

ANTIBODIES AND ANTIGEN BINDING PEPTIDES FOR FACTOR XIA INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of priority to U.S. Provisional Application Serial Number 63/135,016 filed January 8, 2021, U.S. Provisional Application Serial Number 63/148,767 filed February 12, 2021, U.S. Provisional Application Serial Number 63/152,595 filed February 23, 2021 and U.S. Provisional Application Serial Number 63/153,045 filed February 24, 2021, each of which is herein incorporated by reference in its entirety.

REFERENCE TO SEQUENCE LISTING

[0002] This application contains a Sequence Listing file entitled 055920-553P01US_Sequence_Listing.txt, with a file size of about 316,130 bytes and created on 23 December 2020, has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0003] Thromboembolic diseases remain the leading cause of death in developed countries despite the availability of anticoagulants such as dabigatran, apixaban, rivaroxaban, warfarin (COUMADIN®), heparin, low molecular weight heparins (LMWH), and synthetic pentasaccharides and antiplatelet agents such as aspirin and clopidogrel (PLAVIX®). Discovering and developing safe and efficacious oral anticoagulants for the prevention and treatment of a wide range of thromboembolic disorders remains important. One approach is to reduce thrombin generation by targeting the inhibition of coagulation factor XIa (FXIa). FXIa is a plasma serine protease involved in the regulation of blood coagulation, which is initiated *in vivo* by the binding of tissue factor (TF) to factor VII (FVII) to generate factor VIIa (FVIIa). The resulting TF:FVIIa complex activates factor IX (FIX) and factor X (FX) that leads to the production of factor Xa (FXa). The generated FXa catalyzes the transformation of prothrombin into small amounts of thrombin before this pathway is shut down by tissue factor pathway inhibitor (TFPI). The process of coagulation is then further propagated via the feedback activation of Factors V, VIII and XI by catalytic amounts of thrombin. The resulting burst of thrombin converts fibrinogen to fibrin that polymerizes to

form the structural framework of a blood clot, and activates platelets, which are a key cellular component of coagulation. Therefore, FXIa plays a key role in propagating this amplification loop and is thus an attractive target for anti-thrombotic therapy.

[0004] Plasma prekallikrein is a zymogen of a trypsin-like serine protease and is present in plasma at 35 to 50 µg/mL. The structure is similar to that of Factor XI (FXI). Overall, the amino acid sequence of plasma kallikrein has 58% homology to FXI. Plasma kallikrein is thought to play a role in a number of inflammatory disorders. The major inhibitor of plasma kallikrein is the serpin C1 esterase inhibitor. Patients who present with a genetic deficiency in C1 esterase inhibitor suffer from hereditary angioedema (HAE) which results in intermittent swelling of face, hands, throat, gastro-intestinal tract and genitals. Blisters formed during acute episodes contain high levels of plasma kallikrein which cleaves high molecular weight kininogen liberating bradykinin leading to increased vascular permeability. Treatment with a large protein plasma kallikrein inhibitor has been shown to effectively treat HAE by preventing the release of bradykinin which causes increased vascular permeability.

[0005] The plasma kallikrein-kinin system is abnormally abundant in patients with advanced diabetic macular edema. It has been recently published that plasma kallikrein contributes to retinal vascular dysfunctions in diabetic rats. Furthermore, administration of the plasma kallikrein inhibitor ASP-440 ameliorated both retinal vascular permeability and retinal blood flow abnormalities in diabetic rats. Therefore, a plasma kallikrein inhibitor should have utility as a treatment to reduce retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema. Other complications of diabetes such as cerebral hemorrhage, nephropathy, cardiomyopathy and neuropathy, all of which have associations with plasma kallikrein may also be considered as targets for a plasma kallikrein inhibitor. To date, no small molecule synthetic plasma kallikrein inhibitor has been approved for medical use. The large protein plasma kallikrein inhibitors present risks of anaphylactic reactions, as has been reported for Ecallantide.

[0006] Novel and effective selective FXIa inhibitors or dual inhibitors of FXIa and plasma kallikrein have been provided in WO2016053455A1, which is incorporated by reference in its entirety, for treating thromboembolic and/or inflammatory disorders. The development of these selective FXIa inhibitors or dual inhibitors of FXIa and plasma kallikrein, such as the compounds provided in the present invention, is based on the ability to

achieve a high level of antithrombotic efficacy with little or no additional bleeding risk. However, bleeding can occur in rare clinical situations where such FXIa inhibitors have been administered to patients. In humans, FXI-deficiency bleeding can occur for example following trauma, especially in tissues with high fibrinolytic activity, e.g. oral pharynx and urinary tract.

[0007] Pro-hemostatic approaches exist, including coagulation factor concentrates and recombinant activated Factor VII. These agents are approved primarily for use in patients with hemophilia and may be considered for bleeding patients treated with thrombin or FXa inhibitors when a specific reversal agent is not available. However, these approaches have a pro-thrombotic risk. Thus, there is an urgent need to develop compounds that can immediately reverse the antithrombotic effect of these selective FXIa inhibitors or dual inhibitors of FXIa and plasma kallikrein, such as the compounds disclosed herein, in subjects with serious bleeding or who need urgent surgical intervention, without associated pro-thrombotic risk.

BRIEF SUMMARY OF THE INVENTION

[0008] The present invention provides novel antibodies or antigen binding peptides that specifically bind to selective FXIa inhibitors and/or dual inhibitors of FXIa and plasma kallikrein. The present invention further provides methods of reducing the antithrombotic effect of FXIa inhibitors by administering to a subject a pharmaceutically effective dose of the antibodies or antigen binding peptides provided herein. In addition, the present invention provides detection reagents and methods for detecting the level of the inhibitors of FXIa in a biological sample.

[0009] Specific embodiment 1: An isolated antigen binding peptide comprising at least one heavy chain variable region (VH) and at least one light chain variable region (VL), wherein the at least one VH comprises at least one of:

- (a) a VH complementarity-determining region 1 (VH-CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-12;
- (b) a VH-CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 13-22; or

- (c) a VH-CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 23-28; and
wherein the at least one VL comprises at least one of:
- (d) a VL-CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 29-37;
- (e) a VL-CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 38-43; or
- (f) a VL-CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 44-51.

[00010] Specific embodiment 2: An isolated antigen binding peptide comprising:

- (a) at least one heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 52-83; and
- (b) at least one light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 84-99.

[00011] Specific embodiment 3: An isolated antigen binding peptide comprising at least one heavy chain variable region (VH) and at least one light chain variable region (VL), wherein the VH comprises three complementarity determining regions (CDRs): VH-CDR1, VH-CDR2, and VH-CDR3 and the VL comprises three CDRs: VL-CDR1, VL-CDR2, and VL-CDR3, wherein the amino acid sequences of the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3, respectively comprise the sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1, 13, 23, 29, 38, and 44, respectively;
- (b) SEQ ID NOs: 1, 14, 23, 29, 38, and 45, respectively;
- (c) SEQ ID NOs: 1, 13, 24, 30, 38, and 45, respectively;
- (d) SEQ ID NOs: 1, 13, 24, 29, 39, and 45, respectively;

- (e) SEQ ID NOs: 1, 14, 25, 29, 38, and 46, respectively;
- (f) SEQ ID NOs: 2, 13, 26, 31, 40, and 47, respectively;
- (g) SEQ ID NOs: 3, 15, 24, 32, 40, and 47, respectively;
- (h) SEQ ID NOs: 4, 16, 24, 29, 38, and 46, respectively;
- (i) SEQ ID NOs: 5, 15, 24, 29, 38, and 46, respectively;
- (j) SEQ ID NOs: 1, 14, 24, 29, 38, and 46, respectively;
- (k) SEQ ID NOs: 6, 13, 24, 31, 40, and 47, respectively;
- (l) SEQ ID NOs: 3, 15, 24, 32, 41, and 48, respectively;
- (m) SEQ ID NOs: 1, 14, 24, 33, 38, and 49, respectively;
- (n) SEQ ID NOs: 1, 14, 26, 29, 38, and 46, respectively;
- (o) SEQ ID NOs: 7, 17, 26, 29, 38, and 46, respectively;
- (p) SEQ ID NOs: 8, 17, 24, 34, 38, and 46, respectively;
- (q) SEQ ID NOs: 1, 17, 26, 29, 38, and 46, respectively;
- (r) SEQ ID NOs: 1, 17, 26, 35, 38, and 46, respectively;
- (s) SEQ ID NOs: 1, 17, 24, 33, 38, and 49, respectively;
- (t) SEQ ID NOs: 9, 14, 26, 29, 38, and 46, respectively;
- (u) SEQ ID NOs: 9, 14, 26, 35, 38, and 46, respectively;
- (v) SEQ ID NOs: 9, 17, 24, 29, 38, and 46, respectively;
- (w) SEQ ID NOs: 9, 17, 24, 35, 38, and 46, respectively;
- (x) SEQ ID NOs: 9, 17, 24, 34, 38, and 46, respectively;
- (y) SEQ ID NOs: 9, 14, 24, 29, 38, and 46, respectively;
- (z) SEQ ID NOs: 9, 18, 26, 35, 38, and 46, respectively;
- (aa) SEQ ID NOs: 8, 14, 24, 29, 38, and 46, respectively;

- (bb) SEQ ID NOs: 8, 17, 26, 29, 38, and 46, respectively;
- (cc) SEQ ID NOs: 9, 19, 26, 29, 38, and 46, respectively;
- (dd) SEQ ID NOs: 9, 17, 26, 34, 38, and 46, respectively;
- (ee) SEQ ID NOs: 10, 20, 27, 36, 42, and 50, respectively;
- (ff) SEQ ID NOs: 11, 21, 28, 37, 43, and 51, respectively;
- (gg) SEQ ID NOs: 12, 22, 26, 33, 38, and 46, respectively;
- (hh) SEQ ID NOs: 12, 17, 26, 33, 38, and 46, respectively;
- (ii) SEQ ID NOs: 9, 17, 26, 33, 38, and 46, respectively; and
- (jj) variants of (a) to (ii) wherein any of the amino acid sequences have 1, 2, or 3 conservative amino acid substitutions therein.

[00012] Specific embodiment 4: The isolated antigen binding peptide of embodiment 3, wherein the at least one VH region and the at least one VL region, respectively, comprise amino acid sequences selected from the group consisting of:

- (a) SEQ ID NO: 52 and SEQ ID NO: 84, respectively;
- (b) SEQ ID NO: 53 and SEQ ID NO: 85, respectively;
- (c) SEQ ID NO: 54 and SEQ ID NO: 86, respectively;
- (d) SEQ ID NO: 54 and SEQ ID NO: 87, respectively;
- (e) SEQ ID NO: 55 and SEQ ID NO: 88, respectively;
- (f) SEQ ID NO: 56 and SEQ ID NO: 89, respectively;
- (g) SEQ ID NO: 57 and SEQ ID NO: 90, respectively;
- (h) SEQ ID NO: 58 and SEQ ID NO: 88, respectively;
- (i) SEQ ID NO: 59 and SEQ ID NO: 88, respectively;
- (j) SEQ ID NO: 60 and SEQ ID NO: 91, respectively;
- (k) SEQ ID NO: 61 and SEQ ID NO: 89, respectively;

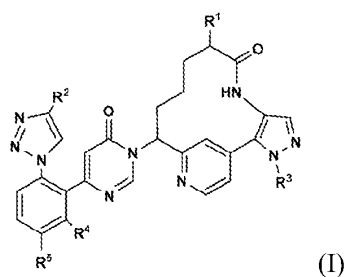
- (l) SEQ ID NO: 57 and SEQ ID NO: 92, respectively;
- (m) SEQ ID NO: 60 and SEQ ID NO: 93, respectively;
- (n) SEQ ID NO: 60 and SEQ ID NO: 88, respectively;
- (o) SEQ ID NO: 62 and SEQ ID NO: 88, respectively;
- (p) SEQ ID NO: 63 and SEQ ID NO: 88, respectively;
- (q) SEQ ID NO: 64 and SEQ ID NO: 88, respectively;
- (r) SEQ ID NO: 65 and SEQ ID NO: 94, respectively;
- (s) SEQ ID NO: 66 and SEQ ID NO: 88, respectively;
- (t) SEQ ID NO: 66 and SEQ ID NO: 95, respectively;
- (u) SEQ ID NO: 67 and SEQ ID NO: 88, respectively;
- (v) SEQ ID NO: 68 and SEQ ID NO: 93, respectively;
- (w) SEQ ID NO: 69 and SEQ ID NO: 88, respectively;
- (x) SEQ ID NO: 69 and SEQ ID NO: 95, respectively;
- (y) SEQ ID NO: 70 and SEQ ID NO: 88, respectively;
- (z) SEQ ID NO: 70 and SEQ ID NO: 95, respectively;
- (aa) SEQ ID NO: 71 and SEQ ID NO: 88, respectively;
- (bb) SEQ ID NO: 71 and SEQ ID NO: 94, respectively;
- (cc) SEQ ID NO: 72 and SEQ ID NO: 88, respectively;
- (dd) SEQ ID NO: 73 and SEQ ID NO: 95, respectively;
- (ee) SEQ ID NO: 74 and SEQ ID NO: 88, respectively;
- (ff) SEQ ID NO: 75 and SEQ ID NO: 88, respectively;
- (gg) SEQ ID NO: 76 and SEQ ID NO: 88, respectively;
- (hh) SEQ ID NO: 77 and SEQ ID NO: 94, respectively;

- (ii) SEQ ID NO: 78 and SEQ ID NO: 96, respectively;
- (jj) SEQ ID NO: 79 and SEQ ID NO: 97 respectively;
- (kk) SEQ ID NO: 80 and SEQ ID NO: 98, respectively;
- (ll) SEQ ID NO: 81 and SEQ ID NO: 99, respectively;
- (mm) SEQ ID NO: 81 and SEQ ID NO: 98, respectively;
- (nn) SEQ ID NO: 82 and SEQ ID NO: 99, respectively;
- (oo) SEQ ID NO: 83 and SEQ ID NO: 98, respectively; and
- (pp) variants of (a) to (oo) comprising 1, 2, 3, or 4 conservative amino acid substitutions.

[00013] Specific embodiment 5: The isolated antigen binding peptide of any one of the preceding embodiments, comprising two heavy chain variable regions, each paired with one light chain variable region.

[00014] Specific embodiment 6: The isolated antigen binding peptide of embodiment 5, further comprising a polypeptide linker comprising a sequence selected from SEQ ID NO: 196-199.

[00015] Specific embodiment 7: The isolated antigen binding peptide of any one of the preceding embodiments, wherein the antigen binding peptide specifically binds to the compound set forth in Formula (I):



or a stereoisomer or a tautomer thereof, wherein:

R¹ is C₁₋₄ alkyl;

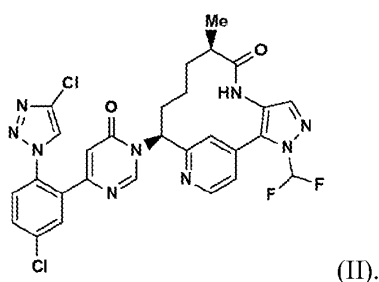
R² is independently selected from F, Cl, CF₃, CHF₂, CH₂F, CH₃;

R^3 is independently selected from CF_3 , CHF_2 , CH_2F , and CH_3 ;

R^4 is H; and

R^5 is independently selected from F and Cl.

[00016] Specific embodiment 8: The isolated antigen binding peptide of embodiment 7, wherein the compound has Formula (II):



[00017] Specific embodiment 9: The isolated antigen binding peptide of any one of the preceding embodiments is an antibody.

[00018] Specific embodiment 10: The isolated antigen binding peptide of any one of the preceding embodiments, wherein said antigen binding peptide is a Fab, Fab', F(ab')₂, Fd, single chain Fv or scFv, disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGACH2, minibody, F(ab')₃, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb², (scFv)₂, scFv-Fc, or a tandem Fab.

[00019] Specific embodiment 11: The isolated antigen binding peptide of any one of the preceding embodiments, comprising sequences selected from the group consisting of:

- (a) SEQ ID NO: 100 and SEQ ID NO: 160, respectively;
- (b) SEQ ID NO: 101 and SEQ ID NO: 160, respectively;
- (c) SEQ ID NO: 102 and SEQ ID NO: 161, respectively;
- (d) SEQ ID NO: 103 and SEQ ID NO: 161, respectively;
- (e) SEQ ID NO: 104 and SEQ ID NO: 162, respectively;
- (f) SEQ ID NO: 105 and SEQ ID NO: 162, respectively;
- (g) SEQ ID NO: 104 and SEQ ID NO: 163, respectively;

- (h) SEQ ID NO: 105 and SEQ ID NO: 163, respectively;
- (i) SEQ ID NO: 106 and SEQ ID NO: 164, respectively;
- (j) SEQ ID NO: 107 and SEQ ID NO: 164, respectively;
- (k) SEQ ID NO: 108 and SEQ ID NO: 165, respectively;
- (l) SEQ ID NO: 109 and SEQ ID NO: 165, respectively;
- (m) SEQ ID NO: 110 and SEQ ID NO: 166, respectively;
- (n) SEQ ID NO: 111 and SEQ ID NO: 166, respectively;
- (o) SEQ ID NO: 112 and SEQ ID NO: 164, respectively;
- (p) SEQ ID NO: 113 and SEQ ID NO: 164, respectively;
- (q) SEQ ID NO: 114 and SEQ ID NO: 164, respectively;
- (r) SEQ ID NO: 115 and SEQ ID NO: 164, respectively;
- (s) SEQ ID NO: 116 and SEQ ID NO: 167, respectively;
- (t) SEQ ID NO: 117 and SEQ ID NO: 167, respectively;
- (u) SEQ ID NO: 118 and SEQ ID NO: 165, respectively;
- (v) SEQ ID NO: 119 and SEQ ID NO: 165, respectively;
- (w) SEQ ID NO: 110 and SEQ ID NO: 168, respectively;
- (x) SEQ ID NO: 111 and SEQ ID NO: 168, respectively;
- (y) SEQ ID NO: 116 and SEQ ID NO: 169, respectively;
- (z) SEQ ID NO: 117 and SEQ ID NO: 169, respectively;
- (aa) SEQ ID NO: 116 and SEQ ID NO: 164, respectively;
- (bb) SEQ ID NO: 117 and SEQ ID NO: 164, respectively;
- (cc) SEQ ID NO: 120 and SEQ ID NO: 164, respectively;
- (dd) SEQ ID NO: 121 and SEQ ID NO: 164, respectively;

- (ee) SEQ ID NO: 122 and SEQ ID NO: 164, respectively;
- (ff) SEQ ID NO: 123 and SEQ ID NO: 164, respectively;
- (gg) SEQ ID NO: 124 and SEQ ID NO: 164, respectively;
- (hh) SEQ ID NO: 125 and SEQ ID NO: 164, respectively;
- (ii) SEQ ID NO: 126 and SEQ ID NO: 170, respectively;
- (jj) SEQ ID NO: 127 and SEQ ID NO: 170, respectively;
- (kk) SEQ ID NO: 128 and SEQ ID NO: 164, respectively;
- (ll) SEQ ID NO: 129 and SEQ ID NO: 164, respectively;
- (mm) SEQ ID NO: 128 and SEQ ID NO: 171, respectively;
- (nn) SEQ ID NO: 129 and SEQ ID NO: 171, respectively;
- (oo) SEQ ID NO: 130 and SEQ ID NO: 164, respectively;
- (pp) SEQ ID NO: 131 and SEQ ID NO: 164, respectively;
- (qq) SEQ ID NO: 132 and SEQ ID NO: 169, respectively;
- (rr) SEQ ID NO: 133 and SEQ ID NO: 169, respectively;
- (ss) SEQ ID NO: 134 and SEQ ID NO: 164, respectively;
- (tt) SEQ ID NO: 135 and SEQ ID NO: 164, respectively;
- (uu) SEQ ID NO: 134 and SEQ ID NO: 171, respectively;
- (vv) SEQ ID NO: 135 and SEQ ID NO: 171, respectively;
- (ww) SEQ ID NO: 136 and SEQ ID NO: 164, respectively;
- (xx) SEQ ID NO: 137 and SEQ ID NO: 164, respectively;
- (yy) SEQ ID NO: 136 and SEQ ID NO: 171, respectively;
- (zz) SEQ ID NO: 137 and SEQ ID NO: 171, respectively;
- (aaa) SEQ ID NO: 138 and SEQ ID NO: 164, respectively;

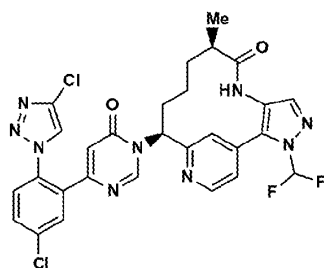
- (bbb) SEQ ID NO: 139 and SEQ ID NO: 164, respectively;
- (ccc) SEQ ID NO: 138 and SEQ ID NO: 170, respectively;
- (ddd) SEQ ID NO: 139 and SEQ ID NO: 170, respectively;
- (eee) SEQ ID NO: 140 and SEQ ID NO: 164, respectively;
- (fff) SEQ ID NO: 141 and SEQ ID NO: 164, respectively;
- (ggg) SEQ ID NO: 142 and SEQ ID NO: 171, respectively;
- (hhh) SEQ ID NO: 143 and SEQ ID NO: 171, respectively;
- (iii) SEQ ID NO: 144 and SEQ ID NO: 164, respectively;
- (jjj) SEQ ID NO: 145 and SEQ ID NO: 164, respectively;
- (kkk) SEQ ID NO: 146 and SEQ ID NO: 164, respectively;
- (lll) SEQ ID NO: 147 and SEQ ID NO: 164, respectively;
- (mmm) SEQ ID NO: 148 and SEQ ID NO: 164, respectively;
- (nnn) SEQ ID NO: 149 and SEQ ID NO: 164, respectively;
- (ooo) SEQ ID NO: 150 and SEQ ID NO: 170, respectively;
- (ppp) SEQ ID NO: 151 and SEQ ID NO: 170, respectively;
- (qqq) SEQ ID NO: 152 and SEQ ID NO: 172, respectively;
- (rrr) SEQ ID NO: 153 and SEQ ID NO: 172, respectively;
- (sss) SEQ ID NO: 154 and SEQ ID NO: 173, respectively;
- (ttt) SEQ ID NO: 155 and SEQ ID NO: 173, respectively;
- (uuu) SEQ ID NO: 156 and SEQ ID NO: 174, respectively;
- (vvv) SEQ ID NO: 157 and SEQ ID NO: 174, respectively;
- (www) SEQ ID NO: 158 and SEQ ID NO: 175, respectively;
- (xxx) SEQ ID NO: 159 and SEQ ID NO: 175, respectively;

(yyy) SEQ ID NO: 158 and SEQ ID NO: 174, respectively; and

(zzz) SEQ ID NO: 159 and SEQ ID NO: 174, respectively;

wherein said isolated antigen binding peptide specifically binds to the compound of Formula

(II):



(II).

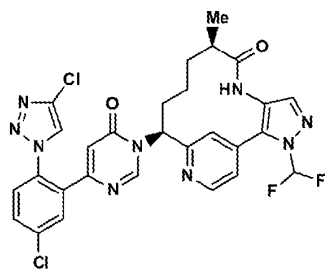
[00020] Specific embodiment 12: The isolated antigen binding peptide of any one of the preceding embodiments, comprising sequences selected from the group consisting of:

- (a) SEQ ID NO: 176 and SEQ ID NO: 160, respectively;
- (b) SEQ ID NO: 177 and SEQ ID NO: 160, respectively;
- (c) SEQ ID NO: 178 and SEQ ID NO: 160, respectively;
- (d) SEQ ID NO: 179 and SEQ ID NO: 160, respectively;
- (e) SEQ ID NO: 180 and SEQ ID NO: 164, respectively;
- (f) SEQ ID NO: 181 and SEQ ID NO: 164, respectively;
- (g) SEQ ID NO: 182 and SEQ ID NO: 164, respectively;
- (h) SEQ ID NO: 183 and SEQ ID NO: 164, respectively;
- (i) SEQ ID NO: 184 and SEQ ID NO: 163, respectively;
- (j) SEQ ID NO: 185 and SEQ ID NO: 163, respectively;
- (k) SEQ ID NO: 186 and SEQ ID NO: 163, respectively;
- (l) SEQ ID NO: 187 and SEQ ID NO: 163, respectively;
- (m) SEQ ID NO: 184 and SEQ ID NO: 162, respectively;

- (n) SEQ ID NO: 185 and SEQ ID NO: 162, respectively;
- (o) SEQ ID NO: 186 and SEQ ID NO: 162, respectively;
- (p) SEQ ID NO: 187 and SEQ ID NO: 162, respectively;
- (q) SEQ ID NO: 188 and SEQ ID NO: 165, respectively;
- (r) SEQ ID NO: 189 and SEQ ID NO: 165, respectively;
- (s) SEQ ID NO: 190 and SEQ ID NO: 165, respectively;
- (t) SEQ ID NO: 191 and SEQ ID NO: 165, respectively;
- (u) SEQ ID NO: 192 and SEQ ID NO: 161, respectively;
- (v) SEQ ID NO: 193 and SEQ ID NO: 161, respectively;
- (w) SEQ ID NO: 194 and SEQ ID NO: 161, respectively; and
- (x) SEQ ID NO: 195 and SEQ ID NO: 161, respectively;

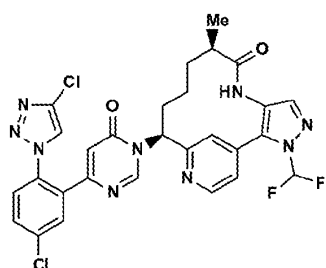
wherein said isolated antigen binding peptide specifically binds to the compound of Formula

(II):



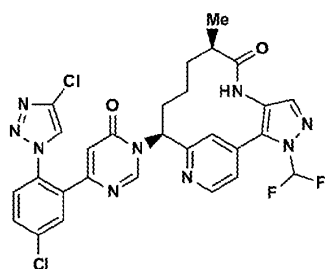
(II)

[00021] Specific embodiment 13: The isolated antigen binding peptide of embodiment 11, comprising sequences SEQ ID NO: 106 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



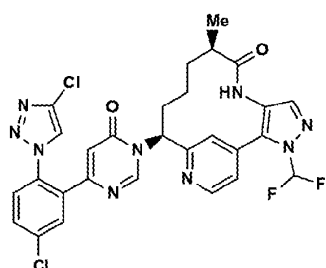
(II)

[00022] Specific embodiment 14: An isolated antibody Fab fragment comprising sequences SEQ ID NO: 106 and SEQ ID NO: 164; wherein said isolated antibody Fab fragment specifically binds to the compound of Formula (II):



(II)

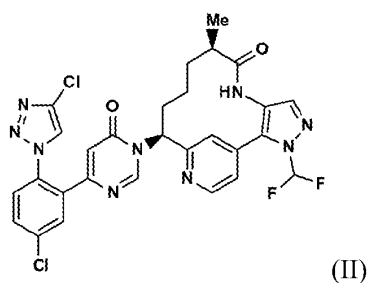
[00023] Specific embodiment 15: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 180 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



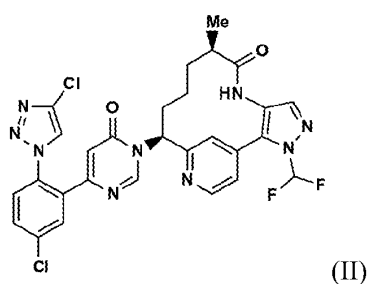
(II)

[00024] Specific embodiment 16: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 180 and SEQ ID NO: 164;

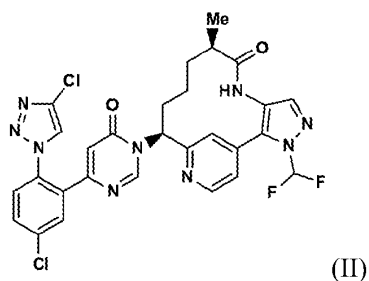
wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):



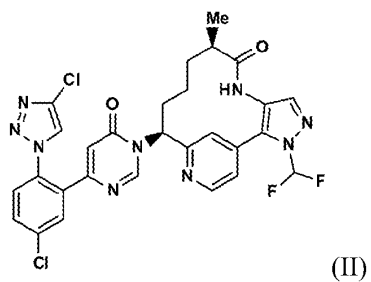
[00025] Specific embodiment 17: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 181 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



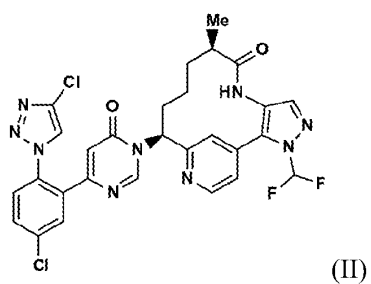
[00026] Specific embodiment 18: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 181 and SEQ ID NO: 164; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):



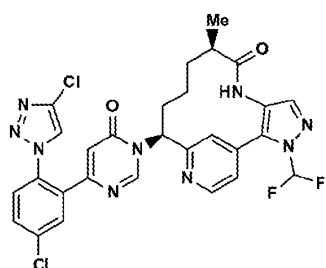
[00027] Specific embodiment 19: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 182 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



[00028] Specific embodiment 20: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 182 and SEQ ID NO: 164; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):

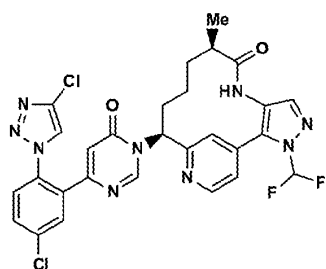


[00029] Specific embodiment 21: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 183 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



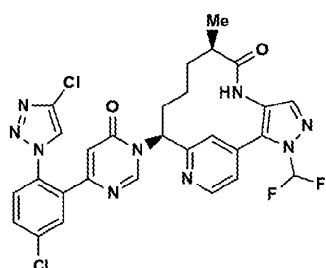
(II)

[00030] Specific embodiment 22: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 183 and SEQ ID NO: 164; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):



(II)

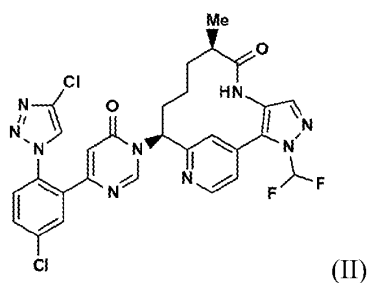
[00031] Specific embodiment 23: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 176 and SEQ ID NO: 160, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



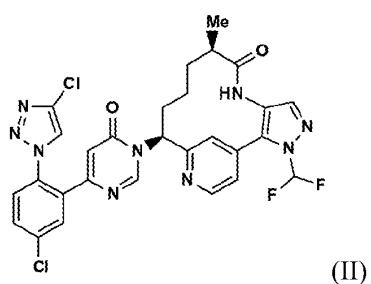
(II)

[00032] Specific embodiment 24: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 176 and SEQ ID NO: 160;

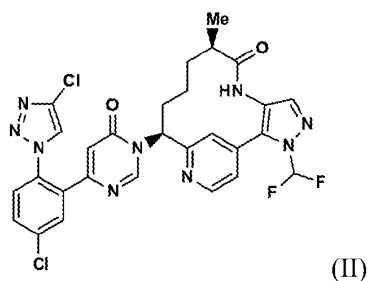
wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):



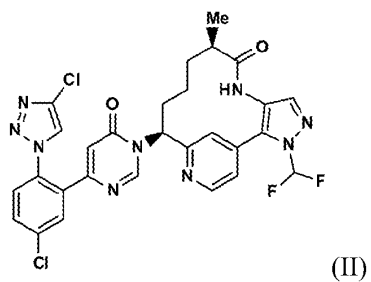
[00033] Specific embodiment 25: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 177 and SEQ ID NO: 160, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



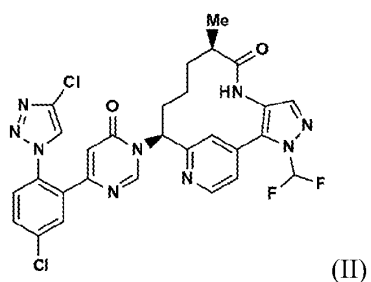
[00034] Specific embodiment 26: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 177 and SEQ ID NO: 160; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):



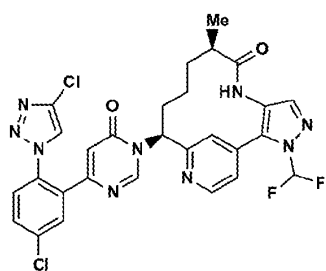
[00035] Specific embodiment 27: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 184 and SEQ ID NO: 162, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



[00036] Specific embodiment 28: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 184 and SEQ ID NO: 162; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):

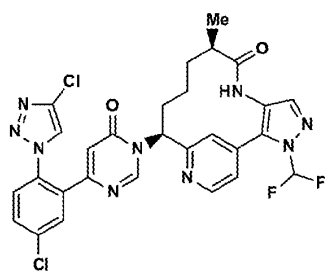


[00037] Specific embodiment 29: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 184 and SEQ ID NO: 163, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



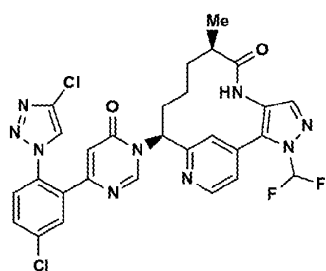
(II)

[00038] Specific embodiment 30: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 184 and SEQ ID NO: 163; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):



(II)

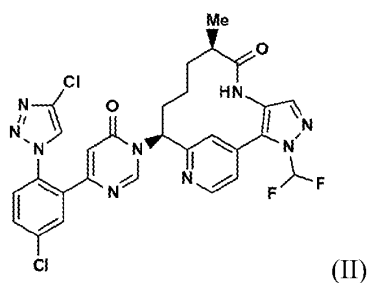
[00039] Specific embodiment 31: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 188 and SEQ ID NO: 165, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



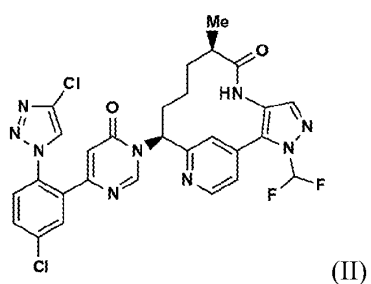
(II)

[00040] Specific embodiment 32: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 188 and SEQ ID NO: 165;

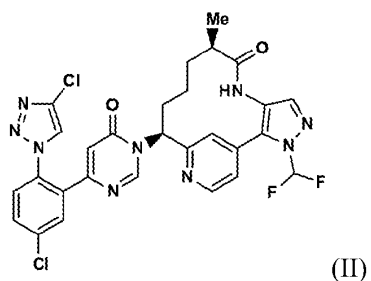
wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):



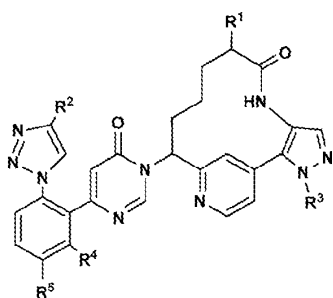
[00041] Specific embodiment 33: The isolated antigen binding peptide of embodiment 12, comprising sequences SEQ ID NO: 192 and SEQ ID NO: 161, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



[00042] Specific embodiment 34: An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 192 and SEQ ID NO: 161; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II):



- [00043] Specific embodiment 35: An isolated polynucleotide comprising a nucleic acid sequence encoding the antigen binding peptide or the antibody Fab fragment or the antibody tandem Fab fragment of any one of embodiments 1-34.
- [00044] Specific embodiment 36: An isolated vector comprising the polynucleotide of embodiment 35.
- [00045] Specific embodiment 37: An isolated host cell comprising the vector of embodiment 36.
- [00046] Specific embodiment 38: A method of making an antigen binding peptide or an antibody Fab fragment or an antibody tandem Fab fragment comprising (a) culturing the host cell of embodiment 37 under culture conditions that promote protein production such that the host cell produces the antigen binding peptide or the antibody Fab fragment or the antibody tandem Fab fragment, and (b) isolating said antigen binding peptide or said antibody Fab fragment or said antibody tandem Fab fragment from said culture.
- [00047] Specific embodiment 39: A detection reagent comprising the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment of any one of embodiments 1-34 and a detectable label.
- [00048] Specific embodiment 40: The detection reagent of embodiment 39, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment is linked to the detectable label.
- [00049] Specific embodiment 41: A method of reducing the antithrombotic effect of the compound of Formula (I) or a stereoisomer or a tautomer thereof, in a subject in need thereof, comprising administering to the subject a pharmaceutically effective dose of the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment of any one of embodiments 1-34, wherein:



R¹ is C₁₋₄ alkyl;

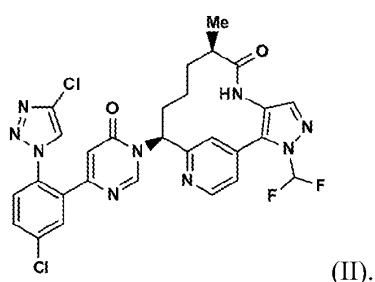
R² is independently selected from F, Cl, CF₃, CHF₂, CH₂F, CH₃;

R³ is independently selected from CF₃, CHF₂, CH₂F, and CH₃;

R⁴ is H; and

R⁵ is independently selected from F and Cl.

