ANTI-TIGIT ANTIGEN-BINDING PROTEINS AND METHODS OF USE THEREOF

[0001] This application claims the benefit of U.S. Provisional Application No. 62/235,990, filed October 1, 2015, which is hereby incorporated by reference in its entirety.

FIELD

[0002] Provided herein are antigen-binding proteins (ABPs) with binding specificity for T cell immunoreceptor with Ig and ITIM domains (TIGIT) and compositions comprising such ABPs, including pharmaceutical compositions, diagnostic compositions, and kits. Also provided are methods of making TIGIT ABPs, and methods of using TIGIT ABPs, for example, for therapeutic purposes, diagnostic purposes, and research purposes.

BACKGROUND

[0003] TIGIT has been identified as a co-inhibitory receptor that limits the response of T cells to cancer and chronic infection. *See* Grogan et al., *J. Immunol.*, 2014, 192: (1 Supplement) 203.15., incorporated by reference in its entirety. Blockade of TIGIT has been shown to contribute to the enhancement CD8+ T cell effector function, and improvement of viral clearance and tumor rejection. *See id.*

[0004] Thus, there is a need for therapeutics that can antagonize TIGIT. Provided herein are ABPs that fulfill this need.

SUMMARY

[0005] Provided herein are ABPs that specifically bind TIGIT and methods of using such ABPs.

[0006] In some embodiments, the TIGIT is selected from human TIGIT ("hTIGIT", SEQ ID NO:1), cynomolgus monkey TIGIT ("cTIGIT", SEQ ID NO:2), and murine TIGIT ("mTIGIT", SEQ ID NO:3 or 138).

[0007] In some embodiments, the ABP comprises an antibody. In some aspects, the antibody is a monoclonal antibody. In some aspects, the antibody is a chimeric antibody. In some aspects, the antibody is a humanized antibody. In some aspects, the antibody is a human antibody. In some aspects, the ABP comprises an antibody fragment. In some embodiments, the ABP comprises an alternative scaffold.

[0008] In some embodiments, the TIGIT is expressed on the surface of a target cell. In some aspects, the ABP antagonizes TIGIT expressed on the surface of the target cell.

[0009] In some embodiments, the target cell is selected from an effector T cell, a regulatory T cell, a natural killer (NK) cell, and a natural killer T (NKT) cell. In some aspects, the target cell is an effector T cell selected from a helper (CD4-positive, "CD4+") T cell, a cytotoxic (CD8-positive, "CD8+") T cell, and combinations thereof. In some aspects, the target cell is a regulatory T cell selected from a

CD4+CD25+Foxp3+ regulatory T cell, a CD8+CD25+ regulatory T cell, and combinations thereof.

[0010] In some embodiments, the ABPs provided herein induce various biological effects associated with inhibition of TIGIT. In some aspects, an ABP provided herein prevents inhibition of an effector T cell. In some aspects, the ABP co-stimulates an effector T cell. In some aspects, the ABP inhibits the suppression of an effector T cell by a regulatory T cell. In some aspects, the ABP increases the number of effector T cells in a tissue or in systemic circulation. In some aspects, the tissue is a tumor. In some aspects, the tissue is a tissue that is infected with a virus.

[0011] Also provided are kits comprising one or more of the ABPs provided herein, and instructions for use of the ABPs. Also provided are kits comprising one or more of the pharmaceutical compositions provided herein, and instructions for use of the pharmaceutical composition.

[0012] Also provided are isolated polynucleotides encoding the ABPs provided herein, and portions thereof.

[0013] Also provided are vectors comprising such polynucleotides.

[0014] Also provided are recombinant host cells comprising such polynucleotides and recombinant host cells comprising such vectors.

[0015] Also provided are methods of producing an ABP provided herein using the polynucleotides, vectors, or host cells provided herein.

[0016] Also provided are pharmaceutical compositions comprising the ABPs provided herein and a pharmaceutically acceptable excipient.

[0017] Also provided are methods of treating or preventing a disease or condition in a subject in need thereof, comprising administering to the subject an effective amount of an ABP provided herein, or a pharmaceutical composition comprising such ABP. In some aspects, the disease or condition is a cancer. In some aspects, the disease or condition is a viral infection. In some aspects the method further comprises administering one or more additional therapeutic agents. In some aspects, the additional therapeutic agent is an immunostimulatory agent.

[0018] In some embodiments, provided herein is a first family of ABPs, wherein an ABP of such family comprises the following six CDR sequences: (a) a CDR-H3 having the sequence A-R-D-G-V-L-X_1-L-N-K-R-S-F-D-I, wherein X_1 is A or T (SEQ ID NO: 128); (b) a CDR-H2 having the sequence S-I-Y-Y-S-G-X_2-T-Y-Y-N-P-S-L-K-S, wherein X_2 is S, Q or G (SEQ ID NO: 129); (c) a CDR-H1 having the sequence G-S-I-X_3-S-G-X_4-Y-Y-W-G, wherein X_3 is E or A, and X_4 is L, V or S (SEQ ID NO: 130); (d) a CDR-L3 having the sequence QQHTVRPPLT (SEQ ID NO: 64); (e) a CDR-L2 having the sequence GASSRAT (SEQ ID NO: 68); and (f) a CDR-L1 having the sequence RASQSVSSSYLA (SEQ ID NO: 71). In some embodiments, provided herein is an ABP within such first family.

[0019] In some embodiments, an ABP of such first family comprises: (a) a CDR-H3 of SEQ ID NO: 32, a CDR-H2 of SEQ ID NO: 40, a CDR-H1 of SEQ ID NO: 54, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71; (b) a CDR-H3 of SEQ ID NO: 31, a

CDR-H2 of SEQ ID NO: 40, a CDR-H1 of SEQ ID NO: 54, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71; (c) a CDR-H3 of SEQ ID NO: 31, a CDR-H2 of SEQ ID NO: 39, a CDR-H1 of SEQ ID NO: 51, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71; (d) a CDR-H3 of SEQ ID NO: 31, a CDR-H2 of SEQ ID NO: 40, a CDR-H1 of SEQ ID NO: 52, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71; or (e) a CDR-H3 of SEQ ID NO: 31, a CDR-H2 of SEQ ID NO: 41, a CDR-H1 of SEQ ID NO: 53, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71.

[0020] In some embodiments, an ABP of such first family comprises: (a) a V_H sequence of SEQ ID NO: 13 and a V_L sequence of SEQ ID NO: 26; (b) a V_H sequence of SEQ ID NO: 12 and a V_L sequence of SEQ ID NO: 26; (c) a V_H sequence of SEQ ID NO: 14 and a V_L sequence of SEQ ID NO: 26; (d) a V_H sequence of SEQ ID NO: 15 and a V_L sequence of SEQ ID NO: 26; (e) a V_H sequence of SEQ ID NO: 9 and a V_L sequence of SEQ ID NO: 26; (f) a V_H sequence of SEQ ID NO: 10 and a V_L sequence of SEQ ID NO: 26; or (g) a V_H sequence of SEQ ID NO: 11 and a V_L sequence of SEQ ID NO: 26.

[0021] In some embodiments, an ABP of such first family comprises: (a) (i) a heavy chain of SEQ ID NO: 99 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 100 and a light chain of SEQ ID NO: 92; (b) (i) a heavy chain of SEQ ID NO: 97 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 98 and a light chain of SEQ ID NO: 92; (c) (i) a heavy chain of SEQ ID NO: 101 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 102 and a light chain of SEQ ID NO: 92; (d) (i) a heavy chain of SEQ ID NO: 103 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 104 and a light chain of SEQ ID NO: 92; (e) (i) a heavy chain of SEQ ID NO: 90 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 91 and a light chain of SEQ ID NO: 92; (f) (i) a heavy chain of SEQ ID NO: 93 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 94 and a light chain of SEQ ID NO: 92; or (g) (i) a heavy chain of SEQ ID NO: 95 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 96 and a light chain of SEQ ID NO: 92.

[0022] In some embodiments, provided herein is a second family of ABPs, wherein an ABP of such family comprises the following six CDR sequences: (a) a CDR-H3 having the sequence A-R-D-A-N-Y-Y-G-X_1-A-W-A-F-D-P, wherein X_1 is S or G (SEQ ID NO: 131); (b) a CDR-H2 having the sequence S-I-Y-Y-S-G-X_2-T-F-Y-N-P-S-L-K-X_3, wherein X_2 is S or A, and X_3 is S or G (SEQ ID NO: 132); (c) a CDR-H1 having the sequence G-S-I-X_4-S-X_5-X_6-X_7-Y-W-G, wherein X_4 is S or T, X_5 is S or T, X_6 is S or K, and X_7 is H or Y (SEQ ID NO: 133); (d) a CDR-L3 having the sequence QQHFNLPT (SEQ ID NO: 63); (e) a CDR-L2 having the sequence DASNRAT (SEQ ID NO: 67); and (f) a CDR-L1 having the sequence RASQSVSSYLA (SEQ ID NO: 70). In some embodiments, provided herein is an ABP within such second family.

[0023] In some embodiments, an ABP of such second family comprises: (a) a CDR-H3 of SEQ ID

NO: 29, a CDR-H2 of SEQ ID NO: 37, a CDR-H1 of SEQ ID NO: 49, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70; (b) a CDR-H3 of SEQ ID NO: 30, a CDR-H2 of SEQ ID NO: 37, a CDR-H1 of SEQ ID NO: 50, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70; (c) a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 38, a CDR-H1 of SEQ ID NO: 50, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70; (d) a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 36, a CDR-H1 of SEQ ID NO: 48, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70; or (e) a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 37, a CDR-H1 of SEQ ID NO: 50, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70.

[0024] In some embodiments, an ABP of such second family comprises: (a) a V_H sequence of SEQ ID NO: 5 and a V_L sequence of SEQ ID NO: 25; (b) a V_H sequence of SEQ ID NO: 7 and a V_L sequence of SEQ ID NO: 25; (c) a V_H sequence of SEQ ID NO: 8 and a V_L sequence of SEQ ID NO: 25; (d) a V_H sequence of SEQ ID NO: 4 and a V_L sequence of SEQ ID NO: 25; or (e) a V_H sequence of SEQ ID NO: 6 and a V_L sequence of SEQ ID NO: 25.

[0025] In some embodiments, an ABP of such second family comprises: (a) (i) a heavy chain of SEQ ID NO: 82 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 83 and a light chain of SEQ ID NO: 81; (b) (i) a heavy chain of SEQ ID NO: 86 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 87 and a light chain of SEQ ID NO: 81; (c) (i) a heavy chain of SEQ ID NO: 88 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 89 and a light chain of SEQ ID NO: 81; (d) (i) a heavy chain of SEQ ID NO: 79 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 80 and a light chain of SEQ ID NO: 81; or (e) (i) a heavy chain of SEQ ID NO: 84 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 85 and a light chain of SEQ ID NO: 81.

[0026] In some embodiments, provided herein is a third family of ABPs, wherein an ABP of such family comprises the following six CDR sequences: (a) a CDR-H3 having the sequence A-R-G-G-R-T-T-W-I-G-A-X_1-D-I, wherein X_1 is F or L (SEQ ID NO: 134); (b) a CDR-H2 having the sequence I-I-N-P-S-X_2-G-L-T-S-Y-A-X_3-K-F-Q-G, wherein X_2 is L or I, and X_3 is Q or R (SEQ ID NO: 135); (c) a CDR-H1 having the sequence Y-T-F-X_4-X_5-Y-Y-X_6-H, wherein X_4 is G, P or R, X_5 is N, A or E, and X_6 is M or I (SEQ ID NO: 136); (d) a CDR-L3 having the sequence QQYVVWPPLT (SEQ ID NO:65); (e) a CDR-L2 having the sequence GASTRAT (SEQ ID NO:69); and (f) a CDR-L1 having the sequence RASQSVSSNLA (SEQ ID NO:72). In some embodiments, provided herein is an ABP within such third family.

[0027] In some embodiments, an ABP of such third family comprises: (a) a CDR-H3 of SEQ ID NO: 33, a CDR-H2 of SEQ ID NO: 43, a CDR-H1 of SEQ ID NO: 60, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; (b) a CDR-H3 of SEQ ID NO: 34, a CDR-H2 of SEQ ID NO: 43, a CDR-H1 of SEQ ID NO: 60, a CDR-L3 of SEQ ID NO: 65, a CDR-

L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; (c) a CDR-H3 of SEQ ID NO: 33, a CDR-H2 of SEQ ID NO: 44, a CDR-H1 of SEQ ID NO: 59, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; (d) a CDR-H3 of SEQ ID NO: 33, a CDR-H2 of SEQ ID NO: 42, a CDR-H1 of SEQ ID NO: 58, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; (e) a CDR-H3 of SEQ ID NO: 33, a CDR-H2 of SEQ ID NO: 42, a CDR-H1 of SEQ ID NO: 59, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; or (f) a CDR-H3 of SEQ ID NO: 34, a CDR-H2 of SEQ ID NO: 44, a CDR-H1 of SEQ ID NO: 61, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72.

[0028] In some embodiments, an ABP of such third family comprises: (a) a V_H sequence of SEQ ID NO: 18 and a V_L sequence of SEQ ID NO: 27; (b) a V_H sequence of SEQ ID NO: 19 and a V_L sequence of SEQ ID NO: 27; (c) a V_H sequence of SEQ ID NO: 21 and a V_L sequence of SEQ ID NO: 27; (d) a V_H sequence of SEQ ID NO: 16 and a V_L sequence of SEQ ID NO: 27; (e) a V_H sequence of SEQ ID NO: 17 and a V_L sequence of SEQ ID NO: 27; or (f) a V_H sequence of SEQ ID NO: 20 and a V_L sequence of SEQ ID NO: 27.

[0029] In some embodiments, an ABP of such third family comprises: (a) (i) a heavy chain of SEQ ID NO: 110 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 111 and a light chain of SEQ ID NO: 107; (b) (i) a heavy chain of SEQ ID NO: 112 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 113 and a light chain of SEQ ID NO: 107; (c) (i) a heavy chain of SEQ ID NO: 116 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 117 and a light chain of SEQ ID NO: 107; (d) (i) a heavy chain of SEQ ID NO: 105 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 106 and a light chain of SEQ ID NO: 107; (e) (i) a heavy chain of SEQ ID NO: 108 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 109 and a light chain of SEQ ID NO: 107; or (f) (i) a heavy chain of SEQ ID NO: 114 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 115 and a light chain of SEQ ID NO: 107.

[0030] In some embodiments, provided herein is a fourth family of ABPs, wherein an ABP of such family comprises the following six CDR sequences: (a) a CDR-H3 having the sequence ARLHVSGSYYPAYLDY (SEQ ID NO: 35); (b) a CDR-H2 having the sequence X_1-I-N-P-S-M-G-A-T-S-Y-X_2-Q-K-F-X_3-G, wherein X_1 is V or I, X_2 is A or T, and X_3 is Q or R (SEQ ID NO: 137); (c) a CDR-H1 having the sequence YTFTSHYMG (SEQ ID NO: 62); (d) a CDR-L3 having the sequence QQYIVFPWT (SEQ ID NO: 66); (e) a CDR-L2 having the sequence GASTRAT (SEQ ID NO: 69); and (f) a CDR-L1 having the sequence RASQSVSSNLA, (SEQ ID NO: 72). In some embodiments, provided herein is an ABP within such fourth family.

[0031] In some embodiments, an ABP of such fourth family comprises: (a) a CDR-H3 of SEQ ID NO: 35, a CDR-H2 of SEQ ID NO: 46, a CDR-H1 of SEQ ID NO: 62, a CDR-L3 of SEQ ID NO: 66, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; (b) a CDR-H3 of SEQ ID NO: 35, a

CDR-H2 of SEQ ID NO: 47, a CDR-H1 of SEQ ID NO: 62, a CDR-L3 of SEQ ID NO: 66, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; or (c) a CDR-H3 of SEQ ID NO: 35, a CDR-H2 of SEQ ID NO: 45, a CDR-H1 of SEQ ID NO: 62, a CDR-L3 of SEQ ID NO: 66, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72.

[0032] In some embodiments, an ABP of such fourth family comprises: (a)a V_H sequence of SEQ ID NO: 23 and a V_L sequence of SEQ ID NO: 28; (b) a V_H sequence of SEQ ID NO: 24 and a V_L sequence of SEQ ID NO: 28; or (c) a V_H sequence of SEQ ID NO: 22 and a V_L sequence of SEQ ID NO: 28.

[0033] In some embodiments, an ABP of such fourth family comprises: (a) (i) a heavy chain of SEQ ID NO: 121 and a light chain of SEQ ID NO: 120; or (ii) a heavy chain of SEQ ID NO: 122 and a light chain of SEQ ID NO: 120; (b) (i) a heavy chain of SEQ ID NO: 123 and a light chain of SEQ ID NO: 120; or (ii) a heavy chain of SEQ ID NO: 124 and a light chain of SEQ ID NO: 120; or (c) (i) a heavy chain of SEQ ID NO: 118 and a light chain of SEQ ID NO: 120; or (ii) a heavy chain of SEQ ID NO: 119 and a light chain of SEQ ID NO: 120.

[0034] In some embodiments, provided herein is an isolated antigen binding protein (ABP) that specifically binds human TIGIT (hTIGIT; SEQ ID NO: 1), comprising: (a) a CDR-H3 having at least about 80% identity to a CDR-H3 of a V_H region selected from SEQ ID NOs: 4-24; (b) a CDR-H2 having at least about 80% identity to a CDR-H2 of a V_H region selected from SEQ ID NOs: 4-24; (c) a CDR-H1 having at least about 80% identity to a CDR-H1 of a V_H region selected from SEQ ID NOs: 4-24; (d) a CDR-L3 having at least about 80% identity to a CDR-L3 of a V_L region selected from SEQ ID NOs: 25-28; (e) a CDR-L2 having at least about 80% identity to a CDR-L2 of a V_L region selected from SEQ ID NOs: 25-28; and (f) a CDR-L1 having at least about 80% identity to a CDR-L1 of a V_L region selected from SEQ ID NOs: 25-28. In some embodiments, the CDR-H3, CDR-H2, CDR-H1, CDR-L3, CDR-L2, and CDR-L1 are each identified according to a numbering scheme selected from the Kabat numbering scheme, the Chothia numbering scheme, or the IMGT numbering scheme. In some embodiments, the CDR-H1 is identified as defined by both the Chothia and Kabat numbering schemes, inclusive of the boundaries of both numbering schemes. In some embodiments: (a) the CDR-H3 comprises a CDR-H3 selected from SEQ ID NOs: 29-35, or a variant thereof having 1, 2, or 3 amino acid substitutions; (b) the CDR-H2 comprises a CDR-H3 selected from SEQ ID NOs: 36-47, or a variant thereof having 1, 2, or 3 amino acid substitutions; (c) the CDR-H1 comprises a CDR-H1 selected from SEQ ID NOs: 48-54 or 58-62, or a variant thereof having 1 or 2 amino acid substitutions; (d) the CDR-L3 comprises a CDR-L3 selected from SEQ ID NOs: 63-66, or a variant thereof having 1 or 2 amino acid substitutions; (e) the CDR-L2 comprises a CDR-L2 selected from SEQ ID NOs: 67-69, or a variant thereof having 1 amino acid substitution; and (f) the CDR-L1 comprises a CDR-L1 selected from SEQ ID NOs: 70-72, or a variant thereof having 1 or 2 amino acid substitutions.

[0035] In some embodiments, provided herein is an isolated antigen binding protein (ABP) that

specifically binds human TIGIT (hTIGIT; SEQ ID NO: 1), comprising: (a) a V_H region having at least about 90% identity to a V_H region selected from SEQ ID NOs: 4-24; and (b) a V_L region having at least about 90% identity to a V_L region selected from SEQ ID NOs: 25-28. In some embodiments: (a) the a V_H region comprises a V_H region selected from SEQ ID NOs: 4-24, or a variant thereof having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid substitutions; and (b) the a V_L region comprises a V_L region selected from SEQ ID NOs: 25-28, or a variant thereof having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions. In some embodiments, the amino acid substitutions are conservative amino acid substitutions.

[0036] In some embodiments, any of the foregoing ABPs: (a) competes for binding to TIGIT with an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each as provided in Table 5 of this disclosure; (b) inhibits binding of CD155 to TIGIT; (c) inhibits binding of CD112 to TIGIT; (d) inhibits association of CD226 with TIGIT; (e) activates an effector T cell or a natural killer (NK) cell; (f) decreases the number of regulatory T cells in a tissue or in circulation; (g) inhibits the suppression of an effector T cell by a regulatory T cell; (h) does not bind specifically to any of PVRL1, PVRL2, PVRL3, or PVRL4; or (i) is capable of any combination of (a)- (h).

[0037] In some embodiments, any of the foregoing ABPs: (a) specifically binds cynomolgus monkey TIGIT (cTIGIT; SEQ ID NO: 2); (b) binds murine TIGIT (mTIGIT; SEQ ID NO: 3) with an affinity lower (as indicated by higher KD) than the affinity of the ABP for hTIGIT, or does not bind mTIGIT; or (c) is capable of any combination of (a) - (b).

[0038] In some embodiments, any of the foregoing ABPs: (a) specifically binds cTIGIT (SEQ ID NO: 2); (b) binds mTIGIT (SEQ ID NO: 3) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hTIGIT and cTIGIT; and (c) inhibits binding of CD155 to TIGIT.

[0039] In some embodiments, provided herein is an ABP that competes for binding to TIGIT with any of the foregoing ABPs, wherein the ABP: (a) specifically binds cTIGIT (SEQ ID NO: 2); (b) binds mTIGIT (SEQ ID NO: 3) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hTIGIT and cTIGIT; and (c) inhibits binding of CD155 to TIGIT.

[0040] In some embodiments, any of the foregoing ABPs comprises an antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is selected from a human antibody, a humanized antibody or a chimeric antibody.

[0041] In some embodiments, any of the foregoing ABPs is multispecific. In some embodiments, the multispecific ABP binds more than one antigen (i.e., TIGIT and a different (non-TIGIT) antigen). In some embodiments, the multispecific ABP binds more than one epitope on a single antigen (i.e., two or more epitopes on TIGIT).

[0042] In some embodiments, any of the foregoing ABPs comprises an antibody fragment.

[0043] In some embodiments, any of the foregoing ABPs comprises an alternative scaffold.

[0044] In some embodiments, any of the foregoing ABPs comprises an immunoglobulin constant region. In some embodiments, the ABP comprises heavy chain constant region of a class selected from IgA, IgD, IgE, IgG, or IgM. In some embodiments, the ABP comprises a heavy chain constant region of the class IgG and a subclass selected from IgG4, IgG1, IgG2, or IgG3.

[0045] In some embodiments, any of the foregoing ABPs binds hTIGIT (SEQ ID NO: 1) with a K_D of less than about 10 nM, as measured by biolayer interferometry. In some embodiments, any of the foregoing ABPs binds hTIGIT (SEQ ID NO: 1) with a K_D of less than about 5 nM, as measured by biolayer interferometry. In some embodiments, any of the foregoing ABPs binds hTIGIT (SEQ ID NO: 1) with a K_D of less than about 2 nM, as measured by biolayer interferometry. In some embodiments, any of the foregoing ABPs binds cTIGIT (SEQ ID NO: 2) with a K_D of less than about 100 nM, as measured by biolayer interferometry. In some embodiments, any of the foregoing ABPs binds cTIGIT (SEQ ID NO: 2) with a K_D of less than about 10 nM, as measured by biolayer interferometry. In some embodiments, any of the foregoing ABPs shows no significant binding to mTIGIT in a biolayer interferometry assay. In some embodiments, any of the foregoing ABPs binds to cell surface mTIGIT with a K_D of less than about 50 nM. In some embodiments, mTIGIT comprises SEQ ID NO: 3. In some embodiments, mTIGIT comprises SEQ ID NO: 138.

[0046] In some embodiments, any of the foregoing ABPs comprises a polypeptide sequence having a pyroglutamate (pE) residue at its N-terminus. In some embodiments, any of the foregoing ABPs comprises a V_H sequence in which an N-terminal Q is substituted with pE. In some embodiments, any of the foregoing ABPs comprises a V_L sequence in which an N-terminal E is substituted with pE. In some embodiments, any of the foregoing ABPs comprises a heavy chain sequence in which an N-terminal Q is substituted with pE. In some embodiments, any of the foregoing ABPs comprises a light chain sequence in which an N-terminal E is substituted with pE.

[0047] In some embodiments, provided herein are any of the foregoing ABPs for use as a medicament. In some embodiments, provided herein are any of the foregoing ABPs for use in the treatment of a cancer or viral infection. In some embodiments, provided herein are any of the foregoing ABPs for use in the treatment of a cancer, wherein the cancer is selected from a solid tumor and a hematological tumor. In some embodiments, provided herein are any of the foregoing ABPs for use as a medicament in the treatment of a disease or condition that was not responsive to a prior therapy. In some embodiments, the prior therapy was a therapy comprising an agent that inhibits the interaction between PD-1 and PD-L1.

[0048] In some embodiments, provided herein is an isolated polynucleotide encoding any of the foregoing ABPs, a V_H thereof, a V_L thereof, a light chain thereof, a heavy chain thereof or an antigen-binding portion thereof. In some embodiments, provided herein is a vector comprising the polynucleotide. In some embodiments, provided herein is a host cell comprising the polynucleotide and/or the vector. In some embodiments, provided herein is a method of producing any of the foregoing ABPs, comprising expressing the ABP in the host cell and isolating the expressed ABP.

[0049] In some embodiments, provided herein is a pharmaceutical composition comprising any of the foregoing ABPs. In some embodiments, the amount of the ABP in the pharmaceutical composition is sufficient to (a) increase effector T cell activity; (b) increase cytolytic T cell activity; (c) increase NK cell activity; (d) inhibit TIGIT-mediated signaling; (e) inhibit or block the binding of CD155 and or CD112 to TIGIT; or (f) any combination of (a) - (e), in a subject. In some embodiments, the any of the foregoing pharmaceutical compositions further comprises an antibody that antagonizes PD-1 or blocks PD-L1 from interacting with PD-1. In some embodiments, any of the foregoing pharmaceutical compositions is for use as a medicament. In some embodiments, any of the foregoing pharmaceutical compositions is for use in the treatment of a cancer or a viral infection. In some embodiments, any of the foregoing pharmaceutical compositions is for use in the treatment of a cancer, wherein the cancer is selected from a solid tumor and a hematological tumor. In some embodiments, any of the foregoing pharmaceutical compositions is for use as a medicament in the treatment of a disease or condition that was not responsive to a prior therapy. In some embodiments, the prior therapy was a therapy comprising an agent that inhibits the interaction between PD-1 and PD-L1.

[0050] In some embodiments, provided herein is a method of treating or preventing a disease or condition in a subject in need thereof, comprising administering to the subject an effective amount of any of the foregoing ABPs or any of the foregoing pharmaceutical compositions. In some embodiments, the disease or condition is a cancer or viral infection. In some embodiments, the disease or condition is a cancer, and the cancer is selected from a solid tumor and a hematological tumor. In some embodiments, provided herein is a method of modulating an immune response in a subject in need thereof, comprising administering to the subject an effective amount of any of the foregoing ABPs or any of the foregoing pharmaceutical compositions. In some embodiments, any of the foregoing methods, further comprise administering one or more additional therapeutic agents to the subject. In some embodiments, the additional therapeutic agent is selected from an agent that inhibits the interaction between PD-1 and PD-L1, a chemotherapy, an immunostimulatory agent, radiation, and combinations thereof.

[0051] In some embodiments, the additional therapeutic agent for use in any of the foregoing methods of treatment, uses of an ABP or uses of a pharmaceutical composition is an agent that inhibits the interaction between PD-1 and PD-L1, and wherein the agent that inhibits the interaction between PD-1 and PD-L1 is selected from an antibody, a peptidomimetic, a small molecule or a nucleic acid encoding such agent. In some embodiments, the agent that inhibits the interaction between PD-1 and PD-L1 is selected from is selected from pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, BMS-936559, sulfamonomethoxine 1, and sulfamethizole 2.

[0052] In some embodiments, the additional therapeutic agent for use in any of the foregoing methods of treatment, uses of an ABP or uses of a pharmaceutical composition is an immunostimulatory agent selected from (a) an agent that blocks signaling of an inhibitory receptor of

an immune cell or a ligand thereof or a nucleic acid encoding such agent; (b) an agonist to a stimulatory receptor of an immune cell or a nucleic acid encoding such agonist; (c) a cytokine or a nucleic acid encoding a cytokine; (d) an oncolytic virus or a nucleic acid encoding an oncolytic virus; (e) a T cell expressing a chimeric antigen receptor; (f) a bi- or multi-specific T cell directed antibody or a nucleic acid encoding such antibody; (g) an anti-TGF-ß antibody or a nucleic acid encoding such antibody; (h) a TGF-ß trap or a nucleic acid encoding such trap; (i) a vaccine to a cancer-associated antigen, including such antigen or a nucleic acid encoding such antigen and (j) combinations thereof. In some embodiments, the additional therapeutic agent is an agent that blocks signaling of an inhibitory receptor of an immune cell or a ligand thereof or a nucleic acid encoding such agent, and the inhibitory receptor or ligand thereof is selected from CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, Tim3, neuritin, BTLA, CECAM-1, CECAM-5, VISTA, LAIR1, CD160, 2B4, TGF-R, KIR, and combinations thereof. In some embodiments, the additional therapeutic agent is an agonist to a stimulatory receptor of an immune cell or a nucleic acid encoding such agonist, and the stimulatory receptor of an immune cell is selected from OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD28, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, CD83 ligand, and combinations thereof. In some embodiments, the additional therapeutic agent is a cytokine or a nucleic acid encoding a cytokine selected from IL-2, IL-5, IL-7, IL-12, IL-15, IL-21, and combinations thereof. In some embodiments, the additional therapeutic agent is an oncolytic virus or a nucleic acid encoding an oncolytic virus selected from herpes simplex virus, vesicular stomatitis virus, adenovirus, Newcastle disease virus, vaccinia virus, a maraba virus, and combinations thereof.

[0053] In some embodiments, the additional therapeutic agent is formulated in the same pharmaceutical composition as the ABP. In some embodiments, the additional therapeutic agent is formulated in a different pharmaceutical composition from the ABP. In some embodiments, the additional therapeutic agent is administered prior to administering the ABP. In some embodiments, the additional therapeutic agent is administered after administering the ABP. In some embodiments, the additional therapeutic agent is administered contemporaneously with the ABP.

[0054] In some embodiments, the subject is a subject that has been treated with an agent that inhibits the interaction between PD-1 and PD-L1 prior to performing such method.

[0055] In some embodiments, the disease or condition afflicting the subject was not responsive to a prior therapy. In some embodiments, the prior therapy was a therapy comprising an agent that inhibits the interaction between PD-1 and PD-L1.

[0056] In some embodiments, provided herein is a kit comprising any of the foregoing pharmaceutical compositions, and instructions for the use of such pharmaceutical composition. In some embodiments, the kit further comprises an additional pharmaceutical composition comprising an additional therapeutic agent and instructions for the use of such additional therapeutic agent. In some embodiments, the additional therapeutic agent is selected from an agent that inhibits the interaction

between PD-1 and PD-L1, a chemotherapy, an immunostimulatory agent, radiation, and combinations thereof. In some embodiments, the additional therapeutic agent is an agent that inhibits the interaction between PD-1 and PD-L1, and wherein the agent inhibits the interaction between PD-1 and PD-L1 is selected from an antibody, a peptidomimetic, a small molecule or a nucleic acid encoding such agent. In some embodiments, the agent that inhibits the interaction between PD-1 and PD-L1 is selected from is selected from pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, BMS-936559, sulfamonomethoxine 1, and sulfamethizole 2. In some embodiments, the additional therapeutic agent is an immunostimulatory agent selected from (a) an agent that blocks signaling of an inhibitory receptor of an immune cell or a ligand thereof or a nucleic acid encoding such agent; (b) an agonist to a stimulatory receptor of an immune cell or a nucleic acid encoding such agonist; (c) a cytokine or a nucleic acid encoding a cytokine; (d) an oncolytic virus or a nucleic acid encoding an oncolytic virus; (e) a T cell expressing a chimeric antigen receptor; (f) a bi- or multi-specific T cell directed antibody or a nucleic acid encoding such antibody; (g) an anti-TGF-ß antibody or a nucleic acid encoding such antibody; (h) a TGF-ß trap or a nucleic acid encoding such trap; (i) a vaccine to a cancer-associated antigen, including such antigen or a nucleic acid encoding such antigen and (j) combinations thereof. In some embodiments, the additional therapeutic agent is an agent that blocks signaling of an inhibitory receptor of an immune cell or a ligand thereof or a nucleic acid encoding such agent, and the inhibitory receptor or ligand thereof is selected from CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, Tim3, neuritin, BTLA, CECAM-1, CECAM-5, VISTA, LAIR1, CD160, 2B4, TGF-R, KIR, and combinations thereof. In some embodiments, the additional therapeutic agent is an agonist to a stimulatory receptor of an immune cell or a nucleic acid encoding such agonist, and the stimulatory receptor of an immune cell is selected from OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD28, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, CD83 ligand, and combinations thereof. In some embodiments, the additional therapeutic agent is a cytokine or a nucleic acid encoding a cytokine selected from IL-2, IL-5, IL-7, IL-12, IL-15, IL-21, and combinations thereof. In some embodiments, the additional therapeutic agent is an oncolytic virus or a nucleic acid encoding an oncolytic virus selected from herpes simplex virus, vesicular stomatitis virus, adenovirus, Newcastle disease virus, vaccinia virus, a maraba virus, and combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] Figures 1A-1B show sequence alignments of various molecules described further in the Examples. **Figure 1A** shows sequence alignments of the TIGIT extracellular domains from human, cynomolgus monkey, mouse (SEQ ID NO: 3), and rat TIGIT reference sequences. **Figure 1B** shows an alignment of the human TIGIT and PVRL4 extracellular domains.

[0058] Figure 2 is an illustration of the similarity between the CD28-CTLA4 and CD226-TIGIT pathways and thus the utility of TIGIT as an immune checkpoint target. The CD226/TIGIT

costimulation/coinhibition biology is analogous to that of CD28/CTLA4; TIGIT provides an inhibitory signal to T cells while CD226 provides a costimulation signal to T cells. TIGIT ligands CD155 and CD112 are widely expressed in tumors providing an immune suppressive environment.

[0059] **Figure 3** shows a schematic diagram of the TIGIT Jurkat/anti-CD3 HT-1080 co-culture assay described in Example 7.

[0060] **Figure 4A** shows the EC_{50} curves from exemplary experiments comparing the ability of MAB10 and an IgG4 isotype control to induce IL-2 production in engineered Jurkat cells expressing human TIGIT. **Figure 4B** shows the EC_{50} curves from exemplary experiments comparing the ability of MAB10 and an IgG4 isotype control to induce IL-2 production in engineered Jurkat cells expressing cynomolgus monkey TIGIT.

[0061] **Figure 5A-5C** show TIGIT expression analysis on human CD4+ T cells by FACS. **Figure 5A** and **Figure 5B** show a series of graphs showing expression analysis of TIGIT, PVR and CD226 on unstimulated (Figure 5A) and stimulated (Figure 5B) CD4+ T cells. **Figure 5C** shows analysis of TIGIT expression on naïve (positive for CD45RA, a marker of naïve T cells, top right panel) and memory (positive for CD45RO, a marker of activated T cells, bottom right panel) CD4+ T cells.

[0062] **Figures 6A-6O** show the effect of treatment with MABs on sub-optimally stimulated PBMCs from human donors. MABs were tested for their ability to induce IFN-γ in PBMCs from human donors, including a control IgG4 antibody (**Figure 6A**), MAB2 (**Figure 6B**), MAB3 (**Figure 6C**), MAB4 (**Figure 6D**), MAB5 (**Figure 6E**), MAB10 (**Figure 6F**), MAB11 (**Figure 6G**), MAB12 (**Figure 6H**), MAB15 (**Figure 6I**), MAB16 (**Figure 6J**), and SEC1 (hamster anti-mouse TIGIT, **Figure 6K**). Treatment of the PBMCs from Donor 1 with MAB10 induces the upregulation of several pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF, **Figure 6L**), lymphotoxin alpha (LT-α, **Figure 6M**), and interferon gamma (IFN-γ, **Figure 6N**). **Figure 6O** shows a graph illustrating the EC_{50} of MAB10 in PBMCs from Donor 1, as measured by IFN-γ production.

[0063] **Figures 7A-7E** provide a series of graphs showing the effect of MAB10 on cytokine secretion in sub-optimally stimulated PBMCs from Donor 2, including IFN-γ (**Figure 7A**), TNF (**Figure 7B**), interleukin 6 (IL-6, **Figure 7C**), granulocyte macrophage colony-stimulating factor (GM-CSF, **Figure 7D**), and LT-α (**Figure 7E**). Data from cells treated with MAB10 are shown as black bars and data from cells treated with the IgG4 isotype control are shown as light gray bars. Antibody concentration for each bar is in μg/mL.

[0064] **Figures 8A-8C** provide a series of graphs showing that the antagonist anti-TIGIT antibody MAB10 increases IFN-γ in a CD4+ cell assay using cells obtained from three different donors. **Figure 8A** shows results obtained from CD4+ cells obtained from Donor 1. **Figure 8B** shows results obtained from CD4+ cells obtained from Donor 2. **Figure 8C** shows results obtained from CD4+ cells obtained from Donor 3. IFN-γ production in cells treated with either MAB10 (black bars) or the IgG4 isotype control (light gray bars) is shown in the left panel of each of Figures 8A-8C. The

average EC_{50} value for MAB10 in this assay was calculated by determining the concentration of MAB10 required to induce 50% of the increase in IFN-γ signal (plotted in the right panel of each of Figures 8A-8C).

[0065] **Figure 9A** shows the results of the assay in which a 1:1 ratio of MAB10 and pembrolizumab (anti-PD-1 antibody) were used in a mechanism-of-action based PD-1/TIGIT Combination Bioassay. Concentrations for each antibody were 25, 10, 4, 1.6, 0.64, 0.256, 0.1024, 0.04096, and 0.016384 μg/ml. An untargeted IgG4 was used as a control. As shown in Figure 9A, only the combination of MAB10 and pembrolizumab (EC_{50} of 5.06 nM) blocked binding sufficiently to induce luciferase activity in the Jurkat cells. **Figure 9B** shows the results of the assay with a fixed dose (1 μg/ml) of pembrolizumab (or IgG4 control) and a varying dose of MAB10 (50, 20, 8, 3.2, 1.28, 0.512, 0.2048, 0.08192, and 0.032768 μg/ml). In Figures 9A and 9B, neither the IgG4 control alone or the IgG4 + MAB10 combination induced luciferase activity.

[0066] **Figures 10A-10D** are a series of graphs showing the effect of MAB10 on CMV-stimulated CD4+ T-cells from a human donor using intracellular cytokine staining. Incubation of CD4+ cells with MAB10 (black bars) increases the production of the effector cytokines in a dose-dependent matter, including TNF (**Figure 10A**), IL-2 (**Figure 10B**), and IFN-γ (**Figure 10C**) compared to cells incubated with the IgG4 control (white bars). **Figure 10D** shows that incubation with MAB10 increases the proportion of antigen-specific activated CD4+ T-cells. In Figure 10D, cells that were treated with 20 μg/ml of the IgG4 control or MAB10 were analyzed by FACS for expression of CD3 (a marker of mature T-cells) and expression of TNF and IL-2. Statistical differences were calculated between MAB10 and IgG4 control groups (same concentration treatments) using Student's T test (*=p<0.05, **=p<0.01, ***=p<0.005, ****=p<0.001).

[0067] **Figures 11A-11D** are a series of graphs similar to Figure 10, but using CD8+ cells, and show the production of TNF (**Figure 11A**), perforin (**Figure 11B**), and granzyme B (**Figure 11C**) by such cells treated with MAB10 or the IgG4 control. **Figure 11D** shows that incubation with MAB10 also increases the proportion of antigen-specific activated CD8+ T-cells. Cells that were treated with 20 μg/ml of the IgG4 control or MAB10 were analyzed by FACS for expression of CD3 and expression of perforin and granzyme B. Statistical differences were calculated between MAB10 and IgG4 control groups (same concentration treatments) using Student's T test (*=p<0.05, **=p<0.01, ***=p<0.005, ****=p<0.001).

[0068] **Figures 12A-12D** show the results of treatment of cells from the same donor, wherein blockade by MAB10 amplifies CMV-specific CD8+ T-cell responses. Cells were incubated with a range of concentrations of MAB10 (black bars) or the IgG4 control (white bars), and the percentage of double positive population perforin + granzyme B+ (**Figure 12A**) or IFN-γ + TNF+ (**Figure 12C**) was analyzed. Statistical differences were calculated between MAB10 and IgG4 control groups (same concentration treatments) using Student's T test (*=p<0.05, **=p<0.01, ***=p<0.005, ****=p<0.001). **Figure 12B** (perforin + granzyme B+ analysis) and **Figure 12D** (IFN-γ + TNF+

analysis) show the proportion of double positive cells comparing cells treated with 20 μg/ml of the control antibody (left panels) or 20 μg/ml of MAB10 (right panels).

[0069] Figure 13 is a graph showing the combinatorial effect of MAB10 and the PD-1 antibody pembrolizumab on cells from the same donor as used for Figures 10-12. Cells were stimulated with CMV lysates and treated with 2 μg/ml pembrolizumab or control IgG4, and 10, 20, or 40 μg/ml control antibody or MAB10, and production of TNF was measured. Four groups of cells were tested, and treated with IgG4 control (white bars, left most group), a constant amount of IgG4 control and a titration of MAB10 (dark gray bars, second group from left), a constant amount of pembrolizumab and a titration of IgG4 control (light gray bars, second group from right), or a constant amount of pembrolizumab and a titration of MAB10 (black bars, right hand group).

[0070] Figures 14A-14C are a series of graphs showing the effect of MAB10 + pembrolizumab treatment on cells from three different donors. Cells were stimulated with 0.1 μg/ml of CMV lysate and treated with 20 μg/ml of MAB10 or 20 μg/ml of control IgG4 antibody and a titration of pembrolizumab, then the production of TNF was measured. **Figure 14A** shows the results of the assay using cells from Donor 1; **Figure 14B** shows the results of the assay using cells from Donor 2; **Figure 14C** shows the results of the assay using cells from Donor 3. The addition of MAB10 (black bars) alone or in combination with increasing concentrations of pembrolizumab results in a greater production of TNF compared to control antibody + pembrolizumab group (white bars). Additionally, MAB10 (black bars) in combination with pembrolizumab also resulted in increased activation compared to MAB10 alone. Statistic differences were calculated between MAB10 alone and MAB10+pembro groups using Student T test analysis (*=$p<0.05$, **=$p<0.01$, ***=$p<0.005$, ****=$p<0.001$)

DETAILED DESCRIPTION

1. Definitions

[0071] Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this invention pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a difference over what is generally understood in the art. The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodologies by those skilled in the art, such as, for example, the widely utilized molecular cloning methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 4th ed. (2012) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. As appropriate, procedures involving the use of commercially available kits and

reagents are generally carried out in accordance with manufacturer-defined protocols and conditions unless otherwise noted.

[0072] As used herein, the singular forms "a," "an," and "the" include the plural referents unless the context clearly indicates otherwise. The terms "include," "such as," and the like are intended to convey inclusion without limitation, unless otherwise specifically indicated.

[0073] As used herein, the term "comprising" also specifically includes embodiments "consisting of" and "consisting essentially of" the recited elements, unless specifically indicated otherwise. For example, a multispecific ABP "comprising a diabody" includes a multispecific ABP "consisting of a diabody" and a multispecific ABP "consisting essentially of a diabody."

[0074] The term "about" indicates and encompasses an indicated value and a range above and below that value. In certain embodiments, the term "about" indicates the designated value ± 10%, ± 5%, or ± 1%. In certain embodiments, where applicable, the term "about" indicates the designated value(s) ± one standard deviation of that value(s).

