEFTPYLETNLGQPTIQ   114
rTF (SEQ ID NO:838)                 DEIVKDVNWTYEARVLSVPWRNSTHGKETLFGTHGEEPPFTNARKFLPYRDTKIGQPVIQ   114
hTF_K68N (SEQ ID NO:865)            DEIVKDVNQTYLARVFSYPAGNVEST-------GSAGEPLYENSPEFTPYLETNLGQPTIQ   114
hTF_K149N (SEQ ID NO:866)           DEIVKDVKQTYLARVFSYPAGNVEST-------GSAGEPLYENSPEFTPYLETNLGQPTIQ   114
hTF_N171H_T197K (SEQ ID NO:867)     DEIVKDVKQTYLARVFSYPAGNVEST------GSAGEPLYENSPEFTPYLETNLGQPTIQ   114
                                    *******: ** ***:* *  *             . ** : *: :* ** :*::***.**

hTF (SEQ ID NO:810)                 SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
rTF (SEQ ID NO:838)                 KYEQGGTKLKVTVKDSFTLVRKNGTFLTLRQVFGNDLGYILTYRKDSSTGRKTNTTHTNE   174
hTF_K68N (SEQ ID NO:865)            SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE   174
hTF_K149N (SEQ ID NO:866)           SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGNDLIYTLYYWKSSSSGKKTAKTNTNE   174
hTF_N171H_T197K (SEQ ID NO:867)     SFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTHTNE   174
                                    .:** ***::***:*. ****:*.***:**:***:** * * * *.**:*:** .*:***