[00050] Specific embodiment 42: The method of embodiment 41, wherein the compound of Formula (I) has Formula (II):



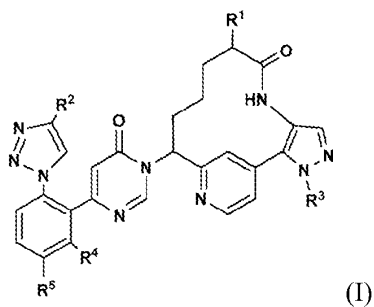
[00051] Specific embodiment 43: The method of embodiment 41 or 42, wherein the pharmaceutically effective dose of the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment comprises the antigen binding peptide or the antibody Fab fragment or the antibody tandem Fab fragment at an at least about 1:1 molar ratio to the dose of the compound of Formula (I) or (II), or an at least about 1:1 molar ratio to the presence of the compound of Formula (I) or (II) in the subject.

[00052] Specific embodiment 44: The method of any one of embodiments 41-43, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment is administered concurrently with or after the administration of the compound of Formula (I) or (II).

[00053] Specific embodiment 45: The method of any one of embodiments 41-44, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment is administered intravenously, intramuscularly, or subcutaneously.

[00054] Specific embodiment 46: The method of any one of embodiments 41-45, wherein the subject is a human.

[00055] Specific embodiment 47: A method of detecting the level of a compound of Formula (I) or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, in a biological sample, wherein:



R^1 is C_{1-4} alkyl;

R^2 is independently selected from F, Cl, CF_3 , CHF_2 , CH_2F , CH_3 ;

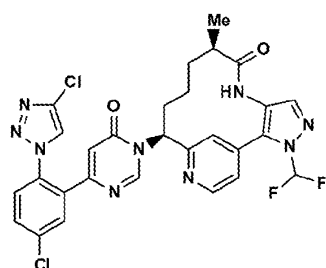
R^3 is independently selected from CF_3 , CHF_2 , CH_2F , and CH_3 ;

R^4 is H; and

R^5 is independently selected from F and Cl; the method comprising:

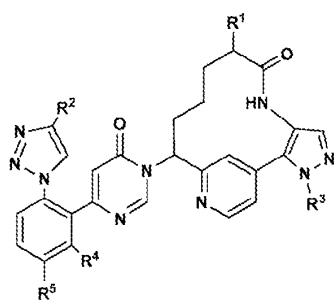
- (a) contacting the biological sample with the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment of any one of embodiments 1-34, and
- (b) detecting the level of a bound complex of the compound and the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment.

[00056] Specific embodiment 48: The method of embodiment 47, wherein the compound of Formula (I) has Formula (II):



(II).

- [00057] Specific embodiment 49: The method of embodiment 47 or 48, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment is labeled.
- [00058] Specific embodiment 50: The method of any one of embodiments 47-49, wherein the detection is performed by an immunological assay.
- [00059] Specific embodiment 51: The method of any one of embodiments 47-50, wherein the biological sample comprises urine, feces, saliva, whole blood, plasma, organ tissue, hair, skin, cells, or cell cultures.
- [00060] Specific embodiment 52: A method of binding a compound of Formula (I) or a stereoisomer or a tautomer thereof, in a subject who is taking therapeutically effective amount of the compound of formula (I) or a stereoisomer or a tautomer thereof, comprising administering to the subject a pharmaceutically effective dose of the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment of any one of claims 1-34, wherein



(I)

R¹ is C1-4 alkyl;

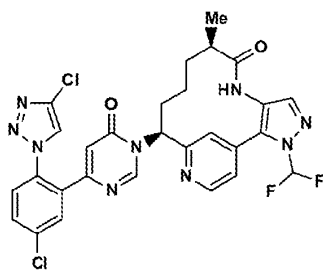
R² is independently selected from F, Cl, CF₃, CHF₂, CH₂F, CH₃;

R³ is independently selected from CF₃, CHF₂, CH₂F, and CH₃;

R⁴ is H; and

R5 is independently selected from F and Cl.

[00061] Specific embodiment 53: The method of embodiment 52, wherein the compound of Formula (I) has Formula (II):



[00062] Specific embodiment 54: The method of any one of embodiments 52 or 53, wherein the pharmaceutically effective dose of the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment comprises the antigen binding peptide or the antibody Fab fragment or the antibody tandem Fab fragment at an at least about 1:1 molar ratio to the dose of the compound of Formula (I) or (II), or an at least about 1:1 molar ratio to the presence of the compound of Formula (I) or (II) in the subject.

[00063] Specific embodiment 55: The method of any one of embodiments 52-54, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated the antibody tandem Fab fragment is administered concurrently with or after the administration of the compound of Formula (I) or (II).

[00064] Specific embodiment 56: The method of any one of embodiments 52-55, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated the antibody tandem Fab fragment is administered intravenously, intramuscularly, or subcutaneously.

[00065] Specific embodiment 57: The method of any one of embodiments 52-56, wherein the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

[00066] FIGURES 1A and 1B depict a comparison of the sequence of the 26D5 mAb to the closest human germline V and J gene sequences. FIGURE 1A: Shows VH sequence of 26D5 compared to IGHV3-53 and IGHJ4 germline sequences. Kabat numbering is shown. Kabat

definitions of HCDR2 and HCDR3 are shown. Kabat and AbM definitions of HCDR1 are shown. Figure 1A discloses SEQ ID NOS 205, 83 and 220, respectively, in order of appearance. FIGURE 1B: Shows VK sequence of 26D5 compared to IGKV1-12 and IGKJ4 germline sequences. Kabat numbering is shown. Kabat definitions of CDRs are shown. Figure 1B discloses SEQ ID NOS 206, 98 and 207, respectively, in order of appearance.

[00067] FIGURE 2 depicts the positions of the 26D5-GV-Q mAb that were randomized for a mutational scan. Kabat numbering is shown for each position randomized in the mutational scan. Kabat definition is shown for LCDR1-3, HCDR2-3 (but last 6 amino acids missing from HCDR2 here); AbM definition is shown for HCDR1. Figure 2 discloses SEQ ID NOS 33, 46, 208-209 and 26, respectively, in order of appearance.

[00068] FIGURES 3A-E depict heat map scans of the positions of the 26D5-GV-Q mAb indicating the effect of mutations at the indicated positions on antibody binding (favorable, neutral or unfavorable). FIGURE 3A shows LCDR1 (SEQ ID NO: 33); FIGURE 3B shows LCDR3 (SEQ ID NO: 46); FIGURE 3C shows HCDR1 (SEQ ID NO: 208); FIGURE 3D shows HCDR2 (SEQ ID NO: 209); FIGURE 3E shows HCDR3 (SEQ ID NO: 26).

[00069] FIGURES 4A and 4B depict the alignment of amino acid sequences of progeny derived from affinity maturation of the 26D5-GV-Q antibody. Kabat definitions are used for CDRs and numbering. FIGURE 4A shows alignment of the heavy chain variable region (SEQ ID NOS 83, 82, 74, 60, 67, 62, 75, 66, 64, 69, 71, 60, 68, 77, 66, 76, 69, 70, 71, 73, 72, 65, 70 and 63, respectively, in order of appearance). FIGURE 4B shows alignment of the light chain variable region (SEQ ID NOS 98, 99, 88, 88, 88, 88, 88, 88, 88, 88, 88, 93, 93, 94, 95, 88, 95, 88, 94, 95, 88, 94, 95 and 88, respectively, in order of appearance).

[00070] FIGURE 5 depicts the positions of the 26D5-295-B08 mAb that were randomized for a mutational scan. Kabat numbering is shown for each position randomized in the mutational scan. Figure 5 discloses SEQ ID NOS 210-215, respectively, in order of appearance.

[00071] FIGURES 6A-F depict heat map scans of the CDRs and adjacent framework positions of the 26D5-295-B08 mAb indicating the effect of mutations at the indicated positions on antibody binding (see FIGURE 3A for further explanation). FIGURE 6A shows LCDR1 (SEQ ID NO: 210); FIGURE 6B shows LCDR2 (SEQ ID NO: 211); FIGURE 6C

shows LCDR3 (SEQ ID NO: 212); FIGURE 6D shows HCDR1 (SEQ ID NO: 213); FIGURE 6E shows HCDR2 (SEQ ID NO: 214); FIGURE 6F shows HCDR3 (SEQ ID NO: 215).

[00072] FIGURES 7A and 7B depict the amino acid positions of the 26D5-295-B08 mAb randomized to create complex libraries (FIGURE 7A, Complex Chip Library (SEQ ID NOS 216-219, respectively, in order of appearance); FIGURE 7B, Complex Doped Library (SEQ ID NO: 215)).

[00073] FIGURES 8A and 8B depict the alignment of amino acid sequences of progeny derived from affinity maturation of the 26D5-295-B08 mAb. Kabat definition is used for CDRs and numbering. FIGURE 8A shows alignment of the heavy chain variable region (SEQ ID NOS 83, 82, 60, 54, 52, 54, 60, 53, 61, 56, 59, 57, 57, 58 and 55, respectively, in order of appearance). FIGURE 8B shows alignment of the light chain variable region (SEQ ID NOS 98, 99, 88, 86, 84, 87, 91, 85, 89, 89, 88, 92, 90, 88 and 88, respectively, in order of appearance).

[00074] FIGURE 9 depicts results from a chromogenic enzymatic assay for determining the amount of antibodies needed for equal to or greater than 50% reversal of activity of Compound A. The activity of Factor XIa enzymatic activity (y-axis) was plotted as a function of the concentration of representative affinity matured mAbs (x-axis), while the concentrations of Factor XIa substrate and Compound A was kept constant. The top graph shows data derived from the use of the mAb IgG1f version of parent 26D5 (SEQ ID NO: 83 and 98; also referred to herein as P1-072224; indicated as “26D5 mAb” in the figure). The bottom graph shows data derived from the use of mAb IgG1f version of 26D5-296-G07 (SEQ ID NO: 65 and 94; also referred to herein as P1-073056; indicated as “26D5-296-G07 mAb” in the figure).

[00075] FIGURE 10 depicts a surface plasmon resonance (SPR) sensograms indicating the binding affinity of parent mAb 26D5 (P1-072224) (indicated as “26D5 mAb” in the figure) to Compound A, measured at various compound concentrations.

[00076] FIGURE 11 depicts surface plasmon resonance (SPR) sensograms indicating the binding affinity of (top) mAb 26D5-GV-Q, (middle) mAb 26D5-295-B08 and (bottom) antibody Fab fragment 26D5-295-B08 to COMPOUND 2, measured at various mAb/Fab concentrations.

[00077] FIGURE 12 depicts surface plasmon resonance (SPR) sensograms indicating the binding affinity of (top) antibody tandem Fab (TanFab) fragment 26D5-75616-348-F10-TanFab and (bottom) antibody tandem Fab (TanFab) fragment 26D5-75214-343-F06-TanFab to COMPOUND 5, measured at various TanFab concentrations.

[00078] FIGURE 13 depicts time-resolved fluorescence energy transfer (TR-FRET) derived competitive binding data of (A) mAb form of 26D5-GVR-Q-FT-Fab-LONG, (B) mAb form of 26D5-295-B08-Fab-LONG and (C) mAb form of 26D5-75747-348-D07-Fab-LONG, each binding to COMPOUND 5.

[00079] FIGURE 14 depicts time-resolved fluorescence energy transfer (TR-FRET) derived competitive binding data of the indicated antibodies and antibody Fab fragments, each binding to COMPOUND 5.

[00080] FIGURE 15 depicts DSC thermograms of the indicated antibody Fab fragments.

[00081] FIGURE 16 depicts the structure as determined by crystallography of the antibody Fab fragment 26D5-GVR-Q-FT Fab bound to Compound A.

[00082] FIGURE 17 depicts the structure as determined by crystallography of the antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT bound to Compound A.

[00083] FIGURE 18 depicts the reversal of the anticoagulant effects of Compound A by the neutralizing antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT. The human plasma clotting time (aPTT) was plotted as a function of the plasma concentrations of Compound A and of neutralizing antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT.

[00084] FIGURE 19 depicts that human plasma clotting time (aPTT) is a function of the plasma concentration of unbound Compound A, regardless whether antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT is present or absent. The human plasma clotting time (aPTT) was plotted as a function of the plasma concentration of Compound A in the absence (filled symbols) and presence (open symbols) of the neutralizing antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT.

[00085] FIGURE 20 depicts the reversal of the anticoagulant effects of Compound A by the neutralizing antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT. An IV dose of Compound A (1 mg/kg), followed 20 minutes later by an IV dose of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT (160 mg/kg) was administered to rabbits. Plasma clotting

time (aPTT) was measured at baseline, shortly before the administration of Compound A and for about 24 hours afterwards.

[00086] FIGURE 21 depicts the pharmacokinetics (rabbit plasma concentrations) of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT, Compound A and free Compound A resulting from an IV dose of Compound A (1 mg/kg) followed 20 minutes later by an IV dose of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT (160 mg/kg).

[00087] FIGURE 22 depicts the pharmacokinetics (rat plasma concentrations) of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT and antibody tandem Fab fragment 26D5-75616-348-F10-TanFab resulting from IV doses each of 10 mg/kg administered by infusion over 10 minutes. Open circles/Tandem Fab indicate antibody tandem Fab fragment 26D5-75616-348-F10-TanFab data points. Open triangles/Fab indicate antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT data points.

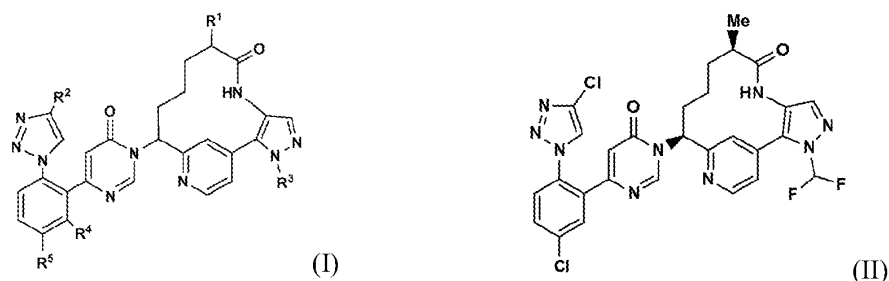
[00088] FIGURE 23 depicts the pharmacokinetics (rabbit plasma concentrations) of antibody tandem Fab fragment 26D5-75616-348-F10-TanFab, Compound A and free Compound A resulting from an IV dose of Compound A of 0.4 mg/kg administered by infusion over 10 minutes, followed 20 minutes later by an IV dose of antibody tandem Fab fragment 26D5-75616-348-F10-TanFab of 40 mg/kg administered by infusion over 10 minutes. Closed circles/tandem Fab indicate antibody tandem Fab fragment 26D5-75616-348-F10-TanFab data points.

[00089] FIGURE 24 depicts the reversal of the anticoagulant effects of Compound A by the neutralizing antibody tandem Fab fragment 26D5-75616-348-F10-TanFab. The human plasma clotting time (aPTT) was plotted as a function of the plasma concentrations of Compound A and of neutralizing antibody tandem Fab fragment 26D5-75616-348-F10-TanFab. “tandem Fab” refers to antibody tandem Fab fragment 26D5-75616-348-F10-TanFab.

DETAILED DESCRIPTION OF THE INVENTION

[00090] The present invention provides novel antibodies or antigen binding peptides that bind to selective FXIa inhibitors and/or dual inhibitors of FXIa and plasma kallikrein. As used herein, FXIa inhibitors are compounds set forth in Formula (I) and have the ability to inhibit the activity or function of FXIa. Accordingly, in some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, provided

herein specifically binds to the compound set forth in Formula (I) or a stereoisomer or a tautomer thereof. In some embodiments, the R^1 in Formula (I) is C_{1-4} alkyl; R^2 in Formula (I) is independently selected from F, Cl, CF_3 , CHF_2 , CH_2F , CH_3 ; the R^3 in Formula (I) is independently selected from CF_3 , CHF_2 , CH_2F , and CH_3 ; the R^4 in Formula (I) is H; and the R^5 in Formula (I) is independently selected from F and Cl. In certain embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, provided herein specifically binds to the compound set forth in Formula (II). As used herein, the term the compound of Formula (I) or (II) encompasses all the compounds with the Formula (I) or (II), or a stereoisomer or a tautomer thereof.



[00091] In a specific embodiment, the antigen to be sequestered by the antigen binding peptides of the present invention is compound of Formula (II) (also referred to as Compound A herein and known as milvexian). Milvexian is a direct-acting, reversible, small molecule therapeutic agent that binds to and inhibits the activated form of human coagulation Factor XI (FXIa) with high affinity and selectivity. Milvexian has the chemical name (5R,9S)-9-(4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-6-oxopyrimidin-1(6H)-yl)-21-(difluoromethyl)-5-methyl-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclonaphan-4-one. Milvexian and a method of preparing milvexian are described in U.S. patent No. 9,453,018, which is hereby incorporated by reference in its entirety.

[00092] As used herein, FXIa refers to a serine protease in the intrinsic pathway involved in the regulation of blood coagulation. The structure and physiologic function of FXIa are generally well known in the art. It is primarily synthesized by hepatocytes and circulates in a zymogen form, FXI. FXI is then physiologically activated by FXIIa and thrombin. See Mohammed B. et al. *Thromb Res.*, 161:94-105 (2018), which is incorporated by reference.

[00093] As used herein, the term “antigen binding peptide” refers to a protein or polypeptide molecule that recognizes and specifically binds to a target molecule (i.e., antigen). Examples of the target molecules include but are not limited to, a small molecule compound, protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or any portion or combination of the foregoing.

[00094] In some embodiments, the antigen binding peptide of the present invention is an antibody or an antibody fragment, such as, but not limited to, (Fab), Fab', F(ab')₂, Fd, single chain Fv or scFv, disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGACH2, minibody, F(ab')₃, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb², (scFv)₂, scFv-Fc, or a tandem Fab.

[00095] In some embodiments, the antigen binding peptides, *e.g.*, antibody or Fab fragment, of the present invention may be isolated. As used herein, the term “isolated” means that the nucleic acid, peptide or protein is removed from its native environment, for example from a cell or organism producing it, or from a fluid in which the nucleic acid, peptide or protein occurs naturally. For peptides or proteins with novel, non-naturally occurring amino acid sequences, an “isolated” peptide or protein means that the protein or peptide has been removed from the engineered cell producing the peptide or protein. For purposes of the present invention, the peptide or protein can still be considered as isolated if the peptide or protein is a component of a mixture or composition, *e.g.*, a pharmaceutical formulation, provided that the protein or peptide is not within the cell producing the peptide or protein and is not otherwise in its native environment.

[00096] In one specific embodiment of the present invention, a Fab is provided as the antigen binding peptide. As used herein, the term “Fab” or “antibody Fab fragment” is a well-known term and refers to the region on a full length antibody that binds to antigens. In some embodiments, an antibody Fab fragment is composed of at least the full length light chain and the N-terminal portion of the heavy chain. As used herein, the full length light chain comprises at least the light chain constant region (CL) and the light chain variable region (VL); and the N-terminal portion of the heavy chain comprises at least the CH1 domain of the heavy chain constant region and the heavy chain variable region (VH).

[00097] In one specific embodiment of the present invention, a tandem Fab is provided as the antigen binding peptide. A tandem Fab, as provided herein, comprises at least one N-

terminal portion of the heavy chain (VH-CH1) and at least one full length light chain (VL-CL). In some embodiments, the tandem Fab provided herein comprises two or more N-terminal portions of the heavy chain linked via a linker (e.g., VH-CH1-linker-CH1-VH or VH-CH1-linker-VH-CH1), each paired with one full length light chain (VL-CL). In an exemplary embodiment, the tandem Fab provided herein comprises two N-terminal portions of the heavy chains linked via a linker (e.g., VH-CH1-linker-CH1-VH or VH-CH1-linker-VH-CH1), each paired with one full length light chain (VL-CL). In some embodiments, the linker is a polypeptide linker. Exemplary tandem Fab are provided in Table 4 of the present invention. The terms “tandem Fab”, “antibody tandem Fab fragment” and “antibody TanFab fragment” are used interchangeably herein.

[00098] A “variable region” of an antibody is a well-known term of art and refers to the end of the light chain or the heavy chains that contributes to an antibody’s specificity for binding its antigen. The terms “heavy chain variable region,” “variable heavy chain,” and “VH” are used interchangeably and refer to the end of the heavy chain that contributes to an antibody’s specificity for binding its antigen. Likewise, the terms “light chain variable region,” “variable light chain,” and “VL” are used interchangeably and refer to the end of the light chain that contributes to an antibody’s specificity for binding its antigen.

[00099] The variable regions of the heavy chain and light chain each generally consist of four framework regions (FRs) connected by three complementarity determining regions (CDRs), also known as hypervariable regions. The CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen-binding domain of antibodies. The techniques for determining CDRs are generally known in the art. For example, there are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability; and (2) an approach based on crystallographic studies of antigen-antibody complexes. In addition, combinations of these two approaches are sometimes used in the art to determine CDRs. The CDRs of each chain are numbered CDR1, CDR2 and CDR3 numbered in the direction from the amino terminal end to the carboxy terminal end.

[000100] A “constant region” of an antibody is a well-known term of art and refers to the part of the antibody that is relatively constant in amino acid sequence between different antibody molecules. Typically, the heavy chain constant region is composed of three distinct

regions, termed CH1, CH2, and CH3, numbered in the direction from the amino terminal (N-terminal) end to the carboxy terminal (C-terminal) end. A typical light chain has only one constant region, termed CL. The constant region of an antibody determines its particular effector function. One of skill in the art will readily understand the terminology and structural features of constant regions of antibodies.

[000101] In some embodiments, the antigen binding peptide encompasses any modified polypeptide molecule comprising at least one antigen recognition site as long as the modified polypeptide molecule exhibits the desired antigen binding activity. The antigen binding peptides provided herein may or may not be conjugated to other molecules, such as toxins, radioisotopes, fluorescent labels, etc.

[000102] As used herein, the term “antibody” is a well-known term of art and refers to an immunoglobulin molecule that recognizes and specifically binds to a target molecule through at least one antigen recognition site within at least a portion of the variable region of the immunoglobulin molecule. The structure of an antibody is generally known in the art and is often composed of at least two full length heavy chains. The majority of antibodies, with the most notable exception being camelid antibodies, are composed of at least two full length heavy chains and at least two full length light chains. As used herein, an antibody encompasses polyclonal antibodies, monoclonal antibodies (also referred to herein as “mAbs”), multispecific antibodies such as bispecific antibodies generated from at least two antibodies, chimeric antibodies, humanized antibodies, human antibodies, and non-human antibodies. An “antibody” as used herein can be any of the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (e.g. IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well known subunit structures and three-dimensional configurations.

[000103] The Kabat numbering system is generally used when referring to a residue in the heavy chain variable domain or light chain variable domains (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain). *See* Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of

Health, Bethesda, MD (1991). The antigen interacting residues of CDRs can also be determined by crystallographic studies of antigen-antibody complexes.

[000104] The terms “polypeptide,” “peptide,” and “protein” are used interchangeably herein to refer to polymers of amino acids of any length. The amino acid polymer can be linear or branched, it can comprise modified amino acids, and it can be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention. In some embodiments, the amino acid polymer is modified by disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification. In some embodiments, the amino acid polymer is modified by conjugation with a labeling component. Also included within the definition are peptides containing one or more analogs of an amino acid known in the art, as well as unnatural amino acids.

[000105] The term “specifically binds to” (or “specific binding”) is well-known in the art and generally means that the antigen binding portion of an antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, specifically recognizing an antigen via its antigen binding domain, and that the binding entails at least some complementarity between the antigen binding domain and the antigen. According to this definition, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is said to “specifically bind” to the epitope of an antigen, via its antigen binding domain more readily than it would bind to a random, unrelated antigen.

[000106] In some embodiments, the antibody or antibody fragment of the present invention comprises the combinations of VH and VL CDR sequences provided in Table 1. In some embodiments, the antibody or antibody fragment of the present invention provided herein specifically binds to the FXIa inhibitors disclosed herein, such as, but not limited to, the FXIa inhibitors of Formula (I), and comprises VH and VL CDRs wherein each CDR independently has up to four (i.e., 0, 1, 2, 3, or 4) conservative amino acid substitutions from the corresponding CDR disclosed in Table 1.

Table 1: Variable heavy chain (VH) and light chain (VL) CDR amino acid sequences

Fab/mAb Name	VH-CDR1	VH-CDR2	VH-CDR3	VL-CDR1	VL-CDR2	VL-CDR3
26D5-75229-343-A10	SNAMS (SEQ ID NO: 1)	YIYPGGRTYYADS VKG (SEQ ID NO: 13)	AGFGGPDY (SEQ ID NO: 23)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANQFPLT (SEQ ID NO: 44)
26D5-75214-343-F06	SNAMS (SEQ ID NO: 1)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	AGFGGPDY (SEQ ID NO: 23)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANEFPLT (SEQ ID NO: 45)
26D5-75202-343-A09	SNAMS (SEQ ID NO: 1)	YIYPGGRTYYADS VKG (SEQ ID NO: 13)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 30)	AASSLQS (SEQ ID NO: 38)	QQANEFPLT (SEQ ID NO: 45)
26D5-75203-343-B09	SNAMS (SEQ ID NO: 1)	YIYPGGRTYYADS VKG (SEQ ID NO: 13)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASTLQS (SEQ ID NO: 39)	QQANEFPLT (SEQ ID NO: 45)
26D5-75616-348-F10	SNAMS (SEQ ID NO: 1)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	AEFGLEDI (SEQ ID NO: 25)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-75768-348-A10	SNAMS (SEQ ID NO: 2)	YIYPGGRTYYADS VKG (SEQ ID NO: 13)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNN Q (SEQ ID NO: 31)	YASSLQS (SEQ ID NO: 40)	QQNEFPLT (SEQ ID NO: 47)
26D5-75747-348-D07	SNAFS (SEQ ID NO: 3)	YIYSGGRTYYADS VKG (SEQ ID NO: 15)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSQV A (SEQ ID NO: 32)	YASSLQS (SEQ ID NO: 40)	QQNEFPLT (SEQ ID NO: 47)
26D5-75602-348-F04	SNQFS (SEQ ID NO: 4)	YFYPGGRTYYADS VKG (SEQ ID NO: 16)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-75576-348-B03	SNDMS (SEQ ID NO: 5)	YIYSGGRTYYADS VKG (SEQ ID NO: 15)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)

Fab/mAb Name	VH-CDR1	VH-CDR2	VH-CDR3	VL-CDR1	VL-CDR2	VL-CDR3
26D5-75017-343-F04	SNAMS (SEQ ID NO: 1)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-75592-348-A04	SNAIA (SEQ ID NO: 6)	YIYPGGRTYYADS VKG (SEQ ID NO: 13)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNN Q (SEQ ID NO: 31)	YASSLQS (SEQ ID NO: 40)	QQGNEFPLT (SEQ ID NO: 47)
26D5-75746-348-C07	SNAFS (SEQ ID NO: 3)	YIYSGGRTYYADS VKG (SEQ ID NO: 15)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSQV A (SEQ ID NO: 32)	PASNLWS (SEQ ID NO: 41)	QQANFPLT (SEQ ID NO: 48)
26D5-296-A07	SNAMS (SEQ ID NO: 1)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSWL A (SEQ ID NO: 33)	AASSLQS (SEQ ID NO: 38)	QQHNSFPLT (SEQ ID NO: 49)
26D5-295-B08	SNAMS (SEQ ID NO: 1)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-295-C08	SNAMS (SEQ ID NO: 1)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-H03	SNAMS (SEQ ID NO: 1)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-295-F07	ENAMS (SEQ ID NO: 7)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-G07	ENYMS (SEQ ID NO: 8)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	AGFGGGDY (SEQ ID NO: 24)	RASQYISSNL A (SEQ ID NO: 34)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-295-E07	SNAMS (SEQ ID NO: 1)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)

Fab/mAb Name	VH-CDR1	VH-CDR2	VH-CDR3	VL-CDR1	VL-CDR2	VL-CDR3
26D5-296-C08	SNAMS (SEQ ID NO: 1)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQYIESNL A (SEQ ID NO: 35)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-295-C07	SNAMS (SEQ ID NO: 1)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-B07	SNAMS (SEQ ID NO: 1)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 33)	AASSLQS (SEQ ID NO: 38)	QQHNSFPLT (SEQ ID NO: 49)
26D5-295-G07	SNYMS (SEQ ID NO: 9)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-D08	SNYMS (SEQ ID NO: 9)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	GGFGGGDY (SEQ ID NO: 26)	RASQYIESNL A (SEQ ID NO: 35)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-F03	SNYMS (SEQ ID NO: 9)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-G08	SNYMS (SEQ ID NO: 9)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	AGFGGGDY (SEQ ID NO: 24)	RASQYIESNL A (SEQ ID NO: 35)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-295-H07	SNYMS (SEQ ID NO: 9)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-F07	SNYMS (SEQ ID NO: 9)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	AGFGGGDY (SEQ ID NO: 24)	RASQYIESNL A (SEQ ID NO: 34)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-G03	SNYMS (SEQ ID NO: 9)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)

Fab/mAb Name	VH-CDR1	VH-CDR2	VH-CDR3	VL-CDR1	VL-CDR2	VL-CDR3
26D5-296-F08	SNYMS (SEQ ID NO: 9)	FIYPGGTTYADS VKG (SEQ ID NO: 18)	GGFGGGDY (SEQ ID NO: 26)	RASQYIESNL A (SEQ ID NO: 35)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-295-A08	ENYMS (SEQ ID NO: 8)	FIYPGGRTYYADS VKG (SEQ ID NO: 14)	AGFGGGDY (SEQ ID NO: 24)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-295-D07	ENYMS (SEQ ID NO: 8)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-D03	SNYMS (SEQ ID NO: 9)	FIYSGGRTYYADS VKG (SEQ ID NO: 19)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSNL A (SEQ ID NO: 29)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-296-C07	SNYMS (SEQ ID NO: 9)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQYISSNL A (SEQ ID NO: 34)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
9C8-VGSKE	SGYYWG (SEQ ID NO: 10)	SIYHSGNTYYSPS LQS (SEQ ID NO: 20)	GGDFDILTGY KGWFE (SEQ ID NO: 27)	RASQGISSAL A (SEQ ID NO: 36)	DASSLES (SEQ ID NO: 42)	QQFNSYPQT (SEQ ID NO: 50)
1H2-K	SGHYWS (SEQ ID NO: 11)	GIYHSGTYYNPS LKS (SEQ ID NO: 21)	DGYDDILTGY NQYFQH (SEQ ID NO: 28)	RASQSVSSSY LA (SEQ ID NO: 37)	GASSRAT (SEQ ID NO: 43)	QQYGSSPFT (SEQ ID NO: 51)
24H1-GQTV	RNYMS (SEQ ID NO: 12)	FIYSGGRTYYADS VKG (SEQ ID NO: 22)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSWL A (SEQ ID NO: 33)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-GVR-Q-FT	RNYMS (SEQ ID NO: 12)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSWL A (SEQ ID NO: 33)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5-GVR-H	RNYMS (SEQ ID NO: 12)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSWL A (SEQ ID NO: 33)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)

Fab/mAb Name	VH-CDR1	VH-CDR2	VH-CDR3	VL-CDR1	VL-CDR2	VL-CDR3
26D5-GV-Q	SNYMS (SEQ ID NO: 9)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSWL A (SEQ ID NO: 33)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)
26D5	SNYMS (SEQ ID NO: 9)	FIYSGGRTYYADS VKG (SEQ ID NO: 17)	GGFGGGDY (SEQ ID NO: 26)	RASQGISSWL A (SEQ ID NO: 33)	AASSLQS (SEQ ID NO: 38)	QQANSFPLT (SEQ ID NO: 46)

[000107] In some embodiments, the antibody or or antibody fragment of the present invention comprises the combinations of VH and VL amino acid sequences provided in Table 2. In some embodiments, the antibody or or antibody fragment of the present invention comprises the combinations of partial heavy chain amino acid sequences and full length light chain amino acid sequences provided in Table 3. In some embodiments, the antibody or or antibody fragment of the present invention comprises the combinations of tandem partial heavy chain amino acid sequences and full length light chain amino acid sequences provided in Table 4.