[0075] The terms "TIGIT," "TIGIT protein," and "TIGIT antigen" are used interchangeably herein to refer to human TIGIT, or any variants (e.g., splice variants and allelic variants), isoforms, and species homologs of human TIGIT that are naturally expressed by cells, or that are expressed by cells transfected with a *tigit* gene. In some aspects, the TIGIT protein is a TIGIT protein naturally expressed by a primate (e.g., a monkey or a human), a rodent (e.g., a mouse or a rat), a dog, a camel, a cat, a cow, a goat, a horse, or a sheep. In some aspects, the TIGIT protein is human TIGIT (hTIGIT; SEQ ID NO:1). Without being bound by theory, it is believed that positions 1-21 of SEQ ID NO:1 encode a signal peptide; positions 22-141 of SEQ ID NO:1 encode the extracellular domain of the mature TIGIT protein; positions 142-162 of SEQ ID NO:1 encode a transmembrane domain; and positions 163-244 of SEQ ID NO:1 encode a cytoplasmic domain. *See* UniProt KB - Q495A1 (TIGIT_HUMAN), at www.uniprot.org/uniprot/Q495A1, accessed September 28, 2015. In some aspects, the TIGIT protein is a cynomolgus monkey TIGIT (cTIGIT; SEQ ID NO:2). In some aspects, the TIGIT protein is a murine TIGIT (mTIGIT) having the sequence provided in SEQ ID NO:3. In some aspects, the TIGIT protein is a murine TIGIT (mTIGIT) having the sequence provided in SEQ ID NO:138. As used herein, if a SEQ ID NO is not specified, the terms "mTIGIT," "murine TIGIT" and "mouse TIGIT mean SEQ ID NO: 3 and/or SEQ ID NO: 138. In some aspects, the TIGIT protein is a full-length or unprocessed TIGIT protein. In some aspects, the TIGIT protein is a truncated or processed TIGIT protein produced by post-translational modification. TIGIT is also known by a variety of synonyms, including WUCAM, VSIG9, and Vstm3.

[0076] The term "immunoglobulin" refers to a class of structurally related proteins generally comprising two pairs of polypeptide chains: one pair of light (L) chains and one pair of heavy (H) chains. In an "intact immunoglobulin," all four of these chains are interconnected by disulfide bonds. The structure of immunoglobulins has been well characterized. *See, e.g.*, Paul, *Fundamental Immunology* 7th ed., Ch. 5 (2013) Lippincott Williams & Wilkins, Philadelphia, PA. Briefly, each

heavy chain typically comprises a heavy chain variable region (V_H) and a heavy chain constant region (C_H). The heavy chain constant region typically comprises three domains, abbreviated C_{H1}, C_{H2}, and C_{H3}. Each light chain typically comprises a light chain variable region (V_L) and a light chain constant region. The light chain constant region typically comprises one domain, abbreviated C_L.

[0077] The term "antigen-binding protein" (ABP) refers to a protein comprising one or more antigen-binding domains that specifically bind to an antigen or epitope. In some embodiments, the antigen-binding domain binds the antigen or epitope with specificity and affinity similar to that of naturally occurring antibodies. In some embodiments, the ABP comprises an antibody. In some embodiments, the ABP consists of an antibody. In some embodiments, the ABP consists essentially of an antibody. In some embodiments, the ABP comprises an alternative scaffold. In some embodiments, the ABP consists of an alternative scaffold. In some embodiments, the ABP consists essentially of an alternative scaffold. In some embodiments, the ABP comprises an antibody fragment. In some embodiments, the ABP consists of an antibody fragment. In some embodiments, the ABP consists essentially of an antibody fragment. A "TIGIT ABP," "anti-TIGIT ABP," or "TIGIT-specific ABP" is an ABP, as provided herein, which specifically binds to the antigen TIGIT. In some embodiments, the ABP binds the extracellular domain of TIGIT. In certain embodiments, a TIGIT ABP provided herein binds to an epitope of TIGIT that is conserved between or among TIGIT proteins from different species.

[0078] The term "antibody" is used herein in its broadest sense and includes certain types of immunoglobulin molecules comprising one or more antigen-binding domains that specifically bind to an antigen or epitope. An antibody specifically includes intact antibodies (e.g., intact immunoglobulins), antibody fragments, and multi-specific antibodies. An antibody is one type of ABP.

[0079] The term "alternative scaffold" refers to a molecule in which one or more regions may be diversified to produce one or more antigen-binding domains that specifically bind to an antigen or epitope. In some embodiments, the antigen-binding domain binds the antigen or epitope with specificity and affinity similar to that of an antibody. Exemplary alternative scaffolds include those derived from fibronectin (e.g., Adnectins™), the β-sandwich (e.g., iMab), lipocalin (e.g., Anticalins®), EETI-II/AGRP, BPTI/LACI-D1/ITI-D2 (e.g., Kunitz domains), thioredoxin peptide aptamers, protein A (e.g., Affibody®), ankyrin repeats (e.g., DARPins), gamma-B-crystallin/ubiquitin (e.g., Affilins), $CTLD_3$ (e.g., Tetranectins), Fynomers, and (LDLR-A module) (e.g., Avimers). Additional information on alternative scaffolds is provided in Binz et al., *Nat. Biotechnol.*, 2005 23:1257-1268; Skerra, *Current Opin. in Biotech.*, 2007 18:295-304; and Silacci et al., *J. Biol. Chem.*, 2014, 289:14392-14398; each of which is incorporated by reference in its entirety. An alternative scaffold is one type of ABP.

[0080] The term "antigen-binding domain" means the portion of an ABP that is capable of specifically binding to an antigen or epitope. One example of an antigen-binding domain is an

antigen-binding domain formed by a V_H -V_L dimer of an antibody. Another example of an antigen-binding domain is an antigen-binding domain formed by diversification of certain loops from the tenth fibronectin type III domain of an Adnectin.

[0081] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a naturally occurring antibody structure and having heavy chains that comprise an Fc region. For example, when used to refer to an IgG molecule, a "full length antibody" is an antibody that comprises two heavy chains and two light chains.

[0082] The term "Fc region" means the C-terminal region of an immunoglobulin heavy chain that, in naturally occurring antibodies, interacts with Fc receptors and certain proteins of the complement system. The structures of the Fc regions of various immunoglobulins, and the glycosylation sites contained therein, are known in the art. *See* Schroeder and Cavacini, *J. Allergy Clin. Immunol.*, 2010, 125:S41-52, incorporated by reference in its entirety. The Fc region may be a naturally occurring Fc region, or an Fc region modified as described in the art or elsewhere in this disclosure.

[0083] The V_H and V_L regions may be further subdivided into regions of hypervariability ("hypervariable regions (HVRs);" also called "complementarity determining regions" (CDRs)) interspersed with regions that are more conserved. The more conserved regions are called framework regions (FRs). Each V_H and V_L generally comprises three CDRs and four FRs, arranged in the following order (from N-terminus to C-terminus): FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4. The CDRs are involved in antigen binding, and influence antigen specificity and binding affinity of the antibody. See Kabat et al., *Sequences of Proteins of Immunological Interest* 5th ed. (1991) Public Health Service, National Institutes of Health, Bethesda, MD, incorporated by reference in its entirety.

[0084] The light chain from any vertebrate species can be assigned to one of two types, called kappa (κ) and lambda (λ), based on the sequence of its constant domain.

[0085] The heavy chain from any vertebrate species can be assigned to one of five different classes (or isotypes): IgA, IgD, IgE, IgG, and IgM. These classes are also designated α, δ, ε, γ, and μ, respectively. The IgG and IgA classes are further divided into subclasses on the basis of differences in sequence and function. Humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[0086] The amino acid sequence boundaries of a CDR can be determined by one of skill in the art using any of a number of known numbering schemes, including those described by Kabat et al., *supra* ("Kabat" numbering scheme); Al-Lazikani et al., 1997, *J. Mol. Biol.*, 273:927-948 ("Chothia" numbering scheme); MacCallum et al., 1996, *J. Mol. Biol.* 262:732-745 ("Contact" numbering scheme); Lefranc et al., *Dev. Comp. Immunol.*, 2003, 27:55-77 ("IMGT" numbering scheme); and Honegge and Plückthun, *J. Mol. Biol.*, 2001, 309:657-70 ("AHo" numbering scheme); each of which is incorporated by reference in its entirety.

[0087] Table 1 provides the positions of CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and CDR-

H3 as identified by the Kabat and Chothia schemes. For CDR-H1, residue numbering is provided using both the Kabat and Chothia numbering schemes.

[0088] CDRs may be assigned, for example, using antibody numbering software, such as Abnum, available at www.bioinf.org.uk/abs/abnum/, and described in Abhinandan and Martin, *Immunology*, 2008, 45:3832-3839, incorporated by reference in its entirety.

Table 1. Residues in CDRs according to Kabat and Chothia numbering schemes.

CDR	Kabat	Chothia
L1	L24-L34	L24-L34
L2	L50-L56	L50-L56
L3	L89-L97	L89-L97
H1 (Kabat Numbering)	H31-H35B	H26-H32 or H34*
H1 (Chothia Numbering)	H31-H35	H26-H32
H2	H50-H65	H52-H56
H3	H95-H102	H95-H102

* The C-terminus of CDR-H1, when numbered using the Kabat numbering convention, varies between H32 and H34, depending on the length of the CDR.

[0089] The "EU numbering scheme" is generally used when referring to a residue in an antibody heavy chain constant region (e.g., as reported in Kabat et al., *supra*). Unless stated otherwise, the EU numbering scheme is used to refer to residues in antibody heavy chain constant regions described herein.

[0090] An "antibody fragment" comprises a portion of an intact antibody, such as the antigen-binding or variable region of an intact antibody. Antibody fragments include, for example, Fv fragments, Fab fragments, $F(ab')_2$ fragments, Fab' fragments, scFv (sFv) fragments, and scFv-Fc fragments.

[0091] "Fv" fragments comprise a non-covalently-linked dimer of one heavy chain variable domain and one light chain variable domain.

[0092] "Fab" fragments comprise, in addition to the heavy and light chain variable domains, the constant domain of the light chain and the first constant domain (C_{H1}) of the heavy chain. Fab fragments may be generated, for example, by recombinant methods or by papain digestion of a full-length antibody.

[0093] "$F(ab')_2$" fragments contain two Fab' fragments joined, near the hinge region, by disulfide bonds. $F(ab')_2$ fragments may be generated, for example, by recombinant methods or by pepsin digestion of an intact antibody. The F(ab') fragments can be dissociated, for example, by treatment with ß-mercaptoethanol.

[0094] "Single-chain Fv" or "sFv" or "scFv" antibody fragments comprise a V_H domain and a V_L domain in a single polypeptide chain. The V_H and V_L are generally linked by a peptide linker. *See* Plückthun A. (1994). Any suitable linker may be used. In some embodiments, the linker is a $(GGGGS)_n$ (SEQ ID NO: 127). In some embodiments, n = 1, 2, 3, 4, 5, or 6. *See* Antibodies from

Escherichia coli. In Rosenberg M. & Moore G.P. (Eds.), *The Pharmacology of Monoclonal Antibodies* vol. 113 (pp. 269-315). Springer-Verlag, New York, incorporated by reference in its entirety.

[0095] "scFv-Fc" fragments comprise an scFv attached to an Fc domain. For example, an Fc domain may be attached to the C-terminal of the scFv. The Fc domain may follow the V_H or V_L, depending on the orientation of the variable domains in the scFv (i.e., V_H -V_L or V_L -V_H). Any suitable Fc domain known in the art or described herein may be used. In some cases, the Fc domain comprises an IgG4 Fc domain.

[0096] The term "single domain antibody" refers to a molecule in which one variable domain of an antibody specifically binds to an antigen without the presence of the other variable domain. Single domain antibodies, and fragments thereof, are described in Arabi Ghahroudi et al., *FEBS Letters*, 1998, 414:521-526 and Muyldermans et al., *Trends in Biochem. Sci.*, 2001, 26:230-245, each of which is incorporated by reference in its entirety. Single domain antibodies are also known as sdAbs or nanobodies.

[0097] A "multispecific ABP" is an ABP that comprises two or more different antigen-binding domains that collectively specifically bind two or more different epitopes. The two or more different epitopes may be epitopes on the same antigen (e.g., a single TIGIT molecule expressed by a cell) or on different antigens (e.g., different TIGIT molecules expressed by the same cell, or a TIGIT molecule and a non-TIGIT molecule). In some aspects, a multi-specific ABP binds two different epitopes (i.e., a "bispecific ABP"). In some aspects, a multi-specific ABP binds three different epitopes (i.e., a "trispecific ABP"). In some aspects, a multi-specific ABP binds four different epitopes (i.e., a "quadspecific ABP"). In some aspects, a multi-specific ABP binds five different epitopes (i.e., a "quintspecific ABP"). In some aspects, a multi-specific ABP binds 6, 7, 8, or more different epitopes. Each binding specificity may be present in any suitable valency. Examples of multispecific ABPs are provided elsewhere in this disclosure.

[0098] A "monospecific ABP" is an ABP that comprises one or more binding sites that specifically bind to a single epitope. An example of a monospecific ABP is a naturally occurring IgG molecule which, while divalent (i.e., having two antigen-binding domains), recognizes the same epitope at each of the two antigen-binding domains. The binding specificity may be present in any suitable valency.

[0099] The term "monoclonal antibody" refers to an antibody from a population of substantially homogeneous antibodies. A population of substantially homogeneous antibodies comprises antibodies that are substantially similar and that bind the same epitope(s), except for variants that may normally arise during production of the monoclonal antibody. Such variants are generally present in only minor amounts. A monoclonal antibody is typically obtained by a process that includes the selection of a single antibody from a plurality of antibodies. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones, yeast clones, bacterial clones, or other recombinant DNA clones. The selected antibody can be further

altered, for example, to improve affinity for the target ("affinity maturation"), to humanize the antibody, to improve its production in cell culture, and/or to reduce its immunogenicity in a subject.

[0100] The term "chimeric antibody" refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0101] "Humanized" forms of non-human antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. A humanized antibody is generally a human antibody (recipient antibody) in which residues from one or more CDRs are replaced by residues from one or more CDRs of a non-human antibody (donor antibody). The donor antibody can be any suitable non-human antibody, such as a mouse, rat, rabbit, chicken, or non-human primate antibody having a desired specificity, affinity, or biological effect. In some instances, selected framework region residues of the recipient antibody are replaced by the corresponding framework region residues from the donor antibody. Humanized antibodies may also comprise residues that are not found in either the recipient antibody or the donor antibody. Such modifications may be made to further refine antibody function. For further details, *see* Jones et al., *Nature*, 1986, 321:522-525; Riechmann et al., *Nature*, 1988, 332:323-329; and Presta, *Curr. Op. Struct. Biol.*, 1992, 2:593-596, each of which is incorporated by reference in its entirety.

[0102] A "human antibody" is one which possesses an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or derived from a non-human source that utilizes a human antibody repertoire or human antibody-encoding sequences (e.g., obtained from human sources or designed *de novo*). Human antibodies specifically exclude humanized antibodies.

[0103] An "isolated ABP" or "isolated nucleic acid" is an ABP or nucleic acid that has been separated and/or recovered from a component of its natural environment. Components of the natural environment may include enzymes, hormones, and other proteinaceous or nonproteinaceous materials. In some embodiments, an isolated ABP is purified to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence, for example by use of a spinning cup sequenator. In some embodiments, an isolated ABP is purified to homogeneity by gel electrophoresis (e.g., SDS-PAGE) under reducing or nonreducing conditions, with detection by Coomassie blue or silver stain. In some embodiments, an isolated ABP may include an ABP *in situ* within recombinant cells, since at least one component of the ABP's natural environment is not present. In some aspects, an isolated ABP or isolated nucleic acid is prepared by at least one purification step. In some embodiments, an isolated ABP or isolated nucleic acid is purified to at least 80%, 85%, 90%, 95%, or 99% by weight. In some embodiments, an isolated ABP or isolated nucleic acid is purified to at least 80%, 85%, 90%, 95%, or 99% by volume. In some embodiments, an isolated ABP or isolated nucleic acid is provided as a solution comprising at least 85%, 90%, 95%, 98%, 99% to 100% ABP or nucleic acid by weight. In some embodiments, an isolated ABP or isolated nucleic acid is provided as a solution comprising at least 85%, 90%, 95%, 98%, 99% to 100% ABP or nucleic acid by volume.

[0104] "Affinity" refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (e.g., an ABP) and its binding partner (e.g., an antigen or epitope). Unless indicated otherwise, as used herein, "affinity" refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of a binding pair (e.g., ABP and antigen or epitope). The affinity of a molecule X for its partner Y can be represented by the dissociation equilibrium constant (K_D). The kinetic components that contribute to the dissociation equilibrium constant are described in more detail below. Affinity can be measured by common methods known in the art, including those described herein, such as surface plasmon resonance (SPR) technology (e.g., BIACORE®) or biolayer interferometry (e.g., FORTEBIO®).

[0105] With regard to the binding of an ABP to a target molecule, the terms "bind," "specific binding," "specifically binds to," "specific for," "selectively binds," and "selective for" a particular antigen (e.g., a polypeptide target) or an epitope on a particular antigen mean binding that is measurably different from a non-specific or non-selective interaction (e.g., with a non-target molecule). Specific binding can be measured, for example, by measuring binding to a target molecule and comparing it to binding to a non-target molecule. Specific binding can also be determined by competition with a control molecule that mimics the epitope recognized on the target molecule. In that case, specific binding is indicated if the binding of the ABP to the target molecule is competitively inhibited by the control molecule. In some aspects, the affinity of a TIGIT ABP for a non-target molecule is less than about 50% of the affinity for TIGIT. In some aspects, the affinity of a TIGIT ABP for a non-target molecule is less than about 40% of the affinity for TIGIT. In some aspects, the affinity of a TIGIT ABP for a non-target molecule is less than about 30% of the affinity for TIGIT. In some aspects, the affinity of a TIGIT ABP for a non-target molecule is less than about 20% of the affinity for TIGIT. In some aspects, the affinity of a TIGIT ABP for a non-target molecule is less than about 10% of the affinity for TIGIT. In some aspects, the affinity of a TIGIT ABP for a non-target molecule is less than about 1% of the affinity for TIGIT. In some aspects, the affinity of a TIGIT ABP for a non-target molecule is less than about 0.1% of the affinity for TIGIT.

[0106] The term "k_d" (sec^{-1}), as used herein, refers to the dissociation rate constant of a particular ABP- antigen interaction. This value is also referred to as the k_{off} value.

[0107] The term "k_a" ($M^{-1}\times sec^{-1}$), as used herein, refers to the association rate constant of a particular ABP-antigen interaction. This value is also referred to as the k_{on} value.

[0108] The term "K_D" (M), as used herein, refers to the dissociation equilibrium constant of a particular ABP-antigen interaction. $K_D = k_d/k_a$. In some embodiments, the affinity of an ABP is described in terms of the K_D for an interaction between such ABP and its antigen. For clarity, as known in the art, a smaller K_D value indicates a higher affinity interaction, while a larger K_D value indicates a lower affinity interaction.

[0109] The term "K_A" (M^{-1}), as used herein, refers to the association equilibrium constant of a particular ABP-antigen interaction. $K_A = k_a/k_d$.

[0110] An "affinity matured" ABP is an ABP with one or more alterations (e.g., in one or more CDRs or FRs) relative to a parent ABP (i.e., an ABP from which the altered ABP is derived or designed) that result in an improvement in the affinity of the ABP for its antigen, compared to the parent ABP which does not possess the alteration(s). In some embodiments, an affinity matured ABP has nanomolar or picomolar affinity for the target antigen. Affinity matured ABPs may be produced using a variety of methods known in the art. For example, Marks et al. (*Bio/Technology*, 1992, 10:779-783, incorporated by reference in its entirety) describes affinity maturation by V_H and V_L domain shuffling. Random mutagenesis of CDR and/or framework residues is described by, for example, Barbas et al. (*Proc. Nat. Acad. Sci. U.S.A.*, 1994, 91:3809-3813); Schier et al., *Gene*, 1995, 169:147-155; Yelton et al., *J. Immunol.*, 1995, 155:1994-2004; Jackson et al., *J. Immunol.*, 1995, 154:3310-33199; and Hawkins et al, *J. Mol. Biol.*, 1992, 226:889-896; each of which is incorporated by reference in its entirety.

[0111] An "immunoconjugate" is an ABP conjugated to one or more heterologous molecule(s), such as a therapeutic or diagnostic agent.

[0112] "Effector functions" refer to those biological activities mediated by the Fc region of an antibody, which activities may vary depending on the antibody isotype. Examples of antibody effector functions include C1q binding to activate complement dependent cytotoxicity (CDC), Fc receptor binding to activate antibody-dependent cellular cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP).

[0113] When used herein in the context of two or more ABPs, the term "competes with" or "cross-competes with" indicates that the two or more ABPs compete for binding to an antigen (e.g., TIGIT). In one exemplary assay, TIGIT is coated on a surface and contacted with a first TIGIT ABP, after which a second TIGIT ABP is added. In another exemplary assay, a first TIGIT ABP is coated on a surface and contacted with TIGIT, and then a second TIGIT ABP is added. If the presence of the first TIGIT ABP reduces binding of the second TIGIT ABP, in either assay, then the ABPs compete with each other. The term "competes with" also includes combinations of ABPs where one ABP reduces binding of another ABP, but where no competition is observed when the ABPs are added in the reverse order. However, in some embodiments, the first and second ABPs inhibit binding of each other, regardless of the order in which they are added. In some embodiments, one ABP reduces binding of another ABP to its antigen by at least 25%, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, or at least 95%. A skilled artisan can select the concentrations of the antibodies used in the competition assays based on the affinities of the ABPs for TIGIT and the valency of the ABPs. The assays described in this definition are illustrative, and a skilled artisan can utilize any suitable assay to determine if antibodies compete with each other. Suitable assays are described, for example, in Cox et al., "Immunoassay Methods," in *Assay Guidance Manual [Internet]*, Updated December 24, 2014 (www.ncbi.nlm.nih.gov/books/NBK92434/; accessed September 29, 2015); Silman et al., *Cytometry*, 2001, 44:30-37; and Finco et al., *J. Pharm. Biomed. Anal.*, 2011,

54:351-358; each of which is incorporated by reference in its entirety.

[0114] The term "epitope" means a portion of an antigen that specifically binds to an ABP. Epitopes frequently consist of surface-accessible amino acid residues and/or sugar side chains and may have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter may be lost in the presence of denaturing solvents. An epitope may comprise amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding. The epitope to which an ABP binds can be determined using known techniques for epitope determination such as, for example, testing for ABP binding to TIGIT variants with different point-mutations, or to chimeric TIGIT variants.

[0115] Percent "identity" between a polypeptide sequence and a reference sequence, is defined as the percentage of amino acid residues in the polypeptide sequence that are identical to the amino acid residues in the reference sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, MEGALIGN (DNASTAR), CLUSTALW, CLUSTAL OMEGA, or MUSCLE software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0116] A "conservative substitution" or a "conservative amino acid substitution," refers to the substitution an amino acid with a chemically or functionally similar amino acid. Conservative substitution tables providing similar amino acids are well known in the art. By way of example, the groups of amino acids provided in Tables 2-4 are, in some embodiments, considered conservative substitutions for one another.

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

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

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

Group 1	A, S, and T
Group 2	D and E
Group 3	N and Q
Group 4	R and K

Group 5	I, L, and M
Group 6	F, Y, and W

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

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

[0117] Additional conservative substitutions may be found, for example, in Creighton, *Proteins: Structures and Molecular Properties* 2nd ed. (1993) W. H. Freeman & Co., New York, NY. An ABP generated by making one or more conservative substitutions of amino acid residues in a parent ABP is referred to as a "conservatively modified variant."

[0118] The term "amino acid" refers to the twenty common naturally occurring amino acids. Naturally occurring amino acids include alanine (Ala; A), arginine (Arg; R), asparagine (Asn; N), aspartic acid (Asp; D), cysteine (Cys; C); glutamic acid (Glu; E), glutamine (Gln; Q), Glycine (Gly; G); histidine (His; H), isoleucine (Ile; I), leucine (Leu; L), lysine (Lys; K), methionine (Met; M), phenylalanine (Phe; F), proline (Pro; P), serine (Ser; S), threonine (Thr; T), tryptophan (Trp; W), tyrosine (Tyr; Y), and valine (Val; V).

[0119] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

[0120] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which an exogenous nucleic acid has been introduced, and the progeny of such cells. Host cells include "transformants" (or "transformed cells") and "transfectants" (or "transfected cells"), which each include the primary transformed or transfected cell and progeny derived therefrom. Such progeny may not be completely identical in nucleic acid content to a parent cell, and may contain mutations.

[0121] The term "treating" (and variations thereof such as "treat" or "treatment") refers to clinical intervention in an attempt to alter the natural course of a disease or condition in a subject in need thereof. Treatment can be performed both for prophylaxis and during the course of clinical pathology. Desirable effects of treatment include preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease,

preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis.

[0122] As used herein, the term "therapeutically effective amount" or "effective amount" refers to an amount of an ABP or pharmaceutical composition provided herein that, when administered to a subject, is effective to treat a disease or disorder.

[0123] As used herein, the term "subject" means a mammalian subject. Exemplary subjects include humans, monkeys, dogs, cats, mice, rats, cows, horses, camels, goats, rabbits, and sheep. In certain embodiments, the subject is a human. In some embodiments the subject has a disease or condition that can be treated with an ABP provided herein. In some aspects, the disease or condition is a cancer. In some aspects, the disease or condition is a viral infection.

[0124] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic or diagnostic products (e.g., kits) that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic or diagnostic products.

[0125] The term "cytotoxic agent," as used herein, refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction.

[0126] A "chemotherapeutic agent" refers to a chemical compound useful in the treatment of cancer. Chemotherapeutic agents include "anti-hormonal agents" or "endocrine therapeutics" which act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer.

[0127] The term "cytostatic agent" refers to a compound or composition which arrests growth of a cell either *in vitro* or *in vivo*. In some embodiments, a cytostatic agent is an agent that reduces the percentage of cells in S phase. In some embodiments, a cytostatic agent reduces the percentage of cells in S phase by at least about 20%, at least about 40%, at least about 60%, or at least about 80%.

[0128] The term "tumor" refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. The terms "cancer," "cancerous," "cell proliferative disorder," "proliferative disorder" and "tumor" are not mutually exclusive as referred to herein. The terms "cell proliferative disorder" and "proliferative disorder" refer to disorders that are associated with some degree of abnormal cell proliferation. In some embodiments, the cell proliferative disorder is a cancer. In some aspects, the tumor is a solid tumor. In some aspects, the tumor is a hematologic malignancy.

[0129] The term "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective in treating a subject, and which contains no additional components which are unacceptably toxic to the subject in the amounts provided in the pharmaceutical composition.

[0130] The terms "modulate" and "modulation" refer to reducing or inhibiting or, alternatively, activating or increasing, a recited variable.

[0131] The terms "increase" and "activate" refer to an increase of 10%, 20%, 30%, 40%, 50%, 60%,

70%, 75%, 80%, 85%, 90%, 95%, 100%, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or greater in a recited variable.

[0132] The terms "reduce" and "inhibit" refer to a decrease of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or greater in a recited variable.

[0133] The term "agonize" refers to the activation of receptor signaling to induce a biological response associated with activation of the receptor. An "agonist" is an entity that binds to and agonizes a receptor.

[0134] The term "antagonize" refers to the inhibition of receptor signaling to inhibit a biological response associated with activation of the receptor. An "antagonist" is an entity that binds to and antagonizes a receptor.

[0135] The term "effector T cell" includes T helper (i.e., CD4+) cells and cytotoxic (i.e., CD8+) T cells. CD4+ effector T cells contribute to the development of several immunologic processes, including maturation of B cells into plasma cells and memory B cells, and activation of cytotoxic T cells and macrophages. CD8+ effector T cells destroy virus-infected cells and tumor cells. *See* Seder and Ahmed, *Nature Immunol.*, 2003, 4:835-842, incorporated by reference in its entirety, for additional information on effector T cells.

[0136] The term "regulatory T cell" includes cells that regulate immunological tolerance, for example, by suppressing effector T cells. In some aspects, the regulatory T cell has a CD4+CD25+Foxp3+ phenotype. In some aspects, the regulatory T cell has a CD8+CD25+ phenotype. *See* Nocentini et al., *Br. J. Pharmacol.*, 2012, 165:2089-2099, incorporated by reference in its entirety, for additional information on regulatory T cells expressing TIGIT.

[0137] The term "dendritic cell" refers to a professional antigen-presenting cell capable of activating a naïve T cell and stimulating growth and differentiation of a B cell.

2. TIGIT Antigen-Binding Proteins

2.1. TIGIT Binding and Target Cells

[0138] Provided herein are ABPs that specifically bind to TIGIT. In some aspects, the TIGIT is hTIGIT (SEQ ID NO:1). In some aspects, the TIGIT is cTIGIT (SEQ ID NO:2). In some aspects, the TIGIT is mTIGIT with the sequence provided in SEQ ID NO:3. In some aspects, the TIGIT is mTIGIT with the sequence provided in SEQ ID NO:138.

[0139] In some embodiments, the ABPs provided herein specifically bind to hTIGIT (SEQ ID NO:1), cTIGIT (SEQ ID NO:2), and mTIGIT of SEQ ID NO:3. In some embodiments, the ABPs provided herein specifically bind to hTIGIT (SEQ ID NO:1), cTIGIT (SEQ ID NO:2), and mTIGIT of SEQ ID NO:138. In some embodiments, the ABPs provided herein specifically bind to hTIGIT (SEQ ID NO:1), and cTIGIT (SEQ ID NO:2). In some embodiments, the ABPs provided herein specifically

bind to hTIGIT (SEQ ID NO:1). In some embodiments, the ABPs provided herein do not bind mTIGIT of SEQ ID NO:3. In some embodiments, the ABPs provided herein do not bind mTIGIT of SEQ ID NO:138.

[0140] In some embodiments, the ABPs provided herein specifically bind to the extracellular domain of TIGIT.

[0141] In some embodiments, an ABP provided herein is an antibody. In some embodiments, an ABP provided herein is an antibody fragment. In some embodiments, an ABP provided herein is an alternative scaffold.

[0142] The TIGIT may be expressed on the surface of any suitable target cell. In some embodiments, the target cell is a T cell. In some embodiments, the target cell is an effector T cell. In some embodiments, the target cell is a regulatory T cell. In some embodiments, the target cell is a natural killer (NK) cell. In some embodiments, the target cell is a natural killer T (NKT) cell.

[0143] In some embodiments, the ABPs provided herein comprise an immunoglobulin molecule. In some embodiments, the ABPs provided herein consist of an immunoglobulin molecule. In some embodiments, the ABPs provided herein consist essentially of an immunoglobulin molecule. In some aspects, the immunoglobulin molecule comprises an antibody. In some aspects, the immunoglobulin molecule consists of an antibody. In some aspects, the immunoglobulin molecule consists essentially of an antibody.

[0144] In some embodiments, the ABPs provided herein comprise a light chain. In some aspects, the light chain is a kappa light chain. In some aspects, the light chain is a lambda light chain.

[0145] In some embodiments, the ABPs provided herein comprise a kappa light chain comprising SEQ ID NO: 126.

[0146] In some embodiments, the ABPs provided herein comprise a heavy chain. In some aspects, the heavy chain is an IgA. In some aspects, the heavy chain is an IgD. In some aspects, the heavy chain is an IgE. In some aspects, the heavy chain is an IgG. In some aspects, the heavy chain is an IgM. In some aspects, the heavy chain is an IgG1. In some aspects, the heavy chain is an IgG2. In some aspects, the heavy chain is an IgG3. In some aspects, the heavy chain is an IgG4. In some aspects, the heavy chain is an IgA1. In some aspects, the heavy chain is an IgA2.

[0147] In some embodiments, the ABPs provided herein comprise an IgG4 heavy chain comprising a sequence selected from SEQ ID NO:55 and SEQ ID NO:56. In some embodiments, the ABPs provided herein comprise an IgG1 heavy chain comprising a sequence selected from SEQ ID NO:57 and SEQ ID NO: 125.

[0148] In some embodiments, the ABPs provided herein comprise an antibody fragment. In some embodiments, the ABPs provided herein consist of an antibody fragment. In some embodiments, the ABPs provided herein consist essentially of an antibody fragment. In some aspects, the antibody fragment is an Fv fragment. In some aspects, the antibody fragment is a Fab fragment. In some aspects, the antibody fragment is a $F(ab')_2$ fragment. In some aspects, the antibody fragment is a Fab'

fragment. In some aspects, the antibody fragment is an scFv (sFv) fragment. In some aspects, the antibody fragment is an scFv-Fc fragment. In some aspects, the antibody fragment is a fragment of a single domain antibody.

[0149] In some embodiments, an antibody fragment provided herein is derived from an illustrative antibody provided herein. In some embodiments, an antibody fragments provided herein is not derived from an illustrative antibody provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibody fragments.

[0150] In some embodiments, an antibody fragment provided specifically binds hTIGIT. In some embodiments, an antibody fragment provided herein specifically binds cTIGIT. In some embodiments, an antibody fragment provided herein specifically binds mTIGIT. In some embodiments, an antibody fragment provided herein specifically binds hTIGIT and cTIGIT. In some embodiments, an antibody fragment provided herein specifically binds hTIGIT and mTIGIT. In some embodiments, an antibody fragment provided herein specifically binds cTIGIT and mTIGIT. In some embodiments, an antibody fragment provided herein specifically binds hTIGIT, cTIGIT and mTIGIT.

[0151] In some embodiments, an antibody fragment derived from an antibody provided herein retains affinity, as measured by K_D, for hTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such antibody. In some embodiments, an antibody fragment derived from an antibody provided herein retains affinity, as measured by K_D, for cTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such antibody. In some embodiments, an antibody fragment derived from an antibody provided herein retains affinity, as measured by K_D, for mTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such antibody. In some embodiments, an antibody fragment derived from an antibody provided herein retains affinity, as measured by K_D, for both hTIGIT and cTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such antibody. In some embodiments, an antibody fragment derived from an antibody provided herein retains affinity, as measured by K_D, for both hTIGIT and mTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such antibody. In some embodiments, an antibody fragment derived from an antibody provided herein retains affinity, as measured by K_D, for both cTIGIT and mTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such antibody. In some embodiments, an antibody fragment derived from an antibody provided herein retains affinity, as measured by K_D, for all three of hTIGIT, cTIGIT and mTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or

about 10-fold the affinity of such antibody.

[0152] In some embodiments, an antibody fragment provided herein retains the ability to antagonize TIGIT, as measured by one or more assays or biological effects described herein. In some embodiments, an antibody fragment provided herein retains the ability to prevent TIGIT from interacting with one or more of its ligands, as described herein.

[0153] In some embodiments, an antibody fragment provided herein competes for binding to TIGIT with an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each as provided in Table 5 of this disclosure.

[0154] In some embodiments, an antibody fragment provided herein inhibits binding of CD155 to TIGIT. In some embodiments, an antibody fragment provided herein inhibits binding of CD112 to TIGIT. In some embodiments, an antibody fragment provided herein inhibits association of CD226 with TIGIT.

[0155] In some embodiments, an antibody fragment provided herein activates an effector T cell or a natural killer (NK) cell. In some embodiments, an antibody fragment provided herein decreases the number of regulatory T cells in a tissue or in circulation. In some embodiments, an antibody fragment provided herein inhibits the suppression of an effector T cell by a regulatory T cell.

[0156] In some embodiments, an antibody fragment provided herein does not bind specifically to any of PVRL1, PVRL2, PVRL3, or PVRL4.

[0157] In some embodiments, an antibody fragment provided herein binds murine TIGIT (mTIGIT; SEQ ID NO: 3) with an affinity lower (as indicated by higher K_D) than the affinity of the antibody fragment for hTIGIT, or does not bind mTIGIT.

[0158] In some embodiments, a fragment of an antibody provided herein binds the same epitope of TIGIT as such antibody.

[0159] In some embodiments, the ABPs provided herein are monoclonal antibodies. In some embodiments, the ABPs provided herein are polyclonal antibodies.

[0160] In some embodiments, the ABPs provided herein comprise a chimeric antibody. In some embodiments, the ABPs provided herein consist of a chimeric antibody. In some embodiments, the ABPs provided herein consist essentially of a chimeric antibody. In some embodiments, the ABPs provided herein comprise a humanized antibody. In some embodiments, the ABPs provided herein consist of a humanized antibody. In some embodiments, the ABPs provided herein consist essentially of a humanized antibody. In some embodiments, the ABPs provided herein comprise a human antibody. In some embodiments, the ABPs provided herein consist of a human antibody. In some embodiments, the ABPs provided herein consist essentially of a human antibody.

[0161] In some embodiments, the ABPs provided herein are affinity matured. In some aspects, the affinity matured ABPs are affinity matured ABPs derived from an illustrative ABP provided herein.

[0162] In some embodiments, the ABPs provided herein comprise an alternative scaffold. In some

embodiments, the ABPs provided herein consist of an alternative scaffold. In some embodiments, the ABPs provided herein consist essentially of an alternative scaffold. Any suitable alternative scaffold may be used. In some aspects, the alternative scaffold is selected from an Adnectin™, an iMab, an Anticalin®, an EETI-II/AGRP, a Kunitz domain, a thioredoxin peptide aptamer, an Affibody®, a DARPin, an Affilin, a Tetranectin, a Fynomer, and an Avimer.

[0163] In some embodiments, an ABP provided herein inhibits binding of TIGIT to one or more ligands of TIGIT. In some aspects, the ligand of TIGIT is selected from one or more of poliovirus receptor (PVR; CD155) and nectin-2 (CD112, PVRL2). In some aspects, the ABP inhibits binding of TIGIT to one or more ligands of TIGIT by at least about 50%. In some aspects, the ABP inhibits binding of TIGIT to one or more ligands of TIGIT by at least about 75%. In some aspects, the ABP inhibits binding of TIGIT to one or more ligands of TIGIT by at least about 90%. In some aspects, the ABP inhibits binding of TIGIT to one or more ligands of TIGIT by at least about 95%.

[0164] In some embodiments, an ABP of the invention is an ABP that competes with an illustrative ABP provided herein. In some aspects, the ABP that competes with the illustrative ABP provided herein binds the same epitope as an illustrative ABP provided herein.

[0165] In some embodiments, an ABP provided herein does not bind PVRL4.

[0166] It is known that when an antibody is expressed in cells, the antibody is modified after translation. Examples of the posttranslational modification include cleavage of lysine at the C terminal of the heavy chain by a carboxypeptidase; modification of glutamine or glutamic acid at the N terminal of the heavy chain and the light chain to pyroglutamic acid by pyroglutamylation; glycosylation; oxidation; deamidation; and glycation, and it is known that such posttranslational modifications occur in various antibodies (*See* Journal of Pharmaceutical Sciences, 2008, Vol. 97, p. 2426-2447, incorporated by reference in its entirety). In some embodiments, an ABP of the invention is an antibody or antigen-binding fragment thereof which has undergone posttranslational modification. Examples of an antibody or antigen-binding fragment thereof which have undergone posttranslational modification include an antibody or antigen-binding fragments thereof which have undergone pyroglutamylation at the N terminal of the heavy chain variable region and/or deletion of lysine at the C terminal of the heavy chain. It is known in the art that such posttranslational modification due to pyroglutamylation at the N terminal and deletion of lysine at the C terminal does not have any influence on the activity of the antibody or fragment thereof (Analytical Biochemistry, 2006, Vol. 348, p. 24-39, incorporated by reference in its entirety).

2.2. Sequences of TIGIT Antigen-Binding Proteins

2.2.1. V_H Domains

[0167] In some embodiments, an ABP provided herein comprises a V_H sequence selected from SEQ ID NOs: 4-24. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID

NO:4. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:5. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:6. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:7. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:8. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:9. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:10. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:11. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:12. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:13. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:14. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:15. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:16. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:17. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:18. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:19. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:20. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:21. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:22. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:23. In some embodiments an ABP provided herein comprises a V_H sequence of SEQ ID NO:24.

[0168] In some embodiments, an ABP provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 4-24. In some embodiments, an ABP provided herein comprises a V_H sequence provided in SEQ ID NOs: 4-24, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

2.2.2.V_L Domains

[0169] In some embodiments, an ABP provided herein comprises a V_L sequence selected from SEQ ID NOs: 25-28. In some embodiments an ABP provided herein comprises a V_L sequence of SEQ ID NO:25. In some embodiments an ABP provided herein comprises a V_L sequence of SEQ ID NO:26. In some embodiments an ABP provided herein comprises a V_L sequence of SEQ ID NO:27. In some

embodiments an ABP provided herein comprises a V_L sequence of SEQ ID NO:28.

[0170] In some embodiments, an ABP provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_L sequence provided in SEQ ID NOs: 25-28. In some embodiments, an ABP provided herein comprises a V_L sequence provided in SEQ ID NOs: 25-28, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

2.2.3.V_H - V_L Combinations

[0171] In some embodiments, an ABP provided herein comprises a V_H sequence selected from SEQ ID NOs: 4-24 and a V_L sequence selected from SEQ ID NOs: 25-28.

[0172] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:4 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:5 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:6 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:7 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:8 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:9 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:10 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:11 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:12 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:13 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:14 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:15 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:16 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:17 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:18 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:19 and a V_L

sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:20 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:21 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:22 and a V_L sequence of SEQ ID NO:28. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:23 and a V_L sequence of SEQ ID NO:28. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:24 and a V_L sequence of SEQ ID NO:28.

[0173] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:4 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:4 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:4 and a V_L sequence of SEQ ID NO:28.

[0174] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:5 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:5 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:5 and a V_L sequence of SEQ ID NO:28.

[0175] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:6 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:6 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:6 and a V_L sequence of SEQ ID NO:28.

[0176] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:7 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:7 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:7 and a V_L sequence of SEQ ID NO:28.

[0177] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:8 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:8 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:8 and a V_L sequence of SEQ ID NO:28.

[0178] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:9 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:9 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:9 and a V_L sequence of SEQ ID NO:28.

[0179] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:10 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:10 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:10 and a V_L sequence of SEQ ID NO:28.

[0180] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:11 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a

V_H sequence of SEQ ID NO:11 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:11 and a V_L sequence of SEQ ID NO:28.

[0181] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:12 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:12 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:12 and a V_L sequence of SEQ ID NO:28.

[0182] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:13 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:13 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:13 and a V_L sequence of SEQ ID NO:28.

[0183] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:14 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:14 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:14 and a V_L sequence of SEQ ID NO:28.

[0184] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:15 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:15 and a V_L sequence of SEQ ID NO:27. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:15 and a V_L sequence of SEQ ID NO:28.

[0185] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:16 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:16 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:16 and a V_L sequence of SEQ ID NO:28.

[0186] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:17 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:17 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:17 and a V_L sequence of SEQ ID NO:28.

[0187] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:18 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:18 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:18 and a V_L sequence of SEQ ID NO:28.

[0188] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:19 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:19 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:19 and a V_L sequence of SEQ ID NO:28.

[0189] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:20 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:20 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP

provided herein comprises a V_H sequence of SEQ ID NO:20 and a V_L sequence of SEQ ID NO:28.

[0190] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:21 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:21 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:21 and a V_L sequence of SEQ ID NO:28.

[0191] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:22 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:22 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:22 and a V_L sequence of SEQ ID NO:27.

[0192] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:23 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:23 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:23 and a V_L sequence of SEQ ID NO:27.

[0193] In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:24 and a V_L sequence of SEQ ID NO:25. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:24 and a V_L sequence of SEQ ID NO:26. In some embodiments, an ABP provided herein comprises a V_H sequence of SEQ ID NO:24 and a V_L sequence of SEQ ID NO:27.

[0194] In some embodiments, an ABP provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 4-24, and a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_L sequence provided in SEQ ID NOs: 25-28. In some embodiments, an ABP provided herein comprises a V_H sequence provided in SEQ ID NOs: 4-24, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions, and a V_L sequence provided in SEQ ID NOs: 25-28, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

2.2.4.CDRs

[0195] In some embodiments, an ABP provided herein comprises one to three CDRs of a V_H domain selected from SEQ ID NOs: 4-24. In some embodiments, an ABP provided herein comprises two to three CDRs of a V_H domain selected from SEQ ID NOs: 4-24. In some embodiments, an ABP provided herein comprises three CDRs of a V_H domain selected from SEQ ID NOs: 4-24. In some

aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are IMGT CDRs.