hTF (SEQ ID NO:810)                 FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE   219
rTF (SEQ ID NO:838)                 FLIDVEKGVSYCFFAQAVIFSRKTNHKSPESITKCTEQWKSVLGE   219
hTF_K68N (SEQ ID NO:865)            FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE   219
hTF_K149N (SEQ ID NO:866)           FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE   219
hTF_N171H_T197K (SEQ ID NO:867)     FLIDVDKGENYCFSVQAVIPSRKVNRKSTDSPVECMGQEKGEFRE   219
                                    *****:** .*** .**** **..*:** :* .:*  * *. : *
```

Figure 39A

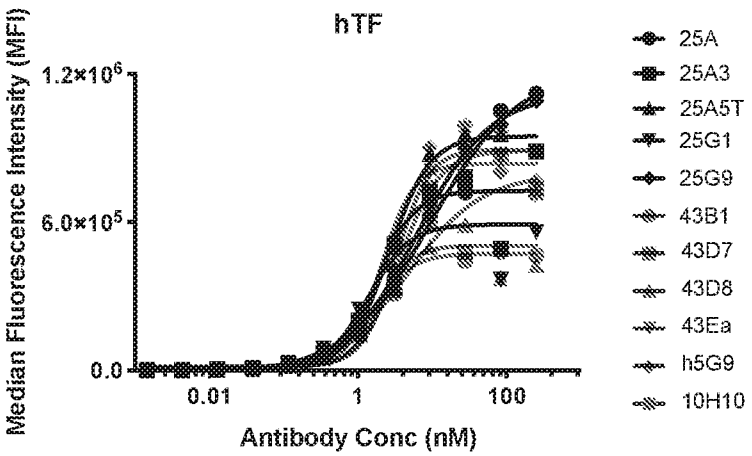


Figure 39B

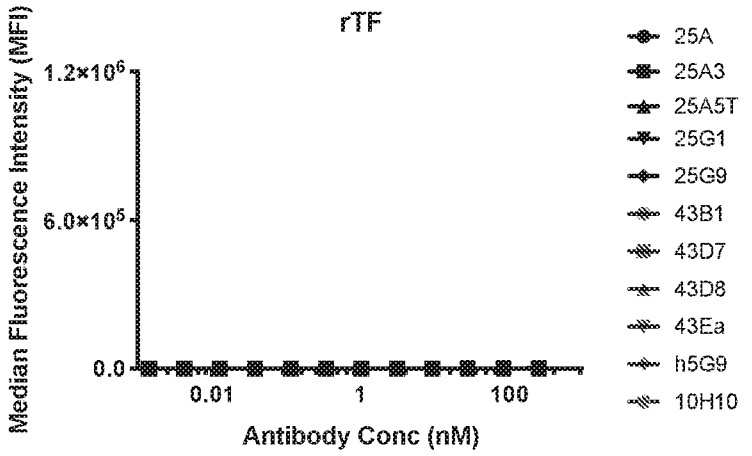


Figure 39C

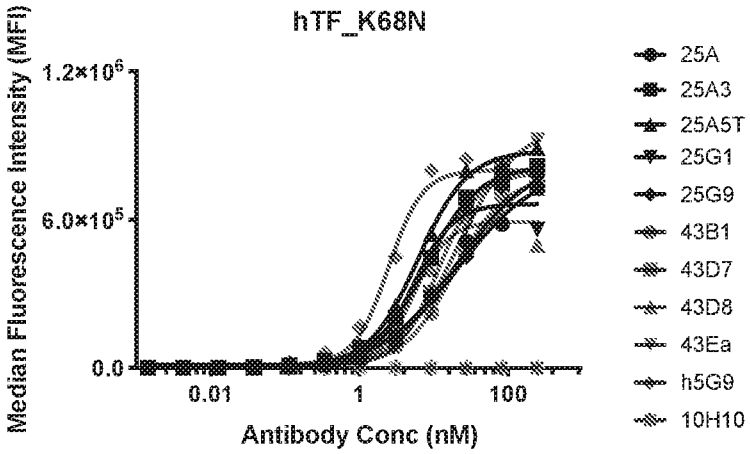


Figure 39D

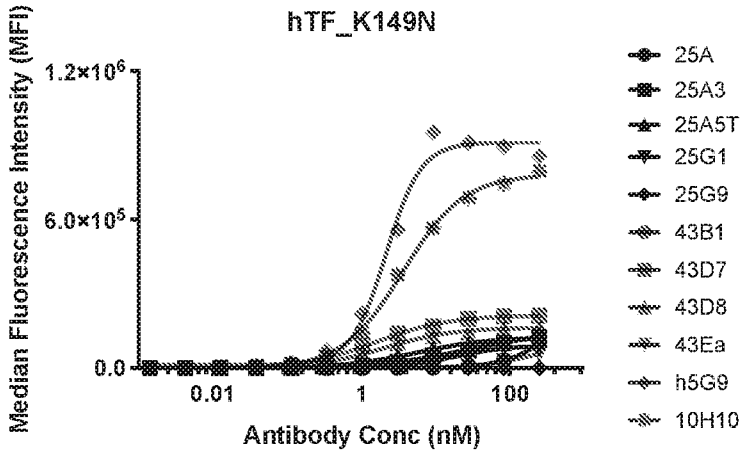


Figure 39E

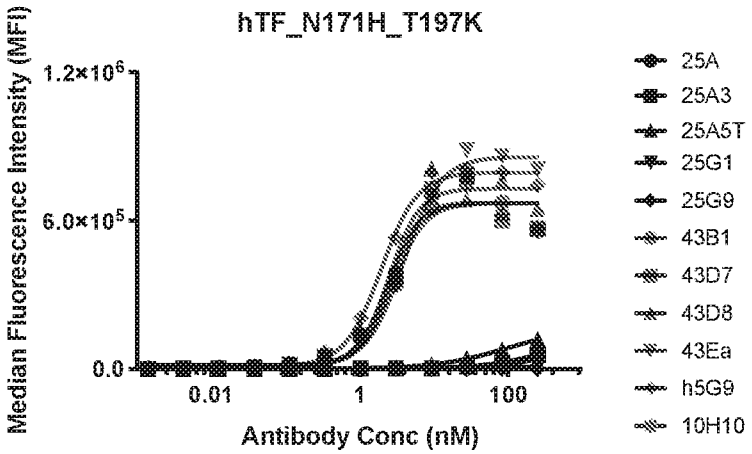


Figure 39F

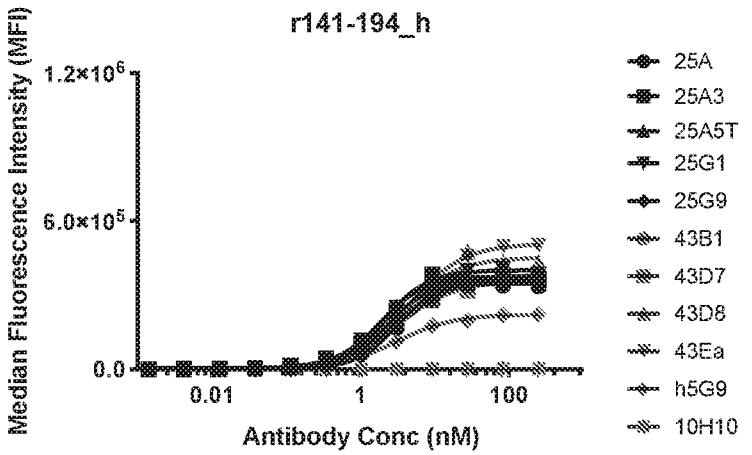
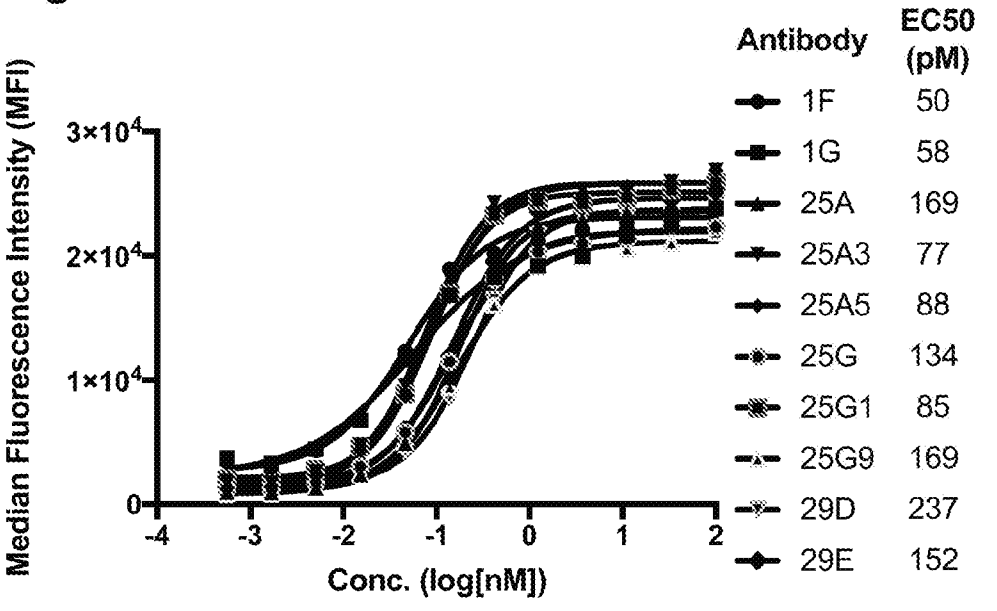


Figure 1A


Median Fluorescence Intensity (MFI)
3×10^4
2×10^4
1×10^4
0
-4
-3
-2
-1
0
1
2
Conc. (log[nM])
Antibody
EC50 (pM)
1F 50
1G 58
25A 169
25A3 77
25A5 88
25G 134
25G1 85
25G9 169
29D 237
29E 152