[000108] In some embodiments, the antibody or antibody fragment of the present invention comprises one or more of the individual variable light chains or variable heavy chains described herein. In some embodiments, the antibody or antibody fragment of the present invention comprises both a variable light chain and a variable heavy chain described herein. In some embodiments, the antibody or antibody fragment of the present invention comprises one variable heavy chain, paired with one variable light chain described herein. In some embodiments, the antibody or antibody fragment of the present invention comprises more than one variable heavy chains, each paired with one variable light chain described herein. In some embodiments, the antibody or antibody fragment of the present invention comprise two variable heavy chains, each paired with one variable light chains described herein.

[000109] The present invention also encompasses antibodies or antibody fragments that comprise VH and VL sequences that are at least about 80%, 85%, 89%, 90%, 95%, or 99% identical to the VH and VL sequences disclosed herein in Table 2.

Table 2: Heavy chain and light chain variable chain amino acid sequences (the underlined portions are the CDRs and the non-underlined portions are the framework regions)

Fab/mAb Name	Heavy Chain Variable Domain (VH)	Light Chain Variable Domain (VL)
26D5-75229-343-A10	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFYIPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYYCARAGFGGPDYWGQGT ^{LVTVSS} (SEQ ID NO: 52)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQQANQFPLTFGGGT ^{KVEIK} (SEQ ID NO: 84)
26D5-75214-343-F06	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFYIPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYYCARAGFGGPDYWGQGT ^{LVTVSS} (SEQ ID NO: 53)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQQANQFPLTFGGGT ^{KVEIK} (SEQ ID NO: 85)
26D5-75202-343-A09	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFYIPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYYCARAGFGGPDYWGQGT ^{LVTVSS} (SEQ ID NO: 54)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQQANQFPLTFGGGT ^{KVEIK} (SEQ ID NO: 86)
26D5-75203-343-B09	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFYIPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYYCARAGFGGPDYWGQGT ^{LVTVSS} (SEQ ID NO: 54)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQQANQFPLTFGGGT ^{KVEIK} (SEQ ID NO: 87)
26D5-75616-348-F10	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFYIPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYYCARAEFGLEDIWGQGT ^{LVTVSS} (SEQ ID NO: 55)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQQANQFPLTFGGGT ^{KVEIK} (SEQ ID NO: 88)
26D5-75768-348-A10	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFYIPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYYCTIGGFGGPDYWGQGT ^{LVTVSS} (SEQ ID NO: 56)	DIQMTQSPSSVSASVGDRVTITCRASQGISSN ^{NQWYQQ} KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQQANQFPLTFGGGT ^{KVEIK} (SEQ ID NO: 89)
26D5-75747-348-D07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFYIPGGRTYYADSVKGRFTISRDN ^{SKNTL}	DIQMTQSPSSVSASVGDRVTITCRASQGISSQ ^{VAWYQQ} KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS}

Fab/mAb Name	Heavy Chain Variable Domain (VH)	Light Chain Variable Domain (VL)
	YLQMNSLRAEDTAVYYCAAAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 57)	SLQPEDFATYYCQQGNEFPLTFGGGTKVEIK (SEQ ID NO: 90)
26D5-75602-348-F04	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNQFSSWRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCAKAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 58)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-75576-348-B03	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNDMSYVRQ APGKGLEWVAIYISGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCVTAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 59)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-75017-343-F04	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 60)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWWQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 91)
26D5-75592-348-A04	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAIAWVRQ APGKGLEWVAIYIPGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCVTAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 61)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNNQWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQGNEFPLTFGGGTKVEIK (SEQ ID NO: 89)
26D5-75746-348-C07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFSSWRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCAAAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 57)	DIQMTQSPSSVSASVGDRVTITCRASQGISSQVAWYQQ KPGKAPKLLIYPASNLSQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANNFPLTFGGGTKVEIK (SEQ ID NO: 92)
26D5-296-A07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 60)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQHNSFPLTFGGGTKVEIK (SEQ ID NO: 93)
26D5-295-B08	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 60)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-295-C08	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDNKNTL	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS

Fab/mAb Name	Heavy Chain Variable Domain (VH)	Light Chain Variable Domain (VL)
	YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 62)	SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-296-H03	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 63)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFS ^{SGSG} TDFTLTIS SLQPEDFATYYCQQANSFPLTFGGG ^{TKVEIK} (SEQ ID NO: 88)
26D5-295-F07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSENAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 64)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFS ^{SGSG} TDFTLTIS SLQPEDFATYYCQQANSFPLTFGGG ^{TKVEIK} (SEQ ID NO: 88)
26D5-296-G07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSENAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 65)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RASQYISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFS ^{SGSG} TDFTLTIS SLQPEDFATYYCQQANSFPLTFGGG ^{TKVEIK} (SEQ ID NO: 94)
26D5-295-E07	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 66)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFS ^{SGSG} TDFTLTIS SLQPEDFATYYCQQANSFPLTFGGG ^{TKVEIK} (SEQ ID NO: 88)
26D5-296-C08	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 66)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RASQYIESNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFS ^{SGSG} TDFTLTIS SLQPEDFATYYCQQANSFPLTFGGG ^{TKVEIK} (SEQ ID NO: 95)
26D5-295-C07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 67)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFS ^{SGSG} TDFTLTIS SLQPEDFATYYCQQANSFPLTFGGG ^{TKVEIK} (SEQ ID NO: 88)
26D5-296-B07	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 68)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFS ^{SGSG} TDFTLTIS SLQPEDFATYYCQQHNSFPLTFGGG ^{TKVEIK} (SEQ ID NO: 93)
26D5-295-G07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL}	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RASQGISSNLA ^{WYQQ} KPGKAPKLLIYAASSLQSGVPSRFS ^{SGSG} TDFTLTIS

Fab/mAb Name	Heavy Chain Variable Domain (VH)	Light Chain Variable Domain (VL)
	YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 69)	SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-296-D08	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 69)	DIQMTQSPSSVSASVGDRTVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 95)
26D5-296-F03	EVQLVESGGGLIQPGGSLRLSCAASGFTQVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 70)	DIQMTQSPSSVSASVGDRTVTITCRASQGISNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-296-G08	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 70)	DIQMTQSPSSVSASVGDRTVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 95)
26D5-295-H07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 71)	DIQMTQSPSSVSASVGDRTVTITCRASQGISNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-296-F07	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 71)	DIQMTQSPSSVSASVGDRTVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 94)
26D5-296-G03	EVQLVESGGGLIQPGGSLRLSCAASGFTQVSSNYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 72)	DIQMTQSPSSVSASVGDRTVTITCRASQGISNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-296-F08	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 73)	DIQMTQSPSSVSASVGDRTVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 95)
26D5-295-A08	EVQLVESGGGLIQPGGSLRLSCAASGFTVSENIMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL	DIQMTQSPSSVSASVGDRTVTITCRASQGISNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS

Fab/mAb Name	Heavy Chain Variable Domain (VH)	Light Chain Variable Domain (VL)
	YLQMNSLRAEDTAVYYCARAGFGGGDYWGQGLTVTVSS (SEQ ID NO: 74)	SLQPEDFATYYCQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-295-D07	EVQLVESGGGLIQPGGSLRLSCAASGFQVSENYSMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGFGGGDYWGQGLTVTVSS (SEQ ID NO: 75)	DIQMTQSPSSVSASVGDRTVITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-296-D03	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGETFYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGFGGGDYWGQGLTVTVSS (SEQ ID NO: 76)	DIQMTQSPSSVSASVGDRTVITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSFPLTFGGGTKVEIK (SEQ ID NO: 88)
26D5-296-C07	EVQLVESGGGLIQPGGSLRLSCAASGITVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGFGGGDYWGQGLTVTVSS (SEQ ID NO: 77)	DIQMTQSPSSVSASVGDRTVITCRASQYISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSFPLTFGGGTKVEIK (SEQ ID NO: 94)
9C8-VGSKE	QVQLQESGPGLVKPSSETLSLTCAVSGYSISSGHHYWSWIR QPPGKGLEWIGSIYHSGNTYYSPSLQSRVTISVDTSKNQ FSLKLSSTAAATAVYYCARGGDFDILTGYKGFWEFPGW QGLTVTVSS (SEQ ID NO: 78)	AIQLTQSPSSLSASVGDRTVITCRASQGISSALAWYQQ KPGKAPKLLIYDASSLESQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQFNQNSYPQTFGGGTKVEIK (SEQ ID NO: 96)
1H2-K	QVQLQESGPGLVKPSSETLSLTCAVSGYSISSGHHYWSWIR QPPGKGLEWIGGIYHSGTYYNPSLKSRTISVDTSKNQ FSLKLSSTAAATAVYYCARDGYDILTGYYNQYFQHWG QGLTVTVSS (SEQ ID NO: 79)	EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYCQQYGSSPFTFGPGTKVDIK (SEQ ID NO: 97)
24H1-GQTV	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYMSWVRQ APGKGLEWVSFIYSGGSTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGFGGGDYWGQGLTVTVSS (SEQ ID NO: 80)	DIQMTQSPSSVSASVGDRTVITCRASQGISSNLAWYQH KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSFPLTFGGGTKVEIK (SEQ ID NO: 98)
26D5-GVR-Q-FT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGFGGGDYWGQGLTVTVSS (SEQ ID NO: 81)	DIQMTQSPSSVSASVGDRTVITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSFPLTFGGGTKVEIK (SEQ ID NO: 99)
26D5-GVR-H	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDNKNTL	DIQMTQSPSSVSASVGDRTVITCRASQGISSNLAWYQH KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS

Fab/mAb Name	Heavy Chain Variable Domain (VH)	Light Chain Variable Domain (VL)
	YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 81)	SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 98)
26D5-GV-Q	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 82)	DIQMTQSPSSVSASVGDRVTITCRASQGISWLA WYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 99)
26D5	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARGGGGGDYWGQGLTVTVSS (SEQ ID NO: 83)	DIQMTQSPSSVSASVGDRVTITCRASQGISWLA WYQH KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 98)

[000110] The present invention also encompasses antibodies or antibody fragments that comprise partial heavy chain amino acid sequences and full length light chain amino acid sequences that are at least about 80%, 85%, 89%, 90%, 95%, or 99% identical to the partial heavy chain amino acid sequences and full length light chain amino acid sequences disclosed herein in Table 3. The present invention also encompasses antibodies or antibody fragments, *e.g.*, antibody Fab fragments, that comprise, consist essentially of, or consist of any one of the N-terminal portion of the heavy chains in Table 3 in combination with any one of the full length light chains in Table 3. The present invention also encompasses antibodies or antibody fragments, *e.g.*, antibody Fab fragments, that comprise, consist essentially of, or consist of any one of the indicated pairs of an N-terminal Portion of the heavy chain in Table 3 and a full length light chain in Table 3. The present invention also encompasses antibodies or antibody fragments, *e.g.*, antibody Fab fragments, that comprise, consist essentially of, or consist of the sequence of SEQ ID NO: 106 and the sequence of SEQ ID NO: 164. The present invention also encompasses antibodies or antibody fragments, *e.g.*, antibody Fab fragments, that comprise the sequence of SEQ ID NO: 106 and the sequence of SEQ ID NO: 164. The present invention also encompasses antibodies or antibody fragments, *e.g.*, antibody Fab fragments, that consist essentially of the sequence of SEQ ID NO: 106 and the sequence of SEQ ID NO: 164. The present invention also encompasses antibodies or antibody fragments, *e.g.*, antibody Fab fragments, that consist of the sequence of SEQ ID NO: 106 and the sequence of SEQ ID NO: 164.

Table 3: Fab Sequences (the non-bolded portions are the variable regions with CDRs being underlined and framework regions not being underlined; bolded amino acids are the constant regions for each of the heavy and light chain portions of the Fab)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
26D5- 75229- 343-A10- Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGPDYWGQGT LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV VS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 100)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TTLTIS SLQPEDFATYYCQQANQFPLTFGGGTKEIKRTVAAPS VFI FP PSDEQLKSGTASVCLLN FN FYP REAKVQWKVDN ALQSGNSQESVTEQDSKDS TY SL ST LT LSKADYEKHK VYACEVTHQGLSSPVT KSFNRGEC (SEQ ID NO: 160)
26D5- 75229- 343-A10- Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGPDYWGQGT LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV VS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKCDKTH (SEQ ID NO: 101)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TTLTIS SLQPEDFATYYCQQANQFPLTFGGGTKEIKRTVAAPS VFI FP PSDEQLKSGTASVCLLN FN FYP REAKVQWKVDN ALQSGNSQESVTEQDSKDS TY SL ST LT LSKADYEKHK VYACEVTHQGLSSPVT KSFNRGEC (SEQ ID NO: 160)
26D5- 75214- 343-F06- Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGPDYWGQGT LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV VS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 102)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TTLTIS SLQPEDFATYYCQQANQFPLTFGGGTKEIKRTVAAPS VFI FP PSDEQLKSGTASVCLLN FN FYP REAKVQWKVDN ALQSGNSQESVTEQDSKDS TY SL ST LT LSKADYEKHK VYACEVTHQGLSSPVT KSFNRGEC (SEQ ID NO: 161)
26D5- 75214- 343-F06- Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGPDYWGQGT LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV VS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 102)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TTLTIS SLQPEDFATYYCQQANQFPLTFGGGTKEIKRTVAAPS VFI FP PSDEQLKSGTASVCLLN FN FYP REAKVQWKVDN ALQSGNSQESVTEQDSKDS TY SL ST LT LSKADYEKHK VYACEVTHQGLSSPVT KSFNRGEC (SEQ ID NO: 161)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	TYICNVNHKPSNTKVKDKRVEPKSCDKTH (SEQ ID NO:103)	VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:161)
26D5-75202-343-A09-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVS ^{YI} YPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLR ^{AEDT} AVYYCARAGFGG ^{DDYWGQ} GLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVKDKRVEPKSC (SEQ ID NO:104)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQGI} SNLAWYQQKPGKAPK ^{LLIYA} ASSLQSGVPS ^{RFSGSGGTDFTLTIS} SLQPEDFA ^{TYCQQAN} E ^{FPLTFGGG} TK ^{VEIKRTVAAPS} V ^{FI} FPSPDEQLKSGTASV ^{CLLN} FN ^{FYP} REAKVQW ^{KVDN} ALQSGNSQESVTEQDSK ^{DSTYSLS} STLTLSKADY ^{EKKH} VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:162)
26D5-75202-343-A09-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVS ^{YI} YPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLR ^{AEDT} AVYYCARAGFGG ^{DDYWGQ} GLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVKDKRVEPKSCDKTH (SEQ ID NO:105)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQGI} SNLAWYQQKPGKAPK ^{LLIYA} ASSLQSGVPS ^{RFSGSGGTDFTLTIS} SLQPEDFA ^{TYCQQAN} E ^{FPLTFGGG} TK ^{VEIKRTVAAPS} V ^{FI} FPSPDEQLKSGTASV ^{CLLN} FN ^{FYP} REAKVQW ^{KVDN} ALQSGNSQESVTEQDSK ^{DSTYSLS} STLTLSKADY ^{EKKH} VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:162)
26D5-75203-343-B09-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVS ^{YI} YPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLR ^{AEDT} AVYYCARAGFGG ^{DDYWGQ} GLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVKDKRVEPKSC (SEQ ID NO:104)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQGI} SNLAWYQQKPGKAPK ^{LLIYA} ASTLQSGVPS ^{RFSGSGGTDFTLTIS} SLQPEDFA ^{TYCQQAN} E ^{FPLTFGGG} TK ^{VEIKRTVAAPS} V ^{FI} FPSPDEQLKSGTASV ^{CLLN} FN ^{FYP} REAKVQW ^{KVDN} ALQSGNSQESVTEQDSK ^{DSTYSLS} STLTLSKADY ^{EKKH} VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:163)
26D5-75203-343-B09-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVS ^{YI} YPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLR ^{AEDT} AVYYCARAGFGG ^{DDYWGQ} GLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVKDKRVEPKSCDKTH (SEQ ID NO:105)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQGI} SNLAWYQQKPGKAPK ^{LLIYA} ASTLQSGVPS ^{RFSGSGGTDFTLTIS} SLQPEDFA ^{TYCQQAN} E ^{FPLTFGGG} TK ^{VEIKRTVAAPS} V ^{FI} FPSPDEQLKSGTASV ^{CLLN} FN ^{FYP} REAKVQW ^{KVDN} ALQSGNSQESVTEQDSK ^{DSTYSLS} STLTLSKADY ^{EKKH} VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:163)
26D5-75616-	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVS ^{FI} YPGGRTYYADSVKGRFTISRDN ^{SKNTL}	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQGI} SNLAWYQQKPGKAPK ^{LLIYA} ASSLQSGVPS ^{RFSGSGGTDFTLTIS}

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
348-F10-Fab-SHORT	YLMNSLRAEDTAVYICARAEFGLEDIWGGTLVTSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 106)	SLQPEDFATYYCQANSFPLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-75616-348-F10-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFWSVRQ APGKGLEWVSYIYPGGRTYYADSVKGRFTISRDN SKNTL YLMNSLRAEDTAVYICARAEFGLEDIWGGTLVTSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 107)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLAAYQQ KPGKAPKLLIYAYASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQANSFPLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-75768-348-A10-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFWSVRQ APGKGLEWVSYIYPGGRTYYADSVKGRFTISRDN SKNTL YLMNSLRAEDTAVYICTIGGFGGDIWGQGTIVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 108)	DIQMTQSPSSVSASVGDRVTITCRASQGISNNAQWYQQ KPGKAPKLLIYAYASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQGNFPLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 165)
26D5-75768-348-A10-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFWSVRQ APGKGLEWVSYIYPGGRTYYADSVKGRFTISRDN SKNTL YLMNSLRAEDTAVYICTIGGFGGDIWGQGTIVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 109)	DIQMTQSPSSVSASVGDRVTITCRASQGISNNAQWYQQ KPGKAPKLLIYAYASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQGNFPLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 165)
26D5-75747-348-D07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFWSVRQ APGKGLEWVSYIYSGGRTYYADSVKGRFTISRDN SKNTL YLMNSLRAEDTAVYICAAAGFGGDIWGQGTIVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ	DIQMTQSPSSVSASVGDRVTITCRASQGISNNAQWYQQ KPGKAPKLLIYAYASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQGNFPLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	TYICNVNHHKPSNTKVDKRVPEPKSC (SEQ ID NO: 110)	VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 166)
26D5-75747-348-D07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFSSWVRQ APGKGLEWVSYYISGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICAAAGFGGDDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHHKPSNTKVDKRVPEPKSCDKTH (SEQ ID NO: 111)	DIQMTQSPSSVSASVGDRTVTITCRASQGISSNLAWYQQ KPGKAPKLLIYYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQGNEFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINFPYPRYAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 166)
26D5-75602-348-F04-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNQFSSWVRQ APGKGLEWVSYYFPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICAAAGFGGDDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHHKPSNTKVDKRVPEPKSC (SEQ ID NO: 112)	DIQMTQSPSSVSASVGDRTVTITCRASQGISSNLAWYQQ KPGKAPKLLIYYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSEFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINFPYPRYAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-75602-348-F04-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNDMSYVRQ APGKGLEWVSYYFPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICAAAGFGGDDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHHKPSNTKVDKRVPEPKSCDKTH (SEQ ID NO: 113)	DIQMTQSPSSVSASVGDRTVTITCRASQGISSNLAWYQQ KPGKAPKLLIYYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSEFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINFPYPRYAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-75576-348-B03-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNDMSYVRQ APGKGLEWVAYIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICVTAAGFGGDDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHHKPSNTKVDKRVPEPKSC (SEQ ID NO: 114)	DIQMTQSPSSVSASVGDRTVTITCRASQGISSNLAWYQQ KPGKAPKLLIYYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSEFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINFPYPRYAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-75576-	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNDMSYVRQ APGKGLEWVAYIYSGGRTYYADSVKGRFTISRDN SKNTL	DIQMTQSPSSVSASVGDRTVTITCRASQGISSNLAWYQQ KPGKAPKLLIYYAASSLQSGVPSRFSGSGSGTDFTLTIS

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
348-B03-Fab-LONG	YLMNSLRAEDTAVYVCVTAGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 115)	SLQPEDFATYYCQANSFPLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-75017-343-F04-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSVFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYVCARAGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 116)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQ} GISSN ^{LAW} WQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQANSFPLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 167)
26D5-75017-343-F04-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSVFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYVCARAGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 117)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQ} GISSN ^{LAW} WQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQANSFPLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 167)
26D5-75592-348-A04-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAIA ^{WVRQ} APGKGLEWVAIYYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYVCVTAGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 118)	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQ} GISSN ^{NQW} YQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQQGN ^{EF} PLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 165)
26D5-75592-348-A04-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAIA ^{WVRQ} APGKGLEWVAIYYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLMNSLRAEDTAVYVCVTAGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ	DIQMTQSPSSVSASVGD ^{RV} TI ^{TC} RA ^{SQ} GISSN ^{NQW} YQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD ^{FTLTIS} SLQPEDFATYYCQQGN ^{EF} PLTFGGGKVEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHK

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 119) EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFSAWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYICAAAGFGGDIWGQGTLVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 110)	VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 165) DIQMTQSPSSVSASVGDRVTITCRASQGISSQVAWYQQ KPGKAPKLLIYPASNLWSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQANFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 168)
26D5-75746-348-C07-Fab-SHORT		
26D5-75746-348-C07-Fab-LONG	TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 111) EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFSAWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYICAAAGFGGDIWGQGTLVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 111)	VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 168) DIQMTQSPSSVSASVGDRVTITCRASQGISSQVAWYQQ KPGKAPKLLIYPASNLWSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQANFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 168)
26D5-296-A07-Fab-SHORT	TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 116) EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFSAWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYICARAGFGGDIWGQGTLVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 116)	VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 169) DIQMTQSPSSVSASVGDRVTITCRASQGISSQVAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQHNSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 169)
26D5-296-A07-Fab-LONG	TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 117) EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAFSAWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYICARAGFGGDIWGQGTLVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 117)	VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 169) DIQMTQSPSSVSASVGDRVTITCRASQGISSQVAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQHNSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 169)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
26D5-295-B08-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARAGFGG ^Q GWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 116)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-B08-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARAGFGG ^Q GWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKCDKTH (SEQ ID NO: 117)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-C08-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMS ^{WVRQ} APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARGFGG ^Q GWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 120)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-C08-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMS ^{WVRQ} APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARGFGG ^Q GWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKCDKTH (SEQ ID NO: 121)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-H03-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARGFGG ^Q GWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 122)	ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-H03-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 123)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINFPYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-F07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 124)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINFPYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-F07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 125)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINFPYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-G07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARAGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 126)	DIQMTQSPSSVSASVGDRVTITCRASQYISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINFPYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 170)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
26D5-296-G07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSENYSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDNKNTL YLMNSLRAEDTAVYICARAGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSCDKTH (SEQ ID NO: 127)	DIQMTQSPSSVSASVGDRVTITCRASQYISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 170)
26D5-295-E07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDNKNTL YLMNSLRAEDTAVYICARGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 128)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-E07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDNKNTL YLMNSLRAEDTAVYICARGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSCDKTH (SEQ ID NO: 129)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-C08-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDNKNTL YLMNSLRAEDTAVYICARGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 128)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 171)
26D5-296-C08-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFQVSSNAMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDNKNTL YLMNSLRAEDTAVYICARGFGGDIWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 129)	ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 171)
26D5-295-C07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARGGGG ^{YWGQGLTVTVSSA} STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSC (SEQ ID NO: 130)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFS ^{GGSGGTDFTLTIS} SLQPEDFATYYCQANSFPLT ^{TFGGGTKEIKRTVAAPS} VFI^{FP}PSDEQLKSGTASVCLLN^{NY}FPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-C07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARGGGG ^{YWGQGLTVTVSSA} STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 131)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFS ^{GGSGGTDFTLTIS} SLQPEDFATYYCQANSFPLT ^{TFGGGTKEIKRTVAAPS} VFI^{FP}PSDEQLKSGTASVCLLN^{NY}FPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-B07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARAGFGG ^{YWGQGLTVTVSSA} STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSC (SEQ ID NO: 132)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFS ^{GGSGGTDFTLTIS} SLQPEDFATYYCQOHNSFPLT ^{TFGGGTKEIKRTVAAPS} VFI^{FP}PSDEQLKSGTASVCLLN^{NY}FPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 169)
26D5-296-B07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ^{WVRQ} APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN ^{SKNTL} YLQMNSLRAEDTAVYICARAGFGG ^{YWGQGLTVTVSSA} STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 133)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFS ^{GGSGGTDFTLTIS} SLQPEDFATYYCQOHNSFPLT ^{TFGGGTKEIKRTVAAPS} VFI^{FP}PSDEQLKSGTASVCLLN^{NY}FPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 169)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
26D5-295-G07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 134)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLA ^{WY} QQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-G07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKCDKTH (SEQ ID NO: 135)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLA ^{WY} QQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-D08-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 134)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLA ^{WY} QQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 171)
26D5-296-D08-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKCDKTH (SEQ ID NO: 135)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLA ^{WY} QQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 171)
26D5-296-F03-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS	DIQMTQSPSSVSASVGDRVTITCRASQGISNLA ^{WY} QQ KPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDN

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSC (SEQ ID NO: 136)	ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-F03-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFGQVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLR AEDTAVYYCARAGFGG DYWGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 137)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFAFYCCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-G08-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFGQVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLR AEDTAVYYCARAGFGG DYWGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSC (SEQ ID NO: 136)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFAFYCCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 171)
26D5-296-G08-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFGQVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLR AEDTAVYYCARAGFGG DYWGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 137)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFAFYCCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 171)
26D5-295-H07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLR AEDTAVYYCARAGFGG DYWGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHHKPSNTKVDKRVKPKSC (SEQ ID NO: 138)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFAFYCCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
26D5-295-H07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSCDKTH (SEQ ID NO: 139)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-F07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 138)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 170)
26D5-296-F07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSCDKTH (SEQ ID NO: 139)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 170)
26D5-296-G03-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 140)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-G03-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARAGFGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVVS	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFI FPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 141)	ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-F08-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGETYYADSVKGRFTISRDN SKNTL YLMNSLRAEDTAVYICARGGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 142)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSFGSGSGTDFLTITIS SLQPEDFATYYCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINFPYPRKAVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 171)
26D5-296-F08-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQ APGKGLEWVSFIYPGGETYYADSVKGRFTISRDN SKNTL YLMNSLRAEDTAVYICARGGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 143)	DIQMTQSPSSVSASVGDRVTITCRASQYIESNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSFGSGSGTDFLTITIS SLQPEDFATYYCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINFPYPRKAVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 171)
26D5-295-A08-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSENMYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLMNSLRAEDTAVYICARAGFGGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 144)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSFGSGSGTDFLTITIS SLQPEDFATYYCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINFPYPRKAVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-A08-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSENMYMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLMNSLRAEDTAVYICARAGFGGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 145)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSFGSGSGTDFLTITIS SLQPEDFATYYCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNINFPYPRKAVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
26D5-295-D07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFGQVSENYSMSWVRQ APGKGLEWVSFIYSGGRTFYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 146)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSEFPLTFGGGTKEIKRTVAAPS VFIIPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-295-D07-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFGQVSENYSMSWVRQ APGKGLEWVSFIYSGGRTFYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKCDKTH (SEQ ID NO: 147)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSEFPLTFGGGTKEIKRTVAAPS VFIIPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-D03-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYSMSWVRQ APGKGLEWVSFIYSGGETFYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 148)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSEFPLTFGGGTKEIKRTVAAPS VFIIPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-D03-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYSMSWVRQ APGKGLEWVSFIYSGGETFYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVKPKCDKTH (SEQ ID NO: 149)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSEFPLTFGGGTKEIKRTVAAPS VFIIPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 164)
26D5-296-C07-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGITVSSNYSMSWVRQ APGKGLEWVSFIYSGGRTFYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYICARGGFGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLAWYQQ KPGKAPKLLIYAASLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQANSEFPLTFGGGTKEIKRTVAAPS VFIIPPSDEQLKSGTASVCLLNINNFYPREAKVQWKVDN

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHNKPSNTKVDKRVKPKSC (SEQ ID NO: 150)	ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 170)
26D5-296-C07-Fab-LONG	EVQLVESGGGLIQPGSLRLSCAASGITVSSNYSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDNKNTL YLMNSLRAEDTAVYICARGGGGQDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPPSSSLGTQ TYICNVNHNKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 151)	DIQMTQSPSSVSASVGDRVTITCRASQYISSNLAWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFAFYCCQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 170)
9C8-VGSKE-Fab-SHORT	QVQLQESGPGLVKPSSETLSLTCAVSGYSISSGYYWGWR QPPGKGLEWIGSIYHSGNTYYSPSLQSRVTISVDTSKNQ FSLKLSSTVTAADTAVYICARGGDFDILTGYKKGWFEPPWG QGTLLTVTVSS ASTKGPSVFFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV TVPPSSSLGTQTYICNVNHNKPSNTKVDKRVKPKSC (SEQ ID NO: 152)	AIQLTQSPSSLSASVGDRVTITCRASQGISALAWYQQ KPGKAPKLLIYDASSLESQVPSRFSGSGSGTDFTLTIS SLQPEDFAFYCCQFNSYPQTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 172)
9C8-VGSKE-Fab-LONG	QVQLQESGPGLVKPSSETLSLTCAVSGYSISSGYYWGWR QPPGKGLEWIGSIYHSGNTYYSPSLQSRVTISVDTSKNQ FSLKLSSTVTAADTAVYICARGGDFDILTGYKKGWFEPPWG QGTLLTVTVSS ASTKGPSVFFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV TVPPSSSLGTQTYICNVNHNKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 153)	AIQLTQSPSSLSASVGDRVTITCRASQGISALAWYQQ KPGKAPKLLIYDASSLESQVPSRFSGSGSGTDFTLTIS SLQPEDFAFYCCQFNSYPQTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 172)
1H2-K-Fab-SHORT	QVQLQESGPGLVKPSSETLSLTCAVSGYSISSGHHYWSWR QPPGKGLEWIGGIYHSGTYYNPSLKSRTVISVDTSKNQ FSLKLSSTVTAADTAVYICARGGDIYDILTYNQNQYFQHWG QGTLLTVTVSS ASTKGPSVFFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV TVPPSSSLGTQTYICNVNHNKPSNTKVDKRVKPKSC (SEQ ID NO: 154)	EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTIS SRLEPEDFAFYCCQYGSPPFTFGPGTKVDIKRTVAAP SVFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVD NALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 173)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
1H2-K-Fab-LONG	QVQLQESGPGLVKPSSETLSLTCAVSGYSISSGHYWSWIR QPPGKLEWIGGIYHSGTTYINPSLKSRVTISVDTSKNQ FSLKLSVTAADTAVYYCARDGYDILTGYNQYFQHWG QGTLTVSSSA ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSNWNGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTH (SEQ ID NO: 155)	EIVLTQSPGTLSPGERATLSCRASQSVSSYLAWYQ QKPGAPRLIIYGASSRATGIPDRFSGSGGTDFTLTI SRLEPEDFAVYCCQQYGSSPFTFGPGTKVDIKRTVAAP SVFI PPSDEQLKSGTASVCLLN NFYPREAKVQWKVD NALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 173)
24H1-GQTV-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYSWVRQ APGKGLEWVSFIYSGGSTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 156)	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQH KPGKAPKLLIIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFAVYCCQANSEFPLTFGGGKVEIKRTVAAPS VFI PPSDEQLKSGTASVCLLN NFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 174)
24H1-GQTV-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYSWVRQ APGKGLEWVSFIYSGGSTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSCDKTH (SEQ ID NO: 157)	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQH KPGKAPKLLIIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFAVYCCQANSEFPLTFGGGKVEIKRTVAAPS VFI PPSDEQLKSGTASVCLLN NFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 174)
26D5-GVR-Q-FT-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYSWVRQ APGKGLEWVSFIYSGGSTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC (SEQ ID NO: 158)	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ KPGKAPKLLIIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFAVYCCQANSEFPLTFGGGKVEIKRTVAAPS VFI PPSDEQLKSGTASVCLLN NFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 175)
26D5-GVR-Q-FT-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYSWVRQ APGKGLEWVSFIYSGGSTYYADSVKGRFTISRDNKNTL YLQMNSLRAEDTAVYYCARGGGGDIWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ KPGKAPKLLIIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFAVYCCQANSEFPLTFGGGKVEIKRTVAAPS VFI PPSDEQLKSGTASVCLLN NFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 175)

Fab/mAb Name	N-terminal Portion of the Heavy Chain	Full Length Light Chain
	WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVEPKCDKTH (SEQ ID NO: 159)	ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 175)
26D5-GVR-H-Fab-SHORT	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDNKNTL YLMNSLRAEDTAVYICARGGGGDIWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVYS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVEPKSC (SEQ ID NO: 158)	DIQMTQSPSSVSASVGDRVTITCRASQGISWLAWYQH KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 174)
26D5-GVR-H-Fab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSRNYSWVRQ APGKGLEWVSFIYSGGRYYADSVKGRFTISRDNKNTL YLMNSLRAEDTAVYICARGGGGDIWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVYS WNSGALTSGVHTFPAVLQSSGLYSLSSVWTVPSSSLGTQ TYICNVNHKPSNTKVDKRVEPKCDKTH (SEQ ID NO: 159)	DIQMTQSPSSVSASVGDRVTITCRASQGISWLAWYQH KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKEIKRTVAAPS VFIFFPSDEQLKSGTASVCLLNFFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 174)

[000111] The present invention also encompasses antibodies or antibody fragments that comprise tandem partial heavy chain amino acid sequences and full length light chain amino acid sequences that are at least about 80%, 85%, 89%, 90%, 95%, or 99% identical to the the partial heavy chain amino acid sequences and full length light chain amino acid sequences disclosed herein in Table 4.