[0196] In some embodiments, the CDRs are CDRs having at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1, CDR-H2, or CDR-H3 of SEQ ID NOs: 4-24. In some embodiments, the CDR-H1 is a CDR-H1 of a V_H domain selected from SEQ ID NOs: 4-24, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some embodiments, the CDR-H2 is a CDR-H2 of a V_H domain selected from SEQ ID NOs: 4-24, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some embodiments, the CDR-H3 is a CDR-H3 of a V_H domain selected from SEQ ID NOs: 4-24, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0197] In some embodiments, an ABP provided herein comprises one to three CDRs of a V_L domain selected from SEQ ID NOs: 25-28. In some embodiments, an ABP provided herein comprises two to three CDRs of a V_L domain selected from SEQ ID NOs: 25-28. In some embodiments, an ABP provided herein comprises three CDRs of a V_L domain selected from SEQ ID NOs: 25-28. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are IMGT CDRs.

[0198] In some embodiments, the CDRs are CDRs having at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1, CDR-L2, or CDR-L3 of SEQ ID NOs: 25-28. In some embodiments, the CDR-L1 is a CDR-L1 of a V_L domain selected from SEQ ID NOs: 25-28, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some embodiments, the CDR-L2 is a CDR-L2 of a V_L domain selected from SEQ ID NOs: 25-28, with up to 1, 2, 3, or 4 amino acid substitutions. In some embodiments, the CDR-L3 is a CDR-L3 of a V_L domain selected from SEQ ID NOs: 25-28, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0199] In some embodiments, an ABP provided herein comprises one to three CDRs of a V_H domain selected from SEQ ID NOs: 4-24 and one to three CDRs of a V_L domain selected from SEQ ID NOs: 25-28. In some embodiments, an ABP provided herein comprises two to three CDRs of a V_H domain

selected from SEQ ID NOs: 4-24 and two to three CDRs of a V_L domain selected from SEQ ID NOs: 25-28. In some embodiments, an ABP provided herein comprises three CDRs of a V_H domain selected from SEQ ID NOs: 4-24 and three CDRs of a V_L domain selected from SEQ ID NOs: 25-28. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are IMGT CDRs.

[0200] In some embodiments, the CDRs are CDRs having at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1, CDR-H2, or CDR-H3 of SEQ ID NOs: 4-24 and at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1, CDR-L2, or CDR-L3 of SEQ ID NOs: 25-28. In some embodiments, the CDR-H1 is a CDR-H1 of a V_H domain selected from SEQ ID NOs: 4-24, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-H2 is a CDR-H2 of a V_H domain selected from SEQ ID NOs: 4-24, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H3 is a CDR-H3 of a V_H domain selected from SEQ ID NOs: 4-24, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-L1 is a CDR-L1 of a V_L domain selected from SEQ ID NOs: 25-28, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions; the CDR-L2 is a CDR-L2 of a V_L domain selected from SEQ ID NOs: 25-28, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L3 is a CDR-L3 of a V_L domain selected from SEQ ID NOs: 25-28, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0201] In some embodiments, an ABP provided herein comprises a CDR-H3 selected from SEQ ID NOs: 29-35. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NOs: 29-35. In some aspects, the CDR-H3 is a CDR-H3 according to the IMGT numbering system. In some embodiments, the CDR-H3 is a CDR-H3 selected from SEQ ID NOs: 29-35, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0202] In some embodiments, an ABP provided herein comprises a CDR-H2 selected from SEQ ID NOs: 36-47. In some aspects, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NOs: 36-47. In some aspects, the CDR-H2 is a CDR-H2

according to the Kabat numbering system. In some embodiments, the CDR-H2 is a CDR-H2 selected from SEQ ID NOs: 36-47, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0203] In some embodiments, an ABP provided herein comprises a CDR-H1 selected from SEQ ID NOs: 48-54 or 58-62. In some aspects, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NOs: 48-54 or 58-62. In some aspects, the CDR-H1 is a CDR-H1 that spans the CDR-H1 as defined by both the Chothia and Kabat numbering systems. In some embodiments, the CDR-H1 is a CDR-H1 selected from SEQ ID NOs: 48-54 or 58-62, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0204] In some embodiments, an ABP provided herein comprises a CDR-H3 selected from SEQ ID NOs: 29-35 and a CDR-H2 selected from SEQ ID NOs: 36-47. In some embodiments, an ABP provided herein comprises a CDR-H3 selected from SEQ ID NOs: 29-35, a CDR-H2 selected from SEQ ID NOs: 36-47, and a CDR-H1 selected from SEQ ID NOs: 48-54 or 58-62. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NOs: 29-35, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NOs: 36-47, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NOs: 48-54 or 58-62. In some embodiments, the CDR-H3 is a CDR-H3 selected from SEQ ID NOs: 29-35, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 selected from SEQ ID NOs: 36-47, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 selected from SEQ ID NOs: 48-54 or 58-62, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example,

be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0205] In some embodiments, an ABP provided herein comprises a CDR-L3 selected from SEQ ID NOs: 63-66. In some aspects, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NOs: 63-66. In some aspects, the CDR-L3 is a CDR-L3 according to the Kabat, Chothia, and IMGT numbering systems. In some embodiments, the CDR-L3 is a CDR-L3 selected from SEQ ID NOs: 63-66, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0206] In some embodiments, an ABP provided herein comprises a CDR-L2 selected from SEQ ID NOs: 67-69. In some aspects, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NOs: 67-69. In some aspects, the CDR-L2 is a CDR-L2 according to the Kabat and Chothia numbering systems. In some embodiments, the CDR-L2 is a CDR-L2 selected from SEQ ID NOs: 67-69, with up to 1, 2, 3, or 4 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0207] In some embodiments, an ABP provided herein comprises a CDR-L1 selected from SEQ ID NOs: 70-72. In some aspects, the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NOs: 70-72. In some aspects, the CDR-L1 is a CDR-L1 according to the Kabat and Chothia numbering systems. In some embodiments, the CDR-L1 is a CDR-L1 selected from SEQ ID NOs: 70-72, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0208] In some embodiments, an ABP provided herein comprises a CDR-L3 selected from SEQ ID

NOs: 63-66 and a CDR-L2 selected from SEQ ID NOs: 67-69. In some embodiments, an ABP provided herein comprises a CDR-L3 selected from SEQ ID NOs: 63-66, a CDR-L2 selected from SEQ ID NOs: 67-69, and a CDR-L1 selected from SEQ ID NOs: 70-72. In some embodiments, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NOs: 63-66, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NOs: 67-69, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NOs: 70-72. In some embodiments, the CDR-L3 is a CDR-L3 selected from SEQ ID NOs: 63-66, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 selected from SEQ ID NOs: 67-69, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 selected from SEQ ID NOs: 70-72, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining ABPs.

[0209] In some embodiments, an ABP provided herein comprises a CDR-H3 selected from SEQ ID NOs: 29-35, a CDR-H2 selected from SEQ ID NOs: 36-47, a CDR-H1 selected from SEQ ID NOs: 48-54 or 58-62, a CDR-L3 selected from SEQ ID NOs: 63-66, a CDR-L2 selected from SEQ ID NOs: 67-69, and a CDR-L1 selected from SEQ ID NOs: 70-72. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NOs: 29-35, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NOs: 36-47, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NOs: 48-54 or 58-62, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NOs: 63-66, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NOs: 67-69, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NOs: 70-72. In some embodiments, the CDR-H3 is a CDR-H3 selected from SEQ ID NOs: 29-35, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 selected from SEQ ID NOs: 36-47, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 selected from SEQ ID NOs: 48-54 or 58-62, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 selected from SEQ ID NOs: 63-66, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 selected from SEQ ID NOs: 67-69, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 selected from SEQ ID NOs: 70-72, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the ABPs described in this paragraph are referred to herein as "variants." In

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

[0210] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:29, a CDR-H2 of SEQ ID NO:36, a CDR-H1 of SEQ ID NO:48, a CDR-L3 of SEQ ID NO:63, a CDR-L2 of SEQ ID NO:67, and a CDR-L1 of SEQ ID NO:70.

[0211] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:29, a CDR-H2 of SEQ ID NO:37, a CDR-H1 of SEQ ID NO:49, a CDR-L3 of SEQ ID NO:63, a CDR-L2 of SEQ ID NO:67, and a CDR-L1 of SEQ ID NO:70.

[0212] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:29, a CDR-H2 of SEQ ID NO:37, a CDR-H1 of SEQ ID NO:50, a CDR-L3 of SEQ ID NO:63, a CDR-L2 of SEQ ID NO:67, and a CDR-L1 of SEQ ID NO:70.

[0213] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:30, a CDR-H2 of SEQ ID NO:37, a CDR-H1 of SEQ ID NO:50, a CDR-L3 of SEQ ID NO:63, a CDR-L2 of SEQ ID NO:67, and a CDR-L1 of SEQ ID NO:70.

[0214] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:29, a CDR-H2 of SEQ ID NO:38, a CDR-H1 of SEQ ID NO:50, a CDR-L3 of SEQ ID NO:63, a CDR-L2 of SEQ ID NO:67, and a CDR-L1 of SEQ ID NO:70.

[0215] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:31, a CDR-H2 of SEQ ID NO:39, a CDR-H1 of SEQ ID NO:51, a CDR-L3 of SEQ ID NO:64, a CDR-L2 of SEQ ID NO:68, and a CDR-L1 of SEQ ID NO:71.

[0216] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:31, a CDR-H2 of SEQ ID NO:40, a CDR-H1 of SEQ ID NO:52, a CDR-L3 of SEQ ID NO:64, a CDR-L2 of SEQ ID NO:68, and a CDR-L1 of SEQ ID NO:71.

[0217] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:31, a CDR-H2 of SEQ ID NO:41, a CDR-H1 of SEQ ID NO:53, a CDR-L3 of SEQ ID NO:64, a CDR-L2 of SEQ ID NO:68, and a CDR-L1 of SEQ ID NO:71.

[0218] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:31, a CDR-H2 of SEQ ID NO:40, a CDR-H1 of SEQ ID NO:54, a CDR-L3 of SEQ ID NO:64, a CDR-L2 of SEQ ID NO:68, and a CDR-L1 of SEQ ID NO:71.

[0219] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:32, a CDR-H2 of SEQ ID NO:40, a CDR-H1 of SEQ ID NO:54, a CDR-L3 of SEQ ID NO:64, a CDR-L2 of SEQ ID NO:68, and a CDR-L1 of SEQ ID NO:71.

[0220] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:32, a CDR-H2 of SEQ ID NO:40, a CDR-H1 of SEQ ID NO:54, a CDR-L3 of SEQ ID NO:64, a CDR-L2

of SEQ ID NO:68, and a CDR-L1 of SEQ ID NO:71.

[0221] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:32, a CDR-H2 of SEQ ID NO:40, a CDR-H1 of SEQ ID NO:54, a CDR-L3 of SEQ ID NO:64, a CDR-L2 of SEQ ID NO:68, and a CDR-L1 of SEQ ID NO:71.

[0222] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:33, a CDR-H2 of SEQ ID NO:42, a CDR-H1 of SEQ ID NO:58, a CDR-L3 of SEQ ID NO:65, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

[0223] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:33, a CDR-H2 of SEQ ID NO:42, a CDR-H1 of SEQ ID NO:59, a CDR-L3 of SEQ ID NO:65, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

[0224] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:33, a CDR-H2 of SEQ ID NO:43, a CDR-H1 of SEQ ID NO:60, a CDR-L3 of SEQ ID NO:65, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

[0225] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:34, a CDR-H2 of SEQ ID NO:43, a CDR-H1 of SEQ ID NO:60, a CDR-L3 of SEQ ID NO:65, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

[0226] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:34, a CDR-H2 of SEQ ID NO:44, a CDR-H1 of SEQ ID NO:61, a CDR-L3 of SEQ ID NO:65, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

[0227] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:33, a CDR-H2 of SEQ ID NO:44, a CDR-H1 of SEQ ID NO:59, a CDR-L3 of SEQ ID NO:65, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

[0228] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:35, a CDR-H2 of SEQ ID NO:45, a CDR-H1 of SEQ ID NO:62, a CDR-L3 of SEQ ID NO:66, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

[0229] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:35, a CDR-H2 of SEQ ID NO:46, a CDR-H1 of SEQ ID NO:62, a CDR-L3 of SEQ ID NO:66, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

[0230] In some embodiments, an ABP provided herein comprises a CDR-H3 of SEQ ID NO:35, a CDR-H2 of SEQ ID NO:47, a CDR-H1 of SEQ ID NO:62, a CDR-L3 of SEQ ID NO:66, a CDR-L2 of SEQ ID NO:69, and a CDR-L1 of SEQ ID NO:72.

2.2.5. Heavy Chains and Light Chains

[0231] In some embodiments, an ABP provided herein comprises a V_H selected from a V_H of SEQ ID NO:4-24 (or a variant described herein) and a constant region selected from SEQ ID NOs: 55-57 or 125. In some embodiments, an ABP provided herein comprises a V_L selected from a V_L of SEQ ID NO:25-28 (or a variant described herein) and a constant region of SEQ ID NO:126.

[0232] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:79. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:80. In some embodiments, an ABP provided herein comprises a light chain of SEQ ID NO:81. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:79 and a light chain of SEQ ID NO: 81. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:80 and a light chain of SEQ ID NO: 81.

[0233] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:82. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:83. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:82 and a light chain of SEQ ID NO: 81. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:83 and a light chain of SEQ ID NO: 81.

[0234] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:84. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:85. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:84 and a light chain of SEQ ID NO: 81. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:85 and a light chain of SEQ ID NO: 81.

[0235] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:86. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:87. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:86 and a light chain of SEQ ID NO: 81. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:87 and a light chain of SEQ ID NO: 81.

[0236] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:88. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:89. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:88 and a light chain of SEQ ID NO: 81. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:89 and a light chain of SEQ ID NO: 81.

[0237] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:90. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:91. In some embodiments, an ABP provided herein comprises a light chain of SEQ ID NO:92. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:90 and a light chain of SEQ ID NO:92. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:91 and a light chain of SEQ ID NO:92.

[0238] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:93. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:94. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:93 and a light chain of SEQ ID NO:92. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:94 and a light chain of SEQ ID NO:92.

[0239] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:95. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:96. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:95 and a light chain of SEQ ID NO:92. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:96 and a light chain of SEQ ID NO:92.

[0240] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:97. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:98. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:97 and a light chain of SEQ ID NO:92. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:98 and a light chain of SEQ ID NO:92.

[0241] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:99. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:100. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:99 and a light chain of SEQ ID NO:92. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:100 and a light chain of SEQ ID NO:92.

[0242] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:101. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:102. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:101 and a light chain of SEQ ID NO:92. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:102 and a light chain of SEQ ID NO:92.

[0243] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:103. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:104. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:103 and a light chain of SEQ ID NO:92. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:104 and a light chain of SEQ ID NO:92.

[0244] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:105. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:106. In some embodiments, an ABP provided herein comprises a light chain of SEQ ID NO:107. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:105 and a light chain of SEQ ID NO:107. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:106 and a light chain of SEQ ID NO:107.

[0245] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:108. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:109. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:108 and a light chain of SEQ ID NO:107. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:109 and a light chain of SEQ ID NO:107.

[0246] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:110.

In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:111. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:110 and a light chain of SEQ ID NO:107. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:111 and a light chain of SEQ ID NO:107.

[0247] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:112. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:113. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:112 and a light chain of SEQ ID NO:107. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:113 and a light chain of SEQ ID NO:107.

[0248] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:114. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:115. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:114 and a light chain of SEQ ID NO:107. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:115 and a light chain of SEQ ID NO:107.

[0249] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:116. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:117. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:116 and a light chain of SEQ ID NO:107. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:117 and a light chain of SEQ ID NO:107.

[0250] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:118. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:119. In some embodiments, an ABP provided herein comprises a light chain of SEQ ID NO:120. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:118 and a light chain of SEQ ID NO:120. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:119 and a light chain of SEQ ID NO:120.

[0251] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:121. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:122. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:121 and a light chain of SEQ ID NO:120. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:122 and a light chain of SEQ ID NO:120.

[0252] In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:123. In some embodiments, an ABP provided herein comprises a heavy chain of SEQ ID NO:124. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:123 and a light chain of SEQ ID NO:120. In some embodiments, an APB provided herein comprises a heavy chain of SEQ ID NO:124 and a light chain of SEQ ID NO:120.

2.2.6. Consensus Sequences

[0253] In some embodiments, provided herein is a first family of ABPs, wherein an ABP of such family comprises the following six CDR sequences: (a) a CDR-H3 having the sequence A-R-D-G-V-L-X_1-L-N-K-R-S-F-D-I, wherein X_1 is A or T (SEQ ID NO: 128); (b) a CDR-H2 having the sequence S-I-Y-Y-S-G-X_2-T-Y-Y-N-P-S-L-K-S, wherein X_2 is S, Q or G (SEQ ID NO: 129); (c) a CDR-H1 having the sequence G-S-I-X_3-S-G-X_4-Y-Y-W-G, wherein X_3 is E or A, and X_4 is L, V or S (SEQ ID NO: 130); (d) a CDR-L3 having the sequence QQHTVRPPLT (SEQ ID NO: 64); (e) a CDR-L2 having the sequence GASSRAT (SEQ ID NO: 68); and (f) a CDR-L1 having the sequence RASQSVSSSYLA (SEQ ID NO: 71). In some embodiments, provided herein is an ABP within such first family.

[0254] In some embodiments, provided herein is a second family of ABPs, wherein an ABP of such family comprises the following six CDR sequences: (a) a CDR-H3 having the sequence A-R-D-A-N-Y-Y-G-X_1-A-W-A-F-D-P, wherein X_1 is S or G (SEQ ID NO: 131); (b) a CDR-H2 having the sequence S-I-Y-Y-S-G-X_2-T-F-Y-N-P-S-L-K-X_3, wherein X_2 is S or A, and X_3 is S or G (SEQ ID NO: 132); (c) a CDR-H1 having the sequence G-S-I-X_4-S-X_5-X_6-X_7-Y-W-G, wherein X_4 is S or T, X_5 is S or T, X_6 is S or K, and X_7 is H or Y (SEQ ID NO: 133); (d) a CDR-L3 having the sequence QQHFNLPT (SEQ ID NO: 63); (e) a CDR-L2 having the sequence DASNRAT (SEQ ID NO: 67); and (f) a CDR-L1 having the sequence RASQSVSSYLA (SEQ ID NO: 70). In some embodiments, provided herein is an ABP within such second family.

[0255] In some embodiments, provided herein is a third family of ABPs, wherein an ABP of such family comprises the following six CDR sequences: (a) a CDR-H3 having the sequence A-R-G-G-R-T-T-W-I-G-A-X_1-D-I, wherein X_1 is F or L (SEQ ID NO: 134); (b) a CDR-H2 having the sequence I-I-N-P-S-X_2-G-L-T-S-Y-A-X_3-K-F-Q-G, wherein X_2 is L or I, and X_3 is Q or R (SEQ ID NO: 135); (c) a CDR-H1 having the sequence Y-T-F-X_4-X_5-Y-Y-X_6-H, wherein X_4 is G, P or R, X_5 is N, A or E, and X_6 is M or I (SEQ ID NO: 136); (d) a CDR-L3 having the sequence QQYVVWPPLT (SEQ ID NO:65); (e) a CDR-L2 having the sequence GASTRAT (SEQ ID NO:69); and (f) a CDR-L1 having the sequence RASQSVSSNLA (SEQ ID NO:72). In some embodiments, provided herein is an ABP within such third family.

[0256] In some embodiments, provided herein is a fourth family of ABPs, wherein an ABP of such family comprises the following six CDR sequences: (a) a CDR-H3 having the sequence ARLHVSGSYYPAYLDY (SEQ ID NO: 35); (b) a CDR-H2 having the sequence X_1-I-N-P-S-M-G-A-T-S-Y-X_2-Q-K-F-X_3-G, wherein X_1 is V or I, X_2 is A or T, and X_3 is Q or R (SEQ ID NO: 137); (c) a CDR-H1 having the sequence YTFTSHYMG (SEQ ID NO: 62); (d) a CDR-L3 having the sequence QQYIVFPWT (SEQ ID NO: 66); (e) a CDR-L2 having the sequence GASTRAT (SEQ ID NO: 69); and (f) a CDR-L1 having the sequence RASQSVSSNLA, (SEQ ID NO: 72). In some embodiments, provided herein is an ABP within such fourth family.

2.2.7. Functional Properties of ABP Variants

[0257] As described above, and elsewhere in this disclosure, provided herein are ABP variants defined based on percent identity to an illustrative ABP sequence provided herein, or substitution of amino acid residues in comparison to an illustrative ABP sequence provided herein.

[0258] In some embodiments, a variant of an ABP provided herein has specificity for hTIGIT. In some embodiments, a variant of an ABP provided herein has specificity for cTIGIT. In some embodiments, a variant of an ABP provided herein has specificity for mTIGIT. In some embodiments, a variant of an ABP provided herein has specificity for hTIGIT and cTIGIT. In some embodiments, a variant of an ABP provided herein has specificity for hTIGIT and mTIGIT. In some embodiments, a variant of an ABP provided herein has specificity for cTIGIT and mTIGIT. In some embodiments, a variant of an ABP provided herein has specificity for hTIGIT, cTIGIT and mTIGIT.

[0259] In some embodiments, a variant of an ABP that is derived from an illustrative ABP sequence provided herein retains affinity, as measured by K_D, for hTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative ABP. In some embodiments, a variant of an ABP that is derived from an illustrative ABP sequence provided herein retains affinity, as measured by K_D, for cTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative ABP. In some embodiments, a variant of an ABP that is derived from an illustrative ABP sequence provided herein retains affinity, as measured by K_D, for mTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative ABP. In some embodiments, a variant of an ABP that is derived from an illustrative ABP sequence provided herein retains affinity, as measured by K_D, for both hTIGIT and cTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative ABP. In some embodiments, a variant of an ABP that is derived from an illustrative ABP sequence provided herein retains affinity, as measured by K_D, for both hTIGIT and mTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative ABP. In some embodiments, a variant of an ABP that is derived from an illustrative ABP sequence provided herein retains affinity, as measured by K_D, for both cTIGIT and mTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative ABP. In some embodiments, a variant of an ABP that is derived from an illustrative ABP sequence provided herein retains affinity, as measured by K_D, for all three of hTIGIT, cTIGIT and mTIGIT that is within about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold or about 10-fold the affinity of such illustrative ABP.

[0260] In some embodiments, a variant of an ABP provided herein retains the ability to antagonize

TIGIT, as measured by one or more assays or biological effects described herein. In some embodiments, a variant of an ABP provided herein retains the ability to prevent TIGIT from interacting with one or more of its ligands, as described herein.

[0261] In some embodiments, a variant of an ABP provided herein competes for binding to TIGIT with an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each as provided in Table 5 of this disclosure.

[0262] In some embodiments, a variant of an ABP provided herein inhibits binding of CD155 to TIGIT. In some embodiments, a variant of an ABP provided herein inhibits binding of CD112 to TIGIT. In some embodiments, a variant of an ABP provided herein inhibits association of CD226 with TIGIT.

[0263] In some embodiments, a variant of an ABP provided herein activates an effector T cell or a natural killer (NK) cell. In some embodiments, a variant of an ABP provided herein decreases the number of regulatory T cells in a tissue or in circulation. In some embodiments, a variant of an ABP provided herein inhibits the suppression of an effector T cell by a regulatory T cell.

[0264] In some embodiments, a variant of an ABP provided herein does not bind specifically to any of PVRL1, PVRL2, PVRL3, or PVRL4.

[0265] In some embodiments, a variant of an ABP provided herein binds murine TIGIT (SEQ ID NO: 3) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hTIGIT, or does not bind mTIGIT. In some embodiments, a variant of an ABP provided herein binds murine TIGIT (SEQ ID NO: 138) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hTIGIT, or does not bind mTIGIT.

[0266] In some embodiments, a variant of an ABP provided herein binds the same epitope of TIGIT as such ABP.

2.2.8. Other Functional Properties of ABPs

[0267] In some embodiments, an ABP provided herein has one or more of the characteristics listed in the following (a)-(j): (a) competes for binding to TIGIT with an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each as provided in Table 5 of this disclosure; (b) inhibits binding of CD155 to TIGIT; (c) inhibits binding of CD112 to TIGIT; (d) inhibits association of CD226 with TIGIT; (e) activates an effector T cell or a natural killer (NK) cell; (f) decreases the number of regulatory T cells in a tissue or in circulation; (g) inhibits the suppression of an effector T cell by a regulatory T cell; (h) does not bind specifically to any of PVRL1, PVRL2, PVRL3, or PVRL4; (i) specifically binds cynomolgus monkey TIGIT (cTIGIT; SEQ ID NO: 2); or (j) binds murine TIGIT (mTIGIT; SEQ ID NO: 3) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hTIGIT, or does not bind mTIGIT. In

some embodiments, an ABP provided herein has two or more of the characteristics listed in the foregoing (a)-(j). In some embodiments, an ABP provided herein has three or more of the characteristics listed in the foregoing (a)-(j). In some embodiments, an ABP provided herein has four or more of the characteristics listed in the foregoing (a)-(j). In some embodiments, an ABP provided herein has five or more of the characteristics listed in the foregoing (a)-(j). In some embodiments, an ABP provided herein has six or more of the characteristics listed in the foregoing (a)-(j). In some embodiments, an ABP provided herein has seven or more of the characteristics listed in the foregoing (a)-(j). In some embodiments, an ABP provided herein has eight or more of the characteristics listed in the foregoing (a)-(j). In some embodiments, an ABP provided herein has nine or more of the characteristics listed in the foregoing (a)-(j). In some embodiments, an ABP provided herein has all ten of the characteristics listed in the foregoing (a)-(j).

[0268] In some embodiments, an ABP provided herein exhibits a combination of the characteristics listed in the following (a)-(j): (a) competes for binding to TIGIT with an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each as provided in Table 5 of this disclosure; (b) inhibits binding of CD155 to TIGIT; (c) inhibits binding of CD112 to TIGIT; (d) inhibits association of CD226 with TIGIT; (e) activates an effector T cell or a natural killer (NK) cell; (f) decreases the number of regulatory T cells in a tissue or in circulation; (g) inhibits the suppression of an effector T cell by a regulatory T cell; (h) does not bind specifically to any of PVRL1, PVRL2, PVRL3, or PVRL4; (i) specifically binds cynomolgus monkey TIGIT (cTIGIT; SEQ ID NO: 2); or (j) binds murine TIGIT (mTIGIT; SEQ ID NO: 3) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hTIGIT, or does not bind mTIGIT. In some embodiments, such ABP exhibits a combination of the characteristics selected from (a and b), (a and c), (a and d), (a and e), (a and f), (a and g), (a and h), (a and i), (a and j), (b and a), (b and c), (b and d), (b and e), (b and f), (b and g), (b and h), (b and i), (b and j), (c and a), (c and b), (c and d), (c and e), (c and f), (c and g), (c and h), (c and i), (c and j), (d and a), (d and b), (d and c), (d and e), (d and f), (d and g), (d and h), (d and i), (d and j), (e and a), (e and b), (e and c), (e and d), (e and f), (e and g), (e and h), (e and i), (e and j), (f and a), (f and b), (f and c), (f and d), (f and e), (f and g), (f and h), (f and i), (f and j), (g and a), (g and b), (g and c), (g and d), (g and e), (g and f), (g and h), (g and i), (g and j), (h and a), (h and b), (h and c), (h and d), (h and e), (h and f), (h and g), (h and i), (h and j), (i and a), (i and b), (i and c), (i and d), (i and e), (i and f), (i and g), (i and h), (i and j), (j and a), (j and b), (j and c), (j and d), (j and e), (j and f), (j and g), (j and h), and (j and i). In some embodiments, such ABP exhibits a combination of the characteristics selected from (a and b and c), (a and b and d), (a and b and e), (a and b and f), (a and b and g), (a and b and h), (a and b and i), (a and b and j), (a and c and b), (a and c and d), (a and c and e), (a and c and f), (a and c and g), (a and c and h), (a and c and i), (a and c and j), (a and d and b), (a and d and c), (a and d and e), (a and d and f), (a and d and g), (a and d and h), (a and d and i), (a and d and j), (a and e and b), (a and e and c), (a and e and d), (a and e

and f), (a and e and g), (a and e and h), (a and e and i), (a and e and j), (a and f and b), (a and f and c), (a and f and d), (a and f and e), (a and f and g), (a and f and h), (a and f and i), (a and f and j), (a and g and b), (a and g and c), (a and g and d), (a and g and e), (a and g and f), (a and g and h), (a and g and i), (a and g and j), (a and h and b), (a and h and c), (a and h and d), (a and h and e), (a and h and f), (a and h and g), (a and h and i), (a and h and j), (a and i and b), (a and i and c), (a and i and d), (a and i and e), (a and i and f), (a and i and g), (a and i and h), (a and i and j), (a and j and b), (a and j and c), (a and j and d), (a and j and e), (a and j and f), (a and j and g), (a and j and h), (a and j and i), (b and a and j), (b and a and c), (b and a and d), (b and a and e), (b and a and f), (b and a and g), (b and a and h), (b and a and i), (b and c and j), (b and c and a), (b and c and d), (b and c and e), (b and c and f), (b and c and g), (b and c and h), (b and c and i), (b and d and j), (b and d and a), (b and d and c), (b and d and e), (b and d and f), (b and d and g), (b and d and h), (b and d and i), (b and e and j), (b and e and a), (b and e and c), (b and e and d), (b and e and f), (b and e and g), (b and e and h), (b and e and i), (b and f and j), (b and f and a), (b and f and c), (b and f and d), (b and f and e), (b and f and g), (b and f and h), (b and f and i), (b and g and j), (b and g and a), (b and g and c), (b and g and d), (b and g and e), (b and g and f), (b and g and h), (b and g and i), (b and h and j), (b and h and a), (b and h and c), (b and h and d), (b and h and e), (b and h and f), (b and h and g), (b and h and i), (b and i and j), (b and i and a), (b and i and c), (b and i and d), (b and i and e), (b and i and f), (b and i and g), (b and i and h), (b and j and i), (b and j and a), (b and j and c), (b and j and d), (b and j and e), (b and j and f), (b and j and g), (b and j and h), (c and a and i), (c and a and j), (c and a and b), (c and a and d), (c and a and e), (c and a and f), (c and a and g), (c and a and h), (c and b and i), (c and b and j), (c and b and a), (c and b and d), (c and b and e), (c and b and f), (c and b and g), (c and b and h), (c and d and i), (c and d and j), (c and d and a), (c and d and b), (c and d and e), (c and d and f), (c and d and g), (c and d and h), (c and e and i), (c and e and j), (c and e and a), (c and e and b), (c and e and d), (c and e and f), (c and e and g), (c and e and h), (c and f and i), (c and f and j), (c and f and a), (c and f and b), (c and f and d), (c and f and e), (c and f and g), (c and f and h), (c and g and i), (c and g and j), (c and g and a), (c and g and b), (c and g and d), (c and g and e), (c and g and f), (c and g and h), (c and h and i), (c and h and j), (c and h and a), (c and h and b), (c and h and d), (c and h and e), (c and h and f), (c and h and g), (c and i and h), (c and i and j), (c and i and a), (c and i and b), (c and i and d), (c and i and e), (c and i and f), (c and i and g), (c and j and h), (c and j and i), (c and j and a), (c and j and b), (c and j and d), (c and j and e), (c and j and f), (c and j and g), (d and a and h), (d and a and i), (d and a and j), (d and a and b), (d and a and c), (d and a and e), (d and a and f), (d and a and g), (d and b and h), (d and b and i), (d and b and j), (d and b and a), (d and b and c), (d and b and e), (d and b and f), (d and b and g), (d and c and h), (d and c and i), (d and c and j), (d and c and a), (d and c and b), (d and c and e), (d and c and f), (d and c and g), (d and e and h), (d and e and i), (d and e and j), (d and e and a), (d and e and b), (d and e and c), (d and e and f), (d and e and g), (d and f and h), (d and f and i), (d and f and j), (d and f and a), (d and f and b), (d and f and c), (d and f and e), (d and f and g), (d and g and h), (d and g and i), (d and g and j), (d and g and a), (d and g and b), (d and g and c), (d and g and e), (d and g and f), (d

and h and g), (d and h and i), (d and h and j), (d and h and a), (d and h and b), (d and h and c), (d and h and e), (d and h and f), (d and i and g), (d and i and h), (d and i and j), (d and i and a), (d and i and b), (d and i and c), (d and i and e), (d and i and f), (d and j and g), (d and j and h), (d and j and i), (d and j and a), (d and j and b), (d and j and c), (d and j and e), (d and j and f), (e and a and g), (e and a and h), (e and a and i), (e and a and j), (e and a and b), (e and a and c), (e and a and d), (e and a and f), (e and b and g), (e and b and h), (e and b and i), (e and b and j), (e and b and a), (e and b and c), (e and b and d), (e and b and f), (e and c and g), (e and c and h), (e and c and i), (e and c and j), (e and c and a), (e and c and b), (e and c and d), (e and c and f), (e and d and g), (e and d and h), (e and d and i), (e and d and j), (e and d and a), (e and d and b), (e and d and c), (e and d and f), (e and f and g), (e and f and h), (e and f and i), (e and f and j), (e and f and a), (e and f and b), (e and f and c), (e and f and d), (e and g and f), (e and g and h), (e and g and i), (e and g and j), (e and g and a), (e and g and b), (e and g and c), (e and g and d), (e and h and f), (e and h and g), (e and h and i), (e and h and j), (e and h and a), (e and h and b), (e and h and c), (e and h and d), (e and i and f), (e and i and g), (e and i and h), (e and i and j), (e and i and a), (e and i and b), (e and i and c), (e and i and d), (e and j and f), (e and j and g), (e and j and h), (e and j and i), (e and j and a), (e and j and b), (e and j and c), (e and j and d), (f and a and e), (f and a and g), (f and a and h), (f and a and i), (f and a and j), (f and a and b), (f and a and c), (f and a and d), (f and b and e), (f and b and g), (f and b and h), (f and b and i), (f and b and j), (f and b and a), (f and b and c), (f and b and d), (f and c and e), (f and c and g), (f and c and h), (f and c and i), (f and c and j), (f and c and a), (f and c and b), (f and c and d), (f and d and e), (f and d and g), (f and d and h), (f and d and i), (f and d and j), (f and d and a), (f and d and b), (f and d and c), (f and e and d), (f and e and g), (f and e and h), (f and e and i), (f and e and j), (f and e and a), (f and e and b), (f and e and c), (f and g and d), (f and g and e), (f and g and h), (f and g and i), (f and g and j), (f and g and a), (f and g and b), (f and g and c), (f and h and d), (f and h and e), (f and h and g), (f and h and i), (f and h and j), (f and h and a), (f and h and b), (f and h and c), (f and i and d), (f and i and e), (f and i and g), (f and i and h), (f and i and j), (f and i and a), (f and i and b), (f and i and c), (f and j and d), (f and j and e), (f and j and g), (f and j and h), (f and j and i), (f and j and a), (f and j and b), (f and j and c), (g and a and d), (g and a and e), (g and a and f), (g and a and h), (g and a and i), (g and a and j), (g and a and b), (g and a and c), (g and b and d), (g and b and e), (g and b and f), (g and b and h), (g and b and i), (g and b and j), (g and b and a), (g and b and c), (g and c and d), (g and c and e), (g and c and f), (g and c and h), (g and c and i), (g and c and j), (g and c and a), (g and c and b), (g and d and c), (g and d and e), (g and d and f), (g and d and h), (g and d and i), (g and d and j), (g and d and a), (g and d and b), (g and e and c), (g and e and d), (g and e and f), (g and e and h), (g and e and i), (g and e and j), (g and e and a), (g and e and b), (g and f and c), (g and f and d), (g and f and e), (g and f and h), (g and f and i), (g and f and j), (g and f and a), (g and f and b), (g and h and c), (g and h and d), (g and h and e), (g and h and f), (g and h and i), (g and h and j), (g and h and a), (g and h and b), (g and i and c), (g and i and d), (g and i and e), (g and i and f), (g and i and h), (g and i and j), (g and i and a), (g and i and b), (g and j and c), (g and j and d), (g and j and e), (g and j and f), (g and j and h), (g and j and i), (g and j

and a), (g and j and b), (h and a and c), (h and a and d), (h and a and e), (h and a and f), (h and a and g), (h and a and i), (h and a and j), (h and a and b), (h and b and c), (h and b and d), (h and b and e), (h and b and f), (h and b and g), (h and b and i), (h and b and j), (h and b and a), (h and c and b), (h and c and d), (h and c and e), (h and c and f), (h and c and g), (h and c and i), (h and c and j), (h and c and a), (h and d and b), (h and d and c), (h and d and e), (h and d and f), (h and d and g), (h and d and i), (h and d and j), (h and d and a), (h and e and b), (h and e and c), (h and e and d), (h and e and f), (h and e and g), (h and e and i), (h and e and j), (h and e and a), (h and f and b), (h and f and c), (h and f and d), (h and f and e), (h and f and g), (h and f and i), (h and f and j), (h and f and a), (h and g and b), (h and g and c), (h and g and d), (h and g and e), (h and g and f), (h and g and i), (h and g and j), (h and g and a), (h and i and b), (h and i and c), (h and i and d), (h and i and e), (h and i and f), (h and i and g), (h and i and j), (h and i and a), (h and j and b), (h and j and c), (h and j and d), (h and j and e), (h and j and f), (h and j and g), (h and j and i), (h and j and a), (i and a and b), (i and a and c), (i and a and d), (i and a and e), (i and a and f), (i and a and g), (i and a and h), (i and a and j), (i and b and a), (i and b and c), (i and b and d), (i and b and e), (i and b and f), (i and b and g), (i and b and h), (i and b and j), (i and c and a), (i and c and b), (i and c and d), (i and c and e), (i and c and f), (i and c and g), (i and c and h), (i and c and j), (i and d and a), (i and d and b), (i and d and c), (i and d and e), (i and d and f), (i and d and g), (i and d and h), (i and d and j), (i and e and a), (i and e and b), (i and e and c), (i and e and d), (i and e and f), (i and e and g), (i and e and h), (i and e and j), (i and f and a), (i and f and b), (i and f and c), (i and f and d), (i and f and e), (i and f and g), (i and f and h), (i and f and j), (i and g and a), (i and g and b), (i and g and c), (i and g and d), (i and g and e), (i and g and f), (i and g and h), (i and g and j), (i and h and a), (i and h and b), (i and h and c), (i and h and d), (i and h and e), (i and h and f), (i and h and g), (i and h and j), (i and j and a), (i and j and b), (i and j and c), (i and j and d), (i and j and e), (i and j and f), (i and j and g), (i and j and h), (j and a and i), (j and a and b), (j and a and c), (j and a and d), (j and a and e), (j and a and f), (j and a and g), (j and a and h), (j and b and i), (j and b and a), (j and b and c), (j and b and d), (j and b and e), (j and b and f), (j and b and g), (j and b and h), (j and c and i), (j and c and a), (j and c and b), (j and c and d), (j and c and e), (j and c and f), (j and c and g), (j and c and h), (j and d and i), (j and d and a), (j and d and b), (j and d and c), (j and d and e), (j and d and f), (j and d and g), (j and d and h), (j and e and i), (j and e and a), (j and e and b), (j and e and c), (j and e and d), (j and e and f), (j and e and g), (j and e and h), (j and f and i), (j and f and a), (j and f and b), (j and f and c), (j and f and d), (j and f and e), (j and f and g), (j and f and h), (j and g and i), (j and g and a), (j and g and b), (j and g and c), (j and g and d), (j and g and e), (j and g and f), (j and g and h), (j and h and i), (j and h and a), (j and h and b), (j and h and c), (j and h and d), (j and h and e), (j and h and f), (j and h and g), (j and i and h), (j and i and a), (j and i and b), (j and i and c), (j and i and d), (j and i and e), (j and i and f), and (j and i and g).

2.3. Germlines

[0269] The ABPs provided herein may comprise any suitable V_H and V_L germline sequences.

[0270] In some embodiments, the V_H region of an ABP provided herein is from the VH4 germline. In some embodiments, the V_H region of an ABP provided herein is from the VH1 germline.

[0271] In some embodiments, the V_H region of an ABP provided herein is from the VH4-39 germline. In some embodiments, the V_H region of an ABP provided herein is from the VH4-31 germline. In some embodiments, the V_H region of an ABP provided herein is from the VH1-46 germline.

[0272] In some embodiments, the V_L region of an ABP provided herein is from the VK3 germline.

[0273] In some embodiments, the V_L region of an ABP provided herein is from the VK3-11 germline. In some embodiments, the V_L region of an ABP provided herein is from the VK3-20 germline. In some embodiments, the V_L region of an ABP provided herein is from the VK3-15 germline.

2.4. Monospecific and Multispecific TIGIT Antigen-Binding Proteins

[0274] In some embodiments, the ABPs provided herein are monospecific ABPs.

[0275] In some embodiments, the ABPs provided herein are multispecific ABPs.

[0276] In some embodiments, a multispecific ABP provided herein binds more than one antigen. In some embodiments, a multispecific antibody binds 2 antigens. In some embodiments, a multispecific antibody binds 3 antigens. In some embodiments, a multispecific antibody binds 4 antigens. In some embodiments, a multispecific antibody binds 5 antigens.

[0277] In some embodiments, a multispecific antibody provided herein binds more than one epitope on a TIGIT antigen. In some embodiments, a multispecific antibody binds 2 epitopes on a TIGIT antigen. In some embodiments, a multispecific antibody binds 3 epitopes on a TIGIT antigen.

[0278] Many multispecific ABP constructs are known in the art, and the ABPs provided herein may be provided in the form of any suitable multispecific suitable construct.

[0279] In some embodiments, the multispecific ABP comprises an immunoglobulin comprising at least two different heavy chain variable regions each paired with a common light chain variable region (i.e., a "common light chain antibody"). The common light chain variable region forms a distinct antigen-binding domain with each of the two different heavy chain variable regions. *See* Merchant et al., *Nature Biotechnol.*, 1998, 16:677-681, incorporated by reference in its entirety.

[0280] In some embodiments, the multispecific ABP comprises an immunoglobulin comprising an antibody or fragment thereof attached to one or more of the N- or C-termini of the heavy or light chains of such immunoglobulin. *See* Coloma and Morrison, *Nature Biotechnol.*, 1997, 15:159-163, incorporated by reference in its entirety. In some aspects, such ABP comprises a tetravalent bispecific antibody.

[0281] In some embodiments, the multispecific ABP comprises a hybrid immunoglobulin comprising at least two different heavy chain variable regions and at least two different light chain variable regions. *See* Milstein and Cuello, *Nature*, 1983, 305:537-540; and Staerz and Bevan, *Proc. Natl.*

Acad. Sci. USA, 1986, 83:1453-1457; each of which is incorporated by reference in its entirety.

[0282] In some embodiments, the multispecific ABP comprises immunoglobulin chains with alterations to reduce the formation of side products that do not have multispecificity. In some aspects, the ABPs comprise one or more "knobs-into-holes" modifications as described in U.S. Pat. No. 5,731,168, incorporated by reference in its entirety.

[0283] In some embodiments, the multispecific ABP comprises immunoglobulin chains with one or more electrostatic modifications to promote the assembly of Fc hetero-multimers. *See* WO 2009/089004, incorporated by reference in its entirety.

[0284] In some embodiments, the multispecific ABP comprises a bispecific single chain molecule. *See* Traunecker et al., *EMBO J.*, 1991, 10:3655-3659; and Gruber et al., *J. Immunol.*, 1994, 152:5368-5374; each of which is incorporated by reference in its entirety.