Table 4 – Tandem Fab sequences (the non-bolded portions are the variable chains with CDRs being underlined and framework regions not being underlined; bolded amino acids are the constant regions for each of the heavy and light chain portions of the Fab; the double underlined portions are the linker sequences)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
26D5-75229-343-A10-TanFab	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ APGKGLEWVSYYIPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLR AEDTAVYYCARAGFGGPDYWGQGTLLTVSSA STKGPSVFPFLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDRVEPKSCASTKGPEVQLVESGG GLIQPGGSLRLSCAASGFTVSSNAMSWVRQAPGKGLEWV SYIYPGGRTYYADSVKGRFTISRDN SKNTLLYLQMNSLRA EDTAVYYCARAGFGGPDYWGQGTLLTVSS ASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK PSNTKVDRVEPKSC (SEQ ID NO: 176)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLPEDFATYYCQANQPFLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 160)
26D5-75229-343-A10-TanFab-long	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ APGKGLEWVSYYIPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLR AEDTAVYYCARAGFGGPDYWGQGTLLTVSSA STKGPSVFPFLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDRVEPKSCASTKGPSVFPLAPEV QLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQAP GKGLEWVSYYIPGGRTYYADSVKGRFTISRDN SKNTLLYL QMNSLR AEDTAVYYCARAGFGGPDYWGQGTLLTVSS AST KGPSVFPFLAPSSKSTSGGTAALGCLVKDYFPEPTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHKPSNTKVDRVEPKSC (SEQ ID NO: 177)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLPEDFATYYCQANQPFLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 160)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
26D5-75229-343-A10-TanFab-ELQ	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVS YIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGPDYWGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC LEESAEEA QEGE LEEVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WV RQAPGKGLEWVS YIYPGGRTYYADSVKGRFTISRDN SKN TLYLQMNSLRAEDTAVYYCARAGFGGPDYWGQGT LVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV VWSNGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLG TQTYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 178)	DIQMTQSPSSVSASVGDRVTITCRASQGIS SNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFS SGSG TDFTLT TISSLPEDFATYYCQ QANQFPLTFGGGT KVEIKRTVAAPS VFIFPPSDEQLKSGTASV VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 160)
26D5-75229-343-A10-TanFab-G4S	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVS YIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGPDYWGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC GGGGSGGGSGGGG EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVS YIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGPDYWGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 179)	DIQMTQSPSSVSASVGDRVTITCRASQGIS SNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFS SGSG TDFTLT TISSLPEDFATYYCQ QANQFPLTFGGGT KVEIKRTVAAPS VFIFPPSDEQLKSGTASV VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 160)
26D5-75616-348-F10-TanFab	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVS FIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAEFGLEDI WGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC ASTKGPEVLVESGG	DIQMTQSPSSVSASVGDRVTITCRASQGIS SNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFS SGSG TDFTLT TISSLPEDFATYYCQ QANSFPLTFGGGT KVEIKRTVAAPS VFIFPPSDEQLKSGTASV VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
	GLIQGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWV SFIYPGGRTYYADSVKGRFTISRDN SKNTLY LQMN SLRA EDTAVYYCARAEFGLEDIWGGT LT TVSSA STKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVT VS WNSGALTSG VHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHK PSNTKVDKRVPEKSC (SEQ ID NO: 180)	STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 164)
26D5-75616-348-F10-TanFab-long	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMN SLRAEDT AVYYCARAEFGLEDIWGGT LT TVSSA STKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVT VS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC ASTKGPSVFPEL AEV QLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ AP GKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTLYL QMN SLRAEDT AVYYCARAEFGLEDIWGGT LT TVSSA ST KGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVT VS WN SGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTY ICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 181)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQANSFPLTFGGGT KVEIKRTVAAPS VFI FP PSDEQLKSGTASV V V C L L NNFY P R E A K V Q W K V D N A L Q S N S Q E S V T E Q D S K D STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 164)
26D5-75616-348-F10-TanFab-ELQ	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMN SLRAEDT AVYYCARAEFGLEDIWGGT LT TVSSA STKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVT VS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC <u>LEELQLEESA</u> <u>EAQEGE</u> <u>LEEVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS</u> WV <u>RQAPGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN</u> SKN <u>TL</u> <u>YLQMN</u> SLRAEDT AVYYCARAEFGLEDIWGGT LT TVS S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V T V P S S L G TQTYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 182)	DIQMTQSPSSVSASVGDRVTITCRASQGISSNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQANSFPLTFGGGT KVEIKRTVAAPS VFI FP PSDEQLKSGTASV V C L L NNFY P R E A K V Q W K V D N A L Q S N S Q E S V T E Q D S K D STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 164)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
26D5-75616-348-F10-TanFab-G4S	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ¹⁸³ WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ¹⁸³ SKNTL YLQMNSLR ¹⁸³ AE ¹⁸³ DTAVYYCARAEFGLEDIWGQGT ¹⁸³ LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 183) EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ¹⁸³ WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ¹⁸³ SKNTL YLQMNSLR ¹⁸³ AE ¹⁸³ DTAVYYCARAEFGLEDIWGQGT ¹⁸³ LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 183)	DIQMTQSPSSVSASVGDRVTITCRASQGIS ¹⁶⁴ NLA WYQQKPGKAPKLLIIYAASLQSGVPSRFS ¹⁶⁴ SGSG TDFTLT ¹⁶⁴ ISSLPEDFATYYCQQANSF ¹⁶⁴ PLTFGGGT KVEIKRTVAAPS ¹⁶⁴ VFIP ¹⁶⁴ PSDEQLKSGTAS ¹⁶⁴ VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFN¹⁶⁴RGEC (SEQ ID NO: 164)
26D5-75203-343-B09-TanFab	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ¹⁸⁴ WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ¹⁸⁴ SKNTL YLQMNSLR ¹⁸⁴ AE ¹⁸⁴ DTAVYYCARAGFGGDIWGQGT ¹⁸⁴ LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 184) GLIQPGGSLRLSCAASGFTVSSNAMS ¹⁸⁴ WVRQAPGKGLEWV SYIYPGGRTYYADSVKGRFTISRDN ¹⁸⁴ SKNTLYLQMN ¹⁸⁴ SLRA EDTAVYYCARAGFGGDIWGQGT ¹⁸⁴ LVTVSSA LAPSSKSTSGGTAALGCLVKDYFPEPTVSN¹⁸⁴SGALTSG VHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHK PSNTKVDKRVPEKSC (SEQ ID NO: 184)	DIQMTQSPSSVSASVGDRVTITCRASQGIS ¹⁶³ NLA WYQQKPGKAPKLLIIYAASLQSGVPSRFS ¹⁶³ SGSG TDFTLT ¹⁶³ ISSLPEDFATYYCQQANEF ¹⁶³ PLTFGGGT KVEIKRTVAAPS ¹⁶³ VFIP ¹⁶³ PSDEQLKSGTAS ¹⁶³ VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFN¹⁶³RGEC (SEQ ID NO: 163)
26D5-75203-343-B09-TanFab-long	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ¹⁸⁴ WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ¹⁸⁴ SKNTL YLQMNSLR ¹⁸⁴ AE ¹⁸⁴ DTAVYYCARAGFGGDIWGQGT ¹⁸⁴ LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 184) QLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ¹⁸⁴ WVRQAP	DIQMTQSPSSVSASVGDRVTITCRASQGIS ¹⁶³ NLA WYQQKPGKAPKLLIIYAASLQSGVPSRFS ¹⁶³ SGSG TDFTLT ¹⁶³ ISSLPEDFATYYCQQANEF ¹⁶³ PLTFGGGT KVEIKRTVAAPS ¹⁶³ VFIP ¹⁶³ PSDEQLKSGTAS ¹⁶³ VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFN¹⁶³RGEC (SEQ ID NO: 163)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
	GKGLEWVS ^{YIYPGGRTYYADSVKGRFTISRDN} SKNTLYLQMN ^{SLRAEDTAVYYCARAGFGGDYWGQGLTVTVSS} ASTKGP ^{SVFFPLAPSSKSTSGGTAALGCLVKDYFPEP} TVTSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS ^{SSLGTQTYICNVNHKPSNTKVDKRV} EPKSC (SEQ ID NO:185)	DIQMTQSPSSVSASVGD ^{RVTITCRASQGI} SSNLA ^{WYQQKPGKAPKLLIIYAAS} TLQSGVPSRFS ^{GSGSGTDFTLTIS} SLQPEDFATYYCQQANEF ^{PLTFGGGT} KVEIKRTVAAPSVFIFPPSDEQLKSGTASV ^{VVCLLN} NNFYPREAKVQWKVDNALQSGNSQESVTEQ ^{DSKDSTYSL} SS ^{TLT} LSKADYEKHKVYACEVTHQGLSSPVT ^{KSFNRGEC} (SEQ ID NO: 163)
26D5-75203-343-B09-TanFab-ELQ	EVQLVESGGGLIQPGGSLRLS ^{CAASGFTVSSNAMS} WVRQAPGKGLEWVS ^{YIYPGGRTYYADSVKGRFTISRDN} SKNTLYLQMN ^{SLRAEDTAVYYCARAGFGGDYWGQGLTVTVSS} A ^{STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEP} TVTSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS ^{SSLGTQTYICNVNHKPSNTKVDKRV} EPKSC ^{LEEVQLVESGGGLIQPGGSLRLS} CAASGFTVSSNAMS ^{WVRQ} RQAPGKGLEWVS ^{YIYPGGRTYYADSVKGRFTISRDN} SKNTLYLQMN ^{SLRAEDTAVYYCARAGFGGDYWGQGLTVTVSS} ASTKGP ^{SVFFPLAPSSKSTSGGTAALGCLVKDYFPEP} TVTSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS ^{SSLGTQTYICNVNHKPSNTKVDKRV} EPKSC ^{LEEVQLVESGGGLIQPGGSLRLS} CAASGFTVSSNAMS ^{WVRQ} RQAPGKGLEWVS ^{YIYPGGRTYYADSVKGRFTISRDN} SKNTLYLQMN ^{SLRAEDTAVYYCARAGFGGDYWGQGLTVTVSS} ASTKGP ^{SVFFPLAPSSKSTSGGTAALGCLVKDYFPEP} TVTSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS ^{SSLGTQTYICNVNHKPSNTKVDKRV} EPKSC (SEQ ID NO:186)	DIQMTQSPSSVSASVGD ^{RVTITCRASQGI} SSNLA ^{WYQQKPGKAPKLLIIYAAS} TLQSGVPSRFS ^{GSGSGTDFTLTIS} SLQPEDFATYYCQQANEF ^{PLTFGGGT} KVEIKRTVAAPSVFIFPPSDEQLKSGTASV ^{VVCLLN} NNFYPREAKVQWKVDNALQSGNSQESVTEQ ^{DSKDSTYSL} SS ^{TLT} LSKADYEKHKVYACEVTHQGLSSPVT ^{KSFNRGEC} (SEQ ID NO: 163)
26D5-75203-343-B09-TanFab-G4S	EVQLVESGGGLIQPGGSLRLS ^{CAASGFTVSSNAMS} WVRQAPGKGLEWVS ^{YIYPGGRTYYADSVKGRFTISRDN} SKNTLYLQMN ^{SLRAEDTAVYYCARAGFGGDYWGQGLTVTVSS} A ^{STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEP} TVTSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS ^{SSLGTQTYICNVNHKPSNTKVDKRV} EPKSC ^{LEEVQLVESGGGLIQPGGSLRLS} CAASGFTVSSNAMS ^{WVRQ} RQAPGKGLEWVS ^{YIYPGGRTYYADSVKGRFTISRDN} SKNTLYLQMN ^{SLRAEDTAVYYCARAGFGGDYWGQGLTVTVSS} ASTKGP ^{SVFFPLAPSSKSTSGGTAALGCLVKDYFPEP} TVTSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS ^{SSLGTQTYICNVNHKPSNTKVDKRV} EPKSC (SEQ ID NO:187)	DIQMTQSPSSVSASVGD ^{RVTITCRASQGI} SSNLA ^{WYQQKPGKAPKLLIIYAAS} TLQSGVPSRFS ^{GSGSGTDFTLTIS} SLQPEDFATYYCQQANEF ^{PLTFGGGT} KVEIKRTVAAPSVFIFPPSDEQLKSGTASV ^{VVCLLN} NNFYPREAKVQWKVDNALQSGNSQESVTEQ ^{DSKDSTYSL} SS ^{TLT} LSKADYEKHKVYACEVTHQGLSSPVT ^{KSFNRGEC} (SEQ ID NO: 163)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
26D5-75202-343-A09-TanFab	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVS YIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMN SLRAEDTAVYYCARAGFGGDYWGQGT LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSCASTKGPEVLVESGG GLIQPGGSLRLSCAASGFTVSSNAMSWVRQAPGKGLEW SYIYPGGRTYYADSVKGRFTISRDN SKNTLYLQMN SLRA EDTAVYYCARAGFGGDYWGQGT LVTVSS ASTKGPSVF LAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHK PSNTKVDKRVPEKSC (SEQ ID NO: 184)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQANEFPLTFGGGT KVEIKRTVAAPS VFIFPPSDEQLKSGTASV VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 162)
26D5-75202-343-A09-TanFab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVS YIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMN SLRAEDTAVYYCARAGFGGDYWGQGT LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSCASTKGPSVFPLAPEV QLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQAP GKGLEWVSYIYPGGRTYYADSVKGRFTISRDNSKNTLYL QMN SLRAEDTAVYYCARAGFGGDYWGQGT LVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTY ICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 185)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQANEFPLTFGGGT KVEIKRTVAAPS VFIFPPSDEQLKSGTASV VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 162)
26D5-75202-343-A09-TanFab-ELQ	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVS YIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMN SLRAEDTAVYYCARAGFGGDYWGQGT LVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQ TYICNVNHKPSNTKVDKRVPEPKSC <u>LEELQLEESA</u> <u>EAQEGE</u> <u>LEEVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ</u> <u>RQAPGKGLEWVSYIYPGGRTYYADSVKGRFTISRDNSKN</u>	DIQMTQSPSSVSASVGDRVTITCRASQGIYSNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQANEFPLTFGGGT KVEIKRTVAAPS VFIFPPSDEQLKSGTASV VVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 162)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
	TLYLQMNSLRAEDTAVYICARAGFGGGDYWGQGLTVTS S ASTKGPSVF PL APSSK STSG TAALGCLVKDY FP EPV T V WNSGALTSGVHTFPAVLQSSGLYSLSSV TV VPSS LG TQ TYICNVNHKPSNTKVDK R VEPK K SC (SEQ ID NO: 186)	
26D5-75202-343-A09-TanFab-G4S	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVSYIYPGGRTYYADSVKGRFTISRDN SKNTL Y LQ MN SL RAEDTAVYICARAGFGGGDYWGQGLTV VSSA ST KGPSVF PL APSSK STSG TAALGCLVKDY FP EPV TVS W NSGALTSGVHTFPAVLQSSGLYSLSSV TV VPSS SLGTQ TY ICNVNHKPSNTKVDK R VEPK SC GGGGGGGGGGGGG S EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQ APGKGLEWVSYIYPGGRTYYADSVKGRFTISRDN SKNTL Y LQ MN SL RAEDTAVYICARAGFGGGDYWGQGLTV VSSA ST KGPSVF PL APSSK STSG TAALGCLVKDY FP EPV TVS W NSGALTSGVHTFPAVLQSSGLYSLSSV TV VPSS SLGTQ TY ICNVNHKPSNTKVDK R VEPK K SC (SEQ ID NO: 187)	DIQMTQSPSSVSASVGD RV TI TC RA SQ GIYS NLA WYQQKPGKAPK LLI YAA SSLQ SGVPS RF SGSG SG TDFT LT IT SSLQ PE DF ATY YCQ Q ANE FP LT FGGG T K VEI K RT V AA P S V FI FP PS DE Q LK SG TA S V V CL L NN FYP RE AK VQ WKVD NALQ SGNS Q ES VT EQ DS K D ST Y SL SS TL TL SK AD YE KK VY ACE V TH Q GL SS P V TK S F N R G E C (SEQ ID NO: 162)
26D5-75768-348-A10-TanFab	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNA VSIVRQ APGKGLEWVAYIYPGGRTYYADSVKGRFTISRDN SKNTL Y LQ MN SL RAEDTAVYICTIGGFGGGDYWGQGLTV VSSA ST KGPSVF PL APSSK STSG TAALGCLVKDY FP EPV TVS W NSGALTSGVHTFPAVLQSSGLYSLSSV TV VPSS SLGTQ TY ICNVNHKPSNTKVDK R VEPK SC ASTKG PEVQ L V ESGG GLIQPGGSLRLSCAASGFTVSSNA VSIVRQ APGK GLEW AYIYPGGRTYYADSVKGRFTISRDN SKNTL Y LQ MN SL RA EDTAVYCTIGGFGGGDYWGQGLTV VSSA STKG PS V FP LAPSSK STSG TAALGCLVKDY FP EPV TVS WNSGALT SG VHTFPAVLQSSGLYSLSSV TV VPSS SLGTQ TYICNVNHK PSNTKVDK R VEPK K SC (SEQ ID NO: 188)	DIQMTQSPSSVSASVGD RV TI TC RA SQ G ISS NN Q WYQQKPGKAPK LLI YAA SSLQ SGVPS RF SGSG SG TDFT LT IT SSLQ PE DF ATY YCQ Q NE FP LT FGGG T K VEI K RT V AA P S V FI FP PS DE Q LK SG TA S V V CL L NN FYP RE AK VQ WKVD NALQ SGNS Q ES VT EQ DS K D ST Y SL SS TL TL SK AD YE KK VY ACE V TH Q GL SS P V TK S F N R G E C (SEQ ID NO: 165)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
26D5-75768-348-A10-TanFab-Long	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAVSIVRQ APGKGLEWVAYIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCTIGGFGGGDYWGQGLTVTVSSA <u>STKGPSVFP</u> PLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSCASTKGPSVFPLAPEV QLVESGGGLIQPGGSLRLSCAASGFTVSSNAVSIVRQAP GKGLEWVAYIYPGGRTYYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCTIGGFGGGDYWGQGLTVTVSSA <u>ST</u> <u>KGPSVFP</u> PLAPSSKSTSGGTAALGCLVKDYFPEPTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO:189)	DIQMTQSPSSVSASVGDRVTITCRASQGISNNQ WYQQKPGKAPKLLIYYASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQGNEFPLTFGGGT KVEIKRTVAAPSFIFFPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 165)
26D5-75768-348-A10-TanFab-ELQ	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAVSIVRQ APGKGLEWVAYIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCTIGGFGGGDYWGQGLTVTVSSA <u>STKGPSVFP</u> PLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC <u>LEQLQEE</u> SAAEAQEGE <u>LE</u> EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAVSIV RQAPGKGLEWVAYIYPGGRTYYADSVKGRFTISRDN SKN TLYLQMNSLRAEDTAVYYCTIGGFGGGDYWGQGLTVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTV VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLG TQTYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 190)	DIQMTQSPSSVSASVGDRVTITCRASQGISNNQ WYQQKPGKAPKLLIYYASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQGNEFPLTFGGGT KVEIKRTVAAPSFIFFPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 165)
26D5-75768-348-A10-TanFab-G4S	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAVSIVRQ APGKGLEWVAYIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCTIGGFGGGDYWGQGLTVTVSSA <u>STKGPSVFP</u> PLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSCGGGGSGGGSGGGGS EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAVSIVRQ	DIQMTQSPSSVSASVGDRVTITCRASQGISNNQ WYQQKPGKAPKLLIYYASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQGNEFPLTFGGGT KVEIKRTVAAPSFIFFPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 165)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
	APGKGLEWVAYIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCTIGGFGGDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHHKPSNTKVDKRVPEKSC (SEQ ID NO: 191)	
26D5-75214-343-F06-TanFab	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGPDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHHKPSNTKVDKRVPEKSC <u>ASTKGPEVQVLVESGG</u> <u>GLIQPGGSLRLSCAASGFTVSSNAMSWVRQAPGKGLEWV</u> <u>SFIYPGGRTYYADSVKGRFTISRDN SKNTLYLQMNSLRA</u> <u>EDTAVYYCARAGFGGPDYWGQGLTVTVSS</u> ASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPTVTSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHHK PSNTKVDKRVPEKSC (SEQ ID NO: 192)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQANEFFPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 161)
26D5-75214-343-F06-TanFab-LONG	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLRAEDTAVYYCARAGFGGPDYWGQGLTVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHHKPSNTKVDKRVPEKSC <u>ASTKGPSVFPLAPEV</u> <u>QLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWVRQAP</u> <u>GKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTLYL</u> <u>QMNSLRAEDTAVYYCARAGFGGPDYWGQGLTVTVSS</u> AST KGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVTSWN SGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHHKPSNTKVDKRVPEKSC (SEQ ID NO: 193)	DIQMTQSPSSVSASVGDRVTITCRASQGISNLA WYQQKPGKAPKLLIIYAASLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQANEFFPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 161)

Construct Name	Tandem Fab Heavy Chain	Tandem Fab Light Chain
26D5-75214-343-F06-TanFab-ELQ	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ¹⁹⁴ WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ¹⁹⁴ SKNTL YLQMNSLR ¹⁹⁴ AE ¹⁹⁴ DTAVYYCARAGFGGPDYWGQGT ¹⁹⁴ LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC ELQ EEESAAEAQEGE LEEVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQAPGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLR AE DTAVYYCARAGFGGPDYWGQGT LVTVSS SATKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS VWSNGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLG TQTYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 194)	DIQMTQSPSSVSASVGD ¹⁶¹ RV ¹⁶¹ TI ¹⁶¹ TCRASQGI ¹⁶¹ SSNLA WYQQKPGKAPK ¹⁶¹ LLI ¹⁶¹ YAAS ¹⁶¹ LSQSGVPS ¹⁶¹ RFSGSGSG TDFT ¹⁶¹ LT ¹⁶¹ ISSLPEDFAT ¹⁶¹ YYCQQANEF ¹⁶¹ PLT ¹⁶¹ FGGGT KVEIK ¹⁶¹ RTVAAPSV ¹⁶¹ FI ¹⁶¹ PPSDEQLKSGTASV ¹⁶¹ V ¹⁶¹ CLL NNFY ¹⁶¹ P ¹⁶¹ REAKVQ ¹⁶¹ W ¹⁶¹ VDNALQ ¹⁶¹ SGNSQ ¹⁶¹ ESVTEQ ¹⁶¹ DSKD STY ¹⁶¹ SL ¹⁶¹ ST ¹⁶¹ LT ¹⁶¹ SKADYE ¹⁶¹ KHKVYACEV ¹⁶¹ THQGL ¹⁶¹ SSP VT ¹⁶¹ KSFNRGEC (SEQ ID NO: 161)
26D5-75214-343-F06-TanFab-G4S	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS ¹⁹⁵ WVRQ APGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN ¹⁹⁵ SKNTL YLQMNSLR ¹⁹⁵ AE ¹⁹⁵ DTAVYYCARAGFGGPDYWGQGT ¹⁹⁵ LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC G4S GGGGSGGGGGSGGGG EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMS WVRQAPGKGLEWVSFIYPGGRTYYADSVKGRFTISRDN SKNTL YLQMNSLR AE DTAVYYCARAGFGGPDYWGQGT LVTVSSA STKGPSVFFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQ TYICNVNHKPSNTKVDKRVPEKSC (SEQ ID NO: 195)	DIQMTQSPSSVSASVGD ¹⁶¹ RV ¹⁶¹ TI ¹⁶¹ TCRASQGI ¹⁶¹ SSNLA WYQQKPGKAPK ¹⁶¹ LLI ¹⁶¹ YAAS ¹⁶¹ LSQSGVPS ¹⁶¹ RFSGSGSG TDFT ¹⁶¹ LT ¹⁶¹ ISSLPEDFAT ¹⁶¹ YYCQQANEF ¹⁶¹ PLT ¹⁶¹ FGGGT KVEIK ¹⁶¹ RTVAAPSV ¹⁶¹ FI ¹⁶¹ PPSDEQLKSGTASV ¹⁶¹ V ¹⁶¹ CLL NNFY ¹⁶¹ P ¹⁶¹ REAKVQ ¹⁶¹ W ¹⁶¹ VDNALQ ¹⁶¹ SGNSQ ¹⁶¹ ESVTEQ ¹⁶¹ DSKD STY ¹⁶¹ SL ¹⁶¹ ST ¹⁶¹ LT ¹⁶¹ SKADYE ¹⁶¹ KHKVYACEV ¹⁶¹ THQGL ¹⁶¹ SSP VT ¹⁶¹ KSFNRGEC (SEQ ID NO: 161)

[000112] “Identity” *per se* has an art-recognized meaning and can be calculated using published techniques. *See, e.g.,* COMPUTATIONAL MOLECULAR BIOLOGY, Lesk, A. M., ed., Oxford University Press, New York, (1988); BIOCOMPUTING: INFORMATICS AND GENOME PROJECTS, Smith, D. W., ed., Academic Press, New York, (1993); COMPUTER ANALYSIS OF SEQUENCE DATA, PART I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, (1994); SEQUENCE ANALYSIS IN MOLECULAR BIOLOGY, von Heinje, G., Academic Press, (1987); and SEQUENCE ANALYSIS PRIMER, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, (1991).) While there exist a number of methods to measure identity between two polynucleotide or polypeptide sequences, the term “identity” is well known to skilled artisans. (Carillo, H., and Lipton, D., SIAM J. Applied Math. 48:1073 (1988).) Methods commonly employed to determine identity or similarity between two sequences include, but are not limited to, those disclosed in “Guide to Huge Computers,” Martin J. Bishop, ed., Academic Press, San Diego, (1994), and Carillo, H., and Lipton, D., SIAM J. Applied Math. 48:1073 (1988). Methods for aligning polynucleotides or polypeptides are codified in computer programs, including the GCG program package (Devereux, J., et al., Nucleic Acids Research 12(1):387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S. F. et al., J. Mol. Biol. 215:403 (1990), Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, Wis. 53711 (using the local homology algorithm of Smith and Waterman, Advances in Applied Mathematics 2:482 489 (1981))).

[000113] By a polynucleotide being at least, for example, 95% “identical” to a reference nucleotide sequence, respectively, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence, except that the polynucleotide sequence may include up to five mutations per each 100 nucleotides of the reference nucleotide sequence. For example, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence.

[000114] As a practical matter, whether any particular nucleic acid molecule is at least 80%, 85%, 89%, 90%, 95%, or 99% identical to a nucleotide sequence of the presence invention can be determined using known computer programs. One method for determining the best overall match between a query sequence and a reference sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a conventional nucleotide sequence alignment, the query and reference sequences are both DNA sequences; however, an RNA sequence can be compared by converting U's to T's. The results of the global sequence alignment are reported in terms of percent identity. In one embodiment of the present invention, the parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

[000115] If the reference sequence is shorter than the query sequence because of, for example, 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the reference sequence when calculating percent identity. For reference sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the reference sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. This percentage is then subtracted from the percent identity, calculated for example by the FASTDB program, using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the reference sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[000116] For example, a 90 base reference sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the reference sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of

bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base reference sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the reference sequence which are not matched/aligned with the query. In this case, the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the reference sequence which are not matched/aligned with the query sequence are manually corrected for.

[000117] By a polypeptide having an amino acid sequence at least, for example, 95% “identical” to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be inserted, deleted or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[000118] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 89%, 90%, 95%, or 99% identical to, for instance, the amino acid sequences shown in any of the **Tables 1-4**, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a reference sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program mentioned above. In a sequence alignment the query and reference sequences are both amino acid sequences. The result of said global sequence alignment is in percent identity. In one embodiment of the present invention, the parameters used in a FASTDB alignment of amino acid sequences to calculate percent identity are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window

Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[000119] If the reference sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the reference sequence when calculating global percent identity. For reference sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the reference sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-terminal of the reference sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the reference sequence.

[000120] For example, a 90 amino acid residue reference sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the reference sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue reference sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the reference sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal

ends of the reference sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected.

[000121] Within the confines of the disclosed percent identity, the invention also relates to substitution variants of disclosed polypeptides of the invention. Substitution variants include those polypeptides in which one or more amino acid residues are removed and replaced with alternative residues. In one aspect, while the percent identity as disclosed above relates to the overall sequence of the specific sequence identified, the amino acid residues that are to remain constant and are not subject to variation would be those of the CDRs, and the amino acid residues that framework would be subject to variation. For example, in one specific embodiment, when the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, of the present invention comprises at least one VH comprising an amino acid sequence that is at least about 80%, 85%, 90%, 95%, or 99% identical to the amino acid sequence of SEQ ID NO: 64, the CDR regions of the VH are to remain constant and the framework regions are permitted to be variable, provided the overall percentage identity of SEQ ID NO:64 falls within the confines of the embodiment. In one aspect, the variations are substitutions that are conservative in nature; however, the invention embraces substitutions that are also non-conservative. Conservative substitutions for the purpose of the present invention may be defined as set out in **Tables 5-7** below. Amino acids can be classified according to physical properties and contribution to secondary and tertiary protein structure. A conservative substitution is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are set out in below.

Table 5: Conservative Substitutions

Side Chain Characteristic	Amino Acid
<u>Aliphatic</u>	
Non-polar	Gly, Ala, Pro, Ile, Leu, Val, Met
Polar-uncharged	Cys, Ser, Thr, Asn, Gln
Polar-charged	Asp, Glu, Lys, Arg
<u>Aromatic</u>	His, Phe, Trp, Tyr

Alternatively, conservative amino acids can be grouped as described in Lehninger (1975) Biochemistry, Second Edition; Worth Publishers, pp. 71-77, as set forth below.

Table 6: Conservative Substitutions

Side Chain Characteristic	Amino Acid
<u>Non-polar (hydrophobic)</u>	
Aliphatic:	Ala, Leu, Iso, Val, Pro
Aromatic	Phe, Trp
Sulfur-containing:	Met
Borderline:	Gly
<u>Uncharged-polar</u>	
Hydroxyl:	Ser, Thr, Tyr
Amides:	Asn, Gln
Sulfhydryl:	Cys
Borderline:	Gly
<u>Positively Charged (Basic):</u>	Lys, Arg, His
<u>Negatively Charged (Acidic)</u>	Asp, Glu

[000122] And still other alternative, exemplary conservative substitutions are set out below.

Table 7: Conservative Substitutions

Original Residue	Exemplary Substitution
Ala (A)	Val, Leu, Ile
Arg (R)	Lys, Gln, Asn
Asn (N)	Gln, His, Lys, Arg
Asp (D)	Glu
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
His (H)	Asn, Gln, Lys, Arg
Ile (I)	Leu, Val, Met, Ala, Phe
Leu (L)	Ile, Val, Met, Ala, Phe
Lys (K)	Arg, Gln, Asn
Met (M)	Leu, Phe, Ile

Phe (F)	Leu, Val, Ile, Ala
Pro (P)	Gly
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser
Val (V)	Ile, Leu, Met, Phe, Ala

[000123] In some embodiments of the antibodies or antibody fragments of the present invention, the CH1 domain comprises a partial heavy chain constant region with amino acid sequence of:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSC (SEQ ID NO: 202). The present invention also encompasses antibodies or antibody fragment of the present invention that comprise a CH1 domain with an amino acid sequence that is at least about 80%, 85%, 89%, 90%, 95%, or 99% identical to the CH1 domain of SEQ ID NO:202. In some embodiments of the antibodies or antibody fragments of the present invention, the CH1 domain comprises a partial heavy chain constant region with amino acid sequence of:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTH (SEQ ID NO: 203). The present invention also encompasses antibodies or antibody fragments that comprise a CH1 domain with an amino acid sequence that is at least about 80%, 85%, 89%, 90%, 95%, or 99% identical to the CH1 domain of SEQ ID NO:203. In some embodiments of the antibodies or antibody fragments of the present invention, the CL domain comprises a light chain constant region with amino acid sequence of:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 204). The present invention also encompasses antibodies or antibody fragments that comprise a CL domain with an amino acid sequence that is at least about 80%, 85%, 89%, 90%, 95%, or 99% identical to the CH1 domain of SEQ ID NO:204.