[0285] In some embodiments, the multispecific ABP comprises a heavy chain variable domain and a light chain variable domain connected by a polypeptide linker, where the length of the linker is selected to promote assembly of multispecific ABPs with the desired multispecificity. For example, monospecific scFvs generally form when a heavy chain variable domain and light chain variable domain are connected by a polypeptide linker of more than 12 amino acid residues. *See* U.S. Pat. Nos. 4,946,778 and 5,132,405, each of which is incorporated by reference in its entirety. In some embodiments, reduction of the polypeptide linker length to less than 12 amino acid residues prevents pairing of heavy and light chain variable domains on the same polypeptide chain, thereby allowing pairing of heavy and light chain variable domains from one chain with the complementary domains on another chain. The resulting ABPs therefore have multispecificity, with the specificity of each binding site contributed by more than one polypeptide chain. Polypeptide chains comprising heavy and light chain variable domains that are joined by linkers between 3 and 12 amino acid residues form predominantly dimers (termed diabodies). With linkers between 0 and 2 amino acid residues, trimers (termed triabodies) and tetramers (termed tetrabodies) are favored. However, the exact type of oligomerization appears to depend on the amino acid residue composition and the order of the variable domain in each polypeptide chain (e.g., V_H-linker-V_L vs. V_L-linker-V_H), in addition to the linker length. A skilled person can select the appropriate linker length based on the desired multispecificity.

[0286] In some embodiments, the multispecific ABP comprises a diabody. *See* Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 1993, 90:6444-6448, incorporated by reference in its entirety. In some embodiments, the multispecific ABP comprises a triabody. *See* Todorovska et al., *J. Immunol. Methods*, 2001, 248:47-66, incorporated by reference in its entirety. In some embodiments, the multispecific ABP comprises a tetrabody. *See id.*, incorporated by reference in its entirety.

[0287] In some embodiments, the multispecific ABP comprises a trispecific F(ab')3 derivative. *See* Tutt et al. *J. Immunol.*, 1991, 147:60-69, incorporated by reference in its entirety.

[0288] In some embodiments, the multispecific ABP comprises a cross-linked antibody. *See* U.S.

Patent No. 4,676,980; Brennan et al., *Science*, 1985, 229:81-83; Staerz, et al. *Nature*, 1985, 314:628-631; and EP 0453082; each of which is incorporated by reference in its entirety.

[0289] In some embodiments, the multispecific ABP comprises antigen-binding domains assembled by leucine zippers. *See* Kostelny et al., *J. Immunol.*, 1992, 148:1547-1553, incorporated by reference in its entirety.

[0290] In some embodiments, the multispecific ABP comprises complementary protein domains. In some aspects, the complementary protein domains comprise an anchoring domain (AD) and a dimerization and docking domain (DDD). In some embodiments, the AD and DDD bind to each other and thereby enable assembly of multispecific ABP structures via the "dock and lock" (DNL) approach. ABPs of many specificities may be assembled, including bispecific ABPs, trispecific ABPs, tetraspecific ABPs, quintspecific ABPs, and hexaspecific ABPs. Multispecific ABPs comprising complementary protein domains are described, for example, in U.S. Pat. Nos. 7,521,056; 7,550,143; 7,534,866; and 7,527,787; each of which is incorporated by reference in its entirety.

[0291] In some embodiments, the multispecific ABP comprises a dual action Fab (DAF) antibody as described in U.S. Pat. Pub. No. 2008/0069820, incorporated by reference in its entirety.

[0292] In some embodiments, the multispecific ABP comprises an antibody formed by reduction of two parental molecules followed by mixing of the two parental molecules and reoxidation to assembly a hybrid structure. *See* Carlring et al., *PLoS One*, 2011, 6:e22533, incorporated by reference in its entirety.

[0293] In some embodiments, the multispecific ABP comprises a DVD-Ig™. A DVD-Ig™ is a dual variable domain immunoglobulin that can bind to two or more antigens. DVD-Igs™ are described in U.S. Pat. No. 7,612,181, incorporated by reference in its entirety.

[0294] In some embodiments, the multispecific ABP comprises a DART™. DARTs™ are described in Moore et al., *Blood*, 2011, 117:454-451, incorporated by reference in its entirety.

[0295] In some embodiments, the multispecific ABP comprises a DuoBody®. DuoBodies® are described in Labrijn et al., *Proc. Natl. Acad. Sci. USA*, 2013, 110:5145-5150; Gramer et al., *mAbs*, 2013, 5:962-972; and Labrijn et al., *Nature Protocols*, 2014, 9:2450-2463; each of which is incorporated by reference in its entirety.

[0296] In some embodiments, the multispecific ABP comprises an antibody fragment attached to another antibody or fragment. The attachment can be covalent or non-covalent. When the attachment is covalent, it may be in the form of a fusion protein or via a chemical linker. Illustrative examples of multispecific ABPs comprising antibody fragments attached to other antibodies include tetravalent bispecific antibodies, where an scFv is fused to the C-terminus of the C_{H3} from an IgG. *See* Coloma and Morrison, *Nature Biotechnol.*, 1997, 15:159-163. Other examples include antibodies in which a Fab molecule is attached to the constant region of an immunoglobulin. *See* Miler et al., *J. Immunol.*, 2003, 170:4854-4861, incorporated by reference in its entirety. Any suitable fragment may be used, including any of the fragments described herein or known in the art.

[0297] In some embodiments, the multispecific ABP comprises a CovX-Body. CovX-Bodies are described, for example, in Doppalapudi et al., *Proc. Natl. Acad. Sci. USA*, 2010, 107:22611-22616, incorporated by reference in its entirety.

[0298] In some embodiments, the multispecific ABP comprises an Fcab antibody, where one or more antigen-binding domains are introduced into an Fc region. Fcab antibodies are described in Wozniak-Knopp et al., *Protein Eng. Des. Sel.*, 2010, 23:289-297, incorporated by reference in its entirety.

[0299] In some embodiments, the multispecific ABP comprises an TandAb® antibody. TandAb® antibodies are described in Kipriyanov et al., *J. Mol. Biol.*, 1999, 293:41-56 and Zhukovsky et al., *Blood*, 2013, 122:5116, each of which is incorporated by reference in its entirety.

[0300] In some embodiments, the multispecific ABP comprises a tandem Fab. Tandem Fabs are described in WO 2015/103072, incorporated by reference in its entirety.

[0301] In some embodiments, the multispecific ABP comprises a Zybody™. Zybodies™ are described in LaFleur et al., *mAbs*, 2013, 5:208-218, incorporated by reference in its entirety.

2.5. TIGIT Antagonism

[0302] In some embodiments, the ABPs provided herein antagonize TIGIT upon binding.

[0303] In some embodiments, antagonism of TIGIT by an ABP provided herein results in dimerization and/or activation of CD226 (also known as DNAM-1), a co-stimulatory receptor whose dimerization and function is impaired by direct interaction with TIGIT. *See* Grogan et al., *J. Immunol.*, 2014, 192 (1 Supplement) 2013.15, incorporated by reference in its entirety. Figure 2 provides an illustration of the CD226-TIGIT pathway in comparison to the CD28/CTLA4 pathway, which has similar costimulation/coinhibition biology.

[0304] In some embodiments, antagonism of TIGIT by an ABP provided herein increases the amount of CD226 and CD155 that interact in comparison to the amount that interact in the absence of the ABP.

[0305] In some embodiments, antagonism of TIGIT by an ABP provided herein results in activation of an effector T cell. In some aspects, the effector T cell is a CD8+ T cell. In some aspects, the effector T cell is a CD4+ T cell.

[0306] In some embodiments, antagonism of TIGIT by an ABP provided herein results in activation of an NK cell. In some embodiments, antagonism of TIGIT by an ABP provided herein results in activation of an NKT cell.

[0307] In some embodiments, antagonism of TIGIT by an ABP provided herein results in a reduction of the inhibitory activity of a regulatory T cell toward an effector T cell.

[0308] In some embodiments, antagonism of TIGIT by an ABP provided herein results in increased secretion of IL-2, IL-6, GM-CSF, TNF, LT-α, and/or IFN-γ by a target cell.

[0309] In some embodiments, antagonism of TIGIT by an ABP provided herein increases the proliferation, survival, and/or function of an effector T cell. In some aspects the effector T cell is a

CD4+ effector T cell. In some aspects, the effector T cell is a CD8+ effector T cell.

[0310] In some embodiments, antagonism of TIGIT by an ABP provided herein abrogates suppression of an effector T cell by a regulatory T cell. In some aspects, the regulatory T cell is a CD4+CD25+Foxp3+ regulator T cell. In some aspects, the regulatory T cell is a CD8+CD25+ regulatory T cell.

[0311] In some embodiments, antagonism of TIGIT by an ABP provided herein results in an enhancement of an immune response.

[0312] In some embodiments, antagonism of TIGIT by an ABP provided herein results in the prevention of a tumor. In some embodiments, antagonism of TIGIT by an ABP provided herein results in the delay of onset of a tumor. In some embodiments, antagonism of TIGIT by an ABP provided herein results in a reduction of the size of a tumor. In some embodiments, antagonism of TIGIT by an ABP provided herein results in elimination of a tumor. In some embodiments, antagonism of TIGIT by an ABP provided herein results in a reduction in the number of metastases.

[0313] In some embodiments, antagonism of TIGIT by an ABP provided herein results in the prevention of a viral disease. In some embodiments, antagonism of TIGIT by an ABP provided herein results in the delay of onset of a viral disease. In some embodiments, antagonism of TIGIT by an ABP provided herein results in a reduction of the viral load in a subject. In some embodiments, antagonism of TIGIT by an ABP provided herein results in the elimination of a viral infection.

2.6. Affinity and Kinetics of Antigen-Binding Proteins for TIGIT; Potency

[0314] In some embodiments, the affinity of an ABP provided herein for TIGIT as indicated by K_D, is less than about 10^{-5} M, less than about 10^{-6} M, less than about 10^{-7} M, less than about 10^{-8} M, less than about 10^{-9} M, less than about 10^{-10} M, less than about 10^{-11} M, or less than about 10^{-12} M. In some embodiments, the affinity of the ABP is between about 10^{-7} M and 10^{-12} M. In some embodiments, the affinity of the ABP is between about 10^{-7} M and 10^{-11} M. In some embodiments, the affinity of the ABP is between about 10^{-7} M and 10^{-10} M. In some embodiments, the affinity of the ABP is between about 10^{-7} M and 10^{-9} M. In some embodiments, the affinity of the ABP is between about 10^{-7} M and 10^{-8} M. In some embodiments, the affinity of the ABP is between about 10^{-8} M and 10^{-12} M. In some embodiments, the affinity of the ABP is between about 10^{-8} M and 10^{-11} M. In some embodiments, the affinity of the ABP is between about 10^{-9} M and 10^{-11} M. In some embodiments, the affinity of the ABP is between about 10^{-10} M and 10^{-11} M.

[0315] In some embodiments, the affinity of an ABP provided herein for hTIGIT as indicated by K_D measured by ForteBio, as set forth in Example 4 is selected from about 5.24×10^{-10} M, about 4.57×10^{-10} M, about 3.32×10^{-10} M, about 2.46×10^{-10} M, about 1.96×10^{-10} M, about 3.11×10^{-9} M, about 2.54×10^{-9} M, about 3.13×10^{-9} M, about 2.83×10^{-9} M, about 1.71×10^{-9} M, about 2.47×10^{-9} M, about 2.35×10^{-9} M, about 1.44×10^{-9} M, about 1.23×10^{-9} M, about 5.26×10^{-10} M, about $3.78 \times 10^{-}$

^{10} M, about 4.29×10^{-10} M, or about 4.48×10^{-10} M. In some embodiments, such affinity ranges from about 3.13×10^{-9} M to about 1.96×10^{-10} M. In some embodiments, such K_D is about 3.13×10^{-9} M or less.

[0316] In some embodiments, the affinity of an ABP provided herein for cTIGIT as indicated by K_D measured by ForteBio, as set forth in Example 4 is selected from about 2.64×10^{-9} M, about 6.55×10^{-9} M, about 8.14×10^{-9} M, about 6.57×10^{-9} M, about 7.94×10^{-8} M, about 7.04×10^{-8} M, about 1.10×10^{-7} M, about 7.20×10^{-8} M, about 1.57×10^{-9} M, about 8.02×10^{-10} M, about 3.67×10^{-10} M, about 8.98×10^{-10} M, about 1.75×10^{-8} M, or about 2.58×10^{-8} M, about 9.35×10^{-9} M. In some embodiments, such affinity ranges from about 1.10×10^{-7} M to about 3.69×10^{-10} M. In some embodiments, such K_D is about 1.10×10^{-7} M or less.

[0317] In some embodiments, the affinity of an ABP provided herein for hTIGIT as indicated by K_D measured by solution equilibrium methods (MSD-SET), as set forth in Example 4 is selected from about 5.40×10^{-11} M, about 1.10×10^{-10} M, about 1.50×10^{-10} M, about 5.60×10^{-11} M, about 4.00×10^{-10} M, about 3.80×10^{-10} M, about 2.10×10^{-10} M, about 7.00×10^{-11} M, about 4.10×10^{-11} M, about 2.50×10^{-11} M, about 3.00×10^{-11} M, about 8.00×10^{-11} M, about 8.10×10^{-12} M, about 5.00×10^{-12} M, or about 4.90×10^{-12} M. In some embodiments, such affinity ranges from about 4.00×10^{-10} M to about 4.90×10^{-12} M. In some embodiments, such K_D is about 4.00×10^{-10} M or less.

[0318] In some embodiments, the affinity of an ABP provided herein for cTIGIT as indicated by K_D measured by MSD-SET, as set forth in Example 4 is selected from about 3.20×10^{-10} M, about 2.30×10^{-10} M, about 3.50×10^{-11} M, about 1.50×10^{-11} M, or about 4.60×10^{-11} M. In some embodiments, such affinity ranges from about 3.20×10^{-10} M to about 1.50×10^{-11} M. In some embodiments, such K_D is about 3.20×10^{-10} M or less.

[0319] In some embodiments, the affinity of an ABP provided herein for hTIGIT as indicated by K_D measured by ForteBio, as set forth in Example 6 is selected from about 7.1×10^{-10} M, about 8.1×10^{-11} M, about 1.9×10^{-10} M, about 5.6×10^{-10} M, about 2.4×10^{-10} M, about 2.8×10^{-10} M, about 1.6×10^{-10} M, about 5.8×10^{-10} M, about 1.1×10^{-9} M, about 8.1×10^{-10} M, about 4.6×10^{-10} M, or about 3.6×10^{-10} M. In some embodiments, such affinity ranges from about 1.1×10^{-9} M to about 8.1×10^{-11} M. In some embodiments, such K_D is about 1.1×10^{-9} M or less.

[0320] In some embodiments, the affinity of an ABP provided herein for hTIGIT as indicated by K_D measured by ForteBio, as set forth in Example 6, is about 2.4×10^{-10} M. In some embodiments, the affinity of an ABP provided herein for cTIGIT as indicated by K_D measured by ForteBio, as set forth in Example 6, is about 6.2×10^{-9} M. In some embodiments, such K_D is about 6.2×10^{-9} M or less.

[0321] In some embodiments, the affinity of an ABP provided herein for hTIGIT expressed on the surface of a Jurkat cell, as indicated by K_D, described in Example 6 is about 5.1×10^{-10} M. In some embodiments, such K_D is about 5.1×10^{-10} M or less.

[0322] In some embodiments, the affinity of an ABP provided herein for cTIGIT expressed on the surface of a Jurkat cell, as indicated by K_D, described in Example 6 is about 4.0×10^{-10} M. In some embodiments, such K_D is about 4.0×10^{-10} M or less.

[0323] In some embodiments, the affinity of an ABP provided herein for mTIGIT (SEQ ID NO: 3) expressed on the surface of a Jurkat cell, as indicated by K_D, described in Example 6 is about 9.8×10^{-9} M. In some embodiments, such K_D is about 9.8×10^{-9} M or less. In some embodiments, such K_D is about 9.8×10^{-9} M or greater.

[0324] In some embodiments, the affinity of an ABP provided herein for hTIGIT expressed on the surface of a human CD8+ T cell, as indicated by K_D, described in Example 6 is about 1.3×10^{-9} M. In some embodiments, such K_D is about 1.3×10^{-9} M or less.

[0325] In some embodiments, the affinity of an ABP provided herein for cTIGIT expressed on the surface of a cynomolgus monkey CD8+ T cell, as indicated by K_D, described in Example 6 is about 2.8×10^{-9} M. In some embodiments, such K_D is about 2.8×10^{-9} M or less.

[0326] In some embodiments, the affinity of an ABP provided herein for mTIGIT expressed on the surface of a murine T regulatory cell (i.e., mTIGIT as it naturally occurs on such cells, whether or not such mTIGIT is of SEQ ID NOs: 3 or 138, but inclusive of such SEQ ID NOs), as indicated by K_D, described in Example 6 is about 2.5×10^{-8} M. In some embodiments, such K_D is about 2.5×10^{-8} M or less.

[0327] In some embodiments, the ABPs provided herein specifically bind to hTIGIT (SEQ ID NO:1) with a K_D of X and to cTIGIT (SEQ ID NO:2) or mTIGIT (SEQ ID NO:3 or 138) with a K_D of $\leq 10X$. In some embodiments, the ABPs provided herein specifically bind to hTIGIT (SEQ ID NO:1) with a K_D of X and to cTIGIT (SEQ ID NO:2) or mTIGIT (SEQ ID NO:3 or 138) with a K_D of $\leq 5X$. In some embodiments, the ABPs provided herein specifically bind to hTIGIT (SEQ ID NO:1) with a K_D of X and to cTIGIT (SEQ ID NO:2) or mTIGIT (SEQ ID NO:3 or 138) with a K_D of $\leq 2X$. In some aspects, X is any K_D described in this disclosure. In some aspects, X is 0.01 nM, 0.1 nM, 1 nM, 10 nM, 20 nM, 50 nM, or 100 nM.

[0328] In some embodiments, the ratio of $K_{D(hTIGIT)}$: $K_{D(cTIGIT)}$ for an ABP provided herein, as measured by ForteBio as set forth in Example 4, is selected from about 1.98×10^{-1}, about 2.61×10^{-1}, about 3.03×10^{-1}, about 3.58×10^{-1}, about 6.62×10^{-3}, about 1.98×10^{-1}, about 5.37×10^{-3}, about 3.90×10^{-3}, about 6.22×10^{-3}, about 2.91×10^{-1}, about 4.14×10^{-1}, about 6.67×10^{-1}, about 2.18×10^{-1}, about 1.78×10^{-1}, about 1.21×10^{-1}, or about 3.03×10^{-1}. In some embodiments, such ratio ranges from about 3.90×10^{-3} to about 6.67×10^{-1}.

[0329] In some embodiments, the ratio of $K_{D(hTIGIT)}$: $K_{D(cTIGIT)}$ for an ABP provided herein, as measured by ForteBio as set forth in Example , is about 3.87×10^{-2}.

[0330] In some embodiments, the ratio of $K_{D(hTIGIT)}$: $K_{D(cTIGIT)}$ for an ABP provided herein, as measured by MSD-SET as set forth in Example 4, is selected from about 3.33×10^{-1}, about 2.31×10^{-1}

^{1}, about 1.09×10^{-1}, about 1.07×10^{-1}, or about 1.69×10^{-1}. In some embodiments, such ratio ranges from about 1.07×10^{-1} M to about 3.33×10^{-1} M.

[0331] In some embodiments an ABP provided herein has a k_a of at least about 10^4 $M^{-1}\times sec^{-1}$. In some embodiments the ABP has a k_a of at least about 10^5 $M^{-1}\times sec^{-1}$. In some embodiments the ABP has a k_a of at least about 10^6 $M^{-1}\times sec^{-1}$. In some embodiments the ABP has a k_a of between about 10^4 $M^{-1}\times sec^{-1}$ and about 10^5 $M^{-1}\times sec^{-1}$. In some embodiments the ABP has a k_a of between about 10^5 $M^{-1}\times sec^{-1}$ and about 10^6 $M^{-1}\times sec^{-1}$. In some embodiments, such k_a is at least about 10^5 $M^{-1}\times sec^{-1}$.

[0332] In some embodiments, an ABP provided herein has a k_a for hTIGIT, as measured by ForteBio as set forth in Example 6, selected from about 3.2×10^5 $M^{-1}\times sec^{-1}$, about 7.0×10^5 $M^{-1}\times sec^{-1}$, about 7.7×10^5 $M^{-1}\times sec^{-1}$, about 1.6×10^6 $M^{-1}\times sec^{-1}$, about 2.0×10^6 $M^{-1}\times sec^{-1}$, about 1.3×10^6 $M^{-1}\times sec^{-1}$, about 1.5×10^6 $M^{-1}\times sec^{-1}$, about 1.1×10^6 $M^{-1}\times sec^{-1}$, about 4.5×10^5 $M^{-1}\times sec^{-1}$, about 7.5×10^5 $M^{-1}\times sec^{-1}$, about 8.9×10^5 $M^{-1}\times sec^{-1}$, or about 1.4×10^6 $M^{-1}\times sec^{-1}$. In some embodiments, such k_a ranges from about 3.2×10^5 $M^{-1}\times sec^{-1}$ to about 2.0×10^6 $M^{-1}\times sec^{-1}$. In some embodiments, such k_d is about 2.0×10^6 M or less.

[0333] In some embodiments, an ABP provided herein has a k_a for hTIGIT, as measured by ForteBio as set forth in Example 6, of about 2.0×10^6 $M^{-1}\times sec^{-1}$. In some embodiments, such k_a is at least about 2.0×10^6 $M^{-1}\times sec^{-1}$.

[0334] In some embodiments, an ABP provided herein has a k_a for cTIGIT, as measured by ForteBio as set forth in Example 6, of about 7.9×10^5 $M^{-1}\times sec^{-1}$. In some embodiments, such k_a is at least about 7.9×10^5 $M^{-1}\times sec^{-1}$.

[0335] In some embodiments an ABP provided herein has a k_d of about 10^{-5} sec^{-1} or less. In some embodiments the ABP has a k_d of about 10^{-4} sec^{-1} or less. In some embodiments the ABP has a k_d of about 10^{-3} sec^{-1} or less. In some embodiments the ABP has a k_d of between about 10^{-2} sec^{-1} and about 10^{-5} sec^{-1}. In some embodiments the ABP has a k_d of between about 10^{-2} sec^{-1} and about 10^{-4} sec^{-1}. In some embodiments the ABP has a k_d of between about 10^{-3} sec^{-1} and about 10^{-5} sec^{-1}.

[0336] In some embodiments, an ABP provided herein has a k_d, for hTIGIT, as measured by ForteBio as set forth in Example 6, selected from about 2.3×10^{-4} sec^{-1}, about 6.3×10^{-5} sec^{-1}, about 1.4×10^{-4} sec^{-1}, about 8.5×10^{-4} sec^{-1}, about 3.8×10^{-4} sec^{-1}, about 3.5×10^{-4} sec^{-1}, about 2.4×10^{-4} sec^{-1}, about 6.6×10^{-4} sec^{-1}, about 5.9×10^{-4} sec^{-1}, or about 5.0×10^{-4} sec^{-1}. In some embodiments, such k_d ranges from about 6.3×10^{-5} sec^{-1} to about 8.5×10^{-4} sec^{-1}. In some embodiments, such k_d is less than about 8.5×10^{-4} sec^{-1}.

[0337] In some embodiments, an ABP provided herein has a k_d for hTIGIT, as measured by ForteBio as set forth in Example 6, of about 3.8×10^{-4} sec^{-1}. In some embodiments, such k_d is less than about 3.8×10^{-4} sec^{-1}.

[0338] In some embodiments, an ABP provided herein has a k_d for cTIGIT, as measured by ForteBio

as set forth in Example 6, of about 4.6×10^{-3} sec^{-1}. In some embodiments, such k_d is less than about 4.6×10^{-3} sec^{-1}.

[0339] In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 3.2×10^5 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 2.3×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 7.1×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 7.0×10^5 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 6.3×10^{-5} sec^{-1}, and a K_D for hTIGIT of about 8.1×10^{-11} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 7.7×10^5 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 1.4×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 1.9×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 1.6×10^6 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 8.5×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 5.6×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 2.0×10^6 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 3.8×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 2.4×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 1.3×10^6 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 3.5×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 2.8×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 1.5×10^6 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 2.4×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 1.6×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 1.1×10^6 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 6.6×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 5.8×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 4.5×10^5 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 3.5×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 1.1×10^{-9} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 7.5×10^5 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 5.9×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 8.1×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 8.9×10^5 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 3.8×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 4.6×10^{-10} M. In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 1.4×10^6 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 5.0×10^{-4} sec^{-1}, and a K_D for hTIGIT of about 3.6×10^{-10} M. In some embodiments, such k_a, k_d and K_D are determined according to the methods provided in Example 6.

[0340] In some embodiments, an ABP provided herein has a k_a for hTIGIT of about 2.0×10^6 $M^{-1} \times sec^{-1}$, a k_d for hTIGIT of about 3.8×10^{-4} sec^{-1}, a K_D for hTIGIT of about 2.4×10^{-10} M, a k_a for cTIGIT of about 7.9×10^5 $M^{-1} \times sec^{-1}$, a k_d for cTIGIT of about 4.6×10^{-3} sec^{-1}, a K_D for cTIGIT of about 6.2×10^{-9} M, and a K_D for mTIGIT (SEQ ID NO: 3) of greater than about 7.0×10^{-7} M. In some embodiments, such k_a, k_d and K_D are determined according to the methods provided in Example 6.

[0341] In some embodiments, K_D, k_a, and k_d are determined using surface plasmon resonance (SPR). In some aspects, the SPR analysis utilizes a BIACORE® instrument. In some aspects, the antigen is immobilized on a carboxymethylated dextran biosensor chip (CM4 or CM5) and contacted with an ABP provided herein. Association and dissociation rate constants may be calculated using the

BIAevaluation® software and a one-to-one Langmuir binding model. In some aspects, the assay is performed at 25°C. In some aspects, the assay is performed at 37°C.

[0342] In some embodiments, K_D, k_a, and k_d are determined using biolayer interferometry (BLI). Any suitable BLI method may be used. In some aspects, the BLI analysis utilizes a FORTEBIO® instrument. In some aspects, an anti-human IgG Fc capture (AHC) biosensor is used to capture ABPs onto the surface of a sensor. Subsequently, association of the ABP and antigen is monitored by contacting the immobilized ABP with different concentrations of TIGIT. Dissociation of the antigen and ABP is then measured in a buffer without TIGIT. Association and dissociation rate constants are calculated using the kinetic modules of the FORTEBIO® Analysis Software. In some aspects, the assay is performed at 30°C.

[0343] In other embodiments, K_D may be determined by a radiolabeled antigen-binding assay, as described in Chen et al. *J. Mol. Biol.*, 1999, 293:865-881, incorporated by reference in its entirety.

[0344] In other embodiments, K_D may be determined by using MSD-SET, as described in Example 4.

[0345] In some embodiments, an ABP provided herein has an EC_{50}, as measured by IL-2 production in a human TIGIT Jurkat co-culture assay as described in Example 7, of about 0.22 nM, about 0.31 nM, about 0.33 nM, about 0.34 nM, about 0.25 nM, about 0.24 nM, about 0.11 nM, about 0.06 nM, about 0.14 nM, about 0.16 nM, about 1.40 nM, about 0.71 nM, about 0.21 nM, about 1.11 nM, about 0.13 nM, about 0.20 nM, about 0.68 nM, or about 0.61 nM. In some embodiments, such EC_{50} ranges from about 0.06 nM to about 1.40 nM. In some embodiments, such EC_{50} is about 1.40 nM or less.

[0346] In some embodiments, an ABP provided herein has an EC_{50}, as measured by IL-2 production in a cynomolgus monkey TIGIT Jurkat co-culture assay as described in Example 7, of about 2.87 nM. In some embodiments, such EC_{50} is about 2.87 nM or less. In some embodiments, the ratio of $EC_{50(cTIGIT)}$: $EC_{50(hTIGIT)}$ in such assay ranges from about 2.05 to about 47.8.

[0347] In some embodiments, an ABP provided herein has an EC_{10}, as measured by TNF production in PBMCs isolated from a human donor and treated as described in Example 9, in a range of about 5.02 nM to about 18.86 nM. In some embodiments, such EC_{10} is about 18.86 nM or less.

[0348] In some embodiments, an ABP provided herein has an EC_{50}, as measured by TNF production in PBMCs isolated from a human donor and treated as described in Example 9, in a range of about 12.60 nM to about 20.60 nM. In some embodiments, such EC_{50} is about 20.60 nM or less.

[0349] In some embodiments, an ABP provided herein has an EC_{90}, as measured by TNF production in PBMCs isolated from a human donor and treated as described in Example 9, in a range of about 22.49 nM to about 31.59 nM. In some embodiments, such EC_{90} is about 31.59 nM or less.

[0350] In some embodiments, an ABP provided herein has an EC_{10} in a range of about 5.02 nM to about 18.86 nM, an EC_{50} in a range of about 12.60 nM to about 20.60 nM, and EC_{90} in a range of about 22.49 nM to about 31.59 nM, in each cases as measured by TNF production in PBMCs isolated from a human donor and treated as described in Example 9.

[0351] In some embodiments, an ABP provided herein has an EC_{10} of about 11.94 nM or less, an EC_{50} of about 16.60 nM or less, and EC_{90} of about 27.04 nM or less, in each cases as measured by TNF production in PBMCs isolated from a human donor and treated as described in Example 9.

[0352] In some embodiments, an ABP provided herein has an EC_{10} of about 18.86 nM or less, an EC_{50} of about 20.06 nM or less, and EC_{90} of about 31.59 nM or less, in each cases as measured by TNF production in PBMCs isolated from a human donor and treated as described in Example 9.

[0353] In some embodiments, an ABP provided herein has an EC_{10} of about 5.02 nM or less, an EC_{50} of about 12.60 nM or less, and EC_{90} of about 22.49 nM or less, in each cases as measured by TNF production in PBMCs isolated from a human donor and treated as described in Example 9.

[0354] In some embodiments, an ABP provided herein has an EC_{10}, as measured by IFN-γ production in CD4+ T cells isolated from a human donor and treated as described in Example 9, in a range of about 0.37 nM to about 1.05 nM. In some embodiments, such EC_{10} is about 1.05 nM or less.

[0355] In some embodiments, an ABP provided herein has an EC_{50}, as measured by IFN-γ production in CD4+ T cells isolated from a human donor and treated as described in Example 9, in a range of about 0.94 nM to about 1.12 nM. In some embodiments, such EC_{50} is about 1.12 nM or less.

[0356] In some embodiments, an ABP provided herein has an EC_{90}, as measured by IFN-γ production in CD4+ T cells isolated from a human donor and treated as described in Example 9, in a range of about 1.04 nM to about 2.72 nM. In some embodiments, such EC_{90} is about 2.72 nM or less.

[0357] In some embodiments, an ABP provided herein has an EC_{10} in a range of about 0.37 nM to about 1.05 nM, an EC_{50} in a range of about 0.94 nM to about 1.12 nM, and EC_{90} in a range of about 1.04 nM to about 2.72 nM, in each cases as measured by IFN-γ production in PBMCs isolated from a human donor and treated as described in Example 9.

[0358] In some embodiments, an ABP provided herein has an EC_{10} of about 0.37 nM or less, an EC_{50} of about 1.00 nM or less, and EC_{90} of about 2.72 nM or less, in each cases as measured by IFN-γ production in PBMCs isolated from a human donor and treated as described in Example 9.

[0359] In some embodiments, an ABP provided herein has an EC_{10} of about 0.85 nM or less, an EC_{50} of about 0.94 nM or less, and EC_{90} of about 1.04 nM or less, in each cases as measured by IFN-γ production in PBMCs isolated from a human donor and treated as described in Example 9.

[0360] In some embodiments, an ABP provided herein has an EC_{10} of about 1.05 nM or less, an EC_{50} of about 1.12 nM or less, and EC_{90} of about 1.19 nM or less, in each cases as measured by IFN-γ production in PBMCs isolated from a human donor and treated as described in Example 9.

[0361] In some embodiments, an ABP provided herein has an EC_{10} of about 0.75 nM or less, an EC_{50} of about 1.02 nM or less, and EC_{90} of about 1.65 nM or less, in each cases as measured by IFN-γ production in PBMCs isolated from a human donor and treated as described in Example 9.

[0362] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 5.24×10^{-10} M (as determined by ForteBio), cTIGIT with a K_D of about 2.64×10^{-9} M (as determined by

ForteBio), hTIGIT with a K_D of about 5.40×10^{-11} M (as determined by MSD-SET), and cTIGIT with a K_D of about 3.20×10^{-10} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0363] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 4.57×10^{-10} M (as determined by ForteBio), cTIGIT with a K_D of about 1.57×10^{-9} M (as determined by ForteBio), hTIGIT with a K_D of about 2.50×10^{-11} M (as determined by MSD-SET), and cTIGIT with a K_D of about 2.30×10^{-10} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0364] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 3.32×10^{-10} M (as determined by ForteBio), cTIGIT with a K_D of about 8.02×10^{-10} M (as determined by ForteBio), hTIGIT with a K_D of about 8.10×10^{-12} M (as determined by MSD-SET), and cTIGIT with a K_D of about 3.50×10^{-1} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0365] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 2.46×10^{-10} M (as determined by ForteBio), cTIGIT with a K_D of about 3.69×10^{-10} M (as determined by ForteBio), hTIGIT with a K_D of about 5.00×10^{-12} M (as determined by MSD-SET), and cTIGIT with a K_D of about 1.50×10^{-11} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0366] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 1.96×10^{-10} M (as determined by ForteBio), cTIGIT with a K_D of about 8.98×10^{-10} M (as determined by ForteBio), hTIGIT with a K_D of about 4.90×10^{-12} M (as determined by MSD-SET), and cTIGIT with a K_D of about 4.60×10^{-11} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0367] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 3.11×10^{-9} M (as determined by ForteBio) and cTIGIT with a K_D of about 1.75×10^{-8} M (as determined by ForteBio), in each case determined according to the methods provided in Example 4.

[0368] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 2.54×10^{-9} M, as determined by ForteBio according to the methods provided in Example 4.

[0369] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 3.13×10^{-9} M (as determined by ForteBio) and cTIGIT with a K_D of about 2.58×10^{-8} M (as determined by ForteBio), in each case determined according to the methods provided in Example 4.

[0370] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 2.83×10^{-9} M (as determined by ForteBio) and cTIGIT with a K_D of about 9.35×10^{-9} M (as determined by ForteBio), in each case determined according to the methods provided in Example 4.

[0371] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 1.71×10^{-9}

M (as determined by ForteBio), cTIGIT with a K_D of about 6.55×10^{-9} M (as determined by ForteBio), and hTIGIT with a K_D of about 1.10×10^{-10} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0372] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 2.47×10^{-9} M (as determined by ForteBio), cTIGIT with a K_D of about 8.14×10^{-9} M (as determined by ForteBio), and hTIGIT with a K_D of about 1.50×10^{-10} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0373] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 2.35×10^{-9} M (as determined by ForteBio), cTIGIT with a K_D of about 6.57×10^{-9} M (as determined by ForteBio), and hTIGIT with a K_D of about 5.60×10^{-11} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0374] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 1.44×10^{-9} M (as determined by ForteBio) and hTIGIT with a K_D of about 4.00×10^{-10} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0375] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 1.23×10^{-9} M (as determined by ForteBio) and hTIGIT with a K_D of about 3.80×10^{-10} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0376] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 5.26×10^{-10} M (as determined by ForteBio), cTIGIT with a K_D of about 7.94×10^{-8} M (as determined by ForteBio), and hTIGIT with a K_D of about 2.10×10^{-10} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0377] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 3.78×10^{-10} M (as determined by ForteBio), cTIGIT with a K_D of about 7.04×10^{-8} M (as determined by ForteBio), and hTIGIT with a K_D of about 7.00×10^{-11} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0378] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 4.29×10^{-10} M (as determined by ForteBio), cTIGIT with a K_D of about 1.10×10^{-7} M (as determined by ForteBio), and hTIGIT with a K_D of about 4.10×10^{-11} M (as determined by MSD-SET), in each case determined according to the methods provided in Example 4.

[0379] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 4.48×10^{-10} M (as determined by ForteBio) and cTIGIT with a K_D of about 7.20×10^{-8} M (as determined by ForteBio), in each case determined according to the methods provided in Example 4.

[0380] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 3.00×10^{-11} M, as determined by MSD-SET according to the methods provided in Example 4.

[0381] In some embodiments, an ABP provided herein binds hTIGIT with a K_D of about 8.00×10^{-11}

M, as determined by MSD-SET according to the methods provided in Example 4.

[0382] In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.2 nM, about 2.3 nM, about 1.6 nM, about 1.9 nM, about 1.7 nM, about 3.2 nM, about 2.6 nM, about 2.9 nM, about 3.3 nM, about 2 nM, about 2.2 nM, about 2.1 nM, about 1.8 nM, about 6.4 nM, or about 1 nM. In some embodiments, such IC_{50} ranges from about 1 nM to about 6.4 nM. In some embodiments, such IC_{50} is about 6.4 nM or less. In some embodiments, such IC_{50} is determined as described in Example 5.

[0383] In some embodiments, an ABP provided herein inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.4 nM, about 1.3 nM, about 1.2 nM, about 1.6 nM, about 2 nM, about 1.2 nM, about 1.1 nM, about 1 nM, about 1.8 nM, about 1.9 nM, about 2 nM, or about 0.8 nM. In some embodiments, such IC_{50} ranges from about 0.8 nM to about 2 nM. In some embodiments, such IC_{50} is about 2 nM or less. In some embodiments, such IC_{50} is determined as described in Example 5.

[0384] In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.2 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.4 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.3 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.3 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 1.6 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.2 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 1.9 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.6 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 1.7 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.4 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 3.2 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.4 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.6 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 2 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.9 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.2 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 1.9 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.1 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 3.3 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.2 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 1.7 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.2 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.1 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.8 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.6 nM and inhibits

binding of PVRL2 to TIGIT with an IC_{50} of about 1.6 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.2 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.1 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.1 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.3 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.6 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.9 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 1.8 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.9 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 6.4 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 2 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 2.3 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 1.9 nM. In some embodiments, an ABP provided herein inhibits binding of PVR to TIGIT with an IC_{50} of about 1 nM and inhibits binding of PVRL2 to TIGIT with an IC_{50} of about 0.8 nM. In some embodiments, such IC_{50} is about 2 nM or less. In some embodiments, such IC_{50} is determined as described in Example 5.

2.6.1. Glycosylation Variants

[0385] In certain embodiments, an ABP provided herein may be altered to increase, decrease or eliminate the extent to which it is glycosylated. Glycosylation of polypeptides is typically either "N-linked" or "O-linked."

[0386] "N-linked" glycosylation refers to the attachment of a carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site.

[0387] "O-linked" glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[0388] Addition or deletion of N-linked glycosylation sites to or from an ABP provided herein may be accomplished by altering the amino acid sequence such that one or more of the above-described tripeptide sequences is created or removed. Addition or deletion of O-linked glycosylation sites may be accomplished by addition, deletion, or substitution of one or more serine or threonine residues in or to (as the case may be) the sequence of an ABP.

[0389] In some embodiments, an ABP provided herein comprises a glycosylation motif that is different from a naturally occurring ABP. Any suitable naturally occurring glycosylation motif can be modified in the ABPs provided herein. The structural and glycosylation properties of immunoglobulins, for example, are known in the art and summarized, for example, in Schroeder and

Cavacini, *J. Allergy Clin. Immunol.*, 2010, 125:S41-52, incorporated by reference in its entirety.

[0390] In some embodiments, an ABP provided herein comprises an IgG1 Fc region with modification to the oligosaccharide attached to asparagine 297 (Asn 297). Naturally occurring IgG1 antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn 297 of the C_{H2} domain of the Fc region. *See* Wright et al., *TIBTECH*, 1997, 15:26-32, incorporated by reference in its entirety. The oligosaccharide attached to Asn 297 may include various carbohydrates such as mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure.

[0391] In some embodiments, the oligosaccharide attached to Asn 297 is modified to create ABPs having altered ADCC. In some embodiments, the oligosaccharide is altered to improve ADCC. In some embodiments, the oligosaccharide is altered to reduce ADCC.

[0392] In some aspects, an ABP provided herein comprises an IgG1 domain with reduced fucose content at position Asn 297 compared to a naturally occurring IgG1 domain. Such Fc domains are known to have improved ADCC. *See* Shields et al., *J. Biol. Chem.*, 2002, 277:26733-26740, incorporated by reference in its entirety. In some aspects, such ABPs do not comprise any fucose at position Asn 297. The amount of fucose may be determined using any suitable method, for example as described in WO 2008/077546, incorporated by reference in its entirety.

[0393] In some embodiments, an ABP provided herein comprises a bisected oligosaccharide, such as a biantennary oligosaccharide attached to the Fc region of the ABP that is bisected by GlcNAc. Such ABP variants may have reduced fucosylation and/or improved ADCC function. Examples of such ABP variants are described, for example, in WO 2003/011878; U.S. Pat. No. 6,602,684; and U.S. Pat. Pub. No. 2005/0123546; each of which is incorporated by reference in its entirety.

[0394] Other illustrative glycosylation variants which may be incorporated into the ABPs provided herein are described, for example, in U.S. Pat. Pub. Nos. 2003/0157108, 2004/0093621, 2003/0157108, 2003/0115614, 2002/0164328, 2004/0093621, 2004/0132140, 2004/0110704, 2004/0110282, 2004/0109865; International Pat. Pub. Nos. 2000/61739, 2001/29246, 2003/085119, 2003/084570, 2005/035586, 2005/035778; 2005/053742, 2002/031140; Okazaki et al., *J. Mol. Biol.*, 2004, 336:1239-1249; and Yamane-Ohnuki et al., *Biotech. Bioeng.*, 2004, 87: 614-622; each of which is incorporated by reference in its entirety.

[0395] In some embodiments, an ABP provided herein comprises an Fc region with at least one galactose residue in the oligosaccharide attached to the Fc region. Such ABP variants may have improved CDC function. Examples of such ABP variants are described, for example, in WO 1997/30087; WO 1998/58964; and WO 1999/22764; each of which his incorporated by reference in its entirety.

[0396] Examples of cell lines capable of producing defucosylated ABPs include Lec13 CHO cells, which are deficient in protein fucosylation (*see* Ripka et al., *Arch. Biochem. Biophys.*, 1986, 249:533-

545; U.S. Pat. Pub. No. 2003/0157108; WO 2004/056312; each of which is incorporated by reference in its entirety), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene or FUT8 knockout CHO cells (*see* Yamane-Ohnuki et al., *Biotech. Bioeng.*, 2004, 87: 614-622; Kanda et al., *Biotechnol. Bioeng.*, 2006, 94:680-688; and WO 2003/085107; each of which is incorporated by reference in its entirety).

[0397] In some embodiments, an ABP provided herein is an aglycosylated ABP. An aglycosylated ABP can be produced using any method known in the art or described herein. In some aspects, an aglycosylated ABP is produced by modifying the ABP to remove all glycosylation sites. In some aspects, the glycosylation sites are removed only from the Fc region of the ABP. In some aspects, an aglycosylated ABP is produced by expressing the ABP in an organism that is not capable of glycosylation, such as *E. coli*, or by expressing the ABP in a cell-free reaction mixture.

[0398] In some embodiments, an ABP provided herein has a constant region with reduced effector function compared to a native IgG1 antibody. In some embodiments, the affinity of a constant region of an Fc region of an ABP provided herein for Fc receptor is less than the affinity of a native IgG1 constant region for such Fc receptor.

2.7. Fc Region Amino Acid Sequence Variants

[0399] In certain embodiments, an ABP provided herein comprises an Fc region with one or more amino acid substitutions, insertions, or deletions in comparison to a naturally occurring Fc region. In some aspects, such substitutions, insertions, or deletions yield ABPs with altered stability, glycosylation, or other characteristics. In some aspects, such substitutions, insertions, or deletions yield aglycosylated ABPs.

[0400] In some aspects, the Fc region of an ABP provided herein is modified to yield an ABP with altered affinity for an Fc receptor, or an ABP that is more immunologically inert. In some embodiments, the ABP variants provided herein possess some, but not all, effector functions. Such ABPs may be useful, for example, when the half-life of the ABP is important *in vivo*, but when certain effector functions (e.g., complement activation and ADCC) are unnecessary or deleterious.

[0401] In some embodiments, the Fc region of an ABP provided herein is a human IgG4 Fc region comprising one or more of the hinge stabilizing mutations S228P and L235E. *See* Aalberse et al., *Immunology*, 2002, 105:9-19, incorporated by reference in its entirety. In some embodiments, the IgG4 Fc region comprises one or more of the following mutations: E233P, F234V, and L235A. *See* Armour et al., *Mol. Immunol.*, 2003, 40:585-593, incorporated by reference in its entirety. In some embodiments, the IgG4 Fc region comprises a deletion at position G236.

[0402] In some embodiments, the Fc region of an ABP provided herein is a human IgG1 Fc region comprising one or more mutations to reduce Fc receptor binding. In some aspects, the one or more mutations are in residues selected from S228 (e.g., S228A), L234 (e.g., L234A), L235 (e.g., L235A), D265 (e.g., D265A), and N297 (e.g., N297A). In some aspects, the ABP comprises a PVA236

mutation. PVA236 means that the amino acid sequence ELLG, from amino acid position 233 to 236 of IgG1 or EFLG of IgG4, is replaced by PVA. *See* U.S. Pat. No. 9,150,641, incorporated by reference in its entirety.

[0403] In some embodiments, the Fc region of an ABP provided herein is modified as described in Armour et al., *Eur. J. Immunol.*, 1999, 29:2613-2624; WO 1999/058572; and/or U.K. Pat. App. No. 98099518; each of which is incorporated by reference in its entirety.

[0404] In some embodiments, the Fc region of an ABP provided herein is a human IgG2 Fc region comprising one or more of mutations A330S and P331S.

[0405] In some embodiments, the Fc region of an ABP provided herein has an amino acid substitution at one or more positions selected from 238, 265, 269, 270, 297, 327 and 329. *See* U.S. Pat. No. 6,737,056, incorporated by reference in its entirety. Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 with alanine. *See* U.S. Pat. No. 7,332,581, incorporated by reference in its entirety. In some embodiments, the ABP comprises an alanine at amino acid position 265. In some embodiments, the ABP comprises an alanine at amino acid position 297.

[0406] In certain embodiments, an ABP provided herein comprises an Fc region with one or more amino acid substitutions which improve ADCC, such as a substitution at one or more of positions 298, 333, and 334 of the Fc region. In some embodiments, an ABP provided herein comprises an Fc region with one or more amino acid substitutions at positions 239, 332, and 330, as described in Lazar et al., *Proc. Natl. Acad. Sci. USA*, 2006,103:4005-4010, incorporated by reference in its entirety.

[0407] In some embodiments, an ABP provided herein comprises one or more alterations that improves or diminishes C1q binding and/or CDC. *See* U.S. Pat. No. 6,194,551; WO 99/51642; and Idusogie et al., *J. Immunol.*, 2000, 164:4178-4184; each of which is incorporated by reference in its entirety.

[0408] In some embodiments, an ABP provided herein comprises one or more alterations to increase half-life. ABPs with increased half-lives and improved binding to the neonatal Fc receptor (FcRn) are described, for example, in Hinton et al., *J. Immunol.*, 2006, 176:346-356; and U.S. Pat. Pub. No. 2005/0014934; each of which is incorporated by reference in its entirety. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 250, 256, 265, 272, 286, 303, 305, 307, 311, 312, 314, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424, 428, and 434 of an IgG.

[0409] In some embodiments, an ABP provided herein comprises one or more Fc region variants as described in U.S. Pat. Nos. 7,371,826 5,648,260, and 5,624,821; Duncan and Winter, *Nature*, 1988, 322:738-740; and WO 94/29351; each of which is incorporated by reference in its entirety.

2.8. Pyroglutamate

[0410] As is known in the art, both glutamate (E) and glutamine (Q) at the N-termini of recombinant

proteins can cyclize spontaneously to form pyroglutamate (pE) *in vitro* and *in vivo*. *See* Liu et al., *J. Biol. Chem.*, 2011, 286:11211-11217, incorporated by reference in its entirety.

[0411] In some embodiments, provided herein are ABPs comprising a polypeptide sequence having a pE residue at the N-terminal position. In some embodiments, provided herein are ABPs comprising a polypeptide sequence in which the N-terminal residue has been converted from Q to pE. In some embodiments, provided herein are ABPs comprising a polypeptide sequence in which the N-terminal residue has been converted from E to pE.

[0412] In some embodiments, provided herein are ABPs comprising V_H sequences having a pE residue at the N-terminal position. In some embodiments, provided herein are ABPs comprising a V_H sequence in which the N-terminal residue has been converted from Q to pE. In some embodiments, provided herein is an ABP comprising a V_H sequence selected from SEQ ID NOs: 4-24, wherein the N-terminal Q residue has been converted to pE. In some embodiments, provided herein is a composition comprising an ABP, wherein the ABP comprises a V_H selected from SEQ ID NOs: 4-24, in which at least about 20%, at least about 40%, at least about 60%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the N-terminal residues of such V_H in such composition have been converted from Q to pE.

[0413] In some embodiments, provided herein are ABPs comprising V_L sequences having a pE residue at the N-terminal position. In some embodiments, provided herein are ABPs comprising a V_L sequence in which the N-terminal residue has been converted from E to pE. In some embodiments, provided herein is an ABP comprising a V_L sequence selected from SEQ ID NOs: 25-28, wherein the N-terminal E residue has been converted to pE. In some embodiments, provided herein is a composition comprising an ABP, wherein the ABP comprises a V_L selected from SEQ ID NOs: 25-28, in which at least about 20%, at least about 40%, at least about 60%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the N-terminal residues of such V_L in such composition have been converted from E to pE.

[0414] In some embodiments, provided herein are ABPs comprising heavy chain sequences having a pE residue at the N-terminal position. In some embodiments, provided herein are ABPs comprising a heavy chain sequence in which the N-terminal residue has been converted from Q to pE. In some embodiments, provided herein is an ABP comprising a heavy chain sequence selected from SEQ ID NOs: 79, 80, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 121, 122, 123 or 124, wherein the N-terminal Q residue has been converted to pE. In some embodiments, provided herein is a composition comprising an ABP, wherein the ABP comprises a heavy chain selected from SEQ ID NOs: 79, 80, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 121, 122, 123 or 124, in which at least about 20%, at least about 40%, at least about 60%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the N-terminal residues of such heavy chain in such

composition have been converted from Q to pE.

[0415] In some embodiments, provided herein are ABPs comprising light chain sequences having a pE residue at the N-terminal position. In some embodiments, provided herein are ABPs comprising a light chain sequence in which the N-terminal residue has been converted from E to pE. In some embodiments, provided herein is an ABP comprising a light chain sequence selected from SEQ ID NOs: 81, 92, 107 or 120, wherein the N-terminal E residue has been converted to pE. In some embodiments, provided herein is a composition comprising an ABP, wherein the ABP comprises a light chain selected from SEQ ID NOs: 81, 92, 107 or 120, in which at least about 20%, at least about 40%, at least about 60%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the N-terminal residues of such light chain in such composition have been converted from E to pE.

2.9. Cysteine Engineered Antigen-Binding Protein Variants

[0416] In certain embodiments, provided herein are cysteine engineered ABPs, also known as "thioMAbs," in which one or more residues of the ABP are substituted with cysteine residues. In particular embodiments, the substituted residues occur at solvent accessible sites of the ABP. By substituting such residues with cysteine, reactive thiol groups are introduced at solvent accessible sites of the ABP and may be used to conjugate the ABP to other moieties, such as drug moieties or linker-drug moieties, for example, to create an immunoconjugate.

[0417] In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 of the light chain; A118 of the heavy chain Fc region; and S400 of the heavy chain Fc region. Cysteine engineered ABPs may be generated as described, for example, in U.S. Pat. No. 7,521,541, which is incorporated by reference in its entirety.

2.9.1. Immunoconjugates

2.9.1.1. Antigen-Binding Protein-Polymer Conjugates

[0418] In some embodiments, an ABP provided herein is derivatized by conjugation with a polymer. Any suitable polymer may be conjugated to the ABP.

[0419] In some embodiments, the polymer is a water soluble polymer. Illustrative examples of water soluble polymers include polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), poly(n-vinyl pyrrolidone)-co-polyethylene glycol, propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. In some aspects, polyethylene glycol propionaldehyde may be useful for manufacturing purposes due to its stability in water.

[0420] The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to each ABP may vary, and if more than one polymer is attached, they may be the same polymer or different polymers. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including the particular properties or functions of the ABP to be improved and the intended use of the ABP.

2.9.1.2. Antigen-Binding Protein-Drug Conjugates

[0421] In some embodiments, the ABPs provided herein are conjugated to one or more therapeutic agents. Any suitable therapeutic agent may be conjugated to the ABP. Exemplary therapeutic agents include cytokines, chemokines, and other agents that induce a desired T cell activity, such as OX40L, 4-1BBL, TNF-alpha (as used herein, "TNF"), IL-2, IL-15 fusion, CXCL9, CXCL10, IL-10 trap, IL-27 trap, and IL-35 trap. Cytokine traps and their use are known in the art and described, for example, in Economides et al., *Nature Medicine*, 2003, 9:47-52, incorporated by reference in its entirety.

3. Methods of Making TIGIT Antigen-Binding Proteins

3.1. TIGIT Antigen Preparation

[0422] The TIGIT antigen used for isolation of the ABPs provided herein may be intact TIGIT or a fragment of TIGIT. The TIGIT antigen may be, for example, in the form of an isolated protein or a protein expressed on the surface of a cell.

[0423] In some embodiments, the TIGIT antigen is a non-naturally occurring variant of TIGIT, such as a TIGIT protein having an amino acid sequence or post-translational modification that does not occur in nature.

[0424] In some embodiments, the TIGIT antigen is truncated by removal of, for example, intracellular or membrane-spanning sequences, or signal sequences. In some embodiments, the TIGIT antigen is fused at its C-terminus to a human IgG1 Fc domain or a polyhistidine tag.

3.2. Methods of Making Monoclonal Antibodies

[0425] Monoclonal antibodies may be obtained, for example, using the hybridoma method first described by Kohler et al., *Nature*, 1975, 256:495-497 (incorporated by reference in its entirety), and/or by recombinant DNA methods (*see e.g.*, U.S. Patent No. 4,816,567, incorporated by reference in its entirety). Monoclonal antibodies may also be obtained, for example, using phage or yeast-based libraries. *See e.g.*, U.S. Patent Nos. 8,258,082 and 8,691,730, each of which is incorporated by reference in its entirety.

[0426] In the hybridoma method, a mouse or other appropriate host animal is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes are then fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form

a hybridoma cell. *See* Goding J.W., *Monoclonal Antibodies: Principles and Practice* 3rd ed. (1986) Academic Press, San Diego, CA, incorporated by reference in its entirety.

[0427] The hybridoma cells are seeded and grown in a suitable culture medium that contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[0428] Useful myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive media conditions, such as the presence or absence of HAT medium. Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOP-21 and MC-11 mouse tumors (available from the Salk Institute Cell Distribution Center, San Diego, CA), and SP-2 or X63-Ag8-653 cells (available from the American Type Culture Collection, Rockville, MD). Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. *See e.g.*, Kozbor, *J. Immunol.*, 1984, 133:3001, incorporated by reference in its entirety.

[0429] After the identification of hybridoma cells that produce antibodies of the desired specificity, affinity, and/or biological activity, selected clones may be subcloned by limiting dilution procedures and grown by standard methods. *See* Goding, *supra.* Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

[0430] DNA encoding the monoclonal antibodies may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). Thus, the hybridoma cells can serve as a useful source of DNA encoding antibodies with the desired properties. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as bacteria (e.g., *E. coli*), yeast (e.g., *Saccharomyces* or *Pichia sp.*), COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody, to produce the monoclonal antibodies.

3.3. Methods of Making Chimeric Antibodies

[0431] Illustrative methods of making chimeric antibodies are described, for example, in U.S. Pat. No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA*, 1984, 81:6851-6855; each of which is incorporated by reference in its entirety. In some embodiments, a chimeric antibody is made by using recombinant techniques to combine a non-human variable region (e.g., a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) with a human constant region.

3.4. Methods of Making Humanized Antibodies

[0432] Humanized antibodies may be generated by replacing most, or all, of the structural portions of a non-human monoclonal antibody with corresponding human antibody sequences. Consequently, a hybrid molecule is generated in which only the antigen-specific variable, or CDR, is composed of non-human sequence. Methods to obtain humanized antibodies include those described in, for example, Winter and Milstein, *Nature*, 1991, 349:293-299; Rader et al., *Proc. Nat. Acad. Sci. U.S.A.*, 1998, 95:8910-8915; Steinberger et al., *J. Biol. Chem.*, 2000, 275:36073-36078; Queen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1989, 86:10029-10033; and U.S. Patent Nos. 5,585,089, 5,693,761, 5,693,762, and 6,180,370; each of which is incorporated by reference in its entirety.

3.5. Methods of making Human Antibodies

[0433] Human antibodies can be generated by a variety of techniques known in the art, for example by using transgenic animals (e.g., humanized mice). *See, e.g.*, Jakobovits et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1993, 90:2551; Jakobovits et al., *Nature*, 1993, 362:255-258; Bruggermann et al., *Year in Immuno.*, 1993, 7:33; and U.S. Patent Nos. 5,591,669, 5,589,369 and 5,545,807; each of which is incorporated by reference in its entirety. Human antibodies can also be derived from phage-display libraries (*see e.g.*, Hoogenboom et al., *J. Mol. Biol.*, 1991, 227:381-388; Marks et al., *J. Mol. Biol.*, 1991, 222:581-597; and U.S. Pat. Nos. 5,565,332 and 5,573,905; each of which is incorporated by reference in its entirety). Human antibodies may also be generated by *in vitro* activated B cells (*see e.g.*, U.S. Patent. Nos. 5,567,610 and 5,229,275, each of which is incorporated by reference in its entirety). Human antibodies may also be derived from yeast-based libraries (*see e.g.*, U.S. Patent No. 8,691,730, incorporated by reference in its entirety).

3.6. Methods of Making Antibody Fragments

[0434] The antibody fragments provided herein may be made by any suitable method, including the illustrative methods described herein or those known in the art. Suitable methods include recombinant techniques and proteolytic digestion of whole antibodies. Illustrative methods of making antibody fragments are described, for example, in Hudson et al., *Nat. Med.*, 2003, 9:129-134, incorporated by reference in its entirety. Methods of making scFv antibodies are described, for example, in Plückthun, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); WO 93/16185; and U.S. Pat. Nos. 5,571,894 and 5,587,458; each of which is incorporated by reference in its entirety.

3.7. Methods of Making Alternative Scaffolds

[0435] The alternative scaffolds provided herein may be made by any suitable method, including the illustrative methods described herein or those known in the art. For example, methods of preparing Adnectins™ are described in Emanuel et al., *mAbs*, 2011, 3:38-48, incorporated by reference in its

entirety. Methods of preparing iMabs are described in U.S. Pat. Pub. No. 2003/0215914, incorporated by reference in its entirety. Methods of preparing Anticalins® are described in Vogt and Skerra, *Chem. Biochem.*, 2004, 5:191-199, incorporated by reference in its entirety. Methods of preparing Kunitz domains are described in Wagner et al., *Biochem. & Biophys. Res. Comm.*, 1992, 186:118-1145, incorporated by reference in its entirety. Methods of preparing thioredoxin peptide aptamers are provided in Geyer and Brent, *Meth. Enzymol.*, 2000, 328:171-208, incorporated by reference in its entirety. Methods of preparing Affibodies are provided in Fernandez, *Curr. Opinion in Biotech.*, 2004, 15:364-373, incorporated by reference in its entirety. Methods of preparing DARPins are provided in Zahnd et al., *J. Mol. Biol.*, 2007, 369:1015-1028, incorporated by reference in its entirety. Methods of preparing Affilins are provided in Ebersbach et al., *J. Mol. Biol.*, 2007, 372:172-185, incorporated by reference in its entirety. Methods of preparing Tetranectins are provided in Graversen et al., *J. Biol. Chem.*, 2000, 275:37390-37396, incorporated by reference in its entirety. Methods of preparing Avimers are provided in Silverman et al., *Nature Biotech.*, 2005, 23:1556-1561, incorporated by reference in its entirety. Methods of preparing Fynomers are provided in Silacci et al., *J. Biol. Chem.*, 2014, 289:14392-14398, incorporated by reference in its entirety.

[0436] Further information on alternative scaffolds is provided in Binz et al., *Nat. Biotechnol.*, 2005 23:1257-1268; and Skerra, *Current Opin. in Biotech.*, 2007 18:295-304, each of which is incorporated by reference in its entirety.

3.8. Methods of Making Multispecific ABPs

[0437] The multispecific ABPs provided herein may be made by any suitable method, including the illustrative methods described herein or those known in the art. Methods of making common light chain antibodies are described in Merchant et al., *Nature Biotechnol.*, 1998, 16:677-681, incorporated by reference in its entirety. Methods of making tetravalent bispecific antibodies are described in Coloma and Morrison, *Nature Biotechnol.*, 1997, 15:159-163, incorporated by reference in its entirety. Methods of making hybrid immunoglobulins are described in Milstein and Cuello, *Nature*, 1983, 305:537-540; and Staerz and Bevan, *Proc. Natl. Acad. Sci. USA*, 1986, 83:1453-1457; each of which is incorporated by reference in its entirety. Methods of making immunoglobulins with knobs-into-holes modification are described in U.S. Pat. No. 5,731,168, incorporated by reference in its entirety. Methods of making immunoglobulins with electrostatic modifications are provided in WO 2009/089004, incorporated by reference in its entirety. Methods of making bispecific single chain antibodies are described in Traunecker et al., *EMBO J.*, 1991, 10:3655-3659; and Gruber et al., *J. Immunol.*, 1994, 152:5368-5374; each of which is incorporated by reference in its entirety. Methods of making single-chain antibodies, whose linker length may be varied, are described in U.S. Pat. Nos. 4,946,778 and 5,132,405, each of which is incorporated by reference in its entirety. Methods of making diabodies are described in Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 1993, 90:6444-6448, incorporated by reference in its entirety. Methods of making triabodies and tetrabodies are described

in Todorovska et al., *J. Immunol. Methods*, 2001, 248:47-66, incorporated by reference in its entirety. Methods of making trispecific F(ab')3 derivatives are described in Tutt et al. *J. Immunol.*, 1991, 147:60-69, incorporated by reference in its entirety. Methods of making cross-linked antibodies are described in U.S. Patent No. 4,676,980; Brennan et al., *Science*, 1985, 229:81-83; Staerz, et al. *Nature*, 1985, 314:628-631; and EP 0453082; each of which is incorporated by reference in its entirety. Methods of making antigen-binding domains assembled by leucine zippers are described in Kostelny et al., *J. Immunol.*, 1992, 148:1547-1553, incorporated by reference in its entirety. Methods of making ABPs via the DNL approach are described in U.S. Pat. Nos. 7,521,056; 7,550,143; 7,534,866; and 7,527,787; each of which is incorporated by reference in its entirety. Methods of making hybrids of antibody and non-antibody molecules are described in WO 93/08829, incorporated by reference in its entirety, for examples of such ABPs. Methods of making DAF antibodies are described in U.S. Pat. Pub. No. 2008/0069820, incorporated by reference in its entirety. Methods of making ABPs via reduction and oxidation are described in Carlring et al., *PLoS One*, 2011, 6:e22533, incorporated by reference in its entirety. Methods of making DVD-Igs™ are described in U.S. Pat. No. 7,612,181, incorporated by reference in its entirety. Methods of making DARTs™ are described in Moore et al., *Blood*, 2011, 117:454-451, incorporated by reference in its entirety. Methods of making DuoBodies® are described in Labrijn et al., *Proc. Natl. Acad. Sci. USA*, 2013, 110:5145-5150; Gramer et al., *mAbs*, 2013, 5:962-972; and Labrijn et al., *Nature Protocols*, 2014, 9:2450-2463; each of which is incorporated by reference in its entirety. Methods of making antibodies comprising scFvs fused to the C-terminus of the C_{H3} from an IgG are described in Coloma and Morrison, *Nature Biotechnol.*, 1997, 15:159-163, incorporated by reference in its entirety. Methods of making antibodies in which a Fab molecule is attached to the constant region of an immunoglobulin are described in Miler et al., *J. Immunol.*, 2003, 170:4854-4861, incorporated by reference in its entirety. Methods of making CovX-Bodies are described in Doppalapudi et al., *Proc. Natl. Acad. Sci. USA*, 2010, 107:22611-22616, incorporated by reference in its entirety. Methods of making Fcab antibodies are described in Wozniak-Knopp et al., *Protein Eng. Des. Sel.*, 2010, 23:289-297, incorporated by reference in its entirety. Methods of making TandAb® antibodies are described in Kipriyanov et al., *J. Mol. Biol.*, 1999, 293:41-56 and Zhukovsky et al., *Blood*, 2013, 122:5116, each of which is incorporated by reference in its entirety. Methods of making tandem Fabs are described in WO 2015/103072, incorporated by reference in its entirety. Methods of making Zybodies™ are described in LaFleur et al., *mAbs*, 2013, 5:208-218, incorporated by reference in its entirety.

3.9. Methods of Making Variants

[0438] In some embodiments, an ABP provided herein is an affinity matured variant of a parent ABP, which may be generated, for example, using phage display-based affinity maturation techniques. Briefly, one or more CDR residues may be mutated and the variant ABPs, or portions thereof, displayed on phage and screened for affinity. Such alterations may be made in CDR

"hotspots," or residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (*see* Chowdhury, *Methods Mol. Biol.*, 2008, 207:179-196, incorporated by reference in its entirety), and/or residues that contact the antigen.

[0439] Any suitable method can be used to introduce variability into a polynucleotide sequence(s) encoding an ABP, including error-prone PCR, chain shuffling, and oligonucleotide-directed mutagenesis such as trinucleotide-directed mutagenesis (TRIM). In some aspects, several CDR residues (e.g., 4-6 residues at a time) are randomized. CDR residues involved in antigen binding may be specifically identified, for example, using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted for mutation.

[0440] The introduction of diversity into the variable regions and/or CDRs can be used to produce a secondary library. The secondary library is then screened to identify ABP variants with improved affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, for example, in Hoogenboom et al., *Methods in Molecular Biology*, 2001, 178:1-37, incorporated by reference in its entirety.

3.10. Vectors, Host Cells, and Recombinant Methods

[0441] Also provided are isolated nucleic acids encoding TIGIT ABPs, vectors comprising the nucleic acids, and host cells comprising the vectors and nucleic acids, as well as recombinant techniques for the production of the ABPs.

[0442] For recombinant production of an ABP, the nucleic acid(s) encoding it may be isolated and inserted into a replicable vector for further cloning (i.e., amplification of the DNA) or expression. In some aspects, the nucleic acid may be produced by homologous recombination, for example as described in U.S. Patent No. 5,204,244, incorporated by reference in its entirety.

[0443] Many different vectors are known in the art. The vector components generally include one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence, for example as described in U.S. Patent No. 5,534,615, incorporated by reference in its entirety.

[0444] Illustrative examples of suitable host cells are provided below. These host cells are not meant to be limiting, and any suitable host cell may be used to produce the ABPs provided herein.

[0445] Suitable host cells include any prokaryotic (e.g., bacterial), lower eukaryotic (e.g., yeast), or higher eukaryotic (e.g., mammalian) cells. Suitable prokaryotes include eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *Escherichia* (*E. coli*), *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella* (*S. typhimurium*), *Serratia* (*S. marcescans*), *Shigella*, *Bacilli* (*B. subtilis* and *B. licheniformis*), *Pseudomonas* (*P. aeruginosa*), and *Streptomyces*. One useful *E. coli* cloning host is *E. coli* 294, although other strains such as *E. coli* B, *E. coli* X1776, and *E. coli* W3110 are also suitable.

[0446] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are also

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

[0447] Useful mammalian host cells include COS-7 cells, HEK293 cells; baby hamster kidney (BHK) cells; Chinese hamster ovary (CHO); mouse sertoli cells; African green monkey kidney cells (VERO-76), and the like.

[0448] The host cells used to produce the TIGIT ABP of this invention may be cultured in a variety of media. Commercially available media such as, for example, Ham's F10, Minimal Essential Medium (MEM), RPMI-1640, and Dulbecco's Modified Eagle's Medium (DMEM) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., *Meth. Enz.*, 1979, 58:44; Barnes et al., *Anal. Biochem.*, 1980, 102:255; and U.S. Patent Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655, and 5,122,469; or WO 90/03430 and WO 87/00195 may be used. Each of the foregoing references is incorporated by reference in its entirety.

[0449] Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics, trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art.

[0450] The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

[0451] When using recombinant techniques, the ABP can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the ABP is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration. For example, Carter et al. (*Bio/Technology*, 1992, 10:163-167, incorporated by reference in its entirety) describes a procedure for isolating ABPs which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation.

[0452] In some embodiments, the ABP is produced in a cell-free system. In some aspects, the cell-free system is an *in vitro* transcription and translation system as described in Yin et al., *mAbs*, 2012,

4:217-225, incorporated by reference in its entirety. In some aspects, the cell-free system utilizes a cell-free extract from a eukaryotic cell or from a prokaryotic cell. In some aspects, the prokaryotic cell is *E. coli*. Cell-free expression of the ABP may be useful, for example, where the ABP accumulates in a cell as an insoluble aggregate, or where yields from periplasmic expression are low.

[0453] Where the ABP is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon® or Millipore® Pellcon® ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

[0454] The ABP composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being a particularly useful purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the ABP. Protein A can be used to purify ABPs that comprise human γ1, γ2, or γ4 heavy chains (Lindmark et al., *J. Immunol. Meth.*, 1983, 62:1-13, incorporated by reference in its entirety). Protein G is useful for all mouse isotypes and for human γ3 (Guss et al., *EMBO J.*, 1986, 5:1567-1575, incorporated by reference in its entirety).

[0455] The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the ABP comprises a C_{H3} domain, the BakerBond ABX® resin is useful for purification.

[0456] Other techniques for protein purification, such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin Sepharose®, chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available, and can be applied by one of skill in the art.

[0457] Following any preliminary purification step(s), the mixture comprising the ABP of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5 to about 4.5, generally performed at low salt concentrations (e.g., from about 0 to about 0.25 M salt).

4. Assays

[0458] A variety of assays known in the art may be used to identify and characterize the TIGIT ABPs provided herein.

4.1. Binding, Competition, and Epitope Mapping Assays

[0459] Specific antigen-binding activity of the ABPs provided herein may be evaluated by any

suitable method, including using SPR, BLI, RIA and MSD-SET, as described elsewhere in this disclosure. Additionally, antigen-binding activity may be evaluated by ELISA assays and Western blot assays.

[0460] Assays for measuring competition between two ABPs, or an ABP and another molecule (e.g., one or more ligands of TIGIT) are described elsewhere in this disclosure and, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual* ch.14, 1988, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y, incorporated by reference in its entirety.

[0461] Assays for mapping the epitopes to which the ABPs provided herein bind are described, for example, in Morris "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66, 1996, Humana Press, Totowa, N.J., incorporated by reference in its entirety. In some embodiments, the epitope is determined by peptide competition. In some embodiments, the epitope is determined by mass spectrometry. In some embodiments, the epitope is determined by crystallography.

4.2. TIGIT Antagonism Assays

[0462] In some embodiments, the ABPs provided herein are screened to identify or characterize ABPs with antagonistic activity against TIGIT. Any suitable assay may be used to identify or characterize such ABPs. In some aspects, the assay measures the amount of a cytokine secreted by an effector T cell after contacting the effector T cell with an ABP provided herein. In some aspects, the cytokine is selected from IL-2, IL-6, LT-α, TNF, GM-CSF, IFNγ, and combinations thereof. In some aspects, the cytokine is selected from sCD40L, VEGF, TGF-α, RANTES, PDGF-AB/BB, PDGF-AA, MIP-1β, MIP-1α, MDC (CCL22), MCP-3, MCP-1, IP-10, IL-17A, IL-2Rα, IL-15, IL-13, IL-12 (p70), IL-12 (p40), IL-10, IL-9, IL-8, IL-7, IL-5, IL-4, IL-3, IL-2, IL-2Rα, IL-1RA, IL-1β, IL-1α, IFNγ, IFNα2, GRO, GM-CSF, G-CSF, fractalkine, Flt-3 ligand, FGF-2, eotaxin, EGF, and combinations thereof.

[0463] In some embodiments, the effector cells are co-stimulated with an agonist of CD3, to promote the secretion of cytokines by the effector cell. In some aspects, the CD3 agonist is provided at a submaximal level.

[0464] In some aspects, such assays may measure the proliferation of an effector T cell after contacting the effector T cell with an ABP provided herein. In some aspects, proliferation of the effector T cell is measured by dilution of a dye (e.g., carboxyfluorescein diacetate succinimidyl ester; CFSE), by tritiated thymidine uptake, by luminescent cell viability assays, or by other assays known in the art.

[0465] In some aspects, such assays may measure the differentiation, cytokine production, viability (e.g., survival), proliferation, or suppressive activity of a regulatory T cell after contacting the regulatory T cell with an ABP provided herein.

[0466] In some aspects, such assays may measure the cytotoxic activity of an NK cell after contacting the NK cell with an ABP provided herein. In some aspects, the cytotoxic activity of the NK

cell is measured using a cytotoxicity assay that quantifies NK-mediated killing of target cells (e.g., a K562 cell line). *See* Jang et al., *Ann. Clin. Lab. Sci.*, 2012, 42:42-49, incorporated by reference in its entirety.

[0467] In some aspects, such assays may measure the amount of granzyme B. In some aspects, such assays may measure the amount of perforin.

4.3. Assays for Effector Functions

[0468] Effector function following treatment with the ABPs provided herein may be evaluated using a variety of *in vitro* and *in vivo* assays known in the art, including those described in Ravetch and Kinet, *Annu. Rev. Immunol.*, 1991, 9:457-492; U.S. Pat. Nos. 5,500,362, 5,821,337; Hellstrom et al., *Proc. Nat'l Acad. Sci. USA*, 1986, 83:7059-7063; Hellstrom et al., *Proc. Nat'l Acad. Sci. USA*, 1985, 82:1499-1502; Bruggemann et al., *J. Exp. Med.*, 1987, 166:1351-1361; Clynes et al., *Proc. Nat'l Acad. Sci. USA*, 1998, 95:652-656; WO 2006/029879; WO 2005/100402; Gazzano-Santoro et al., *J. Immunol. Methods*, 1996, 202:163-171; Cragg et al., *Blood*, 2003, 101:1045-1052; Cragg et al. *Blood*, 2004, 103:2738-2743; and Petkova et al., *Int'l. Immunol.*, 2006, 18:1759-1769; each of which is incorporated by reference in its entirety.

5. Pharmaceutical Compositions

[0469] The ABPs provided herein can be formulated in any appropriate pharmaceutical composition and administered by any suitable route of administration. Suitable routes of administration include, but are not limited to, the intraarterial, intradermal, intramuscular, intraperitoneal, intravenous, nasal, parenteral, pulmonary, and subcutaneous routes.

[0470] The pharmaceutical composition may comprise one or more pharmaceutical excipients. Any suitable pharmaceutical excipient may be used, and one of ordinary skill in the art is capable of selecting suitable pharmaceutical excipients. Accordingly, the pharmaceutical excipients provided below are intended to be illustrative, and not limiting. Additional pharmaceutical excipients include, for example, those described in the *Handbook of Pharmaceutical Excipients*, Rowe et al. (Eds.) 6th Ed. (2009), incorporated by reference in its entirety.

[0471] In some embodiments, the pharmaceutical composition comprises an anti-foaming agent. Any suitable anti-foaming agent may be used. In some aspects, the anti-foaming agent is selected from an alcohol, an ether, an oil, a wax, a silicone, a surfactant, and combinations thereof. In some aspects, the anti-foaming agent is selected from a mineral oil, a vegetable oil, ethylene bis stearamide, a paraffin wax, an ester wax, a fatty alcohol wax, a long chain fatty alcohol, a fatty acid soap, a fatty acid ester, a silicon glycol, a fluorosilicone, a polyethylene glycol-polypropylene glycol copolymer, polydimethylsiloxane-silicon dioxide, ether, octyl alcohol, capryl alcohol, sorbitan trioleate, ethyl alcohol, 2-ethyl-hexanol, dimethicone, oleyl alcohol, simethicone, and combinations thereof.

[0472] In some embodiments, the pharmaceutical composition comprises a cosolvent. Illustrative

examples of cosolvents include ethanol, poly(ethylene) glycol, butylene glycol, dimethylacetamide, glycerin, propylene glycol, and combinations thereof.

[0473] In some embodiments, the pharmaceutical composition comprises a buffer. Illustrative examples of buffers include acetate, borate, carbonate, lactate, malate, phosphate, citrate, hydroxide, diethanolamine, monoethanolamine, glycine, methionine, guar gum, monosodium glutamate, and combinations thereof.

[0474] In some embodiments, the pharmaceutical composition comprises a carrier or filler. Illustrative examples of carriers or fillers include lactose, maltodextrin, mannitol, sorbitol, chitosan, stearic acid, xanthan gum, guar gum, and combinations thereof.

[0475] In some embodiments, the pharmaceutical composition comprises a surfactant. Illustrative examples of surfactants include *d*-alpha tocopherol, benzalkonium chloride, benzethonium chloride, cetrimide, cetylpyridinium chloride, docusate sodium, glyceryl behenate, glyceryl monooleate, lauric acid, macrogol 15 hydroxystearate, myristyl alcohol, phospholipids, polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polyoxylglycerides, sodium lauryl sulfate, sorbitan esters, vitamin E polyethylene(glycol) succinate, and combinations thereof.

[0476] In some embodiments, the pharmaceutical composition comprises an anti-caking agent. Illustrative examples of anti-caking agents include calcium phosphate (tribasic), hydroxymethyl cellulose, hydroxypropyl cellulose, magnesium oxide, and combinations thereof.

[0477] Other excipients that may be used with the pharmaceutical compositions include, for example, albumin, antioxidants, antibacterial agents, antifungal agents, bioabsorbable polymers, chelating agents, controlled release agents, diluents, dispersing agents, dissolution enhancers, emulsifying agents, gelling agents, ointment bases, penetration enhancers, preservatives, solubilizing agents, solvents, stabilizing agents, sugars, and combinations thereof. Specific examples of each of these agents are described, for example, in the *Handbook of Pharmaceutical Excipients*, Rowe et al. (Eds.) 6th Ed. (2009), The Pharmaceutical Press, incorporated by reference in its entirety.

[0478] In some embodiments, the pharmaceutical composition comprises a solvent. In some aspects, the solvent is saline solution, such as a sterile isotonic saline solution or dextrose solution. In some aspects, the solvent is water for injection.

[0479] In some embodiments, the pharmaceutical compositions are in a particulate form, such as a microparticle or a nanoparticle. Microparticles and nanoparticles may be formed from any suitable material, such as a polymer or a lipid. In some aspects, the microparticles or nanoparticles are micelles, liposomes, or polymersomes.

[0480] Further provided herein are anhydrous pharmaceutical compositions and dosage forms comprising an ABP, since water can facilitate the degradation of some ABPs.

[0481] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active

ingredient that comprises a primary or secondary amine can be anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[0482] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

5.1. Parenteral Dosage Forms

[0483] In certain embodiments, the ABPs provided herein are formulated as parenteral dosage forms. Parenteral dosage forms can be administered to subjects by various routes including, but not limited to, subcutaneous, intravenous (including infusions and bolus injections), intramuscular, and intraarterial. Because their administration typically bypasses subjects' natural defenses against contaminants, parenteral dosage forms are typically, sterile or capable of being sterilized prior to administration to a subject. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry (e.g., lyophilized) products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[0484] Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[0485] Excipients that increase the solubility of one or more of the ABPs disclosed herein can also be incorporated into the parenteral dosage forms.

[0486] In some embodiments, the parenteral dosage form is lyophilized. Exemplary lyophilized formulations are described, for example, in U.S. Pat. Nos. 6,267,958 and 6,171,586; and WO 2006/044908; each of which is incorporated by reference in its entirety.

6. Dosage and Unit Dosage Forms

[0487] In human therapeutics, the doctor will determine the posology which he considers most appropriate according to a preventive or curative treatment and according to the age, weight, condition and other factors specific to the subject to be treated.

[0488] In certain embodiments, a composition provided herein is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and single unit dosage forms provided herein comprise a prophylactically or therapeutically effective amount of one or more prophylactic or

therapeutic ABPs.

[0489] The amount of the ABP or composition which will be effective in the prevention or treatment of a disorder or one or more symptoms thereof will vary with the nature and severity of the disease or condition, and the route by which the ABP is administered. The frequency and dosage will also vary according to factors specific for each subject depending on the specific therapy (*e.g.*, therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the subject. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0490] In certain embodiments, exemplary doses of a composition include milligram or microgram amounts of the ABP per kilogram of subject or sample weight (*e.g.*, about 10 micrograms per kilogram to about 50 milligrams per kilogram, about 100 micrograms per kilogram to about 25 milligrams per kilogram, or about 100 microgram per kilogram to about 10 milligrams per kilogram). In certain embodiment, the dosage of the ABP provided herein, based on weight of the ABP, administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is 0.1 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 10 mg/kg, or 15 mg/kg or more of a subject's body weight. It may be necessary to use dosages of the ABP outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

[0491] Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the ABPs provided herein are also encompassed by the dosage amounts and dose frequency schedules provided herein. Further, when a subject is administered multiple dosages of a composition provided herein, not all of the dosages need be the same. For example, the dosage administered to the subject may be increased to improve the prophylactic or therapeutic effect of the composition or it may be decreased to reduce one or more side effects that a particular subject is experiencing.

[0492] In certain embodiments, treatment or prevention can be initiated with one or more loading doses of an ABP or composition provided herein followed by one or more maintenance doses.

[0493] In certain embodiments, a dose of an ABP or composition provided herein can be administered to achieve a steady-state concentration of the ABP in blood or serum of the subject. The steady-state concentration can be determined by measurement according to techniques available to those of skill or can be based on the physical characteristics of the subject such as height, weight and age.

[0494] In certain embodiments, administration of the same composition may be repeated and the

administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

[0495] As discussed in more detail elsewhere in this disclosure, an ABP provided herein may optionally be administered with one or more additional agents useful to prevent or treat a disease or disorder. The effective amount of such additional agents may depend on the amount of ABP present in the formulation, the type of disorder or treatment, and the other factors known in the art or described herein.

7. Therapeutic Applications

[0496] For therapeutic applications, the ABPs of the invention are administered to a mammal, generally a human, in a pharmaceutically acceptable dosage form such as those known in the art and those discussed above. For example, the ABPs of the invention may be administered to a human intravenously as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intra-cerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, or intratumoral routes. The ABPs also are suitably administered by peritumoral, intralesional, or perilesional routes, to exert local as well as systemic therapeutic effects. The intraperitoneal route may be particularly useful, for example, in the treatment of ovarian tumors.

[0497] The ABPs provided herein may be useful for the treatment of any disease or condition involving TIGIT. In some embodiments, the disease or condition is a disease or condition that can benefit from treatment with an anti-TIGIT ABP. In some embodiments, the disease or condition is a tumor. In some embodiments, the disease or condition is a cell proliferative disorder. In some embodiments, the disease or condition is a cancer. In some embodiments, the disease or condition is a viral infection.

[0498] In some embodiments, the ABPs provided herein are provided for use as a medicament. In some embodiments, the ABPs provided herein are provided for use in the manufacture or preparation of a medicament. In some embodiments, the medicament is for the treatment of a disease or condition that can benefit from an anti-TIGIT ABP. In some embodiments, the disease or condition is a tumor. In some embodiments, the disease or condition is a cell proliferative disorder. In some embodiments, the disease or condition is a cancer. In some embodiments, the disease or condition is a viral infection.

[0499] In some embodiments, provided herein is a method of treating a disease or condition in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject. In some aspects, the disease or condition is a cancer. In some aspects, the disease or condition is a viral infection.

[0500] Any suitable cancer may be treated with the ABPs provided herein. Illustrative suitable cancers include, for example, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, basal cell carcinoma, brain tumor, bile duct cancer, bladder cancer, bone cancer, breast cancer, bronchial tumor, carcinoma of

unknown primary origin, cardiac tumor, cervical cancer, chordoma, colon cancer, colorectal cancer, craniopharyngioma, ductal carcinoma, embryonal tumor, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, fibrous histiocytoma, Ewing sarcoma, eye cancer, germ cell tumor, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gestational trophoblastic disease, glioma, head and neck cancer, hepatocellular cancer, histiocytosis, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumor, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ, lung cancer, macroglobulinemia, malignant fibrous histiocytoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer with occult primary, midline tract carcinoma involving *NUT* gene, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, myelodysplastic syndrome, myelodysplastic/myeloproliferative neoplasm, nasal cavity and par nasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-small cell lung cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytomas, pituitary tumor, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell cancer, renal pelvis and ureter cancer, retinoblastoma, rhabdoid tumor, salivary gland cancer, Sezary syndrome, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, spinal cord tumor, stomach cancer, T-cell lymphoma, teratoid tumor, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, vulvar cancer, and Wilms tumor.

[0501] Any suitable virus may be treated with the ABPs provided herein. Illustrative suitable viruses include, for example, adeno-associated virus, Aichi virus, Australian bat lyssavirus, BK polyomavirus, Banna virus, Barmah forest virus, Bunyamwera virus, Bunyavirus La Crosse, Bunyavirus snowshoe hare, Cercopithecine herpesvirus, Chandipura virus, Chikungunya virus, Cosavirus A, cowpox virus, Coxsackievirus, Crimean-Congo hemorrhagic fever virus, Dengue virus, Dhori virus, Dugbe virus, Duvenhage virus, eastern equine encephalitis virus, ebolavirus, echovirus, encephalomyocarditis virus, Epstein-Barr virus, European bat lyssavirus, GB virus C/Hepatitis G virus, Hantaan virus, Hendra virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, hepatitis delta virus, horsepox virus, human adenovirus, human astrovirus, human coronavirus, human cytomegalovirus, human enterovirus, human herpesvirus 1, human herpesvirus 2, human herpesvirus 6, human herpesvirus 7, human herpesvirus 8, human immunodeficiency virus, human papillomavirus 1, human papillomavirus 2, human papillomavirus, human parainfluenza, human parvovirus B19, human respiratory syncytial virus, human rhinovirus, human SARS coronavirus, human spumaretrovirus, human T-lymphotropic virus, human torovirus, influenza A virus, influenza B virus, influenza C virus, Isfahan virus, JC polyomavirus, Japanese encephalitis virus, Junin arenavirus, KI polyomavirus, Kunjin virus, Lagos bat virus, Lake Victoria marburgvirus, Langat virus, Lassa virus, Lordsdale virus, Louping ill virus, lymphocytic choriomeningitis virus, Machupo

virus, Mayaro virus, MERS coronavirus, measles virus, Mengo encephalomyocarditis virus, Merkel cell polyomavirus, Mokola virus, molluscum contagiosum virus, monkeypox virus, mumps virus, Murray valley encephalitis virus, New York virus, Nipah virus, Norwalk virus, O'nyong-nyong virus, Orf virus, Oropouche virus, Pichinde virus, poliovirus, Punta toro phlebovirus, Puumala virus, rabies virus, Rift Valley fever virus, Rosavirus A, Ross River virus, rotavirus A, rotavirus B, rotavirus C, rubella virus, Sagiyama virus, salivirus A, sandfly fever Sicilian virus, Sapporo virus, Semliki Forest virus, Seoul virus, simian foamy virus, simian virus 5, Sindbis virus, Southampton virus, St. Louis encephalitis virus, tick-borne powassan virus, torque teno virus, Toscana virus, Uukuniemi virus, vaccinia virus, varicella-zoster virus, variola virus, Venezuelan equine encephalitis virus, vesicular stomatitis virus, western equine encephalitis virus, WU polyomavirus, West Nile virus, Yaba monkey tumor virus, Yaba-like disease virus, yellow fever virus, and Zika virus.