[000124] In some embodiments, the antibody or antibody fragment of the present invention comprises one or more of the individual N-terminal portion of the heavy chains and full

length light chains described herein. In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, comprises both an N-terminal portion of the heavy chain and a full length light chain sequences described herein. In some embodiments, the antibody or antibody fragment of the present invention comprises one N-terminal portion of the heavy chain, paired with one full length light chain described herein. In some embodiments, the antibody or antibody fragment of the present invention comprises more than one N-terminal portion of the heavy chain, each paired with one full length light chain described herein. In some embodiments, the antibody or antibody fragment of the present invention comprise two N-terminal portions of the heavy chains, each paired with one full length light chain described herein. In certain embodiments, the two N-terminal portions of the heavy chains are linked via a linker.

[000125] Table 4 provides sequences for heavy chains and light chains of exemplary tandem Fabs of the present invention. In some embodiments, the heavy chain of the tandem Fab comprises one or two N-terminal portions of the heavy chain of an antibody linked via a linker, and the light chain of the tandem Fab comprises a full length light chain (VL-CL) of an antibody. In some embodiments, the heavy chain of the tandem Fab can be expressed as VH-CH1-linker-CH1-VH or VH-CH1-linker-VH-CH1.

[000126] The linker encompassed by the present invention can be any suitable molecule of various structures. In certain embodiments, the linker is a polypeptide linker. The polypeptide linker can have various lengths. In some embodiments, the linker is a polypeptide comprising about 20 amino acids or fewer. Exemplary polypeptide linker sequences are provided in Table 8 and double underlined in Table 4.

Table 8: Exemplary linker sequences

Linker sequence	SEQ ID NO
ASTKGP	SEQ ID NO: 196
ASTKGPSVFPLAP	SEQ ID NO: 197
ELQLEESAAEAQEGELE	SEQ ID NO: 198
GGGSGGGGSGGGGS	SEQ ID NO: 199

Table 9: mAb sequences

Name	Sequence

Human IgG1f mAb heavy chain constant region	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 200)
26D5-75616-348-F10-mAb heavy chain	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNAMSWSVRQAPG KGLEWVSFIYPGGRTYYADSVKGRFTISRDNKNTLYLQMNS LRAEDTAVYYCARAEFGLEDIWGGTTLVTVSSASTKGPSVF LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 201)

[000127] In some embodiments, the present invention provides an antigen binding peptide comprising the amino acid sequence of SEQ ID NO: 201.

[000128] In some embodiments, the present invention provides an antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, comprising at least one VH and at least one VL. In some embodiments, the at least one VH comprises a VH complementarity-determining region 1 (VH-CDR1) comprising an amino acid sequence selected from the group comprising SEQ ID NOs: 1-12; a VH-CDR2 comprising an amino acid sequence selected from the group comprising SEQ ID NOs: 13-22; or a VH-CDR3 comprising an amino acid sequence selected from the group comprising SEQ ID NOs: 23-28. In some embodiments, the at least one VL comprises at least one of: a VL-CDR1 comprising an amino acid sequence selected from the group comprising SEQ ID NOs: 29-37; a VL-CDR2 comprising an amino acid sequence selected from the group comprising SEQ ID NOs: 38-43; or a VL-CDR3 comprising an amino acid sequence selected from the group comprising SEQ ID NOs: 44-51. In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, of the present invention comprises VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 that have 1, 2, 3, or 4 conservative amino acid substitutions thereof.

- [000129] In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, comprises at least one VH comprising an amino acid sequence at least about 80%, 85%, 90%, 95%, or 99% identical to a sequence selected from the group comprising SEQ ID NOs: 52-83; and at least one VL comprising an amino acid sequence at least about 80%, 85%, 90%, 95%, or 99% identical to a sequence selected from the group comprising SEQ ID NOs: 84-99.
- [000130] In some embodiments, the at least one VH region and the at least one VL region disclosed in Table 2 herein also encompass variant sequences comprising 1, 2, 3, or 4 conservative amino acid substitutions.
- [000131] In some embodiments, the tandem Fab of the present invention comprises sequences that are at least about 80%, 85%, 90%, 95%, and 99% identical to the sequences to in Table 4.
- [000132] The present invention further encompasses a polynucleotide comprising a nucleic acid sequence that encodes partly or wholly the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, provided herein.
- [000133] In some embodiments, the polynucleotides comprise a nucleic acid sequence encoding any one of the CDR sequences provided in Table 1. In some embodiments, the polynucleotides comprise a nucleic acid sequence encoding any one of the VHs or the VLs provided in Table 2. In some embodiments, the polynucleotides comprise a nucleic acid sequence encoding any one of the N-terminal portion of the heavy chains or full length light chains provided in Table 3. In some embodiments, the polynucleotides comprise a nucleic acid sequence encoding any one of the tandem Fab heavy chain and light chain sequences provided in Table 4.
- [000134] The present invention also encompasses polynucleotides having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to any of the polynucleotides disclosed herein. The present invention further provides variants of the polynucleotides encoding fragments, analogs, and derivatives of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, disclosed herein. The polynucleotide variants can contain alterations in the coding regions, non-coding regions, or both. In some embodiments, the polynucleotide variants contain alterations which produce

silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. In some embodiments, the polynucleotide variants are produced by silent substitutions due to the degeneracy of the genetic code. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host.

[000135] In certain embodiments, the polynucleotides of the present invention comprise the coding sequence for the mature polypeptide fused in the same reading frame to a polynucleotide encoding a polypeptide which aids, for example, in the expression and secretion of a polypeptide from a host cell. In some embodiments, the mature polypeptide is the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, disclosed herein. In certain embodiments, the polynucleotides comprise a sequence encoding a leader polypeptide sequence which functions as a secretory sequence for controlling transport of a polypeptide from the cell. The polypeptide having a leader sequence is a preprotein and can have the leader sequence cleaved by the host cell to form the mature form of the polypeptide. The polynucleotides can also encode for a proprotein which is the mature protein plus additional 5' amino acid residues. A mature polypeptide having a prosequence is a proprotein and is an inactive form of the protein. Once the prosequence is cleaved, an active mature protein remains. In certain embodiments, the polynucleotides comprise the coding sequence for the mature polypeptide fused in the same reading frame to a marker sequence that allows, for example, for purification of the encoded polypeptide.

[000136] In some embodiments, the present invention provides a vector comprising any one of the polynucleotides provided herein. As used herein, the term "vector" refers to a construct, which is capable of delivering, and optionally expressing, one or more polynucleotides, proteins, or sequences of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

[000137] The present invention further provides host cells comprising the vectors provided herein. In some embodiments, the host cell is an isolated cell. In some embodiments, the isolated host cell produces the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, provided herein. Suitable host cells include prokaryotes,

yeast, insect or higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or *bacilli*. Higher eukaryotic cells include established cell lines of mammalian origin as described below. Cell-free translation systems could also be employed. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are generally known in the art. Various mammalian or insect cell culture systems are also advantageously employed to express recombinant protein. Expression of recombinant proteins in mammalian cells can be performed because such proteins are generally correctly folded, appropriately modified and completely functional. Examples of suitable mammalian host cell lines include the COS-7 lines of monkey kidney cells, L cells, C127, 3T3, Chinese hamster ovary (CHO), HeLa, and BHK cell lines. In addition, baculovirus systems for production of heterologous proteins in insect cells are generally known in the art.

[000138] The antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, of the present invention produced by a transformed host can be purified according to any suitable method. Such standard methods include chromatography (e.g., ion exchange, affinity and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for protein purification. Affinity tags such as hexahistidine (SEQ ID NO:221), maltose binding domain, influenza coat sequence and glutathione-S-transferase can be attached to the protein to allow easy purification by passage over an appropriate affinity column. Isolated proteins can also be physically characterized using such techniques as proteolysis, nuclear magnetic resonance, mass spectrometry and x-ray crystallography. Methods for purifying antibodies and other proteins are generally known in the art.

[000139] In certain embodiments, the present invention provides a method of making an antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, disclosed herein. In an exemplary embodiment, the method comprises: (a) culturing the host cell provided hereinabove under culture conditions that promote protein production such that the host cell produces the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment; and (b) isolating the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, from the cultured cell. Methods for making antigen binding peptides that are generally known in the art can be used to produce the antigen

binding peptide, such as, but not limited to, an antibody or antibody fragment, of the present invention.

[000140] In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, provided herein can be used as a detection reagent. In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is detectably labeled. The term “label” when used herein refers to a detectable compound which is conjugated directly or indirectly to the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment. The label can be detectable by itself (e.g. radioisotope labels or fluorescent labels), or, in the case of an enzymatic label, can catalyze chemical alteration of a substrate which is detectable. In certain embodiments, the label is selected from the group consisting of an immunofluorescent label, a chemiluminescent label, a phosphorescent label, an enzyme label, a radiolabel, avidin/biotin, a colloidal gold particle, a colored particle, and a magnetic particle.

[000141] In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, forms a bound complex with the compound of Formula (I) or (II) *in vitro* or *in vivo*. In some embodiments, the bound complex is an immunocomplex. In general, the detection of immunocomplex formation is well known in the art and can be achieved through the application of numerous approaches. In some embodiments, the detection is performed by an immunological assay, or immunoassay.

[000142] As used herein, an immunological assay refers to any assay that capitalizes on the specificity of the antibody-antigen binding *in vitro* or *in vivo*. In some embodiments, the assay can be used to identify the presence or absence of a target molecule in a biological sample. In some embodiments, the assay can be used to measure the amount or level of a target molecule. In some embodiments, the target molecule is an immunocomplex of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, formed with the compound of Formula (I) or (II) *in vitro* or *in vivo*. In some embodiments, the target molecule is the compound of Formula (I) or (II) itself. In some exemplary embodiments, the immunological assay includes, but is not limited to, radioimmunoassay, immunohistochemistry, chemiluminescence immunoassay (CLIA), Enzyme Immunoassays (EIA) or Enzyme-Linked Immuno Sorbent Assay (ELISA), Western blot, counting

immunoassay, flow cytometry, fluoroimmunoassay, and fluorescence-activated cell sorting (FACS).

[000143] A biological sample as used herein can be any sample derived from a subject. In some embodiments, the biological sample is urine, feces, saliva, whole blood, plasma, organ tissue, hair, skin, cells, or cell cultures. In some embodiments, the biological sample is a liquid sample. In some embodiments, the biological sample can be fixed with a fixative. For example, aldehyde fixatives such as formalin (formaldehyde) and glutaraldehyde are typically used.

[000144] The present invention further provides a method of reducing the antithrombotic effect of an FXIa inhibitor, or a dual inhibitor of FXIa and plasma kallikrein, in a subject in need thereof. In some embodiments, the present invention relates to a method of reducing the antithrombotic effect of an FXIa inhibitor. In certain embodiments, the FXIa inhibitor is the compound of Formula (I) or II. In some embodiments, the method comprises administering to the subject a pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, provided herein. In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, can bind to the compound of Formula (I) or (II) with high affinity and reverse its antithrombotic effect *in vitro* or *in vivo*. In some embodiments, the binding of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, to the compound of Formula (I) or (II) can neutralize its antithrombotic effect *in vitro* or *in vivo*. In some embodiments, the antigen binding peptide binds to the FXIa inhibitor, e.g., the compound of Formula (I) or (II), and thereby prevents the FXIa inhibitor from binding to FXIa.

[000145] The term “subject” refers to any animal including, but not limited to humans, non-human primates, and the like. In some embodiments, a subject is the recipient of a particular treatment. In some embodiments, the subject is a human. In certain embodiments, the subject is a human patient who is in need of the treatment provided herein. In some embodiments, the terms “subject” and “patient” are used interchangeably herein.

[000146] Terms such as “treating,” “treatment,” or “to treat” are used interchangeably and refer to therapeutic measures that cure, slow down, reduce or lessen symptoms of, reverse or neutralize the effect of, and/or halt progression of a pathologic condition. As used herein, the term treatment is used to mean receiving at least one of the antigen binding peptides, such as,

but not limited to, an antibody or antibody fragment, of the present invention. The term “prevent” or “reduce the risk” are used to mean prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition, or lessen the risk that a subject will acquire an abnormal condition as compared to an individual not receiving the treatment. Thus, subjects in need of treatment include those already with the condition (such as thrombosis), those prone to have the condition, and those in whom the condition is to be prevented.

[000147] The present invention also provides pharmaceutical compositions comprising the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, disclosed herein. In some embodiments, the pharmaceutical compositions of the present invention encompass therapeutic compositions and/or prophylactic compositions. In some embodiments, the pharmaceutical compositions comprise a therapeutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, and a pharmaceutically acceptable carrier or excipient. Such pharmaceutically acceptable excipients are generally known in the art. Common excipients include, but are not limited to, preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, disintegrants, glidants, lubricants, sorbents, vehicles, sweeteners, flavors, colourants, odourants, salts (substances of the present invention may themselves be provided in the form of a pharmaceutically acceptable salt), buffers, coating agents, and antioxidants. Exemplary excipients include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, sucrose, sorbitol and any combinations thereof. In some embodiments, the pharmaceutically acceptable excipients are inactive ingredients. However, it is understood that the pharmaceutically acceptable excipients can sometimes have impact on the manufacture, quality, safety, or efficacy of the pharmaceutical compositions. In some embodiments, the pharmaceutical compositions may also contain therapeutically active agents in addition to the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, of the present invention.

[000148] The pharmaceutical compositions of the present invention may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water or saline for injections, immediately prior to use. Extemporaneous

injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

- [000149] The pharmaceutical compositions may be administered in a convenient and suitable manner according to the use. In some embodiments, the pharmaceutical compositions may be administered by parenteral routes. In some embodiments, the parenteral administration routes may be intravenous, intraperitoneal, intramuscular, intratumor, subcutaneous, intranasal, or intradermal routes.
- [000150] Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6):318 (1986).
- [000151] Pharmaceutical compositions adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable compositions wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.
- [000152] Pharmaceutical compositions adapted for parenteral administration may include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation substantially isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Excipients which may be used for injectable solutions include water, alcohols, polyols, glycerine, and vegetable oils, for example.
- [000153] The terms “effective dose,” “therapeutically effective dose,” and “pharmaceutically effective dose” are used interchangeably herein and refer to a dose sufficient to produce a physiological effect. In some embodiments, a pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, provided herein refers to an amount of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, effective to reduce or neutralize the

antithrombotic effect of the compounds disclosed herein in a subject in need thereof. In some embodiments, the administration of one pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, can immediately reverse the antithrombotic effect of the compound of Formula (I) or (II) in a subject with serious bleeding. In some embodiments, the administration of one pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, has a limited duration of action. In certain embodiments, a single pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, has a duration of action long enough to reverse the antithrombotic effect of the compound of Formula (I) or (II). In the meantime, the single pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, has a duration of action short enough to allow resumption of antithrombotic therapy soon after the administration of the single pharmaceutically effective dose and to minimize the period of increased risk for thromboembolic events.

[000154] In some embodiments, a pharmaceutically effective dose can be determined empirically and in a routine manner, in relation to the stated purpose. For example, in some embodiments, the dose of the compound of Formula (II) ranges from about 25 milligrams (mg) *quaque die* (*q.d.*, or once a day) to about 375 mg *bis in die* (*b.i.d.*, or twice a day). In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 25 mg *q.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 50 mg *q.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 75 mg *q.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 100 mg *q.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 125 mg *q.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 150 mg *q.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as,

but not limited to, an antibody or antibody fragment, is about 175 mg *q.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 200 mg *q.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 375 mg *q.d.*

[000155] In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 25 mg *b.i.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 50 mg *b.i.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 75 mg *b.i.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 100 mg *b.i.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 125 mg *b.i.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 150 mg *b.i.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 175 mg *b.i.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 200 mg *b.i.d.* In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 375 mg *b.i.d.*

[000156] In some embodiments of the present invention, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is determined primarily in relation to the dose of the compound of Formula (I) or (II) administered before. In some embodiments, a pharmaceutically effective dose comprises the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, at an at least about 1:1 molar ratio to the dose of the compound of Formula (I) or (II) administered to the subject before. In some embodiments, a pharmaceutically effective dose comprises the antigen binding peptide, such as, but not limited to, an antibody or antibody

fragment, at an at least about 2:1 to about 10:1 molar ratio to the dose of the compound of Formula (I) or (II) administered to the subject. In some embodiments, a pharmaceutically effective dose comprises the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, at an at least about 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, 55:1, 60:1, 65:1, 70:1, 75:1, 80:1, 85:1, 90:1, 95:1, or 100:1 molar ratio to the dose of the compound of Formula (I) or (II) administered to the subject before.

[000157] In some embodiments, a pharmaceutically effective dose comprises the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, at an at least about 1:1 molar ratio to the amount of the compound of Formula (I) or (II) present in a subject. In some embodiments, a pharmaceutically effective dose comprises the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, at an at least about 2:1 to about 10:1 molar ratio to the amount of the compound of Formula (I) or (II) present in the subject. In some embodiments, a pharmaceutically effective dose comprises the antigen binding peptide, such as, but not limited, to an antibody or antibody fragment, at an at least about 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, 55:1, 60:1, 65:1, 70:1, 75:1, 80:1, 85:1, 90:1, 95:1, or 100:1 molar ratio to the amount of the compound of Formula (I) or (II) present in the subject.

[000158] In some embodiments, the pharmaceutically effective dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is calculated in mass ratio. For example, the molecular weight (MW) of the antigen binding peptide, such as, but not limited to an antibody or antibody fragment, may be about 75 times the MW of the compound of Formula (II). In this example, for every about 100 mg of the compound of Formula (II), equal molar of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is about 7.5 grams. Thus, one skilled in the art can readily calculate the mass ratio of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, to the compound of Formula (I) or (II) since their molar masses are readily available according to the present invention.

[000159] In some embodiments, the dose of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, will be determined in clinical studies. Prior to those studies, computational modeling and simulation are performed which incorporate (I)

human pharmacokinetic and pharmacodynamic information (from Phase 1 studies), (2) binding kinetics and (3) predicted human PK parameters.

[000160] The antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, of the present invention can be administered concurrently with or after the administration of the compound of Formula (I) or (II). In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered concurrently with the administration of the compound of Formula (I) or (II). In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered immediately after the administration of the compound of Formula (I) or (II). In an exemplary embodiment, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered about 30 minutes after the beginning of the administration of the compound of Formula (I) or (II). In some exemplary embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered about 20 minutes after the administration of the compound of Formula (I) or (II) has finished. However, the administration of the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, and the compound of Formula (I) or (II) can be concurrent or consecutive in any order as deemed appropriate by a person skilled in the art.

[000161] The antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, of the present invention can be administered by any route a skilled person deems suitable. In one embodiment, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered intravenously, intramuscularly, or subcutaneously. In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered once a day. In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered more than once a day. In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered over a period of about 10 minutes. In some embodiments, the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, is administered over a period of about less than about 10 minutes. In some embodiments, the antigen binding peptide, such as, but not limited to, an

antibody or antibody fragment, is administered over a period of about more than about 10 minutes.

[000162] The present invention further provides a method of detecting the level of a compound of Formula (I) or (II) in a biological sample. In some embodiments, the method comprises contacting a biological sample with the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment. In some embodiments, the method comprises detecting the level of a bound complex of the compound of Formula (I) or (II) and the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment. In some embodiments, the method comprises contacting a biological sample with the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment, and then detecting the level of a bound complex of the compound and the antigen binding peptide, such as, but not limited to, an antibody or antibody fragment.

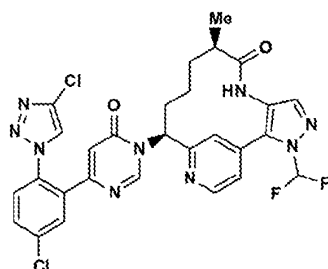
[000163] The breadth and scope of the present disclosure should not be limited by any of the above-described exemplary aspects, but should be defined only in accordance with the following claims and their equivalents.

[000164] The contents of all cited references (including literature references, patents, patent applications, and websites) that may be cited throughout this application are hereby expressly incorporated by reference in their entirety for any purpose, as are the references cited therein.

Examples

[000165] Example 1: Generation of Human Monoclonal Antibodies Against Compound A Using Transgenic Mice that Express Human Antibody Genes – Preparation of Antigen and Related Compounds

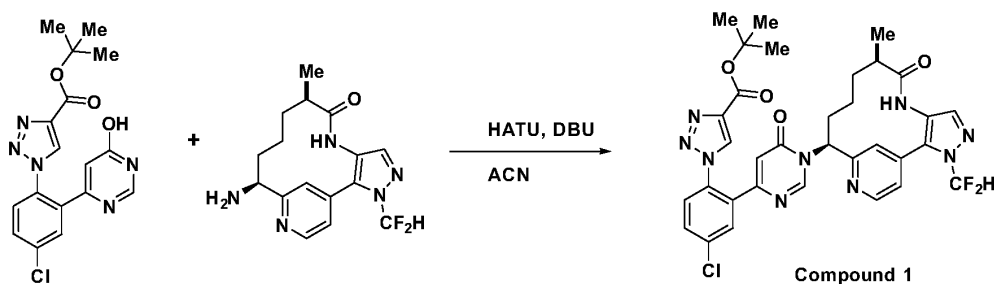
[000166] Fully human monoclonal antibodies to Compound A, a specific inhibitor of Factor XIa, were prepared by immunizing transgenic mice with Keyhole limpet haemocyanin (KLH) conjugated versions of Compound A (shown below).



Compound A

Example 1A. Synthesis of Compound 3

[000167] **Step1:** Synthesis of tert-butyl 1-(4-chloro-2-(1-((5R,9S)-21-(difluoromethyl)-5-methyl-4-oxo-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphane-9-yl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-1H-1,2,3-triazole-4-carboxylate (Compound 1)



[000168] To a 100 mL flask containing a white suspension of tert-butyl 1-(4-chloro-2-(6-hydroxypyrimidin-4-yl)phenyl)-1H-1,2,3-triazole-4-carboxylate (105 mg, 0.28 mmol) in acetonitrile (3.7 mL) was added HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate) (117 mg, 0.31 mmol) and DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) (55.0 μ l, 0.37 mmol). The resulting clear, yellow solution was stirred at room temperature for 5 minutes. (5R,9S)-9-amino-21-(difluoromethyl)-5-methyl-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphan-4-one (94 mg, 0.281 mmol) was added and the resulting suspension was stirred at room temperature for 3 hours, at which point it was concentrated to dryness. The residue was dissolved in 1 mL EtOAc and was loaded onto a 40g Isco column. The product was eluted with a linear gradient of 0% to 100% EtOAc in hexanes over 35 minutes. Product eluted right at 100% EtOAc. Tert-butyl 1-(4-chloro-2-(1-((5R,9S)-21-(difluoromethyl)-5-methyl-4-oxo-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphane-9-yl)-6-oxo-1,6-dihydropyrimidin-4-

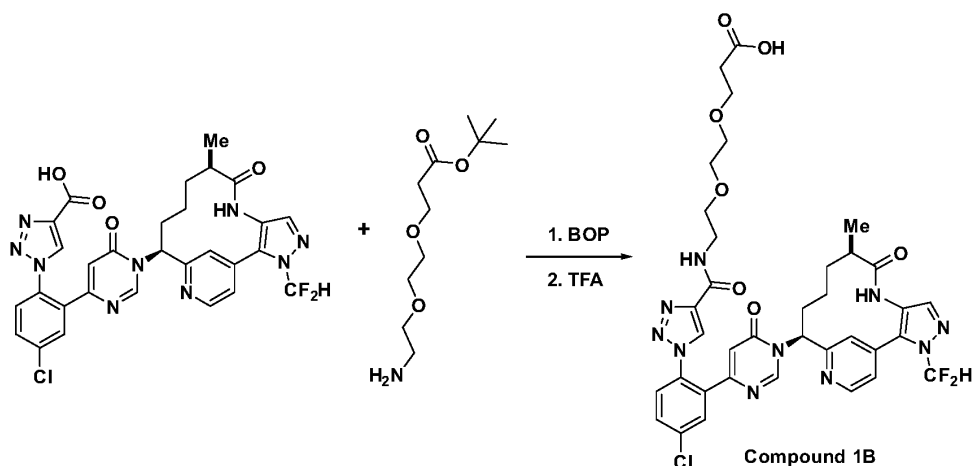
yl)phenyl)-1H-1,2,3-triazole-4-carboxylate (161 mg, 0.233 mmol, 83 % yield) was isolated as a white solid.

Step 2: Synthesis of 1-(4-chloro-2-(1-((5R,9S)-21-(difluoromethyl)-5-methyl-4-oxo-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphane-9-yl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid hydrochloride (Compound 1A)



[000169] Tert-butyl 1-(4-chloro-2-(1-((5R,9S)-21-(difluoromethyl)-5-methyl-4-oxo-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphane-9-yl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-1H-1,2,3-triazole-4-carboxylate (161 mg, 0.233 mmol) was dissolved in HCl in dioxane (3 ml, 12.00 mmol) and stirred for 2 hours at which point the deprotection was complete by LCMS. The reaction mixture was concentrated to dryness and further dried overnight in vacuo. 1-(4-chloro-2-(1-((5R,9S)-21-(difluoromethyl)-5-methyl-4-oxo-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphane-9-yl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid hydrochloride (150 mg, 0.223 mmol, 96 % yield) was isolated as a pale yellow solid.

Step 3: Synthesis of 3-(2-(2-(1-(4-chloro-2-(1-((5R,9S)-21-(difluoromethyl)-5-methyl-4-oxo-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphane-9-yl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-1H-1,2,3-triazole-4-carboxamido)ethoxy)ethoxy)propanoic acid (Compound 1B)



[000170] 1-(4-chloro-2-(1-((5R,9S)-21-(difluoromethyl)-5-methyl-4-oxo-21H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphane-9-yl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid hydrochloride (40 mg, 0.063 mmol), tert-butyl 3-(2-aminoethoxy)ethoxypropanoate (14.67 mg, 0.063 mmol) and triethylamine (8.77 μ l, 0.063 mmol) were dissolved in DMF (N,N-dimethylformamide) (2 mL). BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate) (27.8 mg, 0.063 mmol) was added and the resulting mixture stirred for 4 hours at room temperature. The residue was concentrated to dryness and subsequently diluted with CH_2Cl_2 (4 mL) and TFA (trifluoroacetic acid) (2 mL). The reaction mixture was stirred for 2 hours at room temperature and then concentrated to a dry residue.

[000171] Purification of COMPOUND 1 was accomplished by prep HPLC.

[000172] Prep HPLC - Column = Sunfire Prep C18 OBD 5 micron (30 x 100 mm)

[000173] Solvent A = 10% MeOH, 90% water, 10 mM ammonium acetate

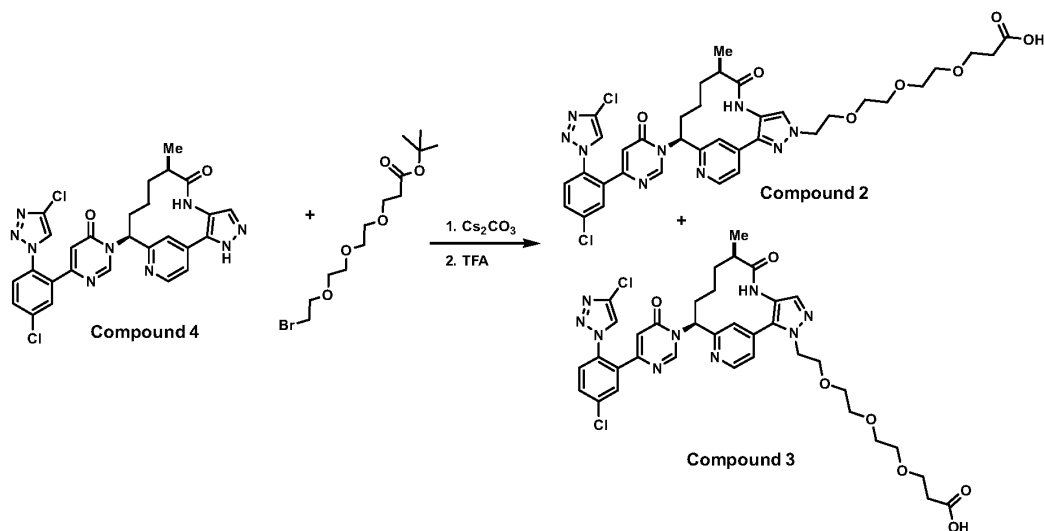
[000174] Solvent B = 90% MeOH, 10% water, 10 mM ammonium acetate

[000175] Linear gradient of 25% B to 100% B

Example 1B. Synthesis of Compound 2 and 3

Synthesis of 3-(2-(2-(2-((5R,9S)-9-(4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-6-oxopyrimidin-1(6H)-yl)-5-methyl-4-oxo-21H-3-aza-1(4,2)-pyridina-2(3,4)-pyrazolacyclononaphane-21-yl)ethoxy)ethoxy)ethoxy)propanoic acid (COMPOUND 2) and

3-(2-(2-(2-((5R,9S)-9-(4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-6-oxopyrimidin-1(6H)-yl)-5-methyl-4-oxo-2H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphane-21-yl)ethoxy)ethoxy)ethoxy)propanoic acid (COMPOUND 3)



[000176] (5R,9S)-9-(4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-6-oxopyrimidin-1(6H)-yl)-5-methyl-2H-3-aza-1(4,2)-pyridina-2(5,4)-pyrazolacyclononaphan-4-one (COMPOUND 4) (70 mg, 0.121 mmol), tert-butyl 3-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)propanoate (41.4 mg, 0.121 mmol), and cesium carbonate (39.6 mg, 0.121 mmol) were heated to 60 °C in DMF (N,N-dimethylformamide) (3 mL) for 1 hour and then cooled to room temperature. The reaction mixture was filtered and then concentrated to dryness. The residue was diluted with CH₂Cl₂ (4 mL) and TFA (2 mL) and then stirred for 1 hour at room temperature. Purification of resulting COMPOUND 2 and COMPOUND 3 was accomplished by prep HPLC.

[000177] Prep HPLC - Column = Sunfire Prep C18 OBD 5 micron (30 x 100 mm)

[000178] Solvent A = 10% MeOH, 90% water, 10 mM ammonium acetate

[000179] Solvent B = 90% MeOH, 10% water, 10 mM ammonium acetate

[000180] Linear gradient of 25% B to 100% B

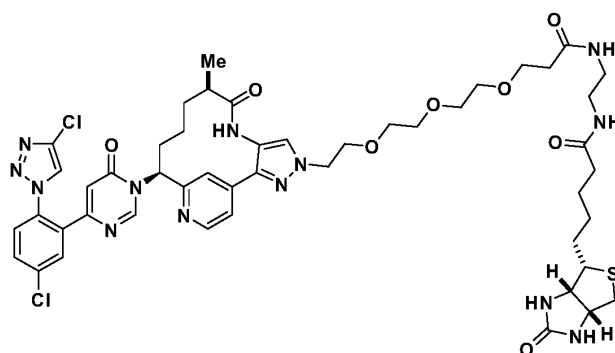
[000181] COMPOUND 2 (40 mg, 0.051 mmol, 41.8 % yield) and COMPOUND 3 (15 mg, 0.019 mmol, 15.51 % yield) were isolated as white solids.

[000182] COMPOUND 2, COMPOUND 3 and COMPOUND 1 were conjugated to BSA and KLH for immunization and ELISA screening.

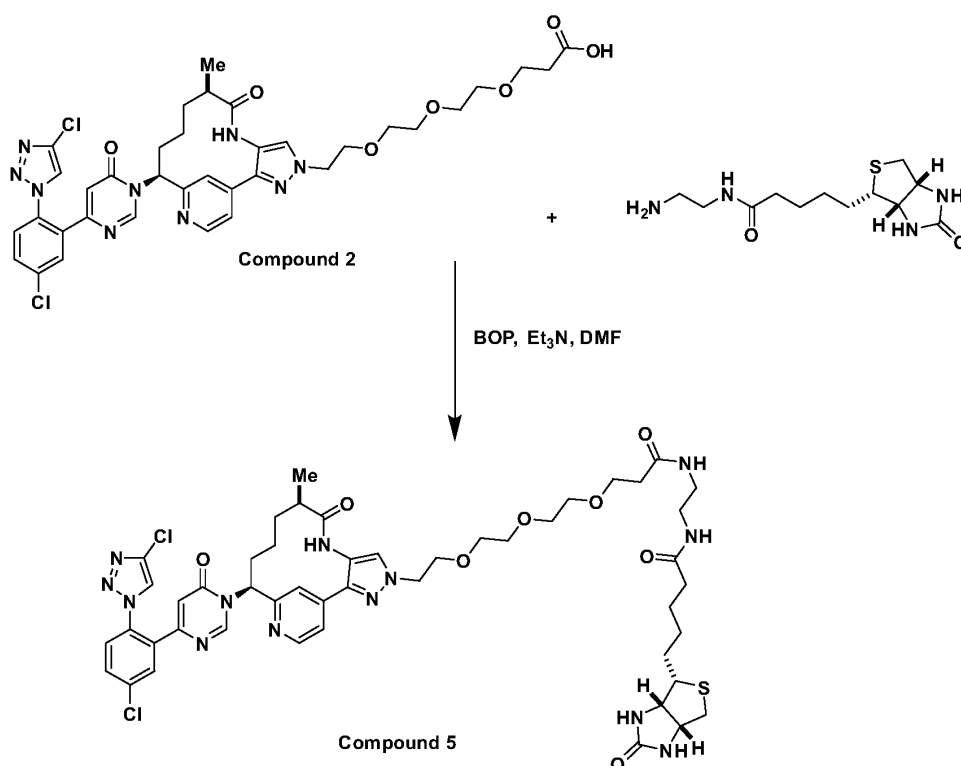
[000183] Conjugation to KLH: A 2mg sample of the COMPOUND 1, 2 or 3 was dissolved with 90 μ L of DMSO followed by 390 μ L of MES buffer and mixed by vortex. Then 200 μ L of KLH (10mg/mL stock) was added to the mixture. Finally 50 μ L of EDC (20mg/mL stock) was added. The samples were Incubated at room temperature for 3hr in the dark and then dialyzed against 5L of 1xDPBS (Lonza, cat# 17-512Q).