[0502] In some embodiments, provided herein is a method of antagonizing TIGIT in a target cell of a subject in need thereof by administering an effective amount of an ABP provided herein to the subject. In some aspects, antagonism of TIGIT by an ABP provided herein results in increased secretion of IL-2, LT-α, IL-6, TNF, GM-CSF, IFNγ or combinations thereof by a target cell.

[0503] In some embodiments, provided herein is a method of increasing the proliferation, survival, and/or function of an effector T cell in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject. In some aspects the effector T cell is a CD4+ effector T cell. In some aspects, the effector T cell is a CD8+ effector T cell.

[0504] In some embodiments, provided herein is a method of abrogating suppression of an effector T cell by a regulatory T cell in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject. In some aspects, the regulatory T cell is a CD4+CD25+Foxp3+ regulator T cell. In some aspects, the regulatory T cell is a CD8+CD25+ regulatory T cell.

[0505] In some embodiments, provided herein is a method of increasing the activity of a natural killer (NK) or natural killer T (NKT) cell in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0506] In some embodiments, provided herein is a method of enhancing an immune response in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0507] In some embodiments, provided herein is a method delaying the onset of a tumor in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0508] In some embodiments, provided herein is a method preventing the onset of a tumor in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0509] In some embodiments, provided herein is a method of delaying the onset of a cancer in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0510] In some embodiments, provided herein is a method of preventing the onset of a cancer in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0511] In some embodiments, provided herein is a method of reducing the size of a tumor in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0512] In some embodiments, provided herein is a method of reducing the number of metastases in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0513] In some embodiments, provided herein is a method of delaying the onset of a viral infection in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0514] In some embodiments, provided herein is a method of preventing the onset of a viral infection in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0515] In some embodiments, provided herein is a method of reducing viral titer a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0516] In some embodiments, provided herein is a method of eliminating a virus from subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0517] In some embodiments, provided herein is a method for extending the period of overall survival, median survival time, or progression-free survival in a subject in need thereof by administering an effective amount of an ABP provided herein to the subject.

[0518] In some embodiments, provided herein is a method for treating a subject who has become resistant to a standard of care therapeutic by administering an effective amount of an ABP provided herein to the subject. In some embodiments, the standard-of-care therapeutic to which the subject has become resistant is a PD-1 inhibitor. In other embodiments, the standard-of-care therapeutic to which the subject has become resistant is a PD-L1 inhibitor. In other embodiments, the standard-of-care therapeutic to which the subject has become resistant is a CTLA-4 inhibitor.

8. Combination Therapies

[0519] In some embodiments, an ABP provided herein is administered with at least one additional therapeutic agent. Any suitable additional therapeutic agent may be administered with an ABP provided herein. In some aspects, the additional therapeutic agent is selected from radiation, a cytotoxic agent, a chemotherapeutic agent, a cytostatic agent, an anti-hormonal agent, an EGFR inhibitor, an immunostimulatory agent, an anti-angiogenic agent, and combinations thereof.

[0520] In some embodiments, the additional therapeutic agent comprises an immunostimulatory agent.

[0521] In some embodiments, the immunostimulatory agent is an agent that blocks signaling of an inhibitory receptor of an immune cell, or a ligand thereof. In some aspects, the inhibitory receptor or ligand is selected from CTLA-4, PD-1, PD-L1, LAG-3, Tim3, TIGIT, neuritin, BTLA, KIR, and combinations thereof. In some aspects, the agent is selected from an anti-PD-1 antibody (e.g., pembrolizumab or nivolumab), and anti-PD-L1 antibody (e.g., atezolizumab), an anti-CTLA-4 antibody (e.g., ipilimumab), and combinations thereof. In some aspects, the agent is pembrolizumab. In some aspects, the agent is nivolumab. In some aspects, the agent is atezolizumab.

[0522] In some embodiments, the additional therapeutic agent is an agent that inhibits the interaction between PD-1 and PD-L1. In some aspects, the additional therapeutic agent that inhibits the interaction between PD-1 and PD-L1 is selected from an antibody, a peptidomimetic and a small molecule. In some aspects, the additional therapeutic agent that inhibits the interaction between PD-1 and PD-L1 is selected from pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, BMS-936559, sulfamonomethoxine 1, and sulfamethizole 2. In some embodiments, the additional therapeutic agent that inhibits the interaction between PD-1 and PD-L1 is any therapeutic known in the art to have such activity, for example as described in Weinmann et al., *Chem Med Chem*, 2016, 14:1576 (DOI: 10.1002/cmdc.201500566), incorporated by reference in its entirety. In some embodiments, the agent that inhibits the interaction between PD-1 and PD-L1 is formulated in the same pharmaceutical composition an ABP provided herein. In some embodiments, the agent that inhibits the interaction between PD-1 and PD-L1 is formulated in a different pharmaceutical composition from an ABP provided herein. In some embodiments, the agent that inhibits the interaction between PD-1 and PD-L1 is administered prior to administration of an ABP provided herein. In some embodiments, the agent that inhibits the interaction between PD-1 and PD-L1 is administered after administration of an ABP provided herein. In some embodiments, the agent that inhibits the interaction between PD-1 and PD-L1 is administered contemporaneously with an ABP provided herein, but the agent and ABP are administered in separate pharmaceutical compositions.

[0523] In some embodiments, the immunostimulatory agent is an agonist of a co-stimulatory receptor of an immune cell. In some aspects, the co-stimulatory receptor is selected from OX40, ICOS, CD27, CD28, 4-1BB, or CD40. In some embodiments, the agonist is an antibody.

[0524] In some embodiments, the immunostimulatory agent is a cytokine. In some aspects, the cytokine is selected from IL-2, IL-5, IL-7, IL-12, IL-15, IL-21, and combinations thereof.

[0525] In some embodiments, the immunostimulatory agent is an oncolytic virus. In some aspects, the oncolytic virus is selected from a herpes simplex virus, a vesicular stomatitis virus, an adenovirus, a Newcastle disease virus, a vaccinia virus, and a maraba virus.

[0526] In some embodiments, the immunostimulatory agent is a T cell with a chimeric antigen receptor (CAR-T cell). In some embodiments, the immunostimulatory agent is a bi- or multi-specific T cell directed antibody. In some embodiments, the immunostimulatory agent is an anti-TGF-ß antibody. In some embodiments, the immunostimulatory agent is a TGF-ß trap.

[0527] In some embodiments, the additional therapeutic agent is a vaccine to a tumor antigen. Any suitable antigen may be targeted by the vaccine, provided that it is present in a tumor treated by the methods provided herein. In some aspects, the tumor antigen is a tumor antigen that is overexpressed in comparison its expression levels in normal tissue. In some aspects, the tumor antigen is selected from cancer testis antigen, differentiation antigen, NY-ESO-1, MAGE-A1, MART, and combinations thereof.

[0528] Further examples of additional therapeutic agents include a taxane (e.g., paclitaxel or docetaxel); a platinum agent (e.g., carboplatin, oxaliplatin, and/or cisplatin); a topoisomerase inhibitor (e.g., irinotecan, topotecan, etoposide, and/or mitoxantrone); folinic acid (e.g., leucovorin); or a nucleoside metabolic inhibitor (e.g., fluorouracil, capecitabine, and/or gemcitabine). In some embodiments, the additional therapeutic agent is folinic acid, 5-fluorouracil, and/or oxaliplatin. In some embodiments, the additional therapeutic agent is 5-fluorouracil and irinotecan. In some embodiments, the additional therapeutic agent is a taxane and a platinum agent. In some embodiments, the additional therapeutic agent is paclitaxel and carboplatin. In some embodiments, the additional therapeutic agent is pemetrexate. In some embodiments, the additional therapeutic agent is a targeted therapeutic such as an EGFR, RAF or MEK-targeted agent.

[0529] The additional therapeutic agent may be administered by any suitable means. In some embodiments, an ABP provided herein and the additional therapeutic agent are included in the same pharmaceutical composition. In some embodiments, an ABP provided herein and the additional therapeutic agent are included in different pharmaceutical compositions.

[0530] In embodiments where an ABP provided herein and the additional therapeutic agent are included in different pharmaceutical compositions, administration of the ABP can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent. In some aspects, administration of an ABP provided herein and the additional therapeutic agent occur within about one month of each other. In some aspects, administration of an ABP provided herein and the additional therapeutic agent occur within about one week of each other. In some aspects, administration of an ABP provided herein and the additional therapeutic agent occur within about one day of each other. In some aspects, administration of an ABP provided herein and the additional therapeutic agent occur within about twelve hours of each other. In some aspects, administration of an ABP provided herein and the additional therapeutic agent occur within about one hour of each other.

9. Diagnostic Methods

[0531] Also provided are methods for detecting the presence of TIGIT on cells from a subject. Such methods may be used, for example, to predict and evaluate responsiveness to treatment with an ABP provided herein.

[0532] In some embodiments, a blood sample is obtained from a subject and the fraction of cells expressing TIGIT is determined. In some aspects, the relative amount of TIGIT expressed by such

cells is determined. The fraction of cells expressing TIGIT and the relative amount of TIGIT expressed by such cells can be determined by any suitable method. In some embodiments, flow cytometry is used to make such measurements. In some embodiments, fluorescence assisted cell sorting (FACS) is used to make such measurement. *See* Li et al., *J. Autoimmunity*, 2003, 21:83-92 for methods of evaluating expression of TIGIT in peripheral blood.

10. Kits

[0533] Also provided are kits comprising the ABPs provided herein. The kits may be used for the treatment, prevention, and/or diagnosis of a disease or disorder, as described herein.

[0534] In some embodiments, the kit comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, and IV solution bags. The containers may be formed from a variety of materials, such as glass or plastic. The container holds a composition that is by itself, or when combined with another composition, effective for treating, preventing and/or diagnosing a disease or disorder. The container may have a sterile access port. For example, if the container is an intravenous solution bag or a vial, it may have a port that can be pierced by a needle. At least one active agent in the composition is an ABP provided herein. The label or package insert indicates that the composition is used for treating the selected condition.

[0535] In some embodiments, the kit comprises (a) a first container with a first composition contained therein, wherein the first composition comprises an ABP provided herein; and (b) a second container with a second composition contained therein, wherein the second composition comprises a further therapeutic agent. The kit in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition.

[0536] Alternatively, or additionally, the kit may further comprise a second (or third) container comprising a pharmaceutically-acceptable excipient. In some aspects, the excipient is a buffer. The kit may further include other materials desirable from a commercial and user standpoint, including filters, needles, and syringes.

11. Other Illustrative Embodiments

[0537] The embodiments provided below are non-limiting and provided by way of illustration of certain embodiments and aspects of the invention, in addition to those described throughout this disclosure.

[0538] **Embodiment 1:** An antigen binding protein that binds specifically to a human TIGIT (hTIGIT) and is capable of at least one of the following: a) inhibits binding of hTIGIT to CD155 and CD112; b) increases a T effector cell function; c) increases a natural killer (NK) cell function; d) decreases the number of regulatory T cells in tissues or in circulation; e) suppresses a regulatory T cell or a regulatory T cell activity; f) inhibits association of TIGIT and CD226; and does not bind

specifically to Nectin-4 (also known as poliovirus-receptor-like 4, PVRL4).

[0539] Embodiment 2: The antigen binding protein of Embodiment 1, wherein the antigen binding protein has one or more of the following characteristics: a) is a monoclonal antibody; b) is a human antibody, a humanized antibody, or a chimeric antibody; c) is a bispecific antibody, a multispecific antibody, a diabody, or a multivalent antibody; d) is of the IgG1, IgG2, IgG3, the IgG4 type, or the IgG4 isotype with a S228P substitution; e) is an antigen-binding antibody fragment; f) is a Fab fragment, a Fab' fragment, a F(ab')2 fragment, or an Fv fragment; g) is a single chain antibody, a single domain antibody, or a nanobody.

[0540] Embodiment 3: A pharmaceutical composition comprising an effective amount of an antibody which binds to hTIGIT and: (a) increases cell-mediated immunity; (b) increases T-cell activity; (c) increases cytolytic T-cell (CTL) activity; (d) increases natural killer (NK) cell activity; (e) is an antagonist of TIGIT-mediated signaling; (f) inhibits TIGIT signaling; (g) inhibits or blocks the interaction between PVR and TIGIT; (h) inhibits or blocks the interaction of TIGIT and CD155 ligand and/or CD112; but does not inhibit the interaction between PVR and CD226.

[0541] Embodiment 4: A pharmaceutical composition comprising the antigen-binding protein of Embodiment 1 or Embodiment 2.

[0542] Embodiment 5: The pharmaceutical composition of Embodiment 4, further comprising an effective amount of an anti-PD-1 antibody.

[0543] Embodiment 6: The antigen binding protein of Embodiment 1, wherein the antigen binding protein has one or more of the following characteristics: a) binds to a human TIGIT polypeptide or a variant thereof, or as otherwise provided herein with a K_D of less than about 20 nM; or b) binds to a cynomolgus monkey (also "cynomolgus" or "cyno") TIGIT polypeptide or a variant thereof, or as otherwise provided herein, with a K_D of less than about 200 nM; c) binds to a murine TIGIT polypeptide or a variant thereof, or as otherwise provided herein, with a K_D of less than about 200 nM; or d) a combination of at least 2 of a), b), and c).

[0544] Embodiment 7: An antigen binding protein that competes or is capable of competing for binding to human TIGIT with a reference antigen binding protein, wherein the reference antigen binding protein is the antigen binding protein of Embodiment 1.

[0545] Embodiment 8: The antigen binding protein of Embodiment 7, wherein the antigen binding protein and the reference antibody cross-compete or are capable of cross-competing for binding to a human TIGIT.

[0546] Embodiment 9: The antigen binding protein of Embodiment 1, comprising a heavy chain constant region comprising a human heavy chain constant region or fragment or a variant thereof, wherein the constant region variant comprises up to 20 conservatively modified amino acid substitutions.

[0547] Embodiment 10: The antigen binding protein of Embodiment 1, that competes or is capable of competing for binding to human TIGIT with a CD155 protein and/or a CD112 protein.

[0548] Embodiment 11: The antigen binding protein of Embodiment 1, that is capable of antagonizing TIGIT signaling in a T cell-specific manner.

[0549] Embodiment 12: An isolated antibody molecule capable of binding to human TIGIT (hTIGIT), comprising a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NOs: 48-62, a VHCDR2 amino acid sequence of SEQ ID NO:36-47, and a VHCDR3 amino acid sequence of SEQ ID NO:29-35; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO:70-72, a VLCDR2 amino acid sequence of SEQ ID NO:67-69, and a VLCDR3 amino acid sequence of SEQ ID NO:63-66.

[0550] Embodiment 13: An isolated nucleic acid encoding an antigen binding protein according to Embodiment 1.

[0551] Embodiment 14: An expression vector comprising the nucleic acid according to Embodiment 13.

[0552] Embodiment 15: A prokaryotic or eukaryotic host cell comprising a vector of Embodiment 14.

[0553] Embodiment 16: A method for the production of a recombinant protein comprising the steps of expressing a nucleic acid according to Embodiment 13 in a prokaryotic or eukaryotic host cell and recovering said protein from said cell or the cell culture supernatant.

[0554] Embodiment 17: A method for treatment of a subject suffering from cancer or from an inflammatory disease, comprising the step of administering to the subject a pharmaceutical composition comprising an effective amount of the antigen binding protein of Embodiment 1.

[0555] Embodiment 18: The method of Embodiment 17, wherein the cancer is a solid cancer.

[0556] Embodiment 19: The method of Embodiment 17, wherein the cancer is a hematological cancer.

[0557] Embodiment 20: A method for modulating immune system function in a human subject in need thereof, comprising the step of contacting a population of T cells of the human subject with a pharmaceutical composition comprising an effective amount of the antigen binding protein of Embodiment 1, under conditions such that the immune system is modulated.

[0558] Embodiment 21: A method for inducing or enhancing an immune response in a subject, comprising the step of administering to the subject a pharmaceutical composition comprising an antigen binding protein or a bispecific antibody or a complexing antigen binding protein, of any of the preceding embodiments, wherein the immune response is generated against a tumor antigen.

[0559] Embodiment 22: The method of Embodiment 21, wherein the antigen binding protein, bispecific antibody or the complexing antigen binding protein is administered in an amount sufficient to achieve one or more of the following in the subject: a) reduce regulatory T cells suppression of activity of effector T cells; b) decrease levels of regulatory T cells; c) activation of effector T cells; d) induce or enhance effector T cell proliferation; e) inhibit tumor growth; and f) induce tumor regression.

[0560] Embodiment 23: The method of Embodiment 22, wherein the method further comprises one or more of the following a) administering chemotherapy; b) administering radiation therapy; or c) administering one or more additional therapeutic agents.

[0561] Embodiment 24: The method of Embodiment 23, wherein the additional therapeutic agent comprises an immunostimulatory agent.

[0562] Embodiment 25: The method of Embodiment 24, wherein the immunostimulatory agent comprises an antagonist to an inhibitory receptor of an immune cell.

[0563] Embodiment 26: The method of Embodiment 25, wherein the inhibitory receptor is CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, Tim3, neuritin, BTLA, CECAM-1, CECAM-5, VISTA, LAIR1, CD160, 2B4, TGF-R, or a KIR.

[0564] Embodiment 27: The method of Embodiment 24, wherein the immunostimulatory agent comprises an agonist of co-stimulatory receptor of an immune cell.

[0565] Embodiment 28: The method of Embodiment 27, wherein the co-stimulatory receptor is OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD28, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand.

[0566] Embodiment 29: The method of Embodiment 24, wherein the immunostimulatory agent comprises a cytokine.

[0567] Embodiment 30: The method of Embodiment 29, wherein the cytokine is IL-2, IL-5, IL-7, IL-12, IL-15 or IL-21.

[0568] Embodiment 31: The method of Embodiment 24, wherein the immunostimulatory agent comprises an oncolytic virus.

[0569] Embodiment 32: The method of Embodiment 31, wherein the oncolytic virus is a Herpes simplex virus, a Vesicular stomatitis virus, an adenovirus, a Newcastle disease virus, a vaccinia virus, or a maraba virus.

[0570] Embodiment 33: The method of Embodiment 24, wherein the immunostimulatory agent comprises a chimeric antigen engineered T cell.

[0571] Embodiment 34: The method of Embodiment 24, wherein the immunostimulatory agent comprises a bi- or multispecific T cell directed antibody.

[0572] Embodiment 35: The method of Embodiment 23, wherein the additional therapeutic agent comprises an anti-TGF-beta antibody or a TGFβ receptor trap.

[0573] Embodiment 36: The method of any one of Embodiments 20-35, wherein administration of the pharmaceutical composition results in induction or enhancement of proliferation of a T-effector cell, or modulation of I-κB and/or NF-κB in the T cell, or modulation of TIGIT activity in the T cell, or T cell receptor induced signaling in a T-effector cell, or a combination thereof.

[0574] Embodiment 37: A method of screening for test compounds comprising an antigen binding protein of Embodiment 1 that are capable of inhibiting the interaction of a TIGIT ligand with TIGIT,

comprising the steps of: contacting a sample containing a TIGIT ligand and TIGIT with the compound; and determining whether the interaction of a TIGIT ligand with TIGIT in the sample is decreased relative to the interaction of a TIGIT ligand with TIGIT in a sample not contacted with the compound, whereby a decrease in the interaction of a TIGIT ligand with TIGIT in the sample contacted with the compound identifies the compound as one that inhibits the interaction of a TIGIT ligand with TIGIT.

[0575] Embodiment 38: The antigen binding protein of Embodiment 1, that is capable of inhibiting phosphorylation of the ITIM domain of the TIGIT polypeptide.

[0576] Embodiment 1A: An isolated antigen-binding protein (ABP) that specifically binds to TIGIT, wherein the antibody: (a) competes for binding to TIGIT with an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each as provided in Table 5 of this disclosure; (b) inhibits binding of CD155 to TIGIT; (c) inhibits binding of CD112 to TIGIT; (d) inhibits association of CD226 with TIGIT; (e) activates an effector T cell or an NK cell; (f) decreases the number of regulatory T cells in a tissue or in circulation; (g) inhibits the suppression of an effector T cell by a regulatory T cell; (h) does not bind specifically to any of PVRL1, PVRL2, PVRL3, or PVRL4; or (i) is capable of any combination of (a) - (h).

[0577] Embodiment 2A: The ABP of Embodiment 1A, wherein the ABP comprises a CDR-H3 of a V_H region selected from SEQ ID NOs: 4-24, or a CDR-H3 having at least about 80% identity to a CDR-H3 of a V_H region selected from SEQ ID NOs: 4-24.

[0578] Embodiment 3A: The ABP of Embodiment 2A, wherein the CDR-H3 is identified according to the Kabat, Chothia, or IMGT numbering schemes.

[0579] Embodiment 4A: The ABP of any of Embodiments 2A-3A, wherein the CDR-H3 is selected from SEQ ID NOs: 29-35.

[0580] Embodiment 5A: The ABP of any of Embodiments 1A-4A, wherein the ABP comprises a CDR-H2 of a V_H region selected from SEQ ID NOs: 4-24, or a CDR-H2 having at least about 80% identity to a CDR-H2 of a V_H region selected from SEQ ID NOs: 4-24

[0581] Embodiment 6A: The ABP of Embodiment 5A, wherein the CDR-H2 is identified according to the Kabat, Chothia, or IMGT numbering schemes.

[0582] Embodiment 7A: The ABP of any of Embodiments 5A-6A, wherein the CDR-H2 is selected from SEQ ID NOs: 36-47.

[0583] Embodiment 8A: The ABP of any of Embodiments 1A-7A, wherein the ABP comprises a CDR-H1 of a V_H region selected from SEQ ID NOs: 4-24, or a CDR-H1 having at least about 80% identity to a CDR-H1 of a V_H region selected from SEQ ID NOs: 4-24

[0584] Embodiment 9A: The ABP of Embodiment 8A, wherein the CDR-H1 is identified according to the Kabat, Chothia, Kabat plus Chothia, or IMGT numbering schemes.

[0585] Embodiment 10A: The ABP of any of Embodiments 8A-9A, wherein the CDR-H1 is

selected from SEQ ID NOs: 48-54 and 58-62.

[0586] Embodiment 11A: The ABP of any of Embodiments 1A-10A, wherein the ABP comprises a CDR-L3 of a V_L region selected from SEQ ID NOs: 25-28, or a CDR-L3 having at least about 80% identity to a CDR-L3 of a V_L region selected from SEQ ID NOs: 25-28.

[0587] Embodiment 12A: The ABP of Embodiment 11A, wherein the CDR-L3 is identified according to the Kabat, Chothia, or IMGT numbering schemes.

[0588] Embodiment 13A: The ABP of any of Embodiments 11A-12A, wherein the CDR-L3 is selected from SEQ ID NOs: 63-66.

[0589] Embodiment 14A: The ABP of any of Embodiments 1A-13A, wherein the ABP comprises a CDR-L2 of a V_L region selected from SEQ ID NOs: 25-28, or a CDR-L2 having at least about 80% identity to a CDR-L2 of a V_L region selected from SEQ ID NOs: 25-28.

[0590] Embodiment 15A: The ABP of Embodiment 14A, wherein the CDR-L2 is identified according to the Kabat, Chothia, or IMGT numbering schemes.

[0591] Embodiment 16A: The ABP of any of Embodiments 14A-15A, wherein the CDR-L2 is selected from SEQ ID NOs: 67-69.

[0592] Embodiment 17A: The ABP of any of Embodiments 1A-16A, wherein the ABP comprises a CDR-L1 of a V_L region selected from SEQ ID NOs: 25-28, or a CDR-L1 having at least about 80% identity to a CDR-L1 of a V_L region selected from SEQ ID NOs: 25-28.

[0593] Embodiment 18A: The ABP of Embodiment 17A, wherein the CDR-L1 is identified according to the Kabat, Chothia, or IMGT numbering schemes.

[0594] Embodiment 19A: The ABP of any of Embodiments 17A-18A, wherein the CDR-L1 is selected from SEQ ID NOs: 70-72.

[0595] Embodiment 20A: The ABP of any of Embodiments 1A-19A, wherein the ABP comprises a V_H region selected from SEQ ID NOs: 4-24.

[0596] Embodiment 21A: The ABP of any of Embodiments 1A-20A, wherein the ABP comprises a V_L region selected from SEQ ID NOs: 25-28.

[0597] Embodiment 22A: The ABP of any of Embodiments 1A-21A, wherein the TIGIT is selected from hTIGIT (SEQ ID NO: 1), cTIGIT (SEQ ID NO: 2), and mTIGIT (SEQ ID NOs: 3 or 138).

[0598] Embodiment 23A: The ABP of any of Embodiments 1A-22A, wherein the ABP comprises an antibody.

[0599] Embodiment 24A: The ABP of Embodiment 23A, wherein the antibody comprises a V_H and V_L paired as provided for an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each as provided in Table 5 of this disclosure.

[0600] Embodiment 25A: The ABP of Embodiment 24A, wherein the ABP is an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each

as provided in Table 5 of this disclosure.

[0601] Embodiment 26A: The ABP of any of Embodiments 23A-25A, wherein the antibody is a monoclonal antibody.

[0602] Embodiment 27A: The ABP of any of Embodiments 23A-26A, wherein the antibody is a chimeric, humanized, or human antibody.

[0603] Embodiment 28A: The ABP of any of Embodiments 1A-27A, wherein the ABP is multispecific.

[0604] Embodiment 29A: The ABP of any of Embodiments 1A-28A, wherein the ABP comprises an antibody fragment.

[0605] Embodiment 30A: The ABP of any of Embodiments 1A-29A, wherein the ABP comprises an alternative scaffold.

[0606] Embodiment 31A: The ABP of any of Embodiments 1A-30A, wherein the ABP comprises an immunoglobulin constant region.

[0607] Embodiment 32A: The ABP of any of Embodiments 1A-31A, wherein the ABP comprises an antibody selected from an IgA, an IgD, an IgE, an IgG, or an IgM.

[0608] Embodiment 33A: The ABP of Embodiment 32A, wherein the ABP comprises an IgG selected from an IgG4, an IgG1, an IgG2, or an IgG3.

[0609] Embodiment 34A: The ABP of any of Embodiments 1A-33A, wherein the ABP binds hTIGIT (SEQ ID NO: 1) with an affinity of less than about 20 nM.

[0610] Embodiment 35A: The ABP of any of Embodiments 1A-34A, wherein the ABP binds cTIGIT (SEQ ID NO: 2) with an affinity of less than about 200 nM.

[0611] Embodiment 36A: The ABP of any of Embodiments 1A-35A, wherein the ABP binds mTIGIT (SEQ ID NO: 3 or 138) with an affinity of less than about 200 nM.

[0612] Embodiment 37A: An isolated polynucleotide encoding an ABP of any of Embodiments 1A-36A, a V_H or V_L thereof, or an antigen-binding portion thereof.

[0613] Embodiment 38A: A vector comprising the polynucleotide of Embodiment 37A.

[0614] Embodiment 39A: A host cell comprising the vector of Embodiment 38A.

[0615] Embodiment 40A: A method of producing an ABP of any of Embodiments 1A-36A, comprising expressing the ABP in the host cell of Embodiment 39A and isolating the expressed ABP.

[0616] Embodiment 41A: A pharmaceutical composition comprising an ABP of any of Embodiments 1A-36A.

[0617] Embodiment 42A: The pharmaceutical composition of Embodiment 41A, wherein the amount of the ABP in the pharmaceutical composition is sufficient to (a) increase effector T cell activity; (b) increase cytolytic T cell activity; (c) increase NK cell activity; (d) inhibit TIGIT-mediated signaling; (e) inhibit or block the binding of CD155 and or CD112 to TIGIT; or (f) any combination of (a) - (e), in a subject.

[0618] Embodiment 43A: The pharmaceutical composition of any of Embodiments 41A-42A,

further comprising an antibody that antagonizes PD-1.

[0619] Embodiment 44A: A method of treating or preventing a disease or condition in a subject in need thereof, comprising administering to the subject an effective amount of an ABP of any of Embodiments 1A-36A or a pharmaceutical composition of any of Embodiments 41A-43A.

[0620] Embodiment 45A: The method of Embodiment 44A, wherein the disease or condition is a cancer or viral infection.

[0621] Embodiment 46A: A method of modulating an immune response in a subject in need thereof, comprising administering to the subject an effective amount of an ABP of any of Embodiments 1A-36A or a pharmaceutical composition of any of Embodiments 41A-43A.

[0622] Embodiment 47A: The method of any of Embodiments 44A-46A, further comprising administering one or more additional therapeutic agents to the subject.

[0623] Embodiment 48A: The method of Embodiment 47A, wherein the additional therapeutic agent is selected from a PD-1 antagonist antibody, a chemotherapy, an immunostimulatory agent, and radiation.

[0624] Embodiment 49A: The method of Embodiments 47A, wherein the additional therapeutic agent is an immunostimulatory agent that blocks signaling of an inhibitory receptor of an immune cell or a ligand thereof.

[0625] Embodiment 50A: The method of Embodiment 49A, wherein the inhibitory receptor or ligand thereof is selected from CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, Tim3, neuritin, BTLA, CECAM-1, CECAM-5, VISTA, LAIR1, CD160, 2B4, TGF-R, KIR, and combinations thereof.

[0626] Embodiment 51A: The method of Embodiment 48A, wherein the additional therapeutic agent is an immunostimulatory agent that is an agonist to a stimulatory receptor of an immune cell.

[0627] Embodiment 52A: The method of Embodiment 51A, wherein the stimulatory receptor of an immune cell is selected from OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD28, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, CD83 ligand, and combinations thereof.

[0628] Embodiment 53A: The method of Embodiment 48A, wherein the additional therapeutic agent is an immunostimulatory agent that is a cytokine.

[0629] Embodiment 54A: The method of Embodiment 53A, wherein the cytokine is selected from IL-2, IL-5, IL-7, IL-12, IL-15, IL-21, and combinations thereof.

[0630] Embodiment 55A: The method of Embodiment 48A, wherein the additional therapeutic agent is an immunostimulatory agent that is an oncolytic virus.

[0631] Embodiment 56A: The method of Embodiment 55A, wherein the oncolytic virus is selected from herpes simplex virus, vesicular stomatitis virus, adenovirus, Newcastle disease virus, vaccinia virus, a maraba virus, and combinations thereof.

[0632] Embodiment 57A: The method of Embodiment 48A, wherein the immunostimulatory agent comprises a T cell expressing a chimeric antigen receptor.

[0633] Embodiment 58A: The method of Embodiment 48A, wherein the immunostimulatory agent comprises a bi- or multi-specific T cell directed antibody.

[0634] Embodiment 59A: The method of Embodiment 48A, wherein the immunostimulatory agent comprises an anti-TGF-ß antibody, a TGF-ß trap, or a combination thereof.

[0635] Embodiment 60A: The method of Embodiment 48A, wherein the immunostimulatory agent comprises a vaccine to a cancer-associated antigen.

[0636] Embodiment 61A: A method of screening for ABPs capable of inhibiting the interaction of a ligand of TIGIT with TIGIT, comprising (a) contacting a sample comprising a ligand of TIGIT and TIGIT with an ABP of any of Embodiments 1A-36A, and (b) determining if the binding of the ligand of TIGIT to TIGIT is decreased in the presence of the ABP, in comparison to the binding of the ligand of TIGIT to TIGIT in the absence of the ABP.

EXAMPLES

[0637] The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided herein.

Example 1: Selection of TIGIT Antigen-Binding Proteins

[0638] TIGIT ABPs were selected from a synthetic library of human antibodies expressed and displayed on the surface of yeast cells in IgG format, as generally described, e.g., in WO2009036379; WO2010105256; WO2012009568; and Xu et al., *Protein Eng. Des. Sel.*, 2013, 26:663-670 (each incorporated by reference in its entirety), and more specifically as provided below. The sequences and characteristics of the ABPs isolated from the recombinant library are provided in Table 5.

[0639] Eight naïve human synthetic yeast libraries each of ~10^9 diversity were propagated as described in WO2009036379; WO2010105256; WO2012009568; and Xu et al., *Protein Eng. Des. Sel.*, 2013, 26:663-670; each incorporated by reference in its entirety. For the first two rounds of selection, a magnetic bead sorting technique utilizing the Miltenyi MACS® system was performed, as described in Siegel et al., *J. Immunol. Meth.*, 2004, 286:141-153. Briefly, yeast cells (~10^{10} cells/library) were incubated with biotinylated TIGIT-Fc antigen in FACS wash buffer (phosphate-buffered saline (PBS)/0.1% bovine serum albumin (BSA)). After washing once with 50 ml ice-cold wash buffer, the cell pellet was resuspended in 40 mL wash buffer, and 500 µl streptavidin MicroBeads™ (Miltenyi Biotec) were added to the yeast and incubated for 15 min at 4°C. Next, the yeast were pelleted, resuspended in 5 mL wash buffer, and loaded onto a Miltenyi LS column. After the 5 mL was loaded, the column was washed 3 times with 3 ml FACS wash buffer. The column was then removed from the magnetic field, and the yeast were eluted with 5 mL of growth media and then grown overnight. The following rounds of sorting were performed using flow cytometry. Approximately 1×10^8 yeast were pelleted, washed three times with wash buffer, and incubated with decreasing concentrations of biotinylated TIGIT-Fc fusion antigen (100 to 1 nM) under equilibrium

conditions at room temperature. Yeast were then washed twice and stained with LC-FITC (diluted 1:100) and either SA-633 (diluted 1:500) or EA-PE (diluted 1:50) secondary reagents for 15 min at 4°C. After washing twice with ice-cold wash buffer, the cell pellets were resuspended in 0.4 mL wash buffer and transferred to strainer-capped sort tubes. Sorting was performed using a FACS ARIA sorter (BD Biosciences) and sort gates were assigned to select for specific binders relative to a background control. Subsequent rounds of selection were employed in order to reduce the number of non-specific binders utilizing soluble membrane proteins from CHO cells (*see* WO2014179363 and Xu et al., *Protein Eng. Des. Sel.*, 2013, 26:663-670, each incorporated by reference in its entirety), and identify binders with improved affinity to TIGIT using the TIGIT-Fc antigen. After the final round of sorting, yeast were plated and individual colonies were picked for characterization and for nomination of clones for affinity maturation.

Example 2: Affinity Maturation

[0640] Optimization of naïve clones was carried out utilizing three maturation strategies: light chain diversification; diversification of CDR-H1 and CDR-H2; and performing VH mutagenesis.

[0641] *Light Chain Diversification:* Heavy chain plasmids were extracted from naïve outputs (described above) and transformed into a light chain library with a diversity of 1 x 10^6. Selections were performed as described above with one round of MACS sorting and two rounds of FACS sorting using 10 nM or 1 nM biotinylated TIGIT-Fc antigen for respective rounds.

[0642] *CDR-H1 and CDR-H2 Selection:* The CDR-H3s from clones selected from the light chain diversification procedure were recombined into a premade library with CDR-H1 and CDR-H2 variants of a diversity of 1 x 10^8 and selections were performed using monomeric HIS-TIGIT antigen. Affinity pressures were applied by using decreasing concentrations of biotinylated HIS-TIGIT antigen (100 to 1 nM) under equilibrium conditions at room temperature.

[0643] *$V_H$mut Selection:* Clones obtained from the CDR-H1 and CDR-H2 selection procedure were subject to additional rounds of affinity maturation via error prone PCR-based mutagenesis of the heavy chain. Selections were performed using HIS-TIGIT as antigen generally as described above but with the addition of employing FACS sorting for all selection rounds.

Example 3: Antibody Production and Purification

[0644] In order to produce sufficient amounts of selected antibodies for further characterization, the yeast clones were grown to saturation and then induced for 48 h at 30°C with shaking. After induction, yeast cells were pelleted and the supernatants were harvested for purification. IgGs were purified using a Protein A column and eluted with acetic acid, pH 2.0. Fab fragments were generated by papain digestion and purified over KappaSelect® (GE Healthcare LifeSciences).

[0645] Antibodies were also produced by transient transfection of Expi293 cells according to the

manufacturer's protocol (Thermo Fisher), transient transfection of CHO cells, or stable expression of CHO cells. Antibodies were purified by Protein A chromatography.

Table 5. Sequences and germlines (GL) of TIGIT ABPs.

Ab	VH GL	CDR-H1[1]	CDR-H2[2]	CDR-H3[3]	VH Protein	VL GL	CDR-L1[4]	CDR-L2[5]	CDR-L3[6]	VL Protein
MAB1-IgG4	VH4-39	GSITSSSYYWG (SEQ ID NO: 48)	SIYYSGATFYNPSLKS (SEQ ID NO: 36)	ARDANYYGSAWAFDP (SEQ ID NO: 29)	QLQLQESGPGLVKPSETLSLTCTVSGGSITSSSYYWGWIRQPPGKGLEWIGSIYYSGATFYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAFDPWGQGTLVTVSS (SEQ ID NO: 4)	VK3-11	RASQSVSSYLA (SEQ ID NO: 70)	DASNRAT (SEQ ID NO: 67)	QQHFNLPT (SEQ ID NO: 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO: 25)
MAB2-IgG4	VH4-39	GSISSSKYYWG (SEQ ID NO: 49)	SIYYSGSTFYNPSLKS (SEQ ID NO: 37)	ARDANYYGSAWAFDP (SEQ ID NO: 29)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSKYYWGWIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAFDPWGQGTLVTVSS (SEQ ID NO: 5)	VK3-11	RASQSVSSYLA (SEQ ID NO: 70)	DASNRAT (SEQ ID NO: 67)	QQHFNLPT (SEQ ID NO: 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO: 25)
MAB3-IgG4	VH4-39	GSISSTSHYWG (SEQ ID NO: 50)	SIYYSGSTFYNPSLKS (SEQ ID NO: 37)	ARDANYYGSAWAFDP (SEQ ID NO: 29)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWGWIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAFDPWGQGTLVTVSS (SEQ ID NO: 6)	VK3-11	RASQSVSSYLA (SEQ ID NO: 70)	DASNRAT (SEQ ID NO: 67)	QQHFNLPT (SEQ ID NO: 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO: 25)

MAB4-IgG4	VH4-39	GSISSTSHYWG (SEQ ID NO: 50)	SIYYSGSTFYNPSLKS (SEQ ID NO: 37)	ARDANYYGGAWAFDP (SEQ ID NO: 30)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWGWIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGGAWAFDPWGQGTLVTVSS (SEQ ID NO: 7)	VK3-11	RASQSVSSYLA (SEQ ID NO: 70)	DASNRAT (SEQ ID NO: 67)	QQHFNLPT (SEQ ID NO: 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO: 25)
MAB5-IgG4	VH4-39	GSISSTSHYWG (SEQ ID NO: 50)	SIYYSGSTFYNPSLKG (SEQ ID NO: 38)	ARDANYYGSAWAFDP (SEQ ID NO: 29)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWGWIRQPPGKGLEWIGSIYYSGSTFYNPSLKGRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAFDPWGQGTLVTVSS (SEQ ID NO: 8)	VK3-11	RASQSVSSYLA (SEQ ID NO: 70)	DASNRAT (SEQ ID NO: 67)	QQHFNLPT (SEQ ID NO: 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO: 25)
MAB6-IgG4	VH4-39	GSIESGSYYWG (SEQ ID NO: 51)	SIYYSGGTYYNPSLKS (SEQ ID NO: 39)	ARDGVLTLNKRSFDI (SEQ ID NO: 31)	QLQLQESGPGLVKPSETLSLTCTVSGGSIESGSYYWGWIRQPPGKGLEWIGSIYYSGGTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSFDIWGQGTMVTVSS (SEQ ID NO: 9)	VK3-20	RASQSVSSSYLA (SEQ ID NO: 71)	GASSRAT (SEQ ID NO: 68)	QQHTVRPPLT (SEQ ID NO: 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO: 26)
MAB7-IgG4	VH4-31	GSIESGVYYWG (SEQ ID NO: 52)	SIYYSGSTYYNPSLKS (SEQ ID NO: 40)	ARDGVLTLNKRSFDI (SEQ ID NO: 31)	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGVYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSFDIWGQGTMVTVSS (SEQ ID NO: 10)	VK3-20	RASQSVSSSYLA (SEQ ID NO: 71)	GASSRAT (SEQ ID NO: 68)	QQHTVRPPLT (SEQ ID NO: 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK

										(SEQ ID NO: 26)
MAB8-IgG4	VH4-39	GSIASGSYYWG (SEQ ID NO: 53)	SIYYSGQTYYNPSLKS (SEQ ID NO: 41)	ARDGVLTLNKRSFDI (SEQ ID NO: 31)	QLQLQESGPGLVKPSETLSLTCTVSGGSIASGSYYWGWIRQPPGKGLEWIGSIYYSGQTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSFDIWGQGTMVTVSS (SEQ ID NO: 11)	VK3-20	RASQSVSSSYLA (SEQ ID NO: 71)	GASSRAT (SEQ ID NO: 68)	QQHTVRPPLT (SEQ ID NO: 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO: 26)
MAB9-IgG4	VH4-31	GSIESGLYYWG (SEQ ID NO: 54)	SIYYSGSTYYNPSLKS (SEQ ID NO: 40)	ARDGVLTLNKRSFDI (SEQ ID NO: 31)	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSFDIWGQGTMVTVSS (SEQ ID NO: 12)	VK3-20	RASQSVSSSYLA (SEQ ID NO: 71)	GASSRAT (SEQ ID NO: 68)	QQHTVRPPLT (SEQ ID NO: 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO: 26)
MAB10-IgG4	VH4-31	GSIESGLYYWG (SEQ ID NO: 54)	SIYYSGSTYYNPSLKS (SEQ ID NO: 40)	ARDGVLALNKRSFDI (SEQ ID NO: 32)	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRATISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKRSFDIWGQGTMVTVSS (SEQ ID NO: 13)	VK3-20	RASQSVSSSYLA (SEQ ID NO: 71)	GASSRAT (SEQ ID NO: 68)	QQHTVRPPLT (SEQ ID NO: 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO: 26)

MAB11-IgG4	VH4-31	GSIESGLYYWG (SEQ ID NO: 54)	SIYYSGSTYYNPSLKS (SEQ ID NO: 40)	ARDGVLALNKRSFDI (SEQ ID NO: 32)	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKRSFDIWGQGTMVTVSS (SEQ ID NO: 14)	VK3-20	RASQSVSSSYLA (SEQ ID NO: 71)	GASSRAT (SEQ ID NO: 68)	QQHTVRPPLT (SEQ ID NO: 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO: 26)
MAB12-IgG4	VH4-31	GSIESGLYYWG (SEQ ID NO: 54)	SIYYSGSTYYNPSLKS (SEQ ID NO: 40)	ARDGVLALNKRSFDI (SEQ ID NO: 32)	QVQLQESGPGLVKPSQTLSLTCTASGGSIESGLYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKRSFDIWGQGTMVTVSS (SEQ ID NO: 15)	VK3-20	RASQSVSSSYLA (SEQ ID NO: 71)	GASSRAT (SEQ ID NO: 68)	QQHTVRPPLT (SEQ ID NO: 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO: 26)
MAB13-IgG4	VH1-46	YTFGNYYMH (SEQ ID NO: 58)	IINPSLGLTSYAQKFQG (SEQ ID NO: 42)	ARGGRTTWIGAFDI (SEQ ID NO: 33)	QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYYMHWVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGAFDIWGQGTMVTVSS (SEQ ID NO: 16)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYVVWPPLT (SEQ ID NO: 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO: 27)
MAB14-IgG4	VH1-46	YTFPAYYMH (SEQ ID NO: 59)	IINPSLGLTSYAQKFQG (SEQ ID NO: 42)	ARGGRTTWIGAFDI (SEQ ID NO: 33)	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMHWVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGAFDIWGQGTMVTVSS (SEQ ID NO: 17)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYVVWPPLT (SEQ ID NO: 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK

										(SEQ ID NO: 27)
MAB15-IgG4	VH1-46	YTFREYYMH (SEQ ID NO: 60)	IINPSIGLTSYARKFQG (SEQ ID NO: 43)	ARGGRTTWIGAFDI (SEQ ID NO: 33)	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMHWVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGAFDIWGQGTMVTVSS (SEQ ID NO: 18)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYVVWPPLT (SEQ ID NO: 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO: 27)
MAB16-IgG4	VH1-46	YTFREYYMH (SEQ ID NO: 60)	IINPSIGLTSYARKFQG (SEQ ID NO: 43)	ARGGRTTWIGALDI (SEQ ID NO: 34)	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMHWVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGALDIWGQGTMVTVSS (SEQ ID NO: 19)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYVVWPPLT (SEQ ID NO: 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO: 27)
MAB17-IgG4	VH1-46	YTFPAYYIH (SEQ ID NO: 61)	IINPSLGLTSYARKFQG (SEQ ID NO: 44)	ARGGRTTWIGALDI (SEQ ID NO: 34)	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYIHWVRQAPGQGLEWMGIINPSLGLTSYARKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGALDIWGQGTMVTVSS (SEQ ID NO: 20)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYVVWPPLT (SEQ ID NO: 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO: 27)

MAB18-IgG4	VH1-46	YTFPAYYMH (SEQ ID NO: 59)	IINPSLGLTSYARKFQG (SEQ ID NO: 44)	ARGGRTTWIGAFDI (SEQ ID NO: 33)	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMHWVRQAPGQGLEWMGIINPSLGLTSYARKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGAFDIWGQGTMVTVSS (SEQ ID NO: 21)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYVVWPPLT (SEQ ID NO: 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO: 27)
MAB19-IgG4	VH1-46	YTFTSHYMG (SEQ ID NO: 62)	VINPSMGATSYAQKFQG (SEQ ID NO: 45)	ARLHVSGSYYPAYLDY (SEQ ID NO: 35)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMGWVRQAPGQGLEWMGVINPSMGATSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYYPAYLDYWGQGTMVTVSS (SEQ ID NO: 22)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYIVFPWT (SEQ ID NO: 66)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIK (SEQ ID NO: 28)
MAB20-IgG4	VH1-46	YTFTSHYMG (SEQ ID NO: 62)	IINPSMGATSYAQKFQG (SEQ ID NO: 46)	ARLHVSGSYYPAYLDY (SEQ ID NO: 35)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMGWVRQAPGQGLEWVGIINPSMGATSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYYPAYLDYWGQGTMVTVSS (SEQ ID NO: 23)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYIVFPWT (SEQ ID NO: 66)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIK (SEQ ID NO: 28)
MAB21-IgG4	VH1-46	YTFTSHYMG (SEQ ID NO: 62)	IINPSMGATSYTQKFRG (SEQ ID NO: 47)	ARLHVSGSYYPAYLDY (SEQ ID NO: 35)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMGWVRQAPGQGLEWMGIINPSMGATSYTQKFRGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYYPAYLDYWGQGTMVTVSS (SEQ ID NO: 24)	VK3-15	RASQSVSSNLA (SEQ ID NO: 72)	GASTRAT (SEQ ID NO: 69)	QQYIVFPWT (SEQ ID NO: 66)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIK

										(SEQ ID NO: 28)

[1] Includes CDR-H1 as defined by both the Chothia and Kabat numbering systems, inclusive of the boundaries of both numbering systems.
[2] According to the Kabat numbering system.
[3] According to the IMGT numbering system.
[4] According to the Kabat and Chothia numbering systems.
[5] According to the Kabat and Chothia numbering systems.
[6] According to the Kabat, Chothia, and IMGT numbering systems.

Example 4: Antibody Characterization

[0646] *ForteBio K_D Measurements:* Quantitative binding of antibodies to recombinant monomeric human, mouse (SEQ ID NO: 3), cynomolgus monkey TIGIT was measured using biolayer interferometry (BLI) with a FORTEBIO®. Affinity measurements of selected antibodies were performed generally as described in Estep et al., *Mabs*, 2013, 5:270-278, incorporated by reference in its entirety. FORTEBIO affinity measurements were performed by loading IgGs on-line onto AHQ sensors. Sensors were equilibrated off-line in assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded IgGs were exposed to a single concentration of antigen (100 nM) for 3 minutes. Afterwards they were transferred to assay buffer for 3 minutes for off-rate measurement. Kinetics were analyzed using the 1:1 binding model. A summary of K_D measurements for antibodies binding a single concentration of human, cynomolgus monkey, and mouse (SEQ ID NO: 3) TIGIT is shown in Table 6 below.

[0647] *MSD-SET K_D Measurements:* Solution equilibrium affinity measurements of selected antibodies binding to monomeric recombinant human and cynomolgus monkey TIGIT were performed generally as previously described. *See* Estep et al., *supra*, incorporated by reference in its entirety. Briefly, solution equilibrium titrations (SET) were performed in PBS + 0.1% IgG-Free BSA (PBSF) with antigen (TIGIT monomer) held constant at 10-100 pM and incubated with 3-to 5-fold serial dilutions of Fab or mAbs starting at 10pM-10nM. Antibodies (20 nM in PBS) were coated onto standard bind MSD-ECL plates overnight at 4°C or at room temperature for 30 min. Plates were then blocked by BSA for 30 min with shaking at 700 rpm, followed by three washes with wash buffer (PBSF + 0.05% Tween 20). SET samples were applied and incubated on the plates for 150s with shaking at 700 rpm followed by one wash. Antigen captured on a plate was detected with 250ng/mL sulfotag-labeled streptavidin in PBSF by incubation on the plate for 3 min. The plates were washed three times with wash buffer and then read on the MSD Sector Imager 2400 instrument using 1x Read Buffer T with surfactant. The percent free antigen was plotted as a function of titrated antibody in Prism and fit to a quadratic equation to extract the K_D. To improve throughput, liquid handling robots were used throughout MSD-SET experiments, including SET sample preparation.

Table 6: K_D Measurements for Human, Cyno, and Mouse (SEQ ID NO: 3) TIGIT

Antibody	ForteBio K_D (M) Human TIGIT His	ForteBio K_D (M) Cyno TIGIT His	ForteBio K_D (M) Mouse TIGIT His	MSD-SET K_D (M) Human TIGIT His	MSD-SET K_D (M) Cyno TIGIT His
MAB1	5.24E-10	2.64E-09	N.B.	5.40E-11	3.20E-10
MAB2	4.57E-10	1.57E-09	N.B.	2.50E-11	2.30E-10
MAB3	3.32E-10	8.02E-10	N.B.	8.10E-12	3.50E-11
MAB4	2.46E-10	3.69E-10	N.B.	5.00E-12	1.50E-11

MAB5	1.96E-10	8.98E-10	N.B.	4.90E-12	4.60E-11
MAB6	3.11E-09	1.75E-08	N.B.	N.D	N.D
MAB7	2.54E-09	P.F.	N.B.	N.D	N.D
MAB8	3.13E-09	2.58E-08	N.B.	N.D	N.D
MAB9	2.83E-09	9.35E-09	N.B.	N.D	N.D
MAB10	1.71E-09	6.55E-09	P.F.	1.10E-10	N.D
MAB11	2.47E-09	8.14E-09	N.B.	1.50E-10	N.D
MAB12	2.35E-09	6.57E-09	P.F.	5.60E-11	N.D
MAB13	1.44E-09	N.B.	N.B.	4.00E-10	N.D
MAB14	1.23E-09	N.B.	N.B.	3.80E-10	N.D
MAB15	5.26E-10	7.94E-08	N.B.	2.10E-10	N.D
MAB16	3.78E-10	7.04E-08	N.B.	7.00E-11	N.D
MAB17	4.29E-10	1.10E-07	N.B.	4.10E-11	N.D
MAB18	4.48E-10	7.20E-08	N.B.	N.D	N.D
MAB19	P.F.	N.B.	N.B.	N.D	N.D
MAB20	P.F.	N.B.	N.B.	3.00E-11	N.D
MAB21	P.F.	N.B.	N.B.	8.00E-11	N.D

N.B.: Non-binder or weak binder

P.F.: Poor Fit (good binding response with unreportable K_D based on a 1:1 fitting model)

N.D.: MSD affinity measurement was not performed

Example 5: Evaluation of Blockade of TIGIT Ligands

[0648] Quantitative ligand blocking studies were conducted by using a cell surface TIGIT binding assay. Binding of fluorescently labeled PVR-Fc or PVRL2-Fc to human TIGIT expressing Jurkat cells was measured by flow cytometry. A dilution series of each test antibody was incubated with the TIGIT Jurkat cells in order to measure each antibody's ability to block PVR-Fc or PVRL2-Fc binding and determine the IC_{50} values shown in Table 7.

Table 7: Ligand blocking IC_{50} Values for Antibody Panel

Antibody	PVR IC_{50} (nM)	PVRL2 IC_{50} (nM)
MAB1-IgG4	2.2	1.4
MAB2-IgG4	2.3	1.3
MAB3-IgG4	1.6	1.2
MAB4-IgG4	1.9	1.6
MAB5-IgG4	1.7	1.4
MAB6-IgG4	3.2	1.4
MAB7-IgG4	2.6	2
MAB8-IgG4	2.9	1.2
MAB9-IgG4	1.9	1.1
MAB10-IgG4	3.3	1
MAB11-IgG4	2	1.2
MAB12-IgG4	1.7	1.2
MAB13-IgG4	2.1	1.8
MAB14-IgG4	2.6	1.6
MAB15-IgG4	2.2	1.1

Antibody	PVR IC_{50} (nM)	PVRL2 IC_{50} (nM)
MAB16-IgG4	2.1	1.3
MAB17-IgG4	2.6	1.9
MAB18-IgG4	1.8	1.9
MAB19-IgG4	6.4	2
MAB20-IgG4	2.3	1.9
MAB21-IgG4	1	0.8

Example 6: Additional TIGIT Binding Assays to Measure Affinity and Cross-Reactivity of Antibodies to TIGIT

[0649] The affinity of antibodies binding to human TIGIT was measured with multiple concentrations of antigen in order to more accurately measure binding kinetics. Additionally, quantitative binding of MAB10 to human, mouse (SEQ ID NO: 3), cynomolgus monkey TIGIT was measured using biolayer interferometry (BLI) and flow cytometry. Figure 1A shows an alignment of TIGIT from different species. The percent identities across the whole TIGIT protein are summarized in Table 8 below.

Table 8: Percent identities between TIGIT proteins of different species.

	Human	**Cynomolgus Monkey**	**Mouse**
Human	100	89.17	68.38
Cynomolgus Monkey	89.17	100	66.67
Mouse	68.38	66.67	100

Kinetic Measurements for Antibodies Binding to Human, Cynomolgus Monkey, and Mouse TIGIT

[0650] The binding affinities and kinetics for antibodies binding to human TIGIT-His were measured using an Octet® QKe instrument (ForteBio) in a method similar to that described above in Example 4 but with multiple concentrations of antigen used. Additionally, binding of MAB10 to cynomolgus monkey and mouse (SEQ ID NO: 3) TIGIT-His was measured. A strategy of capturing anti-TIGIT antibodies on sensors following association/dissociation of monomeric TIGIT proteins was used to avoid avidity effects in the assay. The BLI analysis was performed at 29°C using 1X kinetics buffer (ForteBio) as assay buffer. Anti-human IgG Fc capture (AHC) biosensors (ForteBio) were first presoaked in assay buffer for over five minutes. Anti-TIGIT antibody (5 µg/mL) was captured on the sensor for 300 seconds. Sensors were then dipped in assay buffer for 120 seconds to establish a baseline before measuring binding to each TIGIT protein. Sensors were then dipped into varying concentrations of human TIGIT-His (12.4 to 0.8nM or 6.2 to 0.8nM, 2-fold dilutions in assay buffer), cynomolgus monkey TIGIT-His (24.6 to 1.5nM or 12.3 to 1.5nM, 2-fold dilutions in assay buffer, for MAB10 only), or mouse TIGIT-His (303 to 4.7nM, 2-fold dilutions in assay buffer, for MAB10 only) for 300 seconds or 600 seconds, depending on the experiment, to measure association. Dissociation

of TIGIT was measured by dipping the sensors into assay buffer for 600, 1200, or 1800 seconds, depending on the experiment (600 seconds was only used for mouse TIGIT-His). Agitation at all steps was 1000 rpm.

[0651] Kinetic parameters were generated with Octet® Data Analysis Software Version 8.2.0.7 using reference subtraction, dissociation based inter-step correction, 1-to-1 binding model, and global fit (R_{max} unlinked by sensor). The association rate constant (k_a), dissociation rate constant (k_d) and equilibrium constant (K_D) values were individually averaged across experiments, and a summary of the data for antibodies binding to human TIGIT are shown in Table 9. A summary of MAB10 binding to monomeric human, cynomolgus monkey, and mouse TIGIT (SEQ ID NO: 3) is shown in Table 10.

Table 9: TIGIT Antibody Multi-Concentration Kinetics for Binding Human TIGIT

Antibody	Average of k_a (1/Ms)	Average of k_d (1/s)	Average of K_D (M)	n
MAB2	3.2E+05	2.3E-04	7.1E-10	2
MAB4	7.0E+05	6.3E-05	8.1E-11	3
MAB5	7.7E+05	1.4E-04	1.9E-10	2
MAB9	1.6E+06	8.5E-04	5.6E-10	2
MAB10	2.0E+06	3.8E-04	2.4E-10	6
MAB11	1.3E+06	3.5E-04	2.8E-10	2
MAB12	1.5E+06	2.4E-04	1.6E-10	2
MAB15	1.1E+06	6.6E-04	5.8E-10	2
MAB16	4.5E+05	3.5E-04	1.1E-09	3
MAB18	7.5E+05	5.9E-04	8.1E-10	3
MAB20	8.9E+05	3.8E-04	4.6E-10	2
MAB21	1.4E+06	5.0E-04	3.6E-10	2

Table 10: MAB10 Kinetic Parameters for Binding Human, Cynomolgus Monkey, and Mouse

Species	Average k_a (1/Ms)	Average k_d (1/s)	Average K_D (M)	n
Human	2.0E+06	3.8E-04	2.4E-10	6
Cynomolgus Monkey	7.9E+05	4.6E-03	6.2E-09	5
Mouse	-	-	>7.0E-07*	3

*K_D could not be determined due to minimal binding (very low binding response), indicating that any binding is poorer than the limit of the instrument's sensitivity.

K_D Measurements for Binding to Cells Engineered to Express TIGIT

[0652] The K_D for MAB10 binding to cell surface TIGIT in engineered cell lines was measured using flow cytometry. Jurkat cells (acute T cell leukemia, ATCC® TIB-152™) were engineered to stably express human or cynomolgus monkey TIGIT, and CHO-K1 cells were engineered to stably express mouse TIGIT (SEQ ID NO: 3). The K_D values are shown in Table 11. The K_D values for MAB10

binding to cell surface human and cynomolgus monkey TIGIT are very similar.

Table 11: Measurement of K_D for MAB10 Binding to Cell Surface TIGIT on Engineered Cells

Cell Line	Average K_D (M)	n
Human TIGIT Jurkat	5.1E-10	2
Cynomolgus Monkey TIGIT Jurkat	4.0E-10	1
Mouse TIGIT CHO-K1	9.8E-9	1

K_D Measurements for Binding to Primary Cells

[0653] The K_D for MAB10 binding to cell surface TIGIT on primary cells was measured using flow cytometry. For both human and cynomolgus monkey PBMCs, CD8+ T cells had the greatest detectable TIGIT expression, and therefore were used to calculate the binding of MAB10 to primary cells in these species. For analysis purposes, CD8+ T cells were defined as cells with a lymphocyte size and granularity that expressed the following combination of molecular markers: CD3+CD4-CD8+. Similarly, murine Tregs demonstrated the highest binding of MAB10, and were therefore used for these calculations. Murine Tregs were defined as CD4+CD8-CD25+FoxP3+ cells of lymphocyte size and granularity. The K_D values are shown in Table 12. The K_D values for MAB10 binding to cell surface human and cynomolgus monkey TIGIT on primary cells are very similar.

Table 12: Measurement of K_D for MAB10 Binding to Cell Surface TIGIT on Primary Cells

Cells	Average K_D (M)	n
Human CD8	1.3E-9	2
Cynomolgus Monkey CD8	2.8E-9	2
Mouse Tregs	2.5E-8	2

Antibody binding to human PVRL4

[0654] In order to confirm the specificity of anti-TIGIT antibodies, binding to human PVRL4, the Ig family member most closely related to TIGIT (29% identity in extracellular region of homology), was measured by BLI. Figure 1B shows an alignment of the human TIGIT and PVRL4 extracellular domains. The BLI analysis was performed at 30°C using 1X kinetics buffer as assay buffer. AHC sensors were first presoaked in assay buffer for greater than 5 minutes. Antibody (5 µg/mL) was captured on the sensor for 300 seconds. Sensors were then dipped in assay buffer for 120 seconds to establish a baseline before measuring binding to human PVRL4-His protein. Sensors were then dipped into human PVRL4-His (200nM in assay buffer) for 200 seconds to measure association. Dissociation of PVRL4 was then measured by dipping sensors into assay buffer for 200 seconds. Results were analyzed using Octet® Data Analysis Software Version 8.2.0.7. MAB1 through MAB21 did not bind PVRL4, thus demonstrating that the MABs disclosed herein are highly specific for TIGIT.

Example 7: Production of IL-2 in Jurkat Cells Engineered to Respond to Human TIGIT Signaling Following Treatment with Anti-TIGIT Antibodies

[0655] An assay for testing the ability of antibodies to inhibit the function of TIGIT was developed using two engineered cell lines. This co-culture assay was developed to mimic the interaction of a TIGIT expressing T cell with a second cell expressing TIGIT ligand (PVR and PVRL2), thus replicating TIGIT's ability to suppress T cell activation. This interaction causes an inhibition of T cell function (e.g. cytokine release) in the TIGIT expressing cell. Jurkat cells (acute T cell leukemia) normally express IL-2 upon stimulation of the T cell receptor (using anti-CD3 and anti-CD28 agonist antibodies). The expression of TIGIT in Jurkat cells would reduce IL-2 expression induced by anti-CD3/CD28 agonist antibodies if PVR and/or PVRL2 was present and bound to TIGIT, thus providing a suppressive signal to the Jurkat cell. Therefore, a Jurkat cell line was engineered to express human TIGIT.

[0656] A second cell line, HT-1080 (human fibrosarcoma cell line, ATCC® CCL121™), was engineered to express a membrane tethered anti-CD3 single chain Fv (scFv) antibody that can provide an activating signal to the TIGIT Jurkat cells. The activating signal was also enhanced by including soluble anti-CD28 agonist antibody. HT-1080 cells naturally express high levels of PVR and PVRL2, thus providing ligand for TIGIT in a TIGIT Jurkat/anti-CD3 HT-1080 co-culture assay. In this co-culture assay, TIGIT antagonist antibodies increase the production of IL-2 compared to negative control antibodies. An overview of this assay system is shown in Figure 3.

[0657] The co-culture assay was used to determine the EC_{50} of anti-TIGIT antibodies by treatment with a dose range of antibody. EC_{50} was measured for anti-TIGIT antibodies MAB1-MAB21, as well as the hamster anti-mouse antibody SEC1 (see Example 8) and the commercial anti-human anti-TIGIT antibody MBSA43 (available, e.g., from eBioscience, Cat. No. 16-9500). The supernatants were harvested as described above 24 hours post treatment and analyzed by an IL-2 ELISA. A summary of the experimentally determined EC_{50} values in human TIGIT Jurkat cells is in Table 13. As can be seen in Table 13, all of the MABs except for MAB13, MAB 14, MAB 16, and SEC1, perform better in this assay than the commercial antibody MBSA43.

Table 13: Average EC_{50} Values in Human TIGIT Jurkat Co-Culture Assay

Antibody	Average EC_{50} (nM)
MAB1	0.22
MAB2	0.31
MAB3	0.33
MAB4	0.34
MAB5	0.34
MAB6	data not available
MAB7	0.25
MAB8	0.24

MAB9	0.06
MAB10	0.14
MAB11	0.24
MAB12	0.16
MAB13	1.40
MAB14	0.71
MAB15	0.21
MAB16	1.11
MAB17	0.13
MAB18	0.25
MAB19	0.20
MAB20	0.68
MAB21	0.61
SEC1 (see below)	8.46
MBSA43	0.45

[0658] Additionally, the Jurkat co-culture assay was repeated with MAB10 using a subcloned isolate of the anti-CD3 scFv HT1080 cells. Figure 4A shows the EC_{50} curves from an exemplary experiment comparing MAB10 and an IgG4 control. That experiment was conducted 3 times, and the average EC_{50} was 0.11 nM.

[0659] As described above for human TIGIT expressing Jurkat cells, a co-culture stimulation assay was set up with HT-1080 anti-CD3 scFv cells in the presence of cynomolgus monkey TIGIT expressing Jurkat cells and soluble anti-human CD28. Figure 4B shows the EC_{50} curves from an exemplary experiment comparing MAB10 and IgG4 control. As shown in Figure 4B, MAB10 induces IL-2 production in cynomolgus monkey TIGIT expressing Jurkat cells, whereas the IgG4 isotype control does not. The average EC_{50} for MAB10 in the cynomolgus monkey TIGIT Jurkat/anti-CD3 HT-1080 co-culture assay was determined to be 2.87 nM.

Example 8: Characterization of the anti-TIGIT antibody "SEC1"

[0660] Additional studies were conducted to characterize the hamster anti-TIGIT antibody 10A7 (disclosed, e.g., in U.S. Pat. Pub. No. 20090258013). The antibody 10A7 was reformatted in two different ways for use in this study. The first was to make a chimeric antibody with hamster variable regions and human IgG4 S228P (human S228P heavy chain, SEQ ID NO:73) and kappa constant regions (constant regions used for MAB10, SEQ ID NO:75). The second was to make a chimeric antibody with hamster variable regions and mouse IgG2a N297A and kappa constant regions (heavy chain: SEQ ID NO:77; light chain: SEQ ID NO:79). The variable regions of the antibodies are provided in SEQ ID NOs:74, 76, 78 and 80. The reformatted 10A7 antibodies are referred to herein as "SEC1".

Kinetic Measurements for SEC1 Binding to Recombinant Human, Cynomolgus Monkey, and Mouse

TIGIT

[0661] The binding affinities and kinetics of binding of SEC1 mouse IgG2a N297A to human TIGIT-His, cynomolgus monkey TIGIT-His, and mouse (SEQ ID NO: 3) TIGIT-His were measured using BLI with an Octet QKe instrument. A strategy of capturing SEC1 on sensors followed by association/dissociation of monomeric TIGIT proteins was used to avoid avidity effects in the assay. The BLI analysis was performed at 29°C using 1X Kinetics Buffer (ForteBio) as assay buffer. Anti-Mouse IgG Fc Capture (AMC) biosensors (ForteBio) were first presoaked in assay buffer for greater than 5 minutes. SEC1 mouse IgG2a N297A (5 µg/mL) was captured on the sensor for 300 seconds. Sensors were then dipped in assay buffer for 120 seconds to establish a baseline before measuring binding to each TIGIT protein. Sensors were then dipped into varying concentrations of human TIGIT-His (33.8 to 1.25nM, 3 fold dilutions in assay buffer), cynomolgus monkey TIGIT-His (302.8 to 0.42nM, 3 fold dilutions in assay buffer), or mouse TIGIT-His (33 to 1.22nM, 3 fold dilutions in assay buffer) for 300 seconds to measure

association. Dissociation of TIGIT was then measured by dipping sensors into assay buffer for 600 seconds. Agitation at all steps was 1000 rpm. Kinetic parameters and sensorgrams were generated with Octet® Data Analysis Software using reference subtraction, dissociation based inter-step correction, 1 to 1 binding model, and global fit (Rmax unlinked by sensor). The K_D values are shown in Table 14.

Table 14: SEC1 IgG2a N297A Kinetic Parameters for Binding TIGIT

Species	k_a (1/Ms)	k_d (1/s)	K_D (M)
Human	1.7E+06	7.9E-03	4.7E-09
Cynomolgus Monkey	No Binding		
Mouse	1.9E+06	6.0E-04	3.2E-10

K_D Measurements for Binding to Primary Cells

[0662] The K_D for SEC1 (IgG4 S228P) binding to cell surface TIGIT on primary cells was measured using flow cytometry as described in Example 6. For both human and cynomolgus monkey PBMCs, CD8+ T cells had the greatest detectable TIGIT expression, and therefore were used to calculate the binding of SEC1 to primary cells in these species. For analysis purposes, CD8+ T cells were defined as cells with a lymphocyte size and granularity that expressed the following combination of molecular markers: CD3+CD4-CD8+. Similarly, murine Tregs demonstrated the highest expression of TIGIT, and were therefore used for these calculations. Murine Tregs were defined as CD4+CD8-CD25+FoxP3+ cells of lymphocyte size and granularity. The K_D values are shown in Table 15.

[0663] Table 15: Measurement of K_D for SEC1 Binding to Cell Surface TIGIT on Primary Cells

Cells	Average K_D (M)	n
Human CD8	3.6E-9	1

Cynomolgus Monkey CD8	No binding	1
Mouse Tregs	4.1E-10	2

Engineered TIGIT Jurkat/anti-CD3 HT-1080 Assay

[0664] SEC1 antagonizes TIGIT function in the engineered human TIGIT Jurkat/anti-CD3 HT-1080 co-culture assay described in Example 7. The experiment was conducted 3 times, and the average EC_{50} was 8.5 nM. In comparison, the average EC_{50} for MAB10 in this assay is 0.14nM.

[0665] Like MAB10, SEC1 has been described as a ligand blocking antibody, and both antibodies inhibit the function of TIGIT in an engineered TIGIT Jurkat/anti-CD3 scFv HT-1080 co-culture assay.

Example 9: Increase in cytokine production in sub-optimally stimulated human T cells following treatment with MAB10

[0666] A study was developed in order to determine whether MAB10 is efficacious in a cellular *in vitro* system using human primary T cells obtained from healthy donors. Two different forms of the assay were used: stimulation of T cells within a mix of PBMCs and stimulation of CD4+ T cells after isolation from PBMCs. TIGIT is expressed in exhausted intra-tumoral CD8+ T cells, NK and regulatory T cells. This study was designed to identify and obtain more readily available TIGIT expressing human primary T cells to use as a surrogate system for the intra-tumoral target cells.

[0667] In CD4+ T cells, TIGIT expression is primarily restricted to memory cells (CD45RO+). Suboptimal stimulation of CD4+ T cells permits assaying the efficacy of MAB10 by measuring the increased production of IFN-γ following inhibition of TIGIT – ligand interactions.

[0668] Human primary T cells were obtained from healthy donors. Total peripheral blood mononuclear cells (PBMCs) were isolated from leukapheresis preparations and CD4+ T cells were in turn isolated from PBMCs.

[0669] PBMCs were purified using Ficoll® density gradients. PBMCs were then used to purify CD4+ cells using negative selection (CD4 T cell isolation kit, Miltenyi) following manufacturer's protocol.

FACS Analysis of Key Markers on Human CD4+ T Cells.

[0670] CD4+ T cells were sub-optimally stimulated with plate-bound anti-CD3 antibody (1μg/mL) and soluble anti-CD28 antibody (2μg/mL) for 60 hours. For staining and FACS analysis, cells from unstimulated and stimulated samples were used. The following antibodies were used for staining: anti-TIGIT-PE-Cy7, anti-PVR-PE, anti-CD4-APC-eFluor780 and anti-CD45RA-APC, anti-CD45RO PerCP-eFluor710, and CD226-FITC. Cells were analyzed by flow cytometry using a BD LSRFortessa™ instrument.

[0671] Sub-optimal stimulation of PBMCs was achieved by addition of low concentrations of anti-CD3 antibody (0.2μg/mL). Sub-optimal stimulation of CD4+ T cells was achieved by culturing the

cells on 96-well flat-bottom plates that had been previously coated with 1μg/mL of anti-CD3 antibody and 2μg/mL soluble anti-CD28 antibody. After 60 hours of culture, supernatants were collected and frozen for cytokine quantification using ELISA, AlphaLISA® or multiplex/Luminex® technology. The effect of MAB10 addition was compared to the addition of a non-specific control IgG4 antibody.

[0672] Purified CD4+ T cells were left unstimulated or were stimulated for 60 hours using plate-bound anti-CD3 antibody (1μg/mL) and soluble anti-CD28 antibody (2μg/mL). FACS analysis was performed on both unstimulated (Figure 5A) and stimulated cells (Figure 5B). Population percentages and mean fluorescence intensity (MFI) were calculated. Expression analysis of cell markers TIGIT, PVR, and CD226 prior and post-activation showed that the percentage of both PVR and CD226 positive cells increases upon activation. For TIGIT, the percentage of TIGIT positive cells only increased moderately with these activation conditions, but the MFI values indicated a clear upregulation of TIGIT expression in the positive cell population. FACS analysis also confirmed that TIGIT expression was restricted primarily to memory cells (CD45RO+). CD4+ T cells from a representative donor were stained for CD45RA (naïve T cell marker) and CD45RO (activated or memory T cell marker) markers to differentiate naïve and memory T cells. Expression levels of TIGIT were analyzed within each of these populations (see Figure 5C).

[0673] Purified PBMCs obtained from healthy donors were stimulated for 60 hours using soluble anti-CD3 antibody (0.2μg/mL) in the presence of different concentrations of a MAB or a control IgG4 antibody. Cell culture supernatants were collected and used to measure production of pro-inflammatory cytokines. The analysis of samples from two human donors, illustrated in Figures 6A-6K, show that treatment with each of the MABs induces the upregulation IFN-γ. MAB10 was then used to induce the production of several pro-inflammatory cytokines in PBMCs from Donor 1, including tumor necrosis factor alpha (TNF, Figure 6L), lymphotoxin alpha (LT-α, Figure 6M), and interferon gamma (IFN-γ, Figure 6N). A graphical analysis of the EC_{50} for IFN-γ is shown in Figure 6O. PBMCs from Donor 2 were similarly treated with MAB10 and cytokines induced as shown in Figure 7A (IFN-γ), Figure 7B (TNF), Figure 7C (IL-6), Figure 7D (GM-CSF), and Figure 7E (LT-α). EC_{50} value for MAB10 in this assay in the two donors tested was averaged as ~16nM, by determining the concentration of MAB10 required to induce 50% of the increase in IFN-γ, TNF and LT-α signal. A summary of the TNF data for the two donors (Figure 6) is shown in Table 16.

Table 16: Data Summary for Two Donors (TNF Analyzed)

Donor	EC_{10} (nM)	EC_{50} (nM)	EC_{90} (nM)
1	5.02	12.60	31.59
2	18.86	20.60	22.49
Average	11.94	16.60	27.04

[0674] Purified CD4+ T cells obtained from 3 different healthy donors were stimulated for 60 hours using plate-bound anti-CD3 antibody (1μg/mL) and soluble anti-CD28 antibody (2μg/mL) in the

presence of different concentrations of a control IgG4 antibody or MAB10. Cell culture supernatants were collected and used to measure levels of IFN-γ production.

[0675] In these sub-optimally stimulated CD4+ T cells, MAB10 addition results in an upregulation of IFN-γ in a dose dependent manner in all three donors, demonstrating the anti-TIGIT antagonistic function of MAB10 (see Figure 8A (Donor 1), Figure 8B (Donor 2), and Figure 8C (Donor 3)). IFN-γ production in cells treated with either MAB10 (black bars) or the IgG4 isotype control (light gray bars) is shown in the left panel of each Figure. EC_{50} average value for MAB10 in this assay was calculated as 1.02nM by determining the concentration of MAB10 required to induce 50% of the increase in IFN-γ signal (plotted in the right panel of each of Figures 8A-8C). The data are summarized in Table 17.

Table 17: Data Summary for Three Donors

Donor	EC_{10} (nM)	EC_{50} (nM)	EC_{90} (nM)
1	0.37	1.00	2.72
2	0.85	0.94	1.04
3	1.05	1.12	1.19
Average	0.75	1.02	1.65

[0676] As described above, addition of MAB10 to sub-optimally stimulated human T cells antagonizes TIGIT function and induces the upregulation of pro-inflammatory cytokines (e.g., IFN-γ and TNF) when compared to a non-specific control IgG4 antibody. This effect is dose-dependent with an estimated EC_{50} of 1nM for the isolated CD4+ T cell assay. These data demonstrate *in vitro* efficacy of MAB10 in normal primary human T cells.

Example 10: Characterization of MAB10 in PD-1/TIGIT Combination Bioassay

[0677] PD-1 is an immune inhibitory receptor expressed on activated T cells and B cells and plays a critical role in regulating immune responses to tumor antigens and autoantigens. Engagement of PD-1 by either of its ligands, PD-L1 or PD-L2, on an adjacent cell inhibits T-cell receptor (TCR) signaling and TCR-mediated proliferation, transcriptional activation and cytokine production. Therapeutic antibodies and Fc fusion proteins designed to block the PD-1/PD-L1 interaction show promising results in clinical trials for the treatment of a variety of cancers.

[0678] The PD-1/TIGIT Combination Bioassay (Promega) is a biologically relevant mechanism of action-based assay that can be used to measure the potency and stability of antibodies and other biologics designed to block the PD-1/PD-L1 and TIGIT/CD155 interactions in combination. The assay consists of two genetically engineered cell lines: PD-1/TIGIT Effector Cells, which are Jurkat T-cells stably expressing human PD-1, TIGIT, and a luciferase reporter, and PD-L1/CD155 APC/CHO-K1 Cells, which are CHO-K1 cells stably expressing human PD-L1, human CD155, and a cell surface protein (in this case, TIGIT) designed to activate cognate TCRs in an antigen-independent

manner.

[0679] When the two cell types are co-cultured, the PD-1/PD-L1 and TIGIT/CD155 interactions inhibit TCR signaling and luciferase activity. Addition of an antibody, e.g., an ABP disclosed herein or known in the art, that binds TIGIT and blocks ligand binding (e.g., CD155), in combination with a second antibody that blocks the interaction of PD-1 with its ligand (e.g., PD-L1), releases the inhibitory signal and results in TCR signaling and NFAT-mediated luciferase activity.

[0680] Figure 9A shows the results of the assay in which a 1:1 ratio of MAB10 and pembrolizumab (anti-PD-1 antibody) was used. Concentrations for each antibody were 25, 10, 4, 1.6, 0.64, 0.256, 0.1024, 0.04096, and 0.016384 μg/ml. An untargeted IgG4 was used as a control. As shown in the Figure, only the combination of MAB10 and pembrolizumab (EC_{50} of 5.06 nM) blocked binding sufficiently to induce luciferase activity in the Jurkat cells. Neither the IgG4 control alone or the IgG4 + MAB10 combination induced luciferase activity.

[0681] The assay was then repeated with a 1 μg/ml fixed dose of pembrolizumab (and a 1 μg/ml fixed dose of the IgG4 control) and a varying dose of MAB10 (50, 20, 8, 3.2, 1.28, 0.512, 0.2048, 0.08192, and 0.032768 μg/ml). As shown in Figure 9B, while the fixed dose of pembrolizumab resulted in a low level of activation of luciferase induction, the combination of pembrolizumab and MAB10 was much more effective at induction of luciferase, with an EC_{50} of 0.78 nM. As in Figure 9A, neither the IgG4 control alone or the IgG4 + MAB10 combination induced luciferase activity.

Example 11: Combination therapy of CMV+ T-cells with MAB10 and Pembrolizumab

[0682] A lymphoproliferation assay was used to test for T-cell responses in cytomegalovirus positive (CMV+) T-cells. PBMCs from individual donors that have been screened for CMV antigen reactivity were purchased from Astarte Biologics (Bothell, WA). Cell lysates from CMV-infected cells were also purchased from Astarte Biologics. The PBMCs were plated and the antigen-specific stimulation is performed by the addition of cell lysate, which stimulates the CMV+ T-cells in the sample. MAB10, an IgG4 control, and/or the anti-PD-1 antibody pembrolizumab were added. Cells were cultured for five days, and the supernatants were collected and analyzed for the production of the effector cytokine TNF. Further data were collected performing intracellular cytokine staining for other effector molecules including IL-2, IFN-γ, perforin and granzyme-B.

[0683] Cells from a single donor (Donor 1) were stimulated and cultured as described above. As shown in Figure 10, by gating on CD4+ cells, incubation with MAB10 (black bars) increases the production of the effector cytokines in a dose-dependent matter, as measured by intracellular staining, including TNF (Figure 10A), IL-2 (Figure 10B), and IFN-γ (Figure 10C) to a greater extent than cells incubated with the IgG4 control (white bars). Incubation with MAB10 also increases the proportion of antigen-specific activated CD4+ T-cells, as shown in Figure 10D, in which cells that were treated with 20 μg/ml of the IgG4 control or MAB10 were analyzed by FACS by expression of CD3 (a

marker of mature T-cells) and expression of TNF and IL-2.

[0684] Similar results were obtained by gating on CD8+ cells. As shown in Figure 11, on gated CD8+ cells, incubation with MAB10 (black bars) increases the production of the effector cytokines in a dose-dependent matter, including TNF (Figure 11A), perforin (Figure 11B), and granzyme B (Figure 11C) compared to cells incubated with the IgG4 control (white bars). Perforin and granzyme B are markers of activated cytotoxic T-lymphocytes. Incubation with MAB10 also increases the proportion of antigen-specific activated CD8+ T-cells, as shown in Figure 11D. Cells that were treated with 20 μg/ml of the IgG4 control or MAB10 were analyzed by FACS by expression of CD3 and expression of perforin and granzyme B.

[0685] Cells from the same donor were used in a similar set of experiments to show that blockade by MAB10 amplifies CMV-specific CD8+ T-cell responses. Cells were incubated with a range of concentrations of MAB10 (black bars) or the IgG4 control (white bars) and the percentage of double positive population perforin + granzyme B+ (Figure 12A) or IFN-γ + TNF+ (Figure 12C) was analyzed. Figures 12B (perforin + granzyme B+ analysis) and 12D (IFN-γ + TNF+ analysis) show the proportion of double positive cells comparing cells treated with 20 μg/ml of the control antibody (left panels) or 20 μg/ml of MAB10 (right panels). The cells treated with MAB10 showed a much greater production of effector cytokines compared with control-treated cells.

[0686] The combinatorial effect of MAB10 and the PD-1 antibody pembrolizumab was tested using the same donor as described above. Cells were stimulated with CMV lysates as described above and treated with 2 μg/ml pembrolizumab or control IgG4, and 10, 20, or 40 μg/ml control antibody or MAB10, and production of TNF in the supernatant was measured. As shown in Figure 13, four groups of cells were tested, treated with IgG4 control (white bars, left most group), a constant amount of IgG4 control and a titration of MAB10 (dark gray bars, second group from left), a constant amount of pembrolizumab and a titration of IgG4 control (light gray bars, second group from right), or a constant amount of pembrolizumab and a titration of MAB10 (black bars, right hand group). The combination of pembrolizumab and MAB10 increased the production of TNF above the effect observed with the single agents.

[0687] The combination was again tested in three different donors, using the assay described above. Cells were stimulated with CMV lysate and treated with 20 μg/ml of MAB10 or 20 μg/ml of control IgG4 antibody and a titration of pembrolizumab, and production of TNF was measured. As shown in Figure 14A (Donor 1), Figure 14B (Donor 2), and Figure 14C (Donor 3), the addition of MAB10 (black bars), alone or in combination with increasing concentrations of pembrolizumab, results in greater production of TNF compared to the control antibody + pembrolizumab group (white bars). Additionally, MAB10 (black bars) in combination with pembrolizumab also resulted in increased activation compared to MAB10 alone. Statistical differences were calculated between MAB10 alone and MAB10+pembrolizumab groups using Student T test analysis (*=$p<0.05$, **=$p<0.01$, ***=$p<0.005$, ****=$p<0.001$)

[0688] Taken together, the data presented in the Example demonstrate a clear, dose-dependent effect of MAB10 as a single agent in antigen-specific recall assays. In addition, the data show increased efficacy when combining MAB10 and pembrolizumab in multiple donors, indicating the value of the ABPs disclosed herein and PD-1 inhibitors or PD-L1 inhibitors as combination therapies.

INCORPORATION BY REFERENCE

[0689] The entire disclosures of all patent and non-patent publications cited herein are each incorporated by reference in their entireties for all purposes.

OTHER EMBODIMENTS

[0690] The disclosure set forth above may encompass multiple distinct inventions with independent utility. Although each of these inventions has been disclosed in its preferred form(s), the specific embodiments thereof as disclosed and illustrated herein are not to be considered in a limiting sense, because numerous variations are possible. The subject matter of the inventions includes all novel and nonobvious combinations and subcombinations of the various elements, features, functions, and/or properties disclosed herein. The following claims particularly point out certain combinations and subcombinations regarded as novel and nonobvious. Inventions embodied in other combinations and subcombinations of features, functions, elements, and/or properties may be claimed in this application, in applications claiming priority from this application, or in related applications. Such claims, whether directed to a different invention or to the same invention, and whether broader, narrower, equal, or different in scope in comparison to the original claims, also are regarded as included within the subject matter of the inventions of the present disclosure.