Conjugation BSA: A 2mg sample of the compound (COMPOUND 2, COMPOUND 3, or COMPOUND 1) was dissolved with 200 μ L of DMSO followed by 200 μ L of MES Conjugation buffer (MES pH4.7) and mixed by vortex. Then 400 μ L of BSA (5mg/mL stock) was added to the mixture. Finally, 50 μ L of EDC (20mg/mL stock) was added. (Ratios added were 10xcompound:1xcarrier:2xactivating agent.) The samples were incubated at room temperature for 3hr in the dark and then dialyzed against 5L of 1xDPBS (Lonza, cat# 17-512Q).

[000184] COMPOUND 5 (a biotin-labeled version of COMPOUND 2) has the following structure:



[000185] Synthesis of: N-(1-((5R,9S)-9-(4-(5-chloro-2-(4-chloro-1H-1,2,3-triazol-1-yl)phenyl)-6-oxopyrimidin-1(6H)-yl)-5-methyl-4-oxo-2,3-dihydro-1H-pyridine-2(3,4)-pyrazolacyclononaphane-21-yl)-12-oxo-3,6,9-trioxo-13-azapentadecan-15-yl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide (COMPOUND 5)



[000186] COMPOUND 2 (16 mg, 0.02 mmol), N-(2-aminoethyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide (5.9 mg, 0.02 mmol), biotin and triethylamine (2.9 μ l, 0.02 mmol) were dissolved in DMF (2 mL). BOP (9.1 mg, 0.02 mmol) was added and the reaction mixture was stirred for 4 hours at rt. The reaction mixture was then purified by prep HPLC.

[000187] Prep HPLC - Column = Sunfire Prep C18 OBD 5 micron (30 x 100 mm)

[000188] Solvent A = 10% MeOH, 90% water, 10 mM ammonium acetate

[000189] Solvent B = 90% MeOH, 10% water, 10 mM ammonium acetate

[000190] Linear gradient of 25% B to 100% B

[000191] COMPOUND 5 (18 mg, 80%) was isolated as a white solid.

[000192] Example 2: Generation of Human Monoclonal Antibodies Against Compound A

Using Transgenic Mice that Express Human Antibody Genes – Immunization of Mice

[000193] Human anti-Compound A antibodies were generated by immunizing mice of human Ig transgenic mouse strain HCo42:01 KCo5:01 [J/K] (Lonberg, Handbook of Experimental Pharmacology 113:49, 1994; Lonberg et al. Nature 368:856, 1994). The

immunogen was a mixture of the three KLH-compound conjugated forms: COMPOUND 1-KLH, COMPOUND 2-KLH, and COMPOUND 3-KLH, together with Ribi adjuvant (RA). The immunization protocol consisted of foot pad injections of the immunogen mixture in Ribi adjuvant. Mice were immunized every three to five days for three weeks with a total of seven injections, and the lymph nodes harvested after a pre-fusion boost the day prior to tissue collection. *In vivo* experiments were conducted in accordance with the regulations of the Animal Care and Use Committee of the Bristol-Myers Squibb Company. Lymph nodes from three immunized mice were harvested, homogenized and pooled. Hybridomas were generated by electro-fusion with the mouse myeloma fusion partner SP2/0-Ag14 (ATCC CRL-1581™) by electric field-based electrofusion. Fused cells were plated into multi-well plates in selective HAT medium for 7 days and subsequently screened by ELISA for antigen binding. Based on these results, hybridoma clones 1H2, 9C8, 24H1, and 26D5 from fusion 6938 were selected for further analysis, subcloning, and sequencing. Subcloned hybridomas were expanded to 400ml cultures for purification. Secreted fully human antibodies were purified via Protein A affinity chromatography. The best performing fully human antibody from hybridoma subclone 1873.6938.26D5.D12 (referred to as '26D5' herein) was ultimately advanced to affinity maturation.

[000194] Example 3: Affinity Maturation of Antibodies

[000195] An affinity maturation campaign was conducted on human mAb 26D5 in order to improve its affinity for Compound A. First, the mAb 26D5 sequence was compared to the closest human germline V and J gene sequences (Figure 1A-B). In order to reduce the risk of immunogenicity in humans, the framework positions that differed from germline were mutated or reverted back to germline sequence, generating human mAb 26D5-GV-Q (which in its fully human antibody format is also referred to herein as P1-072226), which retained similar binding to Compound A. mAb 26D5-GV-Q (P1-072226) was then the starting point for a mutational scan, which measured the relative fitness of every possible single amino acid substitution in the antibody CDR positions shown in Figure 2. Deep mutational scanning approaches have been described in Araya et al., *Trends in Biotechnology* 29:435, 2001; Forsynth et al., *mAbs* 5:523, 2013; and Wrenbeck et al., *Curr. Opin. Struct. Biol.* 45:36, 2017. First, an scFv (single chain) library was created where each individual amino acid substitution was generated using NNK oligonucleotides at the CDR positions shown in

Figure 2. In generating this library of single mutants, multiple oligonucleotides were designed that each individually incorporated an NNK codon at a single position, where N=A, C, G, T, and K=G, T. The use of these degenerate codons allowed encoding of all 20 naturally-occurring amino acids (plus a stop codon) at the position where the NNK codon was incorporated. The Kabat definition was used for all CDRs except HCDR1, where the AbM definition was used (Abhinandan and Martin, *Mol. Immunol.* 45:3832, 2008; Swindells et al., *J. Mol. Biol.* 429:356, 2017), and positions 60-65 of HCDR2 were not included in the analysis. Next, using mRNA display (Xu et al., *Chemistry & Biology* 9: 933, 2002; Roberts and Szostak, *Proc. Natl. Acad. Sci. USA* 94:12297, 1997; Kurz et al., *Nucleic Acids Res.* 28: E83, 2000), the DNA library was taken through a single round of *in vitro* transcription and translation, during which the encoding mRNA was fused to its own scFv protein molecule via a puromycin linkage. During selection, any scFvs that bound COMPOUND 5 (a biotin-labeled version of COMPOUND 2) were captured by magnetic streptavidin beads, eluted, and amplified by PCR. Finally, both the initial DNA library generated and the eluted DNA (encoding scFvs binding to COMPOUND 5) were sequenced using next generation sequencing (NGS).

[000196] For the analysis of the NGS data, paired-end forward and reverse read sequences from NGS were assembled using FLASH (Magoc and Salzberg, *Bioinformatics* 27:2957, 2011) and binned according to mutation position and identity of the mutated amino acid. All sequences of poor quality and those containing multiple mutation sites were eliminated from the analysis. Next, the frequency of each sequence in the post-selection population was divided by the frequency in the starting population to derive an enrichment ratio (ER). In other words, the enrichment ratio is the counts of a particular sequence variant in the COMPOUND 5-bound sample divided by the counts in the initial library. This was then normalized to the enrichment ratio of the parental 26D5-GV-Q mAb. In this manner, the effect on COMPOUND 5 binding (and thus, by inference, A) of every single amino acid substitution in the CDR regions as discussed herein was assessed. Figure 3A shows the LCDR1 heat map that was generated using the mutational scan data analysis, and allows for the interpretation of the sequence-activity relationship of single amino acid substitutions. Generally, the error in this method is approximately two-fold. Thus, enrichment ratio (ER) values from 0.5 to 2 are considered to be neutral substitutions, i.e., substitutions that maintain

binding properties to COMPOUND 5. ER values greater than 2 are considered favorable or preferred for binding, and ER values less than 0.5 are considered unfavorable for binding.

Figures 3B-E show the heat maps for the remaining CDRs.

[000197] Based on the calculated enrichment ratios from the NGS data, variable region genes for single and combinations of favorable amino acid substitutions were synthesized and cloned into IgG expression vectors with the human IgG1f Fc region and human LC kappa region (CK). The vectors were transiently transfected into Expi293 HEK cells at a small scale (2ml culture) and purified using a Protein A filter plate. The IgG proteins were assessed using SPR (surface plasmon resonance) and functional activity (see data below). Sequences of the antibodies of interest that were identified following this assessment are shown in Figure 4A-B.

[000198] In particular, progeny 26D5-295-B08 was chosen for further affinity maturation using three different library designs. For the first design, a second mutational scan was performed on 26D5-295-B08, randomizing the residues shown in Figure 5. In this second mutational scan, positions outside of the Kabat and/or AbM CDR definitions were randomized, based on their proximity to Compound A in the co-crystal structure. The heat maps from the mutational scan of 26D5-295-B08 are shown in Figures 6A-F. As previously, variable region genes for single and combinations of favorable amino acid substitutions were synthesized and cloned into IgG1f expression vectors for assays. MAbs of interest that were identified from the mutational scan of 26D5-295-B08 included: 26D5-75202-343-A09, 26D5-75229-343-A10, 26D5-75203-343-B09, 26D5-75017-343-F04, and 26D5-75214-343-F06 (see Tables 1-3 for sequences). All human antibodies disclosed in the Examples were in IgG1f (e.g., SEQ ID NO: 200) and human LC kappa format (e.g., SEQ ID NO: 204), unless specifically indicated otherwise.

[000199] In addition, two complex libraries (chip and doped) based on 26D5-295-B08 were constructed to more fully randomize positions of interest (Figure 7A-B). The chip library was designed to contain single and double substitutions to all amino acids (except cysteine and methionine) within a CDR and flanking framework positions, with some additional modifications as noted in Figure 7A. The design also removed sequences containing chemical liabilities and was synthesized via chip oligonucleotides (Twist Bioscience). The doped library focused randomization on HCDR3 and surrounding framework residues in

order to access more than two mutations within a single CDR. The DNA oligonucleotides encoding this library were generated by “doping” the randomized region based on the 26D5-295-B08 DNA sequence. For each nucleotide in the randomized region, the oligo contained 70% of the 26D5-295-B08 DNA base, and 10% each of the other bases. For example, if the 26D5-295-B08 DNA had a G at a particular position, then the doped oligo would contain 70% G, 10% A, 10% C, and 10% T at that position. This allows deeper randomization of the regions of interest while still biasing the library toward the original parent sequence. The oligos were used to generate separate chip and doped DNA scFv libraries. These libraries were selected using mRNA display according to the above protocol, but with multiple successive rounds incorporating off-rates in later rounds. The resulting populations were sequenced using NGS, and the data were analyzed to pick variable regions for synthesis and cloning into IgG expression vectors for testing. MAbs of interest that were identified from the chip library include: 26D5-75592-348-A04, 26D5-75768-348-A10, 26D5-75576-348-B03, 26D5-75746-348-C07, 26D5-75747-348-D07, and 26D5-75602-348-F04 (see Tables 1-3 for sequences). MAb 26D5-75616-348-F10 was identified as an antibody of interest from the doped library. Figures 8A-B show the sequences of interest from the affinity maturation of mAb 26D5-295-B08.

[000200] For confirmation of small-scale results, the expression vectors of antibodies of interest were transiently transfected into Expi293 HEK cells at a 340mL scale and purified using a prepacked 20mL POROS A column, buffer exchanged into PBS using an Amicon 30K MWCO filter, sterile filtered over 0.2µm PES filter, aliquoted and stored at -80C. Each sample was mass confirmed by LC/MS and characterized by analytical SEC.

[000201] Example 4: Characterization of mAbs by a Chromogenic Enzymatic Assay

[000202] The ability of mAbs to preserve FXIa enzymatic activity in the presence of Compound A was used as a screening assay for antibodies with improved affinity. The assay used an S-2366 chromogenic peptide from Chromogenix as substrate for the Factor XIa enzyme. Each tested mAb was serially diluted from 100 nM to 1.5 nM and incubated with 2.5 nM Compound A or a control compound for 10 minutes at 37°C. Then the chromogenic substrate S-2366 was added to a final concentration 0.5 mM and human FXIa enzyme (Haematologic Technologies, Inc.; HCZIA-0160) was added to a final concentration 0.2 nM. A concentration of 2.5 nM of Compound A produced ~90% inhibition of FXIa activity, i.e.

near full occupancy of FXIa. The assay described here was constructed to produce a meaningful dynamic range. Plates were immediately read at OD 405nm at 37°C on a Molecular Devices SPECTRAmax to measure the rate of substrate hydrolysis. The signal was normalized to 0% activation (FXIa enzyme with Compound A) and 100% activation (FXIa enzyme with no inhibitor). An EC₅₀ was determined for antibodies that reversed 50% or more of the Compound A induced inhibition. Example results are shown in Figure 9.

[000203] Example 5: Production of Recombinant α -Compound A Antibody Fab Fragments

[000204] The selected antibodies were cloned as untagged antibody Fab fragments into the pTT5 vector for Expi293 expression. See SEQ ID NOs for Fab sequences. The optimized DNA sequences were received from GenScript for mammalian expression. For expression at 1L scale, 900 mL of cells at 3×10^6 cells/mL were seeded in a 2L Corning flask. 0.25 mg of each heavy chain and light chain DNA construct were added to 50 mL of Opti-MEM™. 4.1 mL of ExpiFectamine™ in 150 mL of Opti-MEM™ was incubated for 5 minutes at room temperature and then 50 mL of the aforesaid 150 mL were added to the DNA/Opti-MEM™ mixture and incubated for 20 minutes at room temperature. This total 100 mL transfection mixture was added to the 900 mL of cells and placed in 37°C shaker (125 rpm, 8% CO₂ in air). Production was fed with 2 mM VPA and 50 ml of CHO CD efficient Feed B on the first day. Cell viability was tested and productions were harvested on day 5. Average cell viability/cell density was 80%/6 x 10⁶ cells/mL. The productions were centrifuged at 2,000 rpm at 4°C for 20 minutes. The conditioned media supernatant was filtered through 0.2 μ m filters. A 30 mL rProteinA Sepharose FF column was washed with 2 column volumes (CVs) of 6M Guanidine, 2 CVs of 0.033M HCl, and then equilibrated in 1x Dulbecco's PBS. The supernatant pH was verified to be >7.0 and then loaded at 10 mL/min onto the rProteinA Sepharose column. rProteinA binding via framework proteinA interactions was observed for all of the progeny of 1873.6938.26D5.D12 including affinity matured variants. The column was washed in 1xDPBS until baseline was reached and then eluted with 80 mM Sodium Acetate (pH 2.8) into a container filled with ~20 ml Tris HCl (pH 8.0) so protein could neutralize while eluting. The column was then neutralized with 1xDPBS. The eluted sample was concentrated to <10 mL and loaded onto an equilibrated (1xDPBS) S200 26/600 column at 2.5 mL/min. Five mL fractions were collected at 2.5 mL/min and analyzed by SDS-PAGE

and chromatogram for pooling. Typical yields were 150-250 mg/L of purified Antibody Fab Fragment.

[000205] Example 6: Characterization of mAbs and Fabs by Surface Plasmon Resonance (SPR) (Biacore™) Analysis

[000206] The binding of hybridoma expressed 26D5 parent mAb (VH SEQ ID NO: 83 and VL SEQ ID NO: 98 in IgG1f format)(P1-072224) and affinity matured mAbs to Compound A was examined by SPR (Biacore™) using a protein A capture method. The running buffer was 1xPBS (phosphate buffered saline, pH 7.4) with 0.05% Tween 20 and 2% DMSO. Binding experiments were carried out at 37°C. Protein A was coated on a CM5 S-series sensor chip (Cytiva, Cat. No. 29149603) at high density (2000+ RUs of protein A). The immobilization of protein A was carried out using the standard amine coupling immobilization procedure recommended by the manufacturer. The affinity matured antibody was then captured at a concentration of 2µg/mL on the protein A surface at a flow rate of 3µL/min for 2 minutes. Compound A was then injected over the captured antibody at concentrations spanning 100-3 nM (100, 50, 25, 12.5, 6.25, 3.125 nM) (Figure 10) and for screening concentrations spanning 100-3 nM (100, 33, 11 nM) for 2 minutes at a flow rate of 100 µL/min and allowed to dissociate for at least 450 seconds. The chip surface was regenerated after each cycle with a 40 second pulse of 10 mM Glycine, pH 1.5. Background binding to the protein A surface alone was used to subtract non-specific binding. All experiments were run on a Biacore T200 surface plasmon resonance instrument using Biacore T200 Control software v. 2. Data analysis was performed using Biacore T200 evaluation software v 3.1. Apparent affinities were determined for rank ordering only since dissociation rates were too slow to be measured by Biacore. Example binding assay data are shown in Figure 10 and binding assay data are reported in Table 10. The names of the mAbs in Table 10 refer to mAbs having the H and L chain sequences of the corresponding Fabs in Table 3 in an IgG1f format.

Table 10. SPR data

[000207] Biacore Protein A mAb capture

Name	K _a (1/Ms)	K _d (1/s)	K _D (M)	Temperature
26D5-75229-343-A10-mAb	7.7E5	<5E-5	<0.07 nM	37°C

26D5-75214-343-F06-mAb	1.2E6	<5E-5	<0.05 nM	37°C
26D5-75202-343-A09-mAb	5.9E5	<5E-5	<0.09 nM	37°C
26D5-75203-343-B09-mAb	1.2E6	<5E-5	<0.05 nM	37°C
26D5-75616-348-F10-mAb	1.7E6	<5E-5	<0.03 nM	37°C
26D5-75768-348-A10-mAb	3.8E6	<4.1E-4	<0.1 nM	37°C
26D5-75747-348-D07-mAb	2.0E6	<5E-5	<0.02 nM	37°C
26D5-75602-348-F04-mAb	9.1E5	<5E-5	<0.05 nM	37°C
26D5-75576-348-B03-mAb	8.8E5	<5E-5	<0.06 nM	37°C
26D5-075017-343-F04-mAb	1.5E6	1.7E-4	0.11 nM	37°C
25D5-75592-0348-A04-mAb	1.0E6	1.1E-4	0.1nM	37°C
26D5-75017-0343-F04-mAb	1.5E6	1.7E-4	0.11 nM	37°C
26D5-75602-0348-F04-mAb	9.1E5	<5E-5	<0.05 nM	37°C
26D5-75576-0348-B03-mAb	8.8E5	<5E-5	<0.06 nM	37°C
26D5-75746-0348-C07-mAb	2.4E6	2.4E-4	0.1 nM	37°C
26D5-75747-0348-D07-mAb	2.0E6	<5E-5	<0.03 nM	37°C
25D5-296-A07-mAb	1.7 E5	2.7 E-4	1.6 nM	37°C
26D5-296-H03-mAb	1.6 E5	1.8E-4	1.1 nM	37°C
26D5-295-F07-mAb	1.8E5	1.7E-4	0.94 nM	37°C

26D5-296-G07-mAb	8.5E5	3.2E-4	0.38 nM	37°C
26D5-295-E07-mAb	1.9E5	2.3E-4	1.2 nM	37°C
26D5-296-C08-mAb	5.3E5	3.1E-4	0.59 nM	37°C
26D5-295-C07-mAb	2.0E5	3.3E-4	1.6 nM	37°C
26D5-296-B07-mAb	2.9E5	4.2E-4	1.8 nM	37°C
26D5-295-G07-mAb	6.3E5	4.3E-4	0.67 nM	37°C
26D5-296-D08-mAb	7.7E5	4.5E-4	0.59 nM	37°C
26D5-296-F03-mAb	7.2E5	3.9E-4	0.54 nM	37°C
26D5-296-G08-mAb	8.0E5	3.9E-4	0.49 nM	37°C
26D5-296-F07-mAb	7.6E5	4.4E-4	0.58 nM	37°C
26D5-296-G03-mAb	9.4E5	5.8E-4	0.61 nM	37°C
26D5-296-F08-mAb	8.7E5	6.0E-4	0.68 nM	37°C
26D5-295-A08-mAb	1.0E6	5.9E-4	0.58 nM	37°C
26D5-295-D07-mAb	8.0E5	8.1E-4	1.0 nM	37°C
26D5-296-D03-mAb	1.7E6	1.2E-3	0.71 nM	37°C
26D5-296-C07-mAb	9.5E5	1.4E-3	1.4 nM	37°C

[000208] The binding of the first round affinity matured antibody Fab fragments to conjugated versions of Compound A was examined by SPR (Biacore™) using a CM5 S-series sensor chip (Cytiva, Cat. No. 29149603) coated with BSA previously conjugated to

COMPOUND 2, COMPOUND 3 or COMPOUND 1. The immobilization level was 150-250 RUs. The running buffer was 1xPBS (phosphate buffered saline, pH 7.4) with 0.05% Tween 20. Binding experiments were carried out at 25°C. The antibody Fab fragment at a concentration of between 200-0.8 nM was injected over the BSA-compound coated surface for 2 minutes at a flow rate of 30 uL/min. The antibody Fab fragment was then allowed to dissociate for 15 minutes. The chip surface was regenerated after each cycle with a 1 minute pulse of 10 mM Glycine, pH 2, and a 1 minute pulse of 50 mM NaOH. All experiments were run on the same equipment and analyzed with the same software as described before. Apparent affinities were determined for rank ordering only since dissociation rates were too slow to be measured by Biacore. Comparative experiments with selected mAbs were also conducted in a similar fashion (see Figure 11). Example binding assay data are shown in Figure 11 and binding assay data for COMPOUND 2-BSA are reported in Table 11. The sequences of the Fabs in Table 11 are indicated in Table 3.

Table 11. SPR data

Name	Ka (1/Ms)	Kd (1/s)	KD (M)	Temperature
26D5-295-B08-Fab-LONG	2.8E5	2.2E-4	0.8 nM	37°C
26D5-295-C08-Fab-LONG	2.8E5	8.5E-5	0.3 nM	37°C
9C8-VGSKE-Fab-LONG	4.0E5	8.7E-4	2.1 nM	25°C
1H2-K -Fab-LONG	1.8E6	1.5 E-3	0.8 nM	37°C
24H1-GQTV-Fab-LONG	7.9E5	1.0E-3	1.3 nM	37°C
26D5-GVR-Q-FT-Fab-LONG	1.3E6	1.6E-3	1.3 nM	37°C

26D5-GVR-Q-FT-Fab-SHORT	1.6E6	1.3E-3	0.9 nM	37°C
26D5-GVR-H-Fab-LONG	2.8 E5	1.0E-3	3.5 nM	37°C

[000209] The binding of the first and second round affinity matured antibody Fab fragments to conjugated versions of Compound A was examined by SPR (Biacore™) using a Biotin-CAP S-series sensor chip and kit reagents from Cytiva (Cat No. 28920234). The Biotin-CAP chip was hydrated in buffer overnight. Biotin-CAP reagent at 50% in water was flowed over the chip surface for 150 seconds at a flow rate of 2 uL/min. COMPOUND 5 (a biotinylated version of COMPOUND 2) was captured on the Biotin CAP surface at 0.25ug/mL at a flow rate of 10uL/min for a 20 second pulse. The running buffer was 1xPBS (phosphate buffered saline, pH 7.4) with 0.05% Tween 20. Experiments were carried out at 25°C or 37°C. The antibody Fab fragment at a concentrations of 100-3 nM was injected over the Biotin-CAP-COMPOUND 5 surface for 3 minutes at a flow rate of 30 uL/mni. The antibody Fab fragment was allowed to dissociate for 11.7 minutes. The chip surface was regenerated after each cycle with two 2 minute pulses of 6 M Guanidine-HCl in 250 mM NaOH. All experiments were run on the same equipment and analyzed with the same software as described before. Apparent affinities were determined for rank ordering only since dissociation rates were too slow to be measured by Biacore. Example binding assay data are shown in Figure 12 and binding assay data for antibody TanFab fragments are reported in Table 12. The sequences of the TanFabs in Table 12 are indicated in Table 4.

Table 12. SPR data

mAb/Fab	Ka (1/Ms)	Kd (1/s)	KD (M)	Temperature
26D5-75229-343-A10-TanFab	1.7E5	<5E-5	<0.3 nM	25°C
26D5-75229-343-A10-TanFab-long	1.8E5	<5E-5	<0.3 nM	25°C

26D5-75229-343-A10-TanFab-ELQ	1.8E5	<5E-5	<0.3 nM	25°C
26D5-75229-343-A10-TanFab-G4S	1.9E5	<5E-5	<0.3 nM	25°C
26D5-75616-348-F10-TanFab	1.1E5	<5E-5	<0.5 nM	25°C
26D5-75203-343-B09-TanFab	9.2E4	<5E-5	<0.5 nM	25°C
26D5-75202-343-A09-TanFab	3.0E5	<5E-5	<0.2 nM	25°C
26D5-75768-348-A10-TanFab	1.3E5	<5E-5	<0.4 nM	25°C
26D5-75214-343-F06-TanFab	1.2E5	<5E-5	<0.4 nM	25°C

[000210] Example 7: Characterization of mAbs and Fabs by TR-FRET Assay

[000211] A competitive TR-FRET (time-resolved fluorescence resonance energy transfer) assay was developed to rank-order the dissociation of α -Compound A mAbs from Compound A as equilibrium is reached at 37°C. The assay buffer was HBS-N (10 mM HEPES, 150 mM NaCl, pH 7.4; GE Healthcare), 0.1% (w/v) BSA (bovine serum albumin; Sigma), 2% DMSO (dimethyl sulfoxide; Sigma). All reagents were prepared in assay buffer and dispensed in equal volumes into white 384 microplates with final volume of 20 μ l per well at the following final concentrations: 4 nM COMPOUND 5, the biotinylated analog of COMPOUND 2, a 100 – 0.1 nM 7-pt titration of human α -Compound A antibodies, 0.1 nM europium-labeled α -mouse IgG (LANCE Eu-W1024; PerkinElmer), 5 nM streptavidin-D2 (Cisbio), and 4 nM mAb 26D5 VH_A10G_Y33A_S53P_M89V_G95A; VK_W32N_H38Q (P1-075621, the second-round optimization parent 26D5-295-B08 formatted with mouse IgG Fc). COMPOUND 5 and α -Compound A antibody titrations were added first to the

microplate, and were subjected to an initial incubation at 37°C, 1000 rpm, for one hour to facilitate antibody binding to the compound. After the initial incubation period, the europium α -mouse IgG, streptavidin-D2, and 26D5-mouse IgG (P1-075621) were added sequentially, then the plate was returned to 37°C, 1000 rpm incubation. Microplates were read using a Perkin Elmer EnVision plate reader, and the measured FRET signal was defined as $[(665 \text{ nm})/(620 \text{ nm})] * 10,000$. Microplates were read at 30 minutes (T0) and after 24 hour (T24) intervals. For each antibody titration, the FRET signal was converted to % Inhibition relative to wells without α -Compound A antibody: $(100 - ((\text{FRET at [antibody concentration]}/\text{FRET at 0 nM}) * 100))$. The % inhibition antibody titrations were plotted using TIBCO Spotfire (v.7), and the IC₅₀ was determined using a 4-parameter model curve fit. The IC₅₀s at each timepoint were reported, as well as the IC₅₀ curve shift relative to T0. An IC₅₀ curve shift indicated α -Compound A antibody dissociation from the biotinylated compound as the assay reached equilibrium, which subsequently allowed 26D5-mouse IgG1 (P1-075621) competitor to bind and generate the FRET signal detected in the assay.

[000212] Exemplary competitive FRET data collected from α -Compound A 26D5 affinity optimization screening is shown in Figure 13. Three representative human antibodies are shown: 1) IgG1f mAb format of 26D5-GVR-Q-FT-Fab-LONG; also referred to herein as P1-072226 (except that R31 in 26D5-GVR-Q-FT HC is S31 in P1-072226 HC), top panel, 2) IgG1f mAb format of first round optimization progeny 26D5-295-B08-Fab-LONG (also referred to herein as P1-072963), middle panel, and 3) IgG1f mAb format of second round optimization progeny 26D5-75747-348-D07-Fab-LONG (also referred to herein as P1-075747), bottom panel. The IC₅₀s are annotated along each antibody titration curve with a star. The difference between T0 and T24 IC₅₀s is defined as Δ , and the values are reported in each panel. The 26D5-GVR-Q-FT-Fab-LONG mAb parent exhibited the most significant T0 - T24 IC₅₀ shift, 63 nM. As the Compound A dissociation rate (off-rate) was improved through successive rounds of affinity maturation in subsequent progeny (P1-072963: 20.5 nM, then P1-075747: 4.3 nM), the T0 - T24 IC₅₀ shift was minimized. The α -Compound A antibodies were rank-ordered by T24 IC₅₀ and the IC₅₀ shift (Δ) to identify antibodies with improved 37°C Compound A dissociation rates relative to the mAb 26D5-GVR-Q-FT-Fab-LONG parent and mAb 26D5-295-B08 (P1-072963).

[000213] The competitive TR-FRET assay defined above was also modified to assess optimized 26D5 antibody progeny that were reformatted as Fabs. The α -Compound A antibody and Fab titration series were extended to 250 – 0.244 nM (11-pt titration), and replicates of each concentration were collected in quadruplicate. The assay incubation was extended to include an additional 48hr timepoint to ensure equilibrium was reached, and T48hr IC₅₀ and IC₅₀ shifts were reported. The % inhibition titrations were plotted in Graphpad Prism (v.8) and fit to a 4-parameter model. All other experimental setup conditions were otherwise identical to the antibody TF-FRET assay.

[000214] Competitive FRET data collected for affinity-optimized α -Compound A 26D5 progeny comparing human antibodies and Fabs are shown in Figure 14 and Table 13. Each panel represents a single α -Compound A sequence, with antibody (mAb, solid lines, circles) and Fab (dotted lines, triangles) formats overlaid. The 26D5 parent Fab (Fab 26D5-GV-Q; also referred to herein as P1-073708) and first round optimization progeny Fab 26D5-295-C08 (also referred to herein as P1-074468-1) exhibited significant T48 IC₅₀ shifts of at least 26 nM. Second round affinity matured optimized progeny retained slow 37°C dissociation from Compound A in both antibody and Fab formats, exhibiting minimal T48 IC₅₀ shifts. FRET data are provided in Table 13. The names of the mAbs/Fabs in Table 13 refer to the corresponding sequences in Tables 1-3. All mAbs listed in Table 13 were in a human IgG1f/LC kappa format.

Table 13 (“-1”, “-2” etc. refer to lot numbers of otherwise identical mAbs or Fabs)

Sample	T0 IC ₅₀ (nM)	T24hr IC ₅₀ (nM)	T24hr IC ₅₀ shift (nM)	T48hr IC ₅₀ (nM)	T48hr IC ₅₀ shift (nM)
P1-075616-2 (26D5-75616-348-F10 mAb)	1.4	2.5	1.1	2.8	1.4
P1-076827-3 (26D5-75616-348-F10 Fab)	2.8	6.6	3.8	8.8	5.9
P1-076827-4 (26D5-75616-348-F10 Fab)	2.2	5.8	3.5	7.1	4.9

P1-075229-2 (26D5-75229-343-A10 mAb)	1.3	2.4	1.1	2.5	1.1
P1-077178-1 (26D5-75229-343-A10 Fab)	2.5	4.5	2.0	4.9	2.5
P1-075202-2 (26D5-75202-343-A09 mAb)	1.4	2.5	1.1	2.9	1.5
P1-077145-1 (26D5-75202-343-A09 Fab)	2.0	5.8	3.8	7.5	5.5
P1-075768-2 (26D5-75768-348-A10 mAb)	1.2	2.2	1.0	2.3	1.1
P1-077174-2 (26D5-75768-348-A10 Fab)	2.2	5.4	3.2	5.8	3.6
P1-075214-2 (26D5-75214-343-F06 mAb)	1.3	2.5	1.3	2.7	1.4
P1-077176-2 (26D5-75214-343-F06 Fab)	2.6	7.3	4.7	8.7	6.1
P1-075203-2 (26D5-75203-343-B09 mAb)	2.6	3.0	0.4	3.1	0.5
P1-077144-1 (26D5-75203-343-B09 Fab)	2.7	6.1	3.4	8.1	5.4
P1-073708-1 (26D5 parent Fab)	2.6	>28.2	>25.7	>28.8	>26.2
P1-074468-1 (26D5-295-C08 Fab)	2.2	>38.2	>36.0	>43.1	>41.0

[000215] Example 8: Gel Filtration

[000216] Using an Agilent 1260 HPLC system with a Shodex K403-4F and a mobile phase of 100mM Sodium Phosphate 150 mM Sodium Chloride, pH 7.3, at a flow rate of 0.3mL/min, aliquots of purified Fab were injected (20ug) for a run time of 20 minutes. Gel Filtration standards confirmed that most Fabs were at least 98% monomer with greater than 75% recovery.

[000217] Example 9: Thermal Stability Analysis of Fabs

[000218] Thermal stability analysis was performed with UNchained Labs UNcle TM/Tagg analysis with Fabs at a concentration of 20 uM with or without Compound A at a concentration of 50 uM (or control compound). Capillaries were scanned from 25 to 90°C at 0.5°C/min. In addition, select Fabs were also analyzed by Differential Scanning Calorimetry analysis using the Malvern MicroCal VP-Capillary DSC. Samples were buffer matched and loaded with Fabs at a concentration of 10 uM with or without Compound A at a concentration of 15uM (or control compound). Scan temperature range was 15-110°C at a rate of 60°C/Hr (Filter period: 16 sec, Gain: None). Sample analysis was using software provided by the manufacturer for both the UNcle and the Malvern Capillary DSC. Figure 15 and Table 14 below show representative DSC results. The sequences of the Fabs in Table 14 are indicated in Table 3.

Table 14 (Thermal stability by Differential Scanning Calorimetry)

Sample	Conc (mg/ml)	Tm1 (°C)	Tm2 (°C)
26D5-295-C08-Fab-SHORT	1	75.3	
26D5-75616-348-F10-Fab-SHORT	1	75.2	
26D5-75229-343-A10-Fab-SHORT	1	74.9	
26D5-75202-343-A09-Fab-SHORT	1	75.3	
26D5-75203-343-B09-Fab-SHORT	1	76.6	
26D5-75768-348-A10-Fab-SHORT	1	66.3	74.1
26D5-75214-343-F06-Fab-SHORT	1	75.5	

[000219] Example 10: Kinetic Exclusion Analysis (KinExA)

[000220] The solution affinity of the antibody Fab fragments disclosed herein for Compound A was measured using a Kinetic Exclusion Assay (KinExA). Duplicate titrations of Compound A were performed with 26D5 affinity matured antibody Fab fragments at 100, 200, and 300 pM (equilibrated for 24-72 hours). The relative unbound concentration of 26D5

affinity matured antibody Fab fragment was measured by capture on a streptavidin coated bead with COMPOUND 5 followed by detection with a fluorescently labeled antibody that recognizes the human IgG Fab. Kinetic analysis to determine the complex association rate was measured with the same assay format except that a single tube of the mixture was prepared (200 pM Fab and 400 pM Compound A) and time points were removed immediately (no equilibration). Results are shown in Table 15 below. Two Fabs, 26D5-75229-343-A10-Fab-SHORT and 26D5-75616-348-F10-Fab-SHORT, were identified as the top two Fabs by DSC thermal stability and KinExA analysis. Antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT (SEQ ID NO: 106 and SEQ ID NO: 164; see Table 3) was selected for X-ray crystallography as described below and *in vivo* studies as described in Example 12.

Table 15 KinExA (Kinetic Exclusion Analysis)

Name	KinExA KD (M)	KD 95% Confidence Interval	KinExA Ka (1/Ms)
26D5-75229-343-A10-Fab-SHORT	0.22 pM	8 pM to < 1fM	5.0E4
26D5-75214-343-F06-Fab-SHORT	15 pM	4 pM to 37 pM	6.0E5
26D5-75202-343-A09-Fab-SHORT	19 pM	92 pM to <70 fM	1.5E5
26D5-75203-343-B09-Fab-SHORT	10 pM	35 pM to <15 fM	1.4E4
26D5-75616-348-F10-Fab-SHORT	0.13 pM	3.8 pM to <1 fM	9.0E5
26D5-75768-348-A10-Fab-SHORT	0.41 pM	12 pM to <1.5 fM	NM

[000221] Example 11: Crystallization of Fabs

[000222] Fab 26D5-GVR-Q-FT-Fab-SHORT with a GGHHHHHHH (SEQ ID NO:222)

affinity tag was concentrated to 10 mg/ml in DPBS (Dulbecco's Phosphate Buffered Saline) buffer. The protein was complexed with a 5-fold molar excess of Compound A and incubated overnight at 4°C. The complex was crystallized by sitting drop vapor diffusion. The drops consisted of 1 µl of complex and 1 µl of reservoir. The crystallization reservoir consisted of 20 g PEG 3350 dissolved in water to a total volume of 100 ml and 20 mM of unbuffered sodium citrate. The crystals were prepared for flash-cooling in liquid nitrogen by the serial addition of a mixture of 2.5 µl 40% PEG400:40% glycerol (v/v) with 7.5 µl of the reservoir solution to the drop.

[000223] Antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT was concentrated to 20 mg/ml in DPBS buffer. The protein was complexed with a 5-fold molar excess of Compound A and incubated overnight at 4° C. The complex was crystallized by sitting drop vapor diffusion. The drops consisted of 1 µl of complex and 1 µl of reservoir. The crystallization reservoir consist of 100 mM CAPS (N-cyclohexyl-3-aminopropanesulfonic acid), pH 10.5, 200 mM lithium sulfate, 1.2 M sodium phosphate and 0.8 M potassium phosphate. The crystals were prepared for flash-cooling in liquid nitrogen by the serial addition of a mixture of 2.5 µl 40% PEG400:40% glycerol (v/v) with 7.5 µl of the reservoir solution to the drop.

[000224] Data were collected at the Advanced Photon Source at beamline 17-ID using a Pilatus 6M detector. Data were processed with the autoPROC package [Vonnrhein, C., Flensburg, C, Keller, P., Sharff, A., Smart, O., Paciorek, W., Womack, T. & Bricogne, G. (2011). Data processing and analysis with the autoPROC toolbox. *Acta Crystallogr. Sect. D* **67**, 293-302], including the underlying software XDS for processing, XSCALE for scaling and STARANISO for anisotropic extent of the data [W. Kabsch (2010). XDS. *Acta Crystallogr. Sect. D* **66**, 125-132 and W. Kabsch (2010). Integration, scaling, space-group assignment and post-refinement. *Acta Crystallogr. Sect. D* **66**, 133-144; STARANISO (Tickle, I.J., Flensburg, C., Keller, P., Paciorek, W., Sharff, A., Vonnrhein, C., Bricogne, G. (2018). STARANISO (available on the world-wide web at staraniso.globalphasing.org/cgi-bin/staraniso.cgi) Cambridge, United Kingdom: Global Phasing Ltd).

[000225] 26D5-GVR-Q-FT-Fab-SHORT/Compound A crystals had symmetry consistent with space group $P2_12_12_1$ with unit cell edges of $a = 57.7 \text{ \AA}$; $b = 75.1 \text{ \AA}$; and $c = 84.7 \text{ \AA}$ with one complex per asymmetric unit. Data extended to $1.47 \text{ \AA}$ when processed isotropically, but an ellipsoidal cutoff that extended to $1.38 \text{ \AA}$ in a^* , $1.44 \text{ \AA}$ in b^* , and $1.32 \text{ \AA}$ in c^* was used to retain data. The structure was determined by molecular replacement using PHASER (McCoy, A.J., Grosse-Kunstleve, R.W., Adams, P.D., Winn, M.D., Storoni, L.C. & Read, R.J. (2007). Phaser Crystallographic Software. *J. Appl. Crystallogr.* **40**, 658-674.) with models for CL:CH1 derived from PDB 2O5X (Verdino, P., Aldag, C., Hilvert, D., Wilson, I.A. (2008) Closely Related Antibody Receptors Exploit Fundamentally Different Strategies for Steroid Recognition. *Proc. Natl. Acad. Sci., USA* **105**, 11725-11730), VL derived from PDB 4PY7 (Wyrzucki, A., Dreyfus, C., Kohler, I., Steck, M., Wilson, I.A., Hangartner, L. (2014). Alternative Recognition of the Conserved Stem Epitope In Influenza A Virus Hemagglutinin By A VH3-30-Encoded Heterosubtypic Antibody. *J. Virol.* **88**, 7083-7092.), and VH derived from PDB 4TSA (Wensley, B. Structure of a Lysozyme Fab Complex, unpublished.). All CDRs (Complementarity Determining Regions) were removed from the VH and VL models. The initial electron density map showed unambiguous electron density for Compound A. Geometric restraints for the ligand were created using GRADE (Smart, O.S., Womack, T.O., Sharff, A., Flensburg, C., Keller, P., Paciorek, W., Vonnrhein, C. and Bricogne, G., Global Phasing, Ltd., Cambridge, United Kingdom) and initially placed with RHOFIT (Womack, T.O., Smart, O.S., Sharff, A., Flensburg, C., Keller, P., Paciorek, W., Vonnrhein, C. and Bricogne, G., Global Phasing, Ltd., Cambridge, United Kingdom). The structure was improved through alternating rounds of model building with Coot (Emsley, P., Lokhamp, B., Scott, W.G. & Cowtan, K. (2010). Features and Development of Coot. *Acta Crystallogr Sect. D* **66**, 486-501) and refinement with autoBUSTER. (Bricogne, G., Blanc, E., Brandl, M., Flensburg, C., Keller, P., Paciorek, W., Roversi, P., Sharff, A., Smart, O., Vonnrhein, C., Womack, T. BUSTER version 2.11.7. Global Phasing, Ltd., Cambridge, United Kingdom). The image in Figure 16 shows the refined structure for the complex of 26D5-GVR-Q-FT-Fab-SHORT/Compound A.

[000226] 26D5-75616-348-F10-Fab-SHORT/Compound A crystals had symmetry consistent with space group P1 with unit cell edges of $a = 64.8 \text{ \AA}$; $b = 84.9 \text{ \AA}$; $c = 100.9 \text{ \AA}$; $\alpha = 83.4^\circ$; $\beta = 88.4^\circ$; $\gamma = 67.9^\circ$ with four complexes per asymmetric unit. Data extended to 2.7

Å when processed isotropically, but an ellipsoidal cutoff that extended to 1.91 Å in $0.880a^* + 0.436b^* - 0.189c^*$, 2.20 Å in $0.063a^* + 0.898b^* - 0.436c^*$, and 2.98 Å in $0.093a^* + 0.382b^* + 0.920c^*$ was used to retain data. The structure was determined by molecular replacement using PHASER (McCoy, A.J., Grosse-Kunstleve, R.W., Adams, P.D., Winn, M.D., Storoni, L.C. & Read, R.J. (2007). Phaser Crystallographic Software. *J. Appl. Crystallogr.* **40**, 658-674.) with models for CL:CH1, VL and VH derived from that of antibody Fab fragment 26D5-GVR-Q-FT-Fab-SHORT with CDR-H3 removed from the VH model. The initial electron density map showed electron density for Compound A. The structure was improved through alternating rounds of model building with Coot (Emsley, P., Lokhamp, B., Scott, W.G. & Cowtan, K. (2010). Features and Development of Coot. *Acta Crystallogr Sect. D* **66**, 486-501) and refinement with autoBUSTER using automated NCS restraints. (Bricogne, G., Blanc, E., Brandl, M., Flensburg, C., Keller, P., Paciorek, W., Roversi, P., Sharff, A., Smart, O., Vonnrhein, C. & Womack, T. BUSTER version 2.11.7. Global Phasing, Ltd., Cambridge, United Kingdom and Smart, O.S. Womack, T.O., Flensburg, C., Keller, P., Paciorek, W., Sharff, A., Vonnrhein, C. & Bricogne, G. (2012). Exploiting structure similarity in refinement: automated NCS and target-structure restraints in BUSTER. *Acta Crystallogr Sect. D* **68**, 368-380). The image in Figure 17 shows the refined structure for the complex of 26D5-75616-348-F10-Fab-SHORT/Compound A.

[000227] Two Fabs, 26D5-75229-343-A10-Fab-SHORT and 26D5-75616-348-F10-Fab-SHORT, were identified as the top two Fabs by DSC thermal stability and KinExA analysis. X-ray crystallography of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT demonstrated the 1:1 stoichiometry of binding of the antibody Fab fragment with Compound A and the mechanism of binding in the cleft between the heavy and light chains of the antibody Fab fragment.

[000228] Example 12: Plasma Binding Studies of Antibody Fab Fragments

[000229] Studies were conducted to evaluate the ability of 26D5-75616-348-F10-Fab-SHORT to reverse the anticoagulant effects of milvexian in plasma.

[000230] *In vitro studies*

[000231] The ability of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT to neutralize the *in vitro* anticoagulant activity of Factor XIa inhibitor Compound A was determined by combining the Fab fragment with plasma which contained a known amount of

Compound A. The plasma concentration of Compound A was selected to provide a significant increase in the aPTT, where a significant increase may be defined as a coagulation time (for example aPTT) at least 20% greater than the coagulation time in the absence of the Factor XIa inhibitor. An antibody or antibody Fab fragment capable of binding to the Factor XIa inhibitor within the plasma reduces the ability of the Factor XIa inhibitor to bind to Factor XIa, resulting in a reduction in the coagulation time (for example aPTT) relative to the coagulation time in the absence of the antibody or antibody Fab fragment.

[000232] Compound A was added to pooled normal human plasma at concentrations of 8000, 4000, 2000, 1000, 500, 250, 125, 62.5, 31.3 and 15.6 nM. Antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT was added to pooled normal human plasma at the same concentrations of 8000, 4000, 2000, 1000, 500, 250, 125, 62.5, 31.3 and 15.6 nM. Compound A-containing plasma, antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT-containing plasma and normal plasma were combined to produce varying concentrations of each in Compound A:26D5-75616-348-F10-Fab-SHORT molar ratios of 5:5, 5:4, 5:3 and 5:2, including Compound A in the absence of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT.

[000233] The activated partial thromboplastin time (aPTT) (i.e., the human plasma clotting time) was determined for each sample by using ACTIN[®] FS (Siemens/Dade-Behring) following the directions in the package insert. For a description of the aPTT assay see, Goodnight, S.H. et al., "Screening Tests of Hemostasis", *Disorders of Thrombosis and Hemostasis: A Clinical Guide*, 2nd Edition, pp. 41-51, McGraw-Hill, New York (2001). Plasma (0.05 mL) was warmed to 37 °C for 1 minute. ACTIN[®] FS (0.05 mL) was added to the plasma and incubated for an additional 3 minutes. Calcium chloride (25 mM, 0.05 mL) was added to the reaction to initiate coagulation. The clotting time was the time in seconds from the moment calcium chloride was added until a clot was detected.

[000234] Figure 18 shows plasma clotting time (aPTT) as a function of Factor XIa inhibitor, i.e., Compound A, concentration and neutralizing antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT concentration. Figure 19 shows plasma clotting time (aPTT) as a function of the concentration of free Factor XIa inhibitor Compound A in the absence (filled symbols) and presence (open symbols) of the neutralizing antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT. The plot shows that the clotting time (aPTT) is a

function of the unbound Compound A plasma concentration in the absence and the presence of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT.

[000235] The human plasma samples containing various concentrations and molar ratios of Compound A and antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT were processed and the concentrations of Compound A and antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT - unbound and bound - in each sample were determined as described in more detail below.

[000236] The total concentration of Compound A in plasma refers to unbound Compound A, Compound A bound to plasma proteins and Compound A bound to antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT. Free or unbound Compound A refers to Compound A not bound to plasma protein or antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT.

[000237] Unbound Compound A in plasma was obtained via an ultrafiltration method (Centrifree®, MilliporeSigma)(30 kDa molecular weight cut-off). Plasma (0.5 mL) was placed in the upper chamber of the ultrafiltration device (Centrifree®, Ultracel PL membrane, REF# 4104; MilliporeSigma). The device was placed in a fixed angle centrifuge rotor (SORVALL SLA-3000; Thermo Scientific) and ultrafiltrate was collected after centrifugation at 2,000 x g for 20 minutes (SORVALL RC 6 Plus; Thermo Scientific).

[000238] Aliquots of plasma and plasma ultrafiltrate were frozen at -80°C in polypropylene tubes. The total concentration of Compound A in plasma and concentration of unbound Compound A in plasma ultrafiltrate was measured using liquid chromatography tandem mass spectrometry (LC/MS) analysis. The samples for the LC/MS analysis were prepared using a protein precipitation procedure described below.

[000239] An aliquot (20 µL) of biological sample was transferred into a 96-deep well plate (1.2 mL, round bottom polypropylene). A methanol solution (20 µL) containing 50% water and 0.5% formic acid was added. The plate was capped and mixed in a shaker at 95°C for 20 minutes. The protein precipitation process was performed by adding acetonitrile (80 µL) containing an internal standard [10 nM, stable isotope-labeled (13C,15N) Compound A] and 1% formic acid to the resulting solution of the previous step. The plate was further vortex mixed for 15 min at room temperature and then centrifuged at 3,600 rpm for 5 min. An aliquot (100 µL) of supernatant was transferred into an injection plate (96 well, 0.3 mL). The supernatant (5 µL) was injected to an Ultra Performance LC System (Waters® Acquity

UPLC) interfaced with a QTRAP MS/MS (AB Sciex 6500) tandem mass spectrometer. The analytes were separated on a C18 column (Waters HSS T3, 2X 50 mm, 1.8 μ m) at 60°C, with a gradient flow rate of 0.7 ml/min, consisting of two buffer solutions (A: Water, 0.1% formic acid; B: acetonitrile, 0.1% formic acid). The detection was made by using multiple reaction monitoring (MRM) in the positive electrospray ionization mode, representing the precursor (M+H)⁺ species. The MRM transitions monitored were 626→319 for Compound A, 630→323 for the isotope-labeled Compound A. The lowest limit of quantitation was 0.5 nM.

[000240] The concentration of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT in plasma was determined as follows. The plasma concentration of both total antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT and antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT not bound to Compound A in plasma was measured by ligand binding assays on a Gyrolab[®] automated microfluidics platform (Gyros Protein Technologies AB). Biotinylated mouse anti-human kappa (SouthernBiotech, AL) was used as a capture molecule for total antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT. Samples, standards, and QC were brought up to a final matrix concentration of 10% plasma in 1xPTB (1%BSA/0.05%Tween20/PBS), and loaded into the Gyrolab[®] automated microfluidics platform. The 3-step-2-Wash Wizard method with Gyrolab[®] Bioaffy 200 CD was used (Gyros Protein Technologies AB). After final wash steps, the captured total antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT was detected using Alexa Fluor[®] 647 labeled mouse anti-human Ig kappa light chain mAb clone G20-361(BD Catalog No.555861, Lot No. 8333691). The concentrations of total antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT in plasma samples were calculated from fluorescence intensity as measured by the Gyrolab[®] technology using a 4-parameter logistic (4-PL) calibration curve generated from antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT calibrators. The range of the total antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT calibration curve was from 250 to 25000 ng/mL in plasma. The upper and lower limits of quantification were 25000 and 250 ng/mL. Quality control samples were prepared at 20000, 7500, 750 ng/mL in plasma. Calibrators and QC were analyzed in each experiment to ensure acceptable assay performance. Assay performance was within the acceptable range: % CV of the standards and QC was below 20 %, and QC recovery was within $\pm$ 20 % of the nominal values.

[000241] COMPOUND 5 was used as a capture molecule for antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT not bound to Compound A. Samples, standards, and QC were brought up to a final matrix concentration of 10% plasma in 1x PTB (1%BSA/0.05%Tween20/PBS), and loaded into a Gyrolab[®] automated microfluidics platform. The 3-step-2-Wash Wizard method with Gyrolab[®] Bioaffy 200 CD was used. After final wash steps, the captured “active/free” antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT was detected using Alexa Fluor[®] 647 labeled mouse anti-human Ig kappa light chain mAb clone G20-361(BD Catalog No.555861, Lot No. 8333691). The concentrations of “active/free” Fab (26D5-75616-348-F10-Fab-SHORT) in plasma samples were calculated from fluorescence intensity as measured by Gyrolab[®] using a 4-parameter logistic (4-PL) calibration curve generated from antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT calibrators. The range of the “active/free” antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT calibration curve was from 250 to 25000 ng/mL in plasma. The upper and lower limits of quantification were 25000 and 250 ng/mL. Quality control samples were prepared at 20000, 7500, 750 ng/mL in plasma. Calibrators and QC were analyzed in each experiment to ensure acceptable assay performance. Assay performance was within the acceptable range: % CV of the standards and QC was below 20 %, and QC recovery was within ± 20 % of the nominal values.

[000242] *In vivo studies*

[000243] *In vivo* experiments were conducted in accordance with the regulations of the Animal Care and Use Committee of the Bristol-Myers Squibb Company. Rabbits (male New Zealand White, 2 to 4 kg) were instrumented with indwelling catheters in the central ear artery for blood sampling and marginal ear vein for substance administration. Compound A was administered as a constant intravenous infusion at a dose of 1.0 mg/kg over 10 minutes. Beginning 20 minutes after the Compound A infusion was complete, the antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT was administered as a constant intravenous infusion at a dose of 160 mg/kg over 10 minutes. The administered dose of the antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT represented a nominal 2-fold molar excess to the administered dose of Compound A. Blood samples of 1.5 mL were taken prior to the administration of Compound A, at the end of the infusion of compound A, immediately prior to the administration of the antibody Fab fragment, at the end of the administration of the

antibody Fab fragment and at varying intervals after the administration of the antibody Fab fragment for up to 24 hours from the start of Compound A dosing. Blood samples were added to 0.167 mL of 3.8% sodium citrate in a polypropylene tube, inverted at least two times to thoroughly mix and placed on ice. Within one hour of blood sampling, plasma was isolated by centrifuging whole blood at least 1,500 x gravity for at least 10 minutes. Unbound Compound A was obtained by the above-described ultrafiltration method.

[000244] The anticoagulant effects of Compound A were measured in activated partial thromboplastin time (aPTT). The aPTT was determined using ACTIN[®] FS (Siemens/Dade-Behring) following the directions in the package insert. Plasma (0.05 mL) was warmed to 37 °C for 1 minute. ACTIN[®] FS (0.05 mL) was added to the plasma and incubated for an additional 3 minutes. Calcium chloride (25 mM, 0.05 mL) was added to the reaction to initiate coagulation. The clotting time was the time in seconds from the moment calcium chloride was added until a clot was detected.

[000245] After *in vivo* administration of Compound A, rabbit plasma aPTT increased approximately 2-fold relative to baseline. Following administration of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT 20 minutes later, the rabbit plasma aPTT returned to baseline and remained at that level for over 12 hours. Figure 20 shows rabbit plasma clotting time (aPTT) after an IV dose of Compound A (1 mg/kg) followed 20 minutes later by an IV dose of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT (160 mg/kg). Results are the mean from 3 animals.

[000246] Plasma concentrations of Compound A (total and unbound) and antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT were determined as described above. PK parameters were obtained by non-compartmental analysis of plasma concentration versus time data (Phoenix WinNonlin software, Version 6.4, Pharsight Corporation, Mountain View, CA). Values below the lower limit of quantification were not used in calculations. Area under the plasma concentration vs. time curve (AUC [0-T]) was calculated using a combination of linear and log trapezoidal summations. The total plasma clearance (CL), steady-state volume of distribution (V_{ss}), terminal half-life (T-HALF), and mean residence time (MRT) were estimated after IV administration. Estimations of T-HALF were made using a minimum of 3 time points with quantifiable concentrations.

[000247] After administration of Compound A to rabbits (1 mg/kg), the plasma concentration of Compound A was 4.3 μ M and the plasma concentration of unbound Compound A was 290 nM. Following administration of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT (160 mg/kg), the plasma concentration of Compound A was 14 μ M, and the plasma concentration of unbound Compound A was less than 0.2 nM. The decrease in the plasma concentration of unbound Compound A was due to its high binding affinity to antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT. The increase in plasma concentration of Compound A was due to the distribution of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT primarily in the vascular compartment and the redistribution of Compound A from extravascular to vascular space according to the law of mass action. The rabbit plasma concentration of unbound Compound A remained below 10 nM for more than 12 hours. Figure 21 shows rabbit plasma concentration of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT, Compound A and unbound Compound A after an IV dose of Compound A (1 mg/kg) followed 20 minutes later by an IV dose of antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT (160 mg/kg). Results are the mean from 3 animals.

[000248] Example 13: Pharmacokinetics of Antibody Tandem Fab Fragments

[000249] 26D5-75616-348-F10-TanFab (Tandem Fab Heavy Chain SEQ ID NO: 180, Tandem Fab Light Chain SEQ ID NO: 164) was generated and purified according to standard procedures known in the art, similar to the methods described in Example 5 above.

[000250] *Pharmacokinetics in rat*

[000251] In vivo experiments were conducted in accordance with the regulations of the Animal Care and Use Committee of the Bristol-Myers Squibb Company. Rats (male Sprague-Dawley, 0.2 to 0.4 kg) were instrumented with indwelling catheters in the jugular vein for blood sampling and for substance administration. The antibody Fab fragment 26D5-75616-348-F10-Fab-SHORT and antibody tandem Fab fragment 26D5-75616-348-F10-TanFab were each administered as a constant intravenous infusion at a dose of 10 mg/kg over 10 minutes. Blood samples of 0.2 mL were taken at the end of the infusion and at varying intervals for up to 48 hours from the start of dosing. Blood samples were added to EDTA in a polypropylene tube, inverted at least two times to thoroughly mix and placed on ice. Within one hour of blood sampling, plasma was isolated by centrifuging whole blood at least 1,500 x gravity for at least 10 minutes. The concentrations of antibody Fab fragment 26D5-75616-

348-F10-Fab-SHORT and antibody tandem Fab fragment 26D5-75616-348-F10-TanFab in plasma were determined as follows.

[000252] The concentration of 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab in plasma were determined as follows. The plasma concentrations of both total 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab, and 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab not bound to Compound A in plasma were measured by ligand binding assays on a Gyrolab® automated microfluidics platform (Gyros Protein Technologies AB). Biotinylated mouse anti-human kappa (SouthernBiotech Cat No 9230-08, Lot No K5613-X088) was used as a capture molecule for total 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab. Samples, standards, and QC were brought up to a final matrix concentration of 10% plasma in 1xPTB (1%BSA/0.05%Tween20/PBS), and loaded into the Gyrolab® automated microfluidics platform. The 3-step-2-Wash Wizard method with Gyrolab® Bioaffy 200 CD was used (Gyros Protein Technologies AB). After final wash steps, the captured total 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab were detected using Alexa Fluor® 647 labeled mouse anti-human Ig kappa light chain mAb clone G20-361(Becton Dickinson Cat No 555861, Lot No 833694). The concentrations of total 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab in plasma samples were calculated from fluorescence intensity as measured by the Gyrolab® technology using a 4-parameter logistic (4-PL) calibration curve generated from 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab calibrators. The range of the total 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab calibration curves were from 10 to 25000 ng/mL in plasma. The upper and lower limits of quantification were 25000 and 10 ng/mL. Quality control samples were prepared at 20000, 7500, 750, 75 and 30 ng/mL in plasma. Calibrators and QC were analyzed in each experiment to ensure acceptable assay performance. Assay performance was within the acceptable range: % CV of the standards and QC was below 20 %, and QC recovery was within ± 20 % of the nominal values.

[000253] COMPOUND 5 was used as a capture molecule for 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab not bound to Compound A. Samples, standards, and QC were brought up to a final matrix concentration of 10% plasma in 1x PTB (1%BSA/0.05%Tween20/PBS), and loaded into a Gyrolab® automated microfluidics

platform. The 3-step-2-Wash Wizard method with Gyrolab® Bioaffy 200 CD was used. After final wash steps, the captured “active/free” 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab were detected using Alexa Fluor® 647 labeled mouse anti-human Ig kappa light chain mAb clone G20-361 (Becton Dickinson Cat No 555861, Lot No 8333694). The concentrations of “active/free” 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab in plasma samples were calculated from fluorescence intensity as measured by Gyrolab® using a 4-parameter logistic (4-PL) calibration curve generated from 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab calibrators. The range of the “active/free” 26D5-75616-348-F10-Fab-SHORT and 26D5-75616-348-F10-TanFab calibration curves were from 10 to 25000 ng/mL in plasma. The upper and lower limits of quantification were 25000 and 10 ng/mL. Quality control samples were prepared at 20000, 7500, 750, 75 and 30 ng/mL in plasma. Calibrators and QC were analyzed in each experiment to ensure acceptable assay performance. Assay performance was within the acceptable range: % CV of the standards and QC was below 20 %, and QC recovery was within ± 20 % of the nominal values.

[000254] Figure 22 shows the resulting pharmacokinetics data.

[000255] *Pharmacokinetics in rabbit*

[000256] In vivo experiments were conducted in accordance with the regulations of the Animal Care and Use Committee of Bristol-Myers Squibb Company. Rabbits (male New Zealand White, 2 to 4 kg) were instrumented with indwelling catheters in the femoral artery and vein for blood sampling and marginal ear vein for substance administration. Compound A was administered as a constant intravenous infusion at a dose of 0.4 mg/kg (0.64 micromoles/kg) over 10 minutes. Beginning 20 minutes after the Compound A infusion was complete, the antibody tandem Fab fragment 26D5-75616-348-F10-TanFab was administered as a constant intravenous infusion at a dose of 40 mg/kg (0.43 micromoles/kg) over 10 minutes. The administered dose of the antibody tandem Fab fragment 26D5-75616-348-F10-TanFab represented a nominal 1.34-fold molar excess, accounting for 2:1 binding capacity, to the administered dose of Compound A ($2 \times 0.43 / 0.64$). Blood samples of 1.5 mL were taken prior to the administration of Compound A, at the end of the infusion of compound A, immediately prior to the administration of the antibody tandem Fab fragment 26D5-75616-348-F10-TanFab, at the end of the administration of the antibody tandem Fab

fragment 26D5-75616-348-F10-TanFab and at varying intervals after the administration of the antibody tandem Fab fragment 26D5-75616-348-F10-TanFab for up to 24 hours from the start of Compound A dosing.

[000257] Blood samples were added to 0.167 mL of 3.8% sodium citrate in a polypropylene tube, inverted at least two times to thoroughly mix and placed on ice. Within one hour of blood sampling, plasma was isolated by centrifuging whole blood at least 1,500 x gravity for at least 10 minutes. Unbound Compound A was obtained by the above-described ultrafiltration method. Aliquots of plasma and plasma ultrafiltrate were frozen at -80°C in polypropylene tubes. The total concentration of Compound A in plasma and concentration of unbound Compound A in plasma ultrafiltrate were measured using liquid chromatography tandem mass spectrometry (LC/MS) analysis. The samples for the LC/MS analysis were prepared using a protein precipitation procedure described below.

[000258] An aliquot (20 µL) of biological sample was transferred into a 96-deep well plate (1.2 mL, round bottom poly propylene). A methanol solution (20 µL) containing 50% water and 0.5% formic acid was added. The plate was capped and mixed in a shaker at 95°C for 20 minutes. The protein precipitation process was performed by adding acetonitrile (80 µL) containing an internal standard [1 µM] and 1% formic acid to the resulting solution of the previous step. The plate was further vortex mixed for 15 min at room temperature and then centrifuged at 3,700 rpm for 8 min. An aliquot (100 µL) of supernatant was transferred into an injection plate (96 well, 0.3 mL). The supernatant (3 µL) was injected to an Ultra Performance LC System (Waters® Acquity iClass uPLC) interfaced with a Quadrapole MS/MS (Thermo Quantiva) tandem mass spectrometer. The analytes were separated on a C18 column (Waters HSS T3, 2 X 50 mm, 1.8 µm) at 40°C, with a gradient flow rate of 0.6 ml/min, consisting of two buffer solutions (A: Water, 5 mM Ammonium Formate, 0.1% formic acid; B: acetonitrile, 0.1% formic acid). The detection was made by using multiple reaction monitoring (MRM) in the positive electrospray ionization mode, representing the precursor (M+H)⁺ species. The MRM transitions monitored were 626.3→319.1 for Compound A, 474.3→269 for the Internal Standard. The lowest limit of quantitation was 0.5 nM.

[000259] The concentration of antibody tandem Fab fragment 26D5-75616-348-F10-TanFab in plasma was determined as described above in this Example.

[000260] Figure 23 shows the resulting pharmacokinetics data.

[000261] *In vitro studies*

[000262] Compound A was added to pooled normal human plasma at a concentration of 2000 nM. Antibody tandem Fab fragment 26D5-75616-348-F10-TanFab was added to pooled normal human plasma at a concentrations of 1000 nM. Compound A-containing plasma, 26D5-75616-348-F10-TanFab-containing plasma and normal plasma were combined to produce varying concentrations of each in Compound A: 26D5-75616-348-F10-TanFab molar ratios of 2:1, 2:0.8, 2:0.6 and 2:0.4, including Compound A in the absence of 26D5-75616-348-F10-TanFab. The activated partial thromboplastin time (aPTT) (i.e., the human plasma clotting time) was determined for each sample as described above in Example 12. Figure 24 shows the resulting plasma clotting data.

WE CLAIM:

1. An isolated antigen binding peptide comprising at least one heavy chain variable region (VH) and at least one light chain variable region (VL), wherein the at least one VH comprises at least one of:
 - (a) a VH complementarity-determining region 1 (VH-CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-12;
 - (b) a VH-CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 13-22; or
 - (c) a VH-CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 23-28; andwherein the at least one VL comprises at least one of:
 - (d) a VL-CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 29-37;
 - (e) a VL-CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 38-43; or
 - (f) a VL-CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 44-51.
2. An isolated antigen binding peptide comprising:
 - (a) at least one heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 52-83; and
 - (b) at least one light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 84-99.
3. An isolated antigen binding peptide comprising at least one heavy chain variable region (VH) and at least one light chain variable region (VL), wherein the VH comprises three

complementarity determining regions (CDRs): VH-CDR1, VH-CDR2, and VH-CDR3 and the VL comprises three CDRs: VL-CDR1, VL-CDR2, and VL-CDR3, wherein the amino acid sequences of the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3, respectively comprise the sequences selected from the group consisting of:

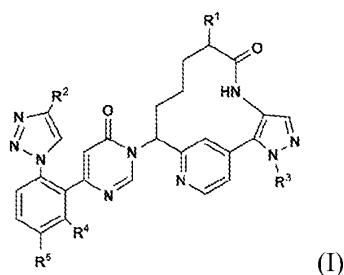
- (a) SEQ ID NOs: 1, 13, 23, 29, 38, and 44, respectively;
- (b) SEQ ID NOs: 1, 14, 23, 29, 38, and 45, respectively;
- (c) SEQ ID NOs: 1, 13, 24, 30, 38, and 45, respectively;
- (d) SEQ ID NOs: 1, 13, 24, 29, 39, and 45, respectively;
- (e) SEQ ID NOs: 1, 14, 25, 29, 38, and 46, respectively;
- (f) SEQ ID NOs: 2, 13, 26, 31, 40, and 47, respectively;
- (g) SEQ ID NOs: 3, 15, 24, 32, 40, and 47, respectively;
- (h) SEQ ID NOs: 4, 16, 24, 29, 38, and 46, respectively;
- (i) SEQ ID NOs: 5, 15, 24, 29, 38, and 46, respectively;
- (j) SEQ ID NOs: 1, 14, 24, 29, 38, and 46, respectively;
- (k) SEQ ID NOs: 6, 13, 24, 31, 40, and 47, respectively;
- (l) SEQ ID NOs: 3, 15, 24, 32, 41, and 48, respectively;
- (m) SEQ ID NOs: 1, 14, 24, 33, 38, and 49, respectively;
- (n) SEQ ID NOs: 1, 14, 26, 29, 38, and 46, respectively;
- (o) SEQ ID NOs: 7, 17, 26, 29, 38, and 46, respectively;
- (p) SEQ ID NOs: 8, 17, 24, 34, 38, and 46, respectively;
- (q) SEQ ID NOs: 1, 17, 26, 29, 38, and 46, respectively;
- (r) SEQ ID NOs: 1, 17, 26, 35, 38, and 46, respectively;

- (s) SEQ ID NOs: 1, 17, 24, 33, 38, and 49, respectively;
 - (t) SEQ ID NOs: 9, 14, 26, 29, 38, and 46, respectively;
 - (u) SEQ ID NOs: 9, 14, 26, 35, 38, and 46, respectively;
 - (v) SEQ ID NOs: 9, 17, 24, 29, 38, and 46, respectively;
 - (w) SEQ ID NOs: 9, 17, 24, 35, 38, and 46, respectively;
 - (x) SEQ ID NOs: 9, 17, 24, 34, 38, and 46, respectively;
 - (y) SEQ ID NOs: 9, 14, 24, 29, 38, and 46, respectively;
 - (z) SEQ ID NOs: 9, 18, 26, 35, 38, and 46, respectively;
 - (aa) SEQ ID NOs: 8, 14, 24, 29, 38, and 46, respectively;
 - (bb) SEQ ID NOs: 8, 17, 26, 29, 38, and 46, respectively;
 - (cc) SEQ ID NOs: 9, 19, 26, 29, 38, and 46, respectively;
 - (dd) SEQ ID NOs: 9, 17, 26, 34, 38, and 46, respectively;
 - (ee) SEQ ID NOs: 10, 20, 27, 36, 42, and 50, respectively;
 - (ff) SEQ ID NOs: 11, 21, 28, 37, 43, and 51, respectively;
 - (gg) SEQ ID NOs: 12, 22, 26, 33, 38, and 46, respectively;
 - (hh) SEQ ID NOs: 12, 17, 26, 33, 38, and 46, respectively;
 - (ii) SEQ ID NOs: 9, 17, 26, 33, 38, and 46, respectively; and
 - (jj) variants of (a) to (ii) wherein any of the amino acid sequences have 1, 2, or 3 conservative amino acid substitutions therein.
4. The isolated antigen binding peptide of claim 3, wherein the at least one VH region and the at least one VL region, respectively, comprise amino acid sequences selected from the group consisting of:
- (a) SEQ ID NO: 52 and SEQ ID NO: 84, respectively;

- (b) SEQ ID NO: 53 and SEQ ID NO: 85, respectively;
- (c) SEQ ID NO: 54 and SEQ ID NO: 86, respectively;
- (d) SEQ ID NO: 54 and SEQ ID NO: 87, respectively;
- (e) SEQ ID NO: 55 and SEQ ID NO: 88, respectively;
- (f) SEQ ID NO: 56 and SEQ ID NO: 89, respectively;
- (g) SEQ ID NO: 57 and SEQ ID NO: 90, respectively;
- (h) SEQ ID NO: 58 and SEQ ID NO: 88, respectively;
- (i) SEQ ID NO: 59 and SEQ ID NO: 88, respectively;
- (j) SEQ ID NO: 60 and SEQ ID NO: 91, respectively;
- (k) SEQ ID NO: 61 and SEQ ID NO: 89, respectively;
- (l) SEQ ID NO: 57 and SEQ ID NO: 92, respectively;
- (m) SEQ ID NO: 60 and SEQ ID NO: 93, respectively;
- (n) SEQ ID NO: 60 and SEQ ID NO: 88, respectively;
- (o) SEQ ID NO: 62 and SEQ ID NO: 88, respectively;
- (p) SEQ ID NO: 63 and SEQ ID NO: 88, respectively;
- (q) SEQ ID NO: 64 and SEQ ID NO: 88, respectively;
- (r) SEQ ID NO: 65 and SEQ ID NO: 94, respectively;
- (s) SEQ ID NO: 66 and SEQ ID NO: 88, respectively;
- (t) SEQ ID NO: 66 and SEQ ID NO: 95, respectively;
- (u) SEQ ID NO: 67 and SEQ ID NO: 88, respectively;
- (v) SEQ ID NO: 68 and SEQ ID NO: 93, respectively;
- (w) SEQ ID NO: 69 and SEQ ID NO: 88, respectively;
- (x) SEQ ID NO: 69 and SEQ ID NO: 95, respectively;

- (y) SEQ ID NO: 70 and SEQ ID NO: 88, respectively;
 - (z) SEQ ID NO: 70 and SEQ ID NO: 95, respectively;
 - (aa) SEQ ID NO: 71 and SEQ ID NO: 88, respectively;
 - (bb) SEQ ID NO: 71 and SEQ ID NO: 94, respectively;
 - (cc) SEQ ID NO: 72 and SEQ ID NO: 88, respectively;
 - (dd) SEQ ID NO: 73 and SEQ ID NO: 95, respectively;
 - (ee) SEQ ID NO: 74 and SEQ ID NO: 88, respectively;
 - (ff) SEQ ID NO: 75 and SEQ ID NO: 88, respectively;
 - (gg) SEQ ID NO: 76 and SEQ ID NO: 88, respectively;
 - (hh) SEQ ID NO: 77 and SEQ ID NO: 94, respectively;
 - (ii) SEQ ID NO: 78 and SEQ ID NO: 96, respectively;
 - (jj) SEQ ID NO: 79 and SEQ ID NO: 97 respectively;
 - (kk) SEQ ID NO: 80 and SEQ ID NO: 98, respectively;
 - (ll) SEQ ID NO: 81 and SEQ ID NO: 99, respectively;
 - (mm) SEQ ID NO: 81 and SEQ ID NO: 98, respectively;
 - (nn) SEQ ID NO: 82 and SEQ ID NO: 99, respectively;
 - (oo) SEQ ID NO: 83 and SEQ ID NO: 98, respectively; and
 - (pp) variants of (a) to (oo) comprising 1, 2, 3, or 4 conservative amino acid substitutions.
5. The isolated antigen binding peptide of any one of the preceding claims, comprising two heavy chain variable regions, each paired with one light chain variable region.
6. The isolated antigen binding peptide of claim 5, further comprising a polypeptide linker comprising a sequence selected from SEQ ID NO: 196-199.

7. The isolated antigen binding peptide of any one of the preceding claims, wherein the isolated antigen binding peptide specifically binds to the compound set forth in Formula (I):



or a stereoisomer or a tautomer thereof, wherein:

R¹ is C₁₋₄ alkyl;

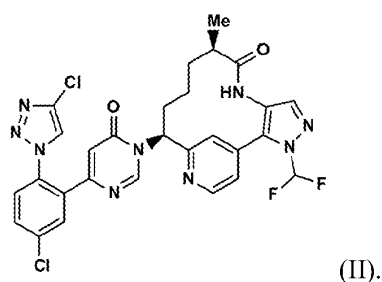
R² is independently selected from F, Cl, CF₃, CHF₂, CH₂F, CH₃;

R³ is independently selected from CF₃, CHF₂, CH₂F, and CH₃;

R⁴ is H; and

R⁵ is independently selected from F and Cl.

8. The isolated antigen binding peptide of claim 7, wherein the compound has Formula (II):



9. The isolated antigen binding peptide of any one of the preceding claims is an antibody.
10. The isolated antigen binding peptide of any one of the preceding claims, wherein said isolated antigen binding peptide is a Fab, Fab', F(ab')₂, Fd, single chain Fv or scFv, disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGACH2, minibody, F(ab')₃,

tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb², (scFv)₂, scFv-Fc, or a tandem Fab.

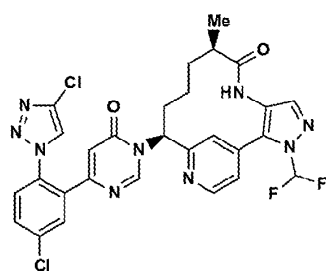
11. The isolated antigen binding peptide of any one of the preceding claims, comprising sequences selected from the group consisting of:
 - (a) SEQ ID NO: 100 and SEQ ID NO: 160, respectively;
 - (b) SEQ ID NO: 101 and SEQ ID NO: 160, respectively;
 - (c) SEQ ID NO: 102 and SEQ ID NO: 161, respectively;
 - (d) SEQ ID NO: 103 and SEQ ID NO: 161, respectively;
 - (e) SEQ ID NO: 104 and SEQ ID NO: 162, respectively;
 - (f) SEQ ID NO: 105 and SEQ ID NO: 162, respectively;
 - (g) SEQ ID NO: 104 and SEQ ID NO: 163, respectively;
 - (h) SEQ ID NO: 105 and SEQ ID NO: 163, respectively;
 - (i) SEQ ID NO: 106 and SEQ ID NO: 164, respectively;
 - (j) SEQ ID NO: 107 and SEQ ID NO: 164, respectively;
 - (k) SEQ ID NO: 108 and SEQ ID NO: 165, respectively;
 - (l) SEQ ID NO: 109 and SEQ ID NO: 165, respectively;
 - (m) SEQ ID NO: 110 and SEQ ID NO: 166, respectively;
 - (n) SEQ ID NO: 111 and SEQ ID NO: 166, respectively;
 - (o) SEQ ID NO: 112 and SEQ ID NO: 164, respectively;
 - (p) SEQ ID NO: 113 and SEQ ID NO: 164, respectively;
 - (q) SEQ ID NO: 114 and SEQ ID NO: 164, respectively;
 - (r) SEQ ID NO: 115 and SEQ ID NO: 164, respectively;
 - (s) SEQ ID NO: 116 and SEQ ID NO: 167, respectively;

- (t) SEQ ID NO: 117 and SEQ ID NO: 167, respectively;
- (u) SEQ ID NO: 118 and SEQ ID NO: 165, respectively;
- (v) SEQ ID NO: 119 and SEQ ID NO: 165, respectively;
- (w) SEQ ID NO: 110 and SEQ ID NO: 168, respectively;
- (x) SEQ ID NO: 111 and SEQ ID NO: 168, respectively;
- (y) SEQ ID NO: 116 and SEQ ID NO: 169, respectively;
- (z) SEQ ID NO: 117 and SEQ ID NO: 169, respectively;
- (aa) SEQ ID NO: 116 and SEQ ID NO: 164, respectively;
- (bb) SEQ ID NO: 117 and SEQ ID NO: 164, respectively;
- (cc) SEQ ID NO: 120 and SEQ ID NO: 164, respectively;
- (dd) SEQ ID NO: 121 and SEQ ID NO: 164, respectively;
- (ee) SEQ ID NO: 122 and SEQ ID NO: 164, respectively;
- (ff) SEQ ID NO: 123 and SEQ ID NO: 164, respectively;
- (gg) SEQ ID NO: 124 and SEQ ID NO: 164, respectively;
- (hh) SEQ ID NO: 125 and SEQ ID NO: 164, respectively;
- (ii) SEQ ID NO: 126 and SEQ ID NO: 170, respectively;
- (jj) SEQ ID NO: 127 and SEQ ID NO: 170, respectively;
- (kk) SEQ ID NO: 128 and SEQ ID NO: 164, respectively;
- (ll) SEQ ID NO: 129 and SEQ ID NO: 164, respectively;
- (mm) SEQ ID NO: 128 and SEQ ID NO: 171, respectively;
- (nn) SEQ ID NO: 129 and SEQ ID NO: 171, respectively;
- (oo) SEQ ID NO: 130 and SEQ ID NO: 164, respectively;
- (pp) SEQ ID NO: 131 and SEQ ID NO: 164, respectively;

- (qq) SEQ ID NO: 132 and SEQ ID NO: 169, respectively;
- (rr) SEQ ID NO: 133 and SEQ ID NO: 169, respectively;
- (ss) SEQ ID NO: 134 and SEQ ID NO: 164, respectively;
- (tt) SEQ ID NO: 135 and SEQ ID NO: 164, respectively;
- (uu) SEQ ID NO: 134 and SEQ ID NO: 171, respectively;
- (vv) SEQ ID NO: 135 and SEQ ID NO: 171, respectively;
- (ww) SEQ ID NO: 136 and SEQ ID NO: 164, respectively;
- (xx) SEQ ID NO: 137 and SEQ ID NO: 164, respectively;
- (yy) SEQ ID NO: 136 and SEQ ID NO: 171, respectively;
- (zz) SEQ ID NO: 137 and SEQ ID NO: 171, respectively;
- (aaa) SEQ ID NO: 138 and SEQ ID NO: 164, respectively;
- (bbb) SEQ ID NO: 139 and SEQ ID NO: 164, respectively;
- (ccc) SEQ ID NO: 138 and SEQ ID NO: 170, respectively;
- (ddd) SEQ ID NO: 139 and SEQ ID NO: 170, respectively;
- (eee) SEQ ID NO: 140 and SEQ ID NO: 164, respectively;
- (fff) SEQ ID NO: 141 and SEQ ID NO: 164, respectively;
- (ggg) SEQ ID NO: 142 and SEQ ID NO: 171, respectively;
- (hhh) SEQ ID NO: 143 and SEQ ID NO: 171, respectively;
- (iii) SEQ ID NO: 144 and SEQ ID NO: 164, respectively;
- (jjj) SEQ ID NO: 145 and SEQ ID NO: 164, respectively;
- (kkk) SEQ ID NO: 146 and SEQ ID NO: 164, respectively;
- (lll) SEQ ID NO: 147 and SEQ ID NO: 164, respectively;
- (mmm) SEQ ID NO: 148 and SEQ ID NO: 164, respectively;

- (nnn) SEQ ID NO: 149 and SEQ ID NO: 164, respectively;
 (ooo) SEQ ID NO: 150 and SEQ ID NO: 170, respectively;
 (ppp) SEQ ID NO: 151 and SEQ ID NO: 170, respectively;
 (qqq) SEQ ID NO: 152 and SEQ ID NO: 172, respectively;
 (rrr) SEQ ID NO: 153 and SEQ ID NO: 172, respectively;
 (sss) SEQ ID NO: 154 and SEQ ID NO: 173, respectively;
 (ttt) SEQ ID NO: 155 and SEQ ID NO: 173, respectively;
 (uuu) SEQ ID NO: 156 and SEQ ID NO: 174, respectively;
 (vvv) SEQ ID NO: 157 and SEQ ID NO: 174, respectively;
 (www) SEQ ID NO: 158 and SEQ ID NO: 175, respectively;
 (xxx) SEQ ID NO: 159 and SEQ ID NO: 175, respectively;
 (yyy) SEQ ID NO: 158 and SEQ ID NO: 174, respectively; and
 (zzz) SEQ ID NO: 159 and SEQ ID NO: 174, respectively;

wherein said isolated antigen binding peptide specifically binds to the compound of
 Formula (II):

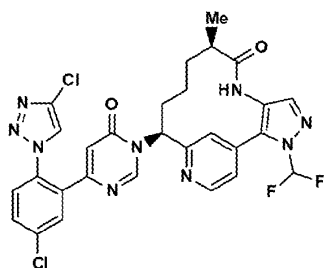


(II).

12. The isolated antigen binding peptide of any one of the preceding claims, comprising sequences selected from the group consisting of:
- (a) SEQ ID NO: 176 and SEQ ID NO: 160, respectively;
 - (b) SEQ ID NO: 177 and SEQ ID NO: 160, respectively;

- (c) SEQ ID NO: 178 and SEQ ID NO: 160, respectively;
- (d) SEQ ID NO: 179 and SEQ ID NO: 160, respectively;
- (e) SEQ ID NO: 180 and SEQ ID NO: 164, respectively;
- (f) SEQ ID NO: 181 and SEQ ID NO: 164, respectively;
- (g) SEQ ID NO: 182 and SEQ ID NO: 164, respectively;
- (h) SEQ ID NO: 183 and SEQ ID NO: 164, respectively;
- (i) SEQ ID NO: 184 and SEQ ID NO: 163, respectively;
- (j) SEQ ID NO: 185 and SEQ ID NO: 163, respectively;
- (k) SEQ ID NO: 186 and SEQ ID NO: 163, respectively;
- (l) SEQ ID NO: 187 and SEQ ID NO: 163, respectively;
- (m) SEQ ID NO: 184 and SEQ ID NO: 162, respectively;
- (n) SEQ ID NO: 185 and SEQ ID NO: 162, respectively;
- (o) SEQ ID NO: 186 and SEQ ID NO: 162, respectively;
- (p) SEQ ID NO: 187 and SEQ ID NO: 162, respectively;
- (q) SEQ ID NO: 188 and SEQ ID NO: 165, respectively;
- (r) SEQ ID NO: 189 and SEQ ID NO: 165, respectively;
- (s) SEQ ID NO: 190 and SEQ ID NO: 165, respectively;
- (t) SEQ ID NO: 191 and SEQ ID NO: 165, respectively;
- (u) SEQ ID NO: 192 and SEQ ID NO: 161, respectively;
- (v) SEQ ID NO: 193 and SEQ ID NO: 161, respectively;
- (w) SEQ ID NO: 194 and SEQ ID NO: 161, respectively; and
- (x) SEQ ID NO: 195 and SEQ ID NO: 161, respectively;

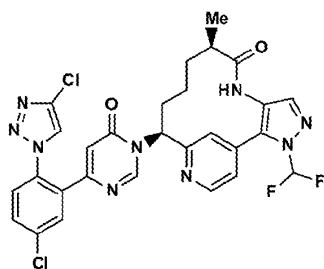
wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



(II).

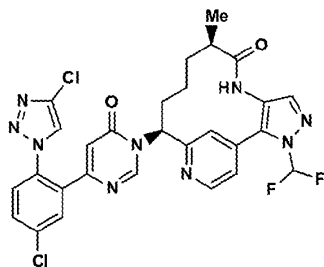
13. The isolated antigen binding peptide of claim 11, comprising sequences SEQ ID NO: 106 and SEQ ID NO: 164, respectively;

wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



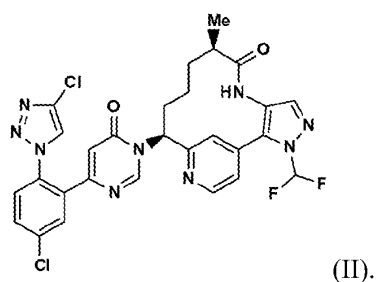
(II).

14. An isolated antibody Fab fragment comprising sequences SEQ ID NO: 106 and SEQ ID NO: 164; wherein said isolated antibody Fab fragment specifically binds to the compound of Formula (II)

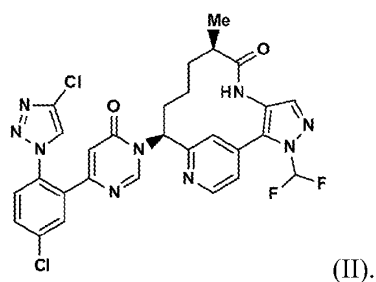


(II).

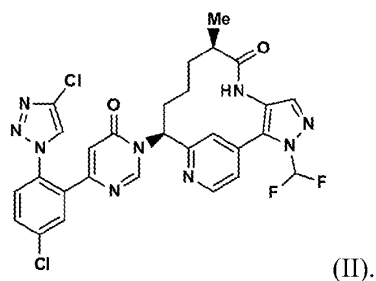
15. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 180 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



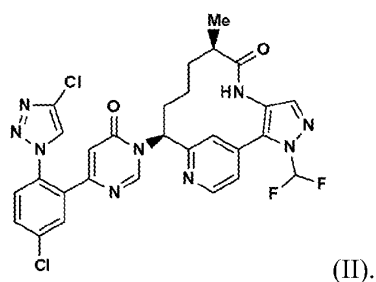
16. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 180 and SEQ ID NO: 164; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



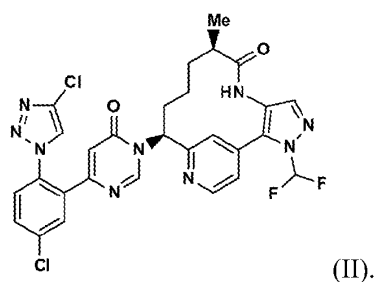
17. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 181 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



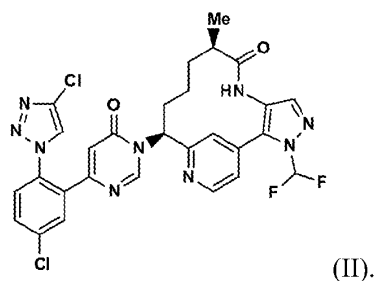
18. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 181 and SEQ ID NO: 164; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



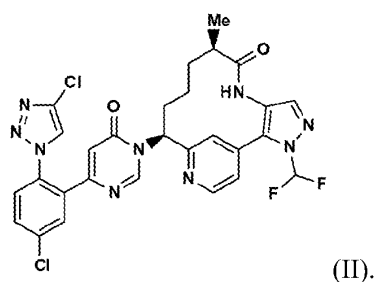
19. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 182 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



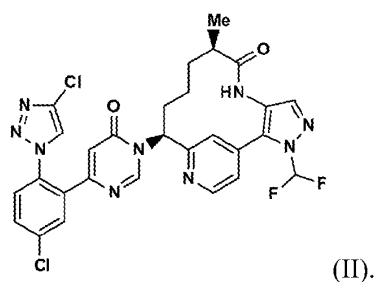
20. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 182 and SEQ ID NO: 164; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



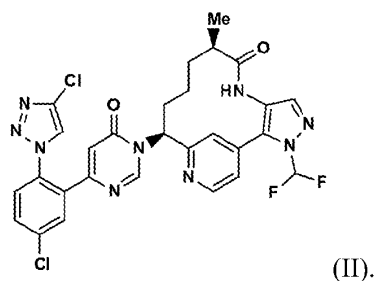
21. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 183 and SEQ ID NO: 164, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



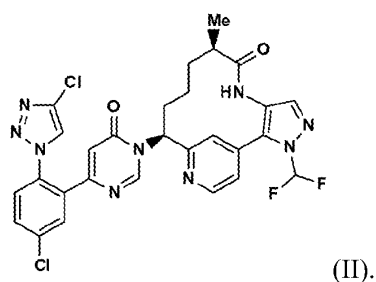
22. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 183 and SEQ ID NO: 164; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



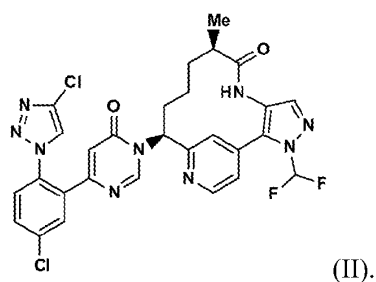
23. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 176 and SEQ ID NO: 160, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



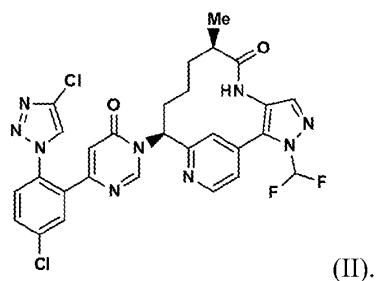
24. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 176 and SEQ ID NO: 160; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



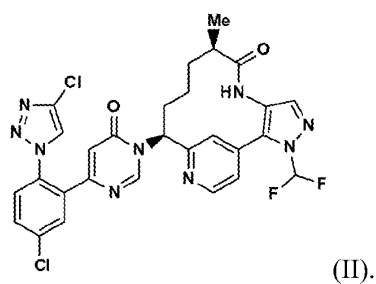
25. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 177 and SEQ ID NO: 160, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



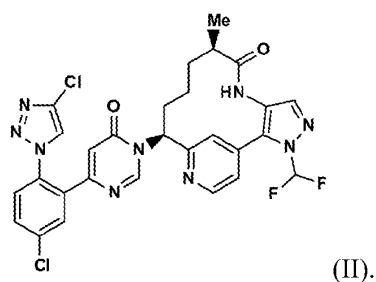
26. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 177 and SEQ ID NO: 160; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



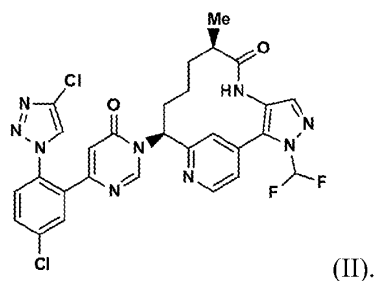
27. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 184 and SEQ ID NO: 162, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



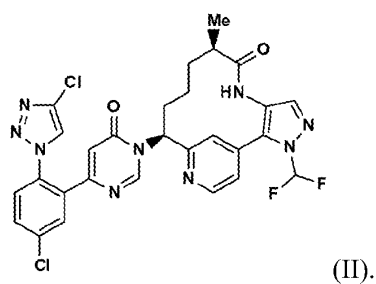
28. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 184 and SEQ ID NO: 162; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



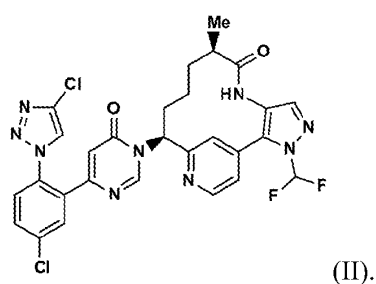
29. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 184 and SEQ ID NO: 163, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



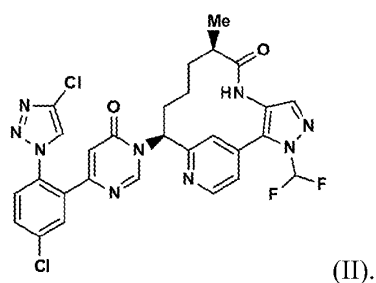
30. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 184 and SEQ ID NO: 163; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



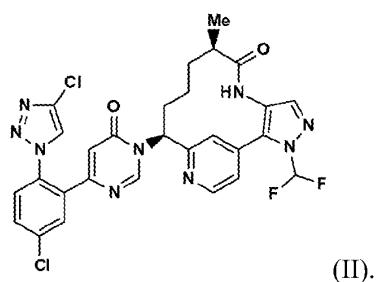
31. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 188 and SEQ ID NO: 165, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):



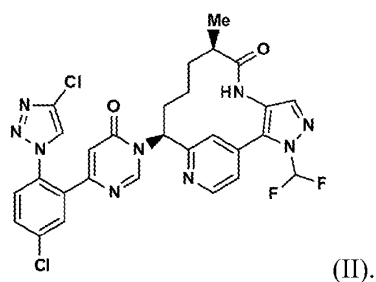
32. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 188 and SEQ ID NO: 165; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



33. The isolated antigen binding peptide of claim 12, comprising sequences SEQ ID NO: 192 and SEQ ID NO: 161, respectively; wherein said isolated antigen binding peptide specifically binds to the compound of Formula (II):

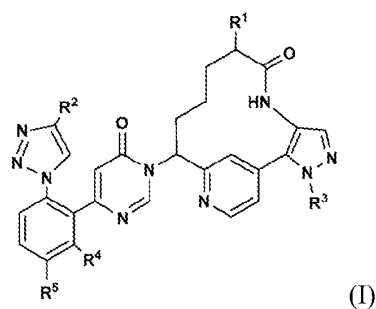


34. An isolated antibody tandem Fab fragment comprising sequences SEQ ID NO: 192 and SEQ ID NO: 161; wherein said isolated antibody tandem Fab fragment specifically binds to the compound of Formula (II)



35. An isolated polynucleotide comprising a nucleic acid sequence encoding the antigen binding peptide or the antibody Fab fragment or the antibody tandem Fab fragment of any one of claims 1-34.
36. A vector comprising the isolated polynucleotide of claim 35.
37. A host cell comprising the vector of claim 36.
38. A method of making an antigen binding peptide or an antibody Fab fragment or an antibody tandem Fab fragment comprising (a) culturing the host cell of claim 37 under culture conditions that promote protein production such that the host cell produces the

- antigen binding peptide or the antibody Fab fragment or the antibody tandem Fab fragment, and (b) isolating said antigen binding peptide or said antibody Fab fragment or said antibody tandem Fab fragment from said culture.
39. A detection reagent comprising the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment of any one of claims 1-34 and a detectable label.
40. The detection reagent of claim 39, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment is linked to the detectable label.
41. A method of reducing the antithrombotic effect of the compound of Formula (I) or a stereoisomer or a tautomer thereof, in a subject in need thereof, comprising administering to the subject a pharmaceutically effective dose of the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment of any one of claims 1-34, wherein:



(I)

R¹ is C₁₋₄ alkyl;

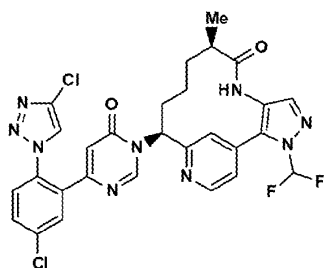
R² is independently selected from F, Cl, CF₃, CHF₂, CH₂F, CH₃;

R³ is independently selected from CF₃, CHF₂, CH₂F, and CH₃;

R⁴ is H; and

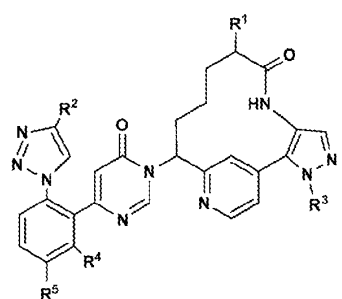
R⁵ is independently selected from F and Cl.

42. The method of claim 41, wherein the compound of Formula (I) has Formula (II):



(II).

43. The method of claim 41 or 42, wherein the pharmaceutically effective dose of the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment comprises the antigen binding peptide or the antibody Fab fragment or the antibody tandem Fab fragment at an at least about 1:1 molar ratio to the dose of the compound of Formula (I) or (II), or an at least about 1:1 molar ratio to the presence of the compound of Formula (I) or (II) in the subject.
44. The method of any one of claims 41-43, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated the antibody tandem Fab fragment is administered concurrently with or after the administration of the compound of Formula (I) or (II).
45. The method of any one of claims 41-44, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated the antibody tandem Fab fragment is administered intravenously, intramuscularly, or subcutaneously.
46. The method of any one of claims 41-45, wherein the subject is a human.
47. A method of detecting the level of a compound of Formula (I) or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, in a biological sample, wherein:



(I)

R¹ is C₁₋₄ alkyl;

R² is independently selected from F, Cl, CF₃, CHF₂, CH₂F, CH₃;

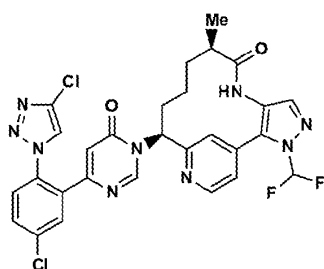
R³ is independently selected from CF₃, CHF₂, CH₂F, and CH₃;

R⁴ is H; and

R⁵ is independently selected from F and Cl; the method comprising:

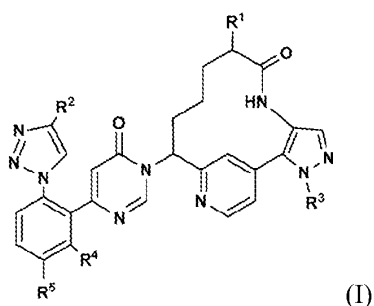
- (a) contacting the biological sample with the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated the antibody tandem Fab fragment of any one of claims 1-34, and
- (b) detecting the level of a bound complex of the compound and the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated the antibody tandem Fab fragment.

48. The method of claim 47, wherein the compound of Formula (I) has Formula (II):



(II).

49. The method of claim 47 or 48, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment is labeled.
50. The method of any one of claims 47-49, wherein the detection is performed by an immunological assay.
51. The method of any one of claims 47-50, wherein the biological sample comprises urine, feces, saliva, whole blood, plasma, organ tissue, hair, skin, cells, or cell cultures.
52. A method of binding a compound of Formula (I) or a stereoisomer or a tautomer thereof, in a subject who is taking therapeutically effective amount of the compound of formula (I) or a stereoisomer or a tautomer thereof, comprising administering to the subject a pharmaceutically effective dose of the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment of any one of claims 1-34, wherein



R^1 is C_{1-4} alkyl;

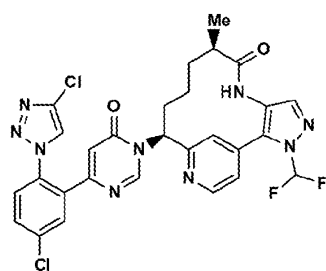
R^2 is independently selected from F, Cl, CF_3 , CHF_2 , CH_2F , CH_3 ;

R^3 is independently selected from CF_3 , CHF_2 , CH_2F , and CH_3 ;

R^4 is H; and

R^5 is independently selected from F and Cl.

53. The method of claim 52, wherein the compound of Formula (I) has Formula (II):



54. The method of claim 52 or 53, wherein the pharmaceutically effective dose of the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated antibody tandem Fab fragment comprises the antigen binding peptide or the antibody Fab fragment or the antibody tandem Fab fragment at an at least about 1:1 molar ratio to the dose of the compound of Formula (I) or (II), or an at least about 1:1 molar ratio to the presence of the compound of Formula (I) or (II) in the subject.
55. The method of any one of claims 52-54, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated the antibody tandem Fab fragment is administered concurrently with or after the administration of the compound of Formula (I) or (II).
56. The method of any one of claims 52-55, wherein the isolated antigen binding peptide or the isolated antibody Fab fragment or the isolated the antibody tandem Fab fragment is administered intravenously, intramuscularly, or subcutaneously.
57. The method of any one of claims 52-56, wherein the subject is a human.