APPENDIX A: SEQUENCE REFERENCE TABLE

SEQ ID NO	Molecule	Region	Sequence
1	hTIGIT		MRWCLLLIWAQGLRQAPLASGMMTGTIETTGNISAE KGGSIILQCHLSSTTAQVTQVNWEQQDQLLAICNAD LGWHISPSFKDRVAPGPGLGLTLQSLTVNDTGEYFCI YHTYPDGTYTGRIFLEVLESSVAEHGARFQIPLLGAM AATLVVICTAVIVVVALTRKKKALRIHSVEGDLRRK SAGQEEWSPSAPSPPGSCVQAEAAPAGLCGEQRGED CAELHDYFNVLSYRSLGNCSFFTETG
2	cTIGIT		MRWCLFLIWAQGLRQAPLASGMMTGTIETTGNISAK KGGSVILQCHLSSTMAQVTQVNWEQHDHSLLAIRN AELGWHIYPAFKDRVAPGPGLGLTLQSLTMNDTGEY FCTYHTYPDGTYRGRIFLEVLESSVAEHSARFQIPLL GAMAMMLVVICIAVIVVVVLARKKKSLRIHSVESGL QRKSTGQEEQIPSAPSPPGSCVQAEAAPAGLCGEQQ GDDCAELHDYFNVLSYRSLGSCSFFTETG
3	mTIGIT		MHGWLLLVWVQGLIQAAFLATGATAGTIDTKRNIS AEEGGSVILQCHFSSDTAEVTQVDWKQQDQLLAIYS VDLGWHVASVFSDRVVPGPSLGLTFQSLTMNDTGE YFCTYHTYPGGIYKGRIFLKVQESSVAQFQTAPLGGT MAAVLGLICLMVTGVTVLARKKSIRMHSIESGLGRT EAEPQEWNLRSLSSPGSPVQTQTAPAGPCGEQAEDD YADPQEYFNVLSYRSLESFIAVSKTG
4	MAB1-IgG4	VH	QLQLQESGPGLVKPSETLSLTCTVSGGSITSSSYYWG WIRQPPGKGLEWIGSIYYSGATFYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWA FDPWGQGTLVTVSS
5	MAB2-IgG4	VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSKYYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAF DPWGQGTLVTVSS
6	MAB3-IgG4	VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAF DPWGQGTLVTVSS
7	MAB4-IgG4	VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGGAWAF DPWGQGTLVTVSS
8	MAB5-IgG4	VH	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKGRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWA FDPWGQGTLVTVSS
9	MAB6-IgG4	VH	QLQLQESGPGLVKPSETLSLTCTVSGGSIESGSYYWG WIRQPPGKGLEWIGSIYYSGGTYYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSF DIWGQGTMVTVSS
10	MAB7-IgG4	VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGVYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRS FDIWGQGTMVTVSS

11	MAB8-IgG4	VH	QLQLQESGPGLVKPSETLSLTCTVSGGSIASGSYYWG WIRQPPGKGLEWIGSIYYSGQTYYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSF DIWGQGTMVTVSS
12	MAB9-IgG4	VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRS FDIWGQGTMVTVSS
13	MAB10-IgG4	VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRATISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSS
14	MAB11-IgG4	VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSS
15	MAB12-IgG4	VH	QVQLQESGPGLVKPSQTLSLTCTASGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSS
16	MAB13-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYYM HWVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWI GAFDIWGQGTMVTVSS
17	MAB14-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMH WVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG AFDIWGQGTMVTVSS
18	MAB15-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMH WVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGA FDIWGQGTMVTVSS
19	MAB16-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMH WVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGA LDIWGQGTMVTVSS
20	MAB17-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYIH WVRQAPGQGLEWMGIINPSLGLTSYARKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG ALDIWGQGTMVTVSS
21	MAB18-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMH WVRQAPGQGLEWMGIINPSLGLTSYARKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG AFDIWGQGTMVTVSS
22	MAB19-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWMGVINPSMGATSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSY YPAYLDYWGQGTMVTVSS
23	MAB20-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWVGIINPSMGATSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYY PAYLDYWGQGTMVTVSS

24	MAB21-IgG4	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWMGIINPSMGATSYTQKFRGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYY PAYLDYWGQGTMVTVSS
25	MAB1-IgG4	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK
25	MAB2-IgG4	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK
25	MAB3-IgG4	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK
25	MAB4-IgG4	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK
25	MAB5-IgG4	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK
26	MAB6-IgG4	VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK
26	MAB7-IgG4	VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK
26	MAB8-IgG4	VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK
26	MAB9-IgG4	VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK
26	MAB10-IgG4	VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK
26	MAB11-IgG4	VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK
26	MAB12-IgG4	VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK
27	MAB13-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK
27	MAB14-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK
27	MAB15-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK
27	MAB16-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK

27	MAB17-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK
27	MAB18-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK
28	MAB19-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIK
28	MAB20-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIK
28	MAB21-IgG4	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIK
29	MAB1-IgG4	H3-IMGT	ARDANYYGSAWAFDP
29	MAB2-IgG4	H3-IMGT	ARDANYYGSAWAFDP
29	MAB3-IgG4	H3-IMGT	ARDANYYGSAWAFDP
30	MAB4-IgG4	H3-IMGT	ARDANYYGGAWAFDP
29	MAB5-IgG4	H3-IMGT	ARDANYYGSAWAFDP
31	MAB6-IgG4	H3-IMGT	ARDGVLTLNKRSFDI
31	MAB7-IgG4	H3-IMGT	ARDGVLTLNKRSFDI
31	MAB8-IgG4	H3-IMGT	ARDGVLTLNKRSFDI
31	MAB9-IgG4	H3-IMGT	ARDGVLTLNKRSFDI
32	MAB10-IgG4	H3-IMGT	ARDGVLALNKRSFDI
32	MAB11-IgG4	H3-IMGT	ARDGVLALNKRSFDI
32	MAB12-IgG4	H3-IMGT	ARDGVLALNKRSFDI
33	MAB13-IgG4	H3-IMGT	ARGGRTTWIGAFDI
33	MAB14-IgG4	H3-IMGT	ARGGRTTWIGAFDI
33	MAB15-IgG4	H3-IMGT	ARGGRTTWIGAFDI
34	MAB16-IgG4	H3-IMGT	ARGGRTTWIGALDI
34	MAB17-IgG4	H3-IMGT	ARGGRTTWIGALDI
33	MAB18-IgG4	H3-IMGT	ARGGRTTWIGAFDI
35	MAB19-IgG4	H3-IMGT	ARLHVSGSYYPAYLDY
35	MAB20-	H3-IMGT	ARLHVSGSYYPAYLDY

	IgG4		
35	MAB21-IgG4	H3-IMGT	ARLHVSGSYYPAYLDY
36	MAB1-IgG4	H2-Kabat	SIYYSGATFYNPSLKS
37	MAB2-IgG4	H2-Kabat	SIYYSGSTFYNPSLKS
37	MAB3-IgG4	H2-Kabat	SIYYSGSTFYNPSLKS
37	MAB4-IgG4	H2-Kabat	SIYYSGSTFYNPSLKS
38	MAB5-IgG4	H2-Kabat	SIYYSGSTFYNPSLKG
39	MAB6-IgG4	H2-Kabat	SIYYSGGTYYNPSLKS
40	MAB7-IgG4	H2-Kabat	SIYYSGSTYYNPSLKS
41	MAB8-IgG4	H2-Kabat	SIYYSGQTYYNPSLKS
40	MAB9-IgG4	H2-Kabat	SIYYSGSTYYNPSLKS
40	MAB10-IgG4	H2-Kabat	SIYYSGSTYYNPSLKS
40	MAB11-IgG4	H2-Kabat	SIYYSGSTYYNPSLKS
40	MAB12-IgG4	H2-Kabat	SIYYSGSTYYNPSLKS
42	MAB13-IgG4	H2-Kabat	IINPSLGLTSYAQKFQG
42	MAB14-IgG4	H2-Kabat	IINPSLGLTSYAQKFQG
43	MAB15-IgG4	H2-Kabat	IINPSIGLTSYARKFQG
43	MAB16-IgG4	H2-Kabat	IINPSIGLTSYARKFQG
44	MAB17-IgG4	H2-Kabat	IINPSLGLTSYARKFQG
44	MAB18-IgG4	H2-Kabat	IINPSLGLTSYARKFQG
45	MAB19-IgG4	H2-Kabat	VINPSMGATSYAQKFQG
46	MAB20-IgG4	H2-Kabat	IINPSMGATSYAQKFQG
47	MAB21-IgG4	H2-Kabat	IINPSMGATSYTQKFRG
48	MAB1-IgG4	H1-Chothia + Kabat	GSITSSSYYWG
49	MAB2-IgG4	H1-Chothia + Kabat	GSISSSKYYWG
50	MAB3-IgG4	H1-Chothia + Kabat	GSISSTSHYWG
50	MAB4-IgG4	H1-Chothia + Kabat	GSISSTSHYWG
50	MAB5-	H1-Chothia +	GSISSTSHYWG

	IgG4	Kabat	
51	MAB6-IgG4	H1-Chothia + Kabat	GSIESGSYYWG
52	MAB7-IgG4	H1-Chothia + Kabat	GSIESGVYYWG
53	MAB8-IgG4	H1-Chothia + Kabat	GSIASGSYYWG
54	MAB9-IgG4	H1-Chothia + Kabat	GSIESGLYYWG
54	MAB10-IgG4	H1-Chothia + Kabat	GSIESGLYYWG
54	MAB11-IgG4	H1-Chothia + Kabat	GSIESGLYYWG
54	MAB12-IgG4	H1-Chothia + Kabat	GSIESGLYYWG
55	IgG4	Constant, S228P hinge stabilizing	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCP APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG K
56	IgG4	Constant S228P, N297A, C terminal Lys deleted	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCP APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFASTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
57	IgG1	Constant (G1m(3) allotype)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
58	MAB13-IgG4	H1-Chothia + Kabat	YTFGNYYMH
59	MAB14-IgG4	H1-Chothia + Kabat	YTFPAYYMH
60	MAB15-IgG4	H1-Chothia + Kabat	YTFREYYMH
60	MAB16-IgG4	H1-Chothia + Kabat	YTFREYYMH
61	MAB17-IgG4	H1-Chothia + Kabat	YTFPAYYIH

59	MAB18-IgG4	H1-Chothia + Kabat	YTFPAYYMH
62	MAB19-IgG4	H1-Chothia + Kabat	YTFTSHYMG
62	MAB20-IgG4	H1-Chothia + Kabat	YTFTSHYMG
62	MAB21-IgG4	H1-Chothia + Kabat	YTFTSHYMG
63	MAB1-IgG4	L3 - Chothia/Kabat/IMGT	QQHFNLPT
63	MAB2-IgG4	L3 - Chothia/Kabat/IMGT	QQHFNLPT
63	MAB3-IgG4	L3 - Chothia/Kabat/IMGT	QQHFNLPT
63	MAB4-IgG4	L3 - Chothia/Kabat/IMGT	QQHFNLPT
63	MAB5-IgG4	L3 - Chothia/Kabat/IMGT	QQHFNLPT
64	MAB6-IgG4	L3 - Chothia/Kabat/IMGT	QQHTVRPPLT
64	MAB7-IgG4	L3 - Chothia/Kabat/IMGT	QQHTVRPPLT
64	MAB8-IgG4	L3 - Chothia/Kabat/IMGT	QQHTVRPPLT
64	MAB9-IgG4	L3 - Chothia/Kabat/IMGT	QQHTVRPPLT
64	MAB10-IgG4	L3 - Chothia/Kabat/IMGT	QQHTVRPPLT
64	MAB11-IgG4	L3 - Chothia/Kabat/IMGT	QQHTVRPPLT
64	MAB12-IgG4	L3 - Chothia/Kabat/IMGT	QQHTVRPPLT
65	MAB13-IgG4	L3 - Chothia/Kabat/IMGT	QQYVVWPPLT
65	MAB14-IgG4	L3 - Chothia/Kabat/IMGT	QQYVVWPPLT
65	MAB15-IgG4	L3 - Chothia/Kabat/IMGT	QQYVVWPPLT
65	MAB16-	L3 -	QQYVVWPPLT

	IgG4	Chothia/Kabat/IMGT	
65	MAB17-IgG4	L3 - Chothia/Kabat/IMGT	QQYVVWPPLT
65	MAB18-IgG4	L3 - Chothia/Kabat/IMGT	QQYVVWPPLT
66	MAB19-IgG4	L3 - Chothia/Kabat/IMGT	QQYIVFPWT
66	MAB20-IgG4	L3 - Chothia/Kabat/IMGT	QQYIVFPWT
66	MAB21-IgG4	L3 - Chothia/Kabat/IMGT	QQYIVFPWT
67	MAB1-IgG4	L2 - Chothia/Kabat	DASNRAT
67	MAB2-IgG4	L2 - Chothia/Kabat	DASNRAT
67	MAB3-IgG4	L2 - Chothia/Kabat	DASNRAT
67	MAB4-IgG4	L2 - Chothia/Kabat	DASNRAT
67	MAB5-IgG4	L2 - Chothia/Kabat	DASNRAT
68	MAB6-IgG4	L2 - Chothia/Kabat	GASSRAT
68	MAB7-IgG4	L2 - Chothia/Kabat	GASSRAT
68	MAB8-IgG4	L2 - Chothia/Kabat	GASSRAT
68	MAB9-IgG4	L2 - Chothia/Kabat	GASSRAT
68	MAB10-IgG4	L2 - Chothia/Kabat	GASSRAT
68	MAB11-IgG4	L2 - Chothia/Kabat	GASSRAT
68	MAB12-IgG4	L2 - Chothia/Kabat	GASSRAT
69	MAB13-IgG4	L2 - Chothia/Kabat	GASTRAT
69	MAB14-IgG4	L2 - Chothia/Kabat	GASTRAT
69	MAB15-IgG4	L2 - Chothia/Kabat	GASTRAT
69	MAB16-IgG4	L2 - Chothia/Kabat	GASTRAT
69	MAB17-IgG4	L2 - Chothia/Kabat	GASTRAT
69	MAB18-IgG4	L2 - Chothia/Kabat	GASTRAT
69	MAB19-	L2 -	GASTRAT

	IgG4	Chothia/Kabat	
69	MAB20-IgG4	L2 - Chothia/Kabat	GASTRAT
69	MAB21-IgG4	L2 - Chothia/Kabat	GASTRAT
70	MAB1-IgG4	L1 - Chothia/Kabat	RASQSVSSYLA
70	MAB2-IgG4	L1 - Chothia/Kabat	RASQSVSSYLA
70	MAB3-IgG4	L1 - Chothia/Kabat	RASQSVSSYLA
70	MAB4-IgG4	L1 - Chothia/Kabat	RASQSVSSYLA
70	MAB5-IgG4	L1 - Chothia/Kabat	RASQSVSSYLA
71	MAB6-IgG4	L1 - Chothia/Kabat	RASQSVSSSYLA
71	MAB7-IgG4	L1 - Chothia/Kabat	RASQSVSSSYLA
71	MAB8-IgG4	L1 - Chothia/Kabat	RASQSVSSSYLA
71	MAB9-IgG4	L1 - Chothia/Kabat	RASQSVSSSYLA
71	MAB10-IgG4	L1 - Chothia/Kabat	RASQSVSSSYLA
71	MAB11-IgG4	L1 - Chothia/Kabat	RASQSVSSSYLA
71	MAB12-IgG4	L1 - Chothia/Kabat	RASQSVSSSYLA
72	MAB13-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
72	MAB14-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
72	MAB15-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
72	MAB16-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
72	MAB17-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
72	MAB18-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
72	MAB19-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
72	MAB20-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
72	MAB21-IgG4	L1 - Chothia/Kabat	RASQSVSSNLA
73	SEC1	Human IgG4 S228P Heavy Chain	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHW VRQSPGKGLEWVAFIRSGSGIVFYADAVRGRFTISRD NAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDS WGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRT

			PEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK
74	SEC1	Heavy Chain Variable Region	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHW VRQSPGKGLEWVAFIRSGSGIVFYADAVRGRFTISRD NAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDS WGQGTLVTVSS
75	SEC1	SEC1 Human Kappa Chain	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKE NLLAWYQQKPGQSPKLLIYYASIRFTGVPDRFTGSGS GTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTK LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC
76	SEC1	Light Chain Variable Region	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKE NLLAWYQQKPGQSPKLLIYYASIRFTGVPDRFTGSGS GTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTK LEIK
77	SEC1	Mouse IgG2a N297A Heavy Chain	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHW VRQSPGKGLEWVAFIRSGSGIVFYADAVRGRFTISRD NAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDS WGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDL YTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEP RGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISL SPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQT HREDYASTLRVVSALPIQHQDWMSGKEFKCKVNNK DLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQV TLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVL DSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLH NHHTTKSFSRTPGK
74	SEC1	Heavy Chain Variable region	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHW VRQSPGKGLEWVAFIRSGSGIVFYADAVRGRFTISRD NAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDS WGQGTLVTVSS
78	SEC1	Mouse Kappa Chain	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKE NLLAWYQQKPGQSPKLLIYYASIRFTGVPDRFTGSGS GTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTK LEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYP KDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMS STLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNE C
76	SEC1	Light Chain Variable Region	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKE NLLAWYQQKPGQSPKLLIYYASIRFTGVPDRFTGSGS GTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTK LEIK
79	MAB1	Full length IgG4 S228P	QLQLQESGPGLVKPSETLSLTCTVSGGSITSSSYYWG WIRQPPGKGLEWIGSIYYSGATFYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWA FDPWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS

			SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
80	MAB1	Full length IgG1	QLQLQESGPGLVKPSETLSLTCTVSGGSITSSSYYWG WIRQPPGKGLEWIGSIYYSGATFYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWA FDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
81	MAB1	Full length Kappa	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
82	MAB2	Full length IgG4 S228P	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSKYYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAF DPWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK
83	MAB2	Full length IgG1	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSKYYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAF DPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
81	MAB2	Full length	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ

		Kappa	QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
84	MAB3	Full length IgG4 S228P	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAF DPWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK
85	MAB3	Full length IgG1	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAF DPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
81	MAB3	Full length Kappa	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
86	MAB4	Full length IgG4 S228P	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGGAWAF DPWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK
87	MAB4	Full length IgG1	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDANYYGGAWAF DPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA

			ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
81	MAB4	Full length Kappa	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
88	MAB5	Full length IgG4 S228P	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKGRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWA FDPWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
89	MAB5	Full length IgG1	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWG WIRQPPGKGLEWIGSIYYSGSTFYNPSLKGRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWA FDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
81	MAB5	Full length Kappa	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQHFNLPTFGGGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
90	MAB6	Full length IgG4 S228P	QLQLQESGPGLVKPSETLSLTCTVSGGSIESGSYYWG WIRQPPGKGLEWIGSIYYSGGTYYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSF DIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMIS

			RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK
91	MAB6	Full length IgG1	QLQLQESGPGLVKPSETLSLTCTVSGGSIESGSYYWG WIRQPPGKGLEWIGSIYYSGGTYYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSF DIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
92	MAB6	Full length Kappa	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
93	MAB7	Full length IgG4 S228P	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGVYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRS FDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
94	MAB7	Full length IgG1	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGVYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRS FDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
92	MAB7	Full length Kappa	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIKRT

			VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
95	MAB8	Full length IgG4 S228P	QLQLQESGPGLVKPSETLSLTCTVSGGSIASGSYYWG WIRQPPGKGLEWIGSIYYSGQTYYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSF DIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK
96	MAB8	Full length IgG1	QLQLQESGPGLVKPSETLSLTCTVSGGSIASGSYYWG WIRQPPGKGLEWIGSIYYSGQTYYNPSLKSRVTISVD TSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSF DIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
92	MAB8	Full length Kappa	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
97	MAB9	Full length IgG4 S228P	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRS FDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
98	MAB9	Full length IgG1	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRS FDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK

			RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
92	MAB9	Full length Kappa	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
99	MAB10	Full length IgG4 S228P	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRATISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
100	MAB10	Full length IgG1	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRATISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
92	MAB10	Full length Kappa	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
101	MAB11	Full length IgG4 S228P	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV

			SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
102	MAB11	Full length IgG1	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
92	MAB11	Full length Kappa	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
103	MAB12	Full length IgG4 S228P	QVQLQESGPGLVKPSQTLSLTCTASGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
104	MAB12	Full length IgG1	QVQLQESGPGLVKPSQTLSLTCTASGGSIESGLYYW GWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKR SFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
92	MAB12	Full length Kappa	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS

			KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
105	MAB13	Full length IgG4 S228P	QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYYM HWVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWI GAFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLGK
106	MAB13	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYYM HWVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWI GAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK
107	MAB13	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
108	MAB14	Full length IgG4 S228P	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMH WVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG AFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
109	MAB14	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMH WVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG AFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV

			HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
107	MAB14	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
110	MAB15	Full length IgG4 S228P	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMH WVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGA FDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
111	MAB15	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMH WVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGA FDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
107	MAB15	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
112	MAB16	Full length IgG4 S228P	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMH WVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGA LDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP

			VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
113	MAB16	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMH WVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGA LDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK
107	MAB16	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
114	MAB17	Full length IgG4 S228P	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYIH WVRQAPGQGLEWMGIINPSLGLTSYARKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG ALDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
115	MAB17	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYIH WVRQAPGQGLEWMGIINPSLGLTSYARKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG ALDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
107	MAB17	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
116	MAB18	Full length IgG4	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMH

		S228P	WVRQAPGQGLEWMGIINPSLGLTSYARKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG AFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
117	MAB18	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMH WVRQAPGQGLEWMGIINPSLGLTSYARKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIG AFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
107	MAB18	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
118	MAB19	Full length IgG4 S228P	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWMGVINPSMGATSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSY YPAYLDYWGQGTMVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSN TKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK
119	MAB19	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWMGVINPSMGATSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSY YPAYLDYWGQGTMVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP

			PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
120	MAB19	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
121	MAB20	Full length IgG4 S228P	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWVGIINPSMGATSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYY PAYLDYWGQGTMVTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK
122	MAB20	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWVGIINPSMGATSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYY PAYLDYWGQGTMVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
120	MAB20	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
123	MAB21	Full length IgG4 S228P	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWMGIINPSMGATSYTQKFRGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYY PAYLDYWGQGTMVTVSSASTKGPSVFPLAPCSRSTS ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK

124	MAB21	Full length IgG1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMG WVRQAPGQGLEWMGIINPSMGATSYTQKFRGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARLHVSGSYY PAYLDYWGQGTMVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
120	MAB21	Full length Kappa	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWY QQKPGQAPRHLIYGASTRATGIPARFSGSGSGTEFTL TISSLQSEDFAVYYCQQYIVFPWTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
125	IgG1	Constant (G1m(17,1) allotype, N297A	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
126	Kappa	Constant	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
127	Linker		GGGGS
128 . . . 137 - *See* other portions of this disclosure and the electronic version of the Sequence Listing submitted herewith.			
138	mTIGIT2		MHGWLLLVWVQGLIQAAFLATAIGATAGTIDTKRNI SAEEGGSVILQCHFSSDTAEVTQVDWKQQDQLLAIY SVDLGWHVASVFSDRVVPGPSLGLTFQSLTMNDTGE YFCTYHTYPGGIYKGRIFLKVQESSDDRNGLAQFQT APLGGTMAAVLGLICLMVTGVTVLARKDKSIRMHSI ESGLGRTEAEPQEWNLRSLSSPGSPVQTQTAPAGPC GEQAEDDYADPQEYFNVLSYRSLESFIAVSKTG

WHAT IS CLAIMED IS:

1. An isolated antigen binding protein (ABP) that specifically binds human TIGIT (hTIGIT; SEQ ID NO: 1), comprising the following six CDR sequences:

   (a) a CDR-H3 having the sequence A-R-D-G-V-L-X_1-L-N-K-R-S-F-D-I, wherein X_1 is A or T (SEQ ID NO: 128);

   (b) a CDR-H2 having the sequence S-I-Y-Y-S-G-X_2-T-Y-Y-N-P-S-L-K-S, wherein X_2 is S, Q or G (SEQ ID NO: 129);

   (c) a CDR-H1 having the sequence G-S-I-X_3-S-G-X_4-Y-Y-W-G, wherein X_3 is E or A, and X_4 is L, V or S (SEQ ID NO: 130);

   (d) a CDR-L3 having the sequence QQHTVRPPLT (SEQ ID NO: 64);

   (e) a CDR-L2 having the sequence GASSRAT (SEQ ID NO: 68); and

   (f) a CDR-L1 having the sequence RASQSVSSSYLA (SEQ ID NO: 71).

2. The ABP of claim 1, wherein the ABP comprises:

   (a) a CDR-H3 of SEQ ID NO: 32, a CDR-H2 of SEQ ID NO: 40, a CDR-H1 of SEQ ID NO: 54, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71;

   (b) a CDR-H3 of SEQ ID NO: 31, a CDR-H2 of SEQ ID NO: 40, a CDR-H1 of SEQ ID NO: 54, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71;

   (c) a CDR-H3 of SEQ ID NO: 31, a CDR-H2 of SEQ ID NO: 39, a CDR-H1 of SEQ ID NO: 51, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71;

   (d) a CDR-H3 of SEQ ID NO: 31, a CDR-H2 of SEQ ID NO: 40, a CDR-H1 of SEQ ID NO: 52, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71; or

   (e) a CDR-H3 of SEQ ID NO: 31, a CDR-H2 of SEQ ID NO: 41, a CDR-H1 of SEQ ID NO: 53, a CDR-L3 of SEQ ID NO: 64, a CDR-L2 of SEQ ID NO: 68, and a CDR-L1 of SEQ ID NO: 71.

3. The ABP of claim 2, wherein:

   (a) the ABP of claim 2(a) comprises a V_H sequence of SEQ ID NO: 13 and a V_L sequence of SEQ ID NO: 26;

(b) the ABP of claim 2(b) comprises a V_H sequence of SEQ ID NO: 12 and a V_L sequence of SEQ ID NO: 26;

(c) the ABP of claim 2(a) comprises a V_H sequence of SEQ ID NO: 14 and a V_L sequence of SEQ ID NO: 26;

(d) the ABP of claim 2(a) comprises a V_H sequence of SEQ ID NO: 15 and a V_L sequence of SEQ ID NO: 26;

(e) the ABP of claim 2(c) comprises a V_H sequence of SEQ ID NO: 9 and a V_L sequence of SEQ ID NO: 26;

(f) the ABP of claim 2(d) comprises a V_H sequence of SEQ ID NO: 10 and a V_L sequence of SEQ ID NO: 26; or

(g) the ABP of claim 2(e) comprises a V_H sequence of SEQ ID NO: 11 and a V_L sequence of SEQ ID NO: 26.

4. The ABP of claim 3, wherein:

(a) the ABP of claim 3(a) comprises (i) a heavy chain of SEQ ID NO: 99 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 100 and a light chain of SEQ ID NO: 92;

(b) the ABP of claim 3(b) comprises (i) a heavy chain of SEQ ID NO: 97 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 98 and a light chain of SEQ ID NO: 92;

(c) the ABP of claim 3(c) comprises (i) a heavy chain of SEQ ID NO: 101 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 102 and a light chain of SEQ ID NO: 92;

(d) the ABP of claim 3(d) comprises (i) a heavy chain of SEQ ID NO: 103 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 104 and a light chain of SEQ ID NO: 92;

(e) the ABP of claim 3(e) comprises (i) a heavy chain of SEQ ID NO: 90 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 91 and a light chain of SEQ ID NO: 92;

(f) the ABP of claim 3(f) comprises (i) a heavy chain of SEQ ID NO: 93 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 94 and a light chain of SEQ ID NO: 92; or

(g) the ABP of claim 3(g) comprises (i) a heavy chain of SEQ ID NO: 95 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 96 and a light chain of SEQ ID NO: 92.

5. An isolated antigen binding protein (ABP) that specifically binds human TIGIT (hTIGIT; SEQ ID NO: 1), comprising the following six CDR sequences:

(a) a CDR-H3 having the sequence A-R-D-A-N-Y-Y-G-X_1-A-W-A-F-D-P, wherein X_1 is S or G (SEQ ID NO: 131);

(b) a CDR-H2 having the sequence S-I-Y-Y-S-G-X_2-T-F-Y-N-P-S-L-K-X_3, wherein X_2 is S or A, and X_3 is S or G (SEQ ID NO: 132);

(c) a CDR-H1 having the sequence G-S-I-X_4-S-X_5-X_6-X_7-Y-W-G, wherein X_4 is S or T, X_5 is S or T, X_6 is S or K, and X_7 is H or Y (SEQ ID NO: 133);

(d) a CDR-L3 having the sequence QQHFNLPT (SEQ ID NO: 63);

(e) a CDR-L2 having the sequence DASNRAT (SEQ ID NO: 67); and

(f) a CDR-L1 having the sequence RASQSVSSYLA (SEQ ID NO: 70).

6. The ABP of claim 5, wherein the ABP comprises:

(a) a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 37, a CDR-H1 of SEQ ID NO: 49, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70;

(b) a CDR-H3 of SEQ ID NO: 30, a CDR-H2 of SEQ ID NO: 37, a CDR-H1 of SEQ ID NO: 50, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70;

(c) a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 38, a CDR-H1 of SEQ ID NO: 50, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70;

(d) a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 36, a CDR-H1 of SEQ ID NO: 48, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70; or

(e) a CDR-H3 of SEQ ID NO: 29, a CDR-H2 of SEQ ID NO: 37, a CDR-H1 of SEQ ID NO: 50, a CDR-L3 of SEQ ID NO: 63, a CDR-L2 of SEQ ID NO: 67, and a CDR-L1 of SEQ ID NO: 70.

7. The ABP of claim 6, wherein:

(a) the ABP of claim 6(a) comprises a V_H sequence of SEQ ID NO: 5 and a V_L sequence of SEQ ID NO: 25;

(b) the ABP of claim 6(b) comprises a V_H sequence of SEQ ID NO: 7 and a V_L sequence of SEQ ID NO: 25;

(c) the ABP of claim 6(c) comprises a V_H sequence of SEQ ID NO: 8 and a V_L sequence of SEQ ID NO: 25;

(d) the ABP of claim 6(d) comprises a V_H sequence of SEQ ID NO: 4 and a V_L sequence of SEQ ID NO: 25; or

(e) the ABP of claim 6(e) comprises a V_H sequence of SEQ ID NO: 6 and a V_L sequence of SEQ ID NO: 25.

8. The ABP of claim 7, wherein:

(a) the ABP of claim 7(a) comprises (i) a heavy chain of SEQ ID NO: 82 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 83 and a light chain of SEQ ID NO: 81;

(b) the ABP of claim 7(b) comprises (i) a heavy chain of SEQ ID NO: 86 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 87 and a light chain of SEQ ID NO: 81;

(c) the ABP of claim 7(c) comprises (i) a heavy chain of SEQ ID NO: 88 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 89 and a light chain of SEQ ID NO: 81;

(d) the ABP of claim 7(d) comprises (i) a heavy chain of SEQ ID NO: 79 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 80 and a light chain of SEQ ID NO: 81; or

(e) the ABP of claim 7(e) comprises (i) a heavy chain of SEQ ID NO: 84 and a light chain of SEQ ID NO: 81; or (ii) a heavy chain of SEQ ID NO: 85 and a light chain of SEQ ID NO: 81.

9. An isolated antigen binding protein (ABP) that specifically binds human TIGIT (hTIGIT; SEQ ID NO: 1), comprising the following six CDR sequences:

(a) a CDR-H3 having the sequence A-R-G-G-R-T-T-W-I-G-A-X_1-D-I, wherein X_1 is F or L (SEQ ID NO: 134);

(b) a CDR-H2 having the sequence I-I-N-P-S-X_2-G-L-T-S-Y-A-X_3-K-F-Q-G, wherein X_2 is L or I, and X_3 is Q or R (SEQ ID NO: 135);

(c) a CDR-H1 having the sequence Y-T-F-X_4-X_5-Y-Y-X_6-H, wherein X_4 is G, P or R, X_5 is N, A or E, and X_6 is M or I (SEQ ID NO: 136);

(d) a CDR-L3 having the sequence QQYVVWPPLT (SEQ ID NO:65);

(e) a CDR-L2 having the sequence GASTRAT (SEQ ID NO:69); and

(f) a CDR-L1 having the sequence RASQSVSSNLA (SEQ ID NO:72).

10. The ABP of claim 9, wherein the ABP comprises:

(a) a CDR-H3 of SEQ ID NO: 33, a CDR-H2 of SEQ ID NO: 43, a CDR-H1 of SEQ ID NO: 60, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72;

(b) a CDR-H3 of SEQ ID NO: 34, a CDR-H2 of SEQ ID NO: 43, a CDR-H1 of SEQ ID NO: 60, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72;

(c) a CDR-H3 of SEQ ID NO: 33, a CDR-H2 of SEQ ID NO: 44, a CDR-H1 of SEQ ID NO: 59, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72;

(d) a CDR-H3 of SEQ ID NO: 33, a CDR-H2 of SEQ ID NO: 42, a CDR-H1 of SEQ ID NO: 58, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72;

(e) a CDR-H3 of SEQ ID NO: 33, a CDR-H2 of SEQ ID NO: 42, a CDR-H1 of SEQ ID NO: 59, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; or

(f) a CDR-H3 of SEQ ID NO: 34, a CDR-H2 of SEQ ID NO: 44, a CDR-H1 of SEQ ID NO: 61, a CDR-L3 of SEQ ID NO: 65, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72.

11. The ABP of claim 10, wherein:

(a) the ABP of claim 10(a) comprises a V_H sequence of SEQ ID NO: 18 and a V_L sequence of SEQ ID NO: 27;

(b) the ABP of claim 10(b) comprises a V_H sequence of SEQ ID NO: 19 and a V_L sequence of SEQ ID NO: 27;

(c) the ABP of claim 10(c) comprises a V_H sequence of SEQ ID NO: 21 and a V_L sequence of SEQ ID NO: 27;

(d) the ABP of claim 10(d) comprises a V_H sequence of SEQ ID NO: 16 and a V_L sequence of SEQ ID NO: 27;

(e) the ABP of claim 10(e) comprises a V_H sequence of SEQ ID NO: 17 and a V_L sequence of SEQ ID NO: 27; or

(f) the ABP of claim 10(f) comprises a V_H sequence of SEQ ID NO: 20 and a V_L sequence of SEQ ID NO: 27.

12. The ABP of claim 11, wherein:

(a) the ABP of claim 11(a) comprises (i) a heavy chain of SEQ ID NO: 110 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 111 and a light chain of SEQ ID NO: 107;

(b) the ABP of claim 11(b) comprises (i) a heavy chain of SEQ ID NO: 112 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 113 and a light chain of SEQ ID NO: 107;

(c) the ABP of claim 11(c) comprises (i) a heavy chain of SEQ ID NO: 116 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 117 and a light chain of SEQ ID NO: 107;

(d) the ABP of claim 11(d) comprises (i) a heavy chain of SEQ ID NO: 105 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 106 and a light chain of SEQ ID NO: 107;

(e) the ABP of claim 11(e) comprises (i) a heavy chain of SEQ ID NO: 108 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 109 and a light chain of SEQ ID NO: 107; or

(f) the ABP of claim 11(f) comprises (i) a heavy chain of SEQ ID NO: 114 and a light chain of SEQ ID NO: 107; or (ii) a heavy chain of SEQ ID NO: 115 and a light chain of SEQ ID NO: 107.

13. An isolated antigen binding protein (ABP) that specifically binds human TIGIT (hTIGIT; SEQ ID NO: 1), comprising the following six CDR sequences:

(a) a CDR-H3 having the sequence ARLHVSGSYYPAYLDY (SEQ ID NO: 35);

(b) a CDR-H2 having the sequence X_1-I-N-P-S-M-G-A-T-S-Y-X_2-Q-K-F-X_3-G, wherein X_1 is V or I, X_2 is A or T, and X_3 is Q or R (SEQ ID NO: 137);

(c) a CDR-H1 having the sequence YTFTSHYMG (SEQ ID NO: 62);

(d) a CDR-L3 having the sequence QQYIVFPWT (SEQ ID NO: 66);

(e) a CDR-L2 having the sequence GASTRAT (SEQ ID NO: 69); and

(f) a CDR-L1 having the sequence RASQSVSSNLA, (SEQ ID NO: 72).

14. The ABP of claim 13, wherein the ABP comprises:

(a) a CDR-H3 of SEQ ID NO: 35, a CDR-H2 of SEQ ID NO: 46, a CDR-H1 of SEQ ID NO: 62, a CDR-L3 of SEQ ID NO: 66, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72;

(b) a CDR-H3 of SEQ ID NO: 35, a CDR-H2 of SEQ ID NO: 47, a CDR-H1 of SEQ ID NO: 62, a CDR-L3 of SEQ ID NO: 66, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72; or

(c) a CDR-H3 of SEQ ID NO: 35, a CDR-H2 of SEQ ID NO: 45, a CDR-H1 of SEQ ID NO: 62, a CDR-L3 of SEQ ID NO: 66, a CDR-L2 of SEQ ID NO: 69, and a CDR-L1 of SEQ ID NO: 72.

15. The ABP of claim 14, wherein:

(a) the ABP of claim 14(a) comprises a V_H sequence of SEQ ID NO: 23 and a V_L sequence of SEQ ID NO: 28;

(b) the ABP of claim 14(b) comprises a V_H sequence of SEQ ID NO: 24 and a V_L sequence of SEQ ID NO: 28; or

(c) the ABP of claim 14(c) comprises a V_H sequence of SEQ ID NO: 22 and a V_L sequence of SEQ ID NO: 28.

16. The ABP of claim 15, wherein:

(a) the ABP of claim 15(a) comprises (i) a heavy chain of SEQ ID NO: 121 and a light chain of SEQ ID NO: 120; or (ii) a heavy chain of SEQ ID NO: 122 and a light chain of SEQ ID NO: 120;

(b) the ABP of claim 15(b) comprises (i) a heavy chain of SEQ ID NO: 123 and a light chain of SEQ ID NO: 120; or (ii) a heavy chain of SEQ ID NO: 124 and a light chain of SEQ ID NO: 120; or

(c) the ABP of claim 15(c) comprises (i) a heavy chain of SEQ ID NO: 118 and a light chain of SEQ ID NO: 120; or (ii) a heavy chain of SEQ ID NO: 119 and a light chain of SEQ ID NO: 120.

17. An isolated antigen binding protein (ABP) that specifically binds human TIGIT (hTIGIT; SEQ ID NO: 1), comprising:

(a) a CDR-H3 having at least about 80% identity to a CDR-H3 of a V_H region selected from SEQ ID NOs: 4-24;

(b) a CDR-H2 having at least about 80% identity to a CDR-H2 of a V_H region selected from SEQ ID NOs: 4-24;

(c) a CDR-H1 having at least about 80% identity to a CDR-H1 of a V_H region selected from SEQ ID NOs: 4-24;

(d) a CDR-L3 having at least about 80% identity to a CDR-L3 of a V_L region selected from SEQ ID NOs: 25-28;

(e) a CDR-L2 having at least about 80% identity to a CDR-L2 of a V_L region selected from SEQ ID NOs: 25-28; and

(f) a CDR-L1 having at least about 80% identity to a CDR-L1 of a V_L region selected from SEQ ID NOs: 25-28.

18. The ABP of claim 17, wherein the CDR-H3, CDR-H2, CDR-H1, CDR-L3, CDR-L2, and CDR-L1 are each identified according to a numbering scheme selected from the Kabat numbering scheme, the Chothia numbering scheme, or the IMGT numbering scheme.

19. The ABP of any one of claims 17-18, wherein the CDR-H1 is identified as defined by both the Chothia and Kabat numbering schemes, inclusive of the boundaries of both numbering schemes.

20. The ABP of any one of claims 17-19, wherein:

(a) the CDR-H3 comprises a CDR-H3 selected from SEQ ID NOs: 29-35, or a variant thereof having 1, 2, or 3 amino acid substitutions;

(b) the CDR-H2 comprises a CDR-H3 selected from SEQ ID NOs: 36-47, or a variant thereof having 1, 2, or 3 amino acid substitutions;

(c) the CDR-H1 comprises a CDR-H1 selected from SEQ ID NOs: 48-54 or 58-62, or a variant thereof having 1 or 2 amino acid substitutions;

(d) the CDR-L3 comprises a CDR-L3 selected from SEQ ID NOs: 63-66, or a variant thereof having 1 or 2 amino acid substitutions;

(e) the CDR-L2 comprises a CDR-L2 selected from SEQ ID NOs: 67-69, or a variant thereof having 1 amino acid substitution; and

(f) the CDR-L1 comprises a CDR-L1 selected from SEQ ID NOs: 70-72, or a variant thereof having 1 or 2 amino acid substitutions.

21. An isolated antigen binding protein (ABP) that specifically binds human TIGIT (hTIGIT; SEQ ID NO: 1), comprising:

    (a) a V_H region having at least about 90% identity to a V_H region selected from SEQ ID NOs: 4-24; and

    (b) a V_L region having at least about 90% identity to a V_L region selected from SEQ ID NOs: 25-28.

22. The ABP of claim 21, wherein:

    (a) the a V_H region comprises a V_H region selected from SEQ ID NOs: 4-24, or a variant thereof having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid substitutions; and

    (b) the a V_L region comprises a V_L region selected from SEQ ID NOs: 25-28, or a variant thereof having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions.

23. The ABP of any one of claims 20 or 22, wherein the amino acid substitutions are conservative amino acid substitutions.

24. The ABP of any one of claims 1-23, wherein the ABP:

    (a) competes for binding to TIGIT with an antibody selected from MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, MAB19, MAB20, or MAB21, each as provided in Table 5 of this disclosure;

    (b) inhibits binding of CD155 to TIGIT;

    (c) inhibits binding of CD112 to TIGIT;

    (d) inhibits association of CD226 with TIGIT;

    (e) activates an effector T cell or a natural killer (NK) cell;

    (f) decreases the number of regulatory T cells in a tissue or in circulation;

    (g) inhibits the suppression of an effector T cell by a regulatory T cell;

    (h) does not bind specifically to any of PVRL1, PVRL2, PVRL3, or PVRL4; or

    (i) is capable of any combination of (a)- (h).

25. The ABP of any one of claims 1-24, wherein the ABP (a) specifically binds cynomolgus monkey TIGIT (cTIGIT; SEQ ID NO: 2); (b) binds murine TIGIT (mTIGIT; SEQ ID NO: 3) with an affinity lower (as indicated by higher KD) than the affinity of the ABP for hTIGIT, or does not bind mTIGIT; or (c) is capable of any combination of (a) - (b).

26. The ABP of any one of claims 1-25, wherein the ABP: (a) specifically binds cTIGIT (SEQ ID NO: 2); (b) binds mTIGIT (SEQ ID NO: 3) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hTIGIT and cTIGIT; and (c) inhibits binding of CD155 to TIGIT.

27. An ABP that competes for binding to TIGIT with an ABP of any one of claims 1-26, wherein the ABP: (a) specifically binds cTIGIT (SEQ ID NO: 2); (b) binds mTIGIT (SEQ ID NO: 3) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hTIGIT and cTIGIT; and (c) inhibits binding of CD155 to TIGIT.

28. The ABP of any one of claims 1-27, wherein the ABP comprises an antibody.

29. The ABP of claim 28, wherein the antibody is a monoclonal antibody.

30. The ABP of any one of claims 28-29, wherein the antibody is selected from a human antibody, a humanized antibody or a chimeric antibody.

31. The ABP of any one of claims 1-30, wherein the ABP is multispecific.

32. The ABP of claim 31, wherein the ABP binds more than one antigen or more than one epitope on a single antigen.

33. The ABP of any one of claims 1-32, wherein the ABP comprises an antibody fragment.

34. The ABP of any one of claims 1-33, wherein the ABP comprises an alternative scaffold.

35. The ABP of any one of claims 1-34, wherein the ABP comprises an immunoglobulin constant region.

36. The ABP of any one of claims 1-3, 5-7, 9-11,13-15 or 17-35, wherein the ABP comprises heavy chain constant region of a class selected from IgA, IgD, IgE, IgG, or IgM.

37. The ABP of claim 36, wherein the ABP comprises a heavy chain constant region of the class IgG and a subclass selected from IgG4, IgG1, IgG2, or IgG3.

38. The ABP of any one of claims 1-37, wherein the ABP binds hTIGIT (SEQ ID NO: 1) with a K_D of less than about 10 nM, as measured by biolayer interferometry.

39. The ABP of any one of claims 1-38, wherein the ABP binds hTIGIT (SEQ ID NO: 1) with a K_D of less than about 5 nM, as measured by biolayer interferometry.

40. The ABP of any one of claims 1-39, wherein the ABP binds hTIGIT (SEQ ID NO: 1) with a K_D of less than about 2 nM, as measured by biolayer interferometry.

41. The ABP of any one of claims 1-40, wherein the ABP binds cTIGIT (SEQ ID NO: 2) with a K_D of less than about 100 nM, as measured by biolayer interferometry.

42. The ABP of any one of claims 1-41, wherein the ABP binds cTIGIT (SEQ ID NO: 2) with a K_D of less than about 10 nM, as measured by biolayer interferometry.

43. The ABP of any one of claims 1-42, wherein the ABP shows no significant binding to mTIGIT in a biolayer interferometry assay.

44. The ABP of any one of claims 1-43, wherein the ABP binds to cell surface mTIGIT with a K_D of less than about 50 nM.

45. The ABP of any one of claims 43-44, wherein the mTIGIT comprises SEQ ID NO: 3.

46. The ABP of any one of claims 1-45, wherein the ABP comprises a polypeptide sequence having a pyroglutamate (pE) residue at its N-terminus.

47. The ABP of any one of claims 1-46, wherein the ABP comprises a V_H sequence in which an N-terminal Q is substituted with pE.

48. The ABP of any one of claims 1-47, wherein the ABP comprises a V_L sequence in which an N-terminal E is substituted with pE.

49. The ABP of any one of claims 1-48, wherein the ABP comprises a heavy chain sequence in which an N-terminal Q is substituted with pE.

50. The ABP of any one of claims 1-49, wherein the ABP comprises a light chain sequence in which an N-terminal E is substituted with pE.

51. The ABP of any one of claims 1-50 for use as a medicament.

52. The ABP of any one of claims 1-51 for use in the treatment of a cancer or viral infection.

53. The ABP of claim 52 for use in the treatment of a cancer, wherein the cancer is selected from a solid tumor and a hematological tumor.

54. The ABP of any one of claims 1-53 for use as a medicament in the treatment of a disease or condition that was not responsive to a prior therapy.

55. The ABP of claim 54, wherein the prior therapy was a therapy comprising an agent that inhibits the interaction between PD-1 and PD-L1.

56. An isolated polynucleotide encoding an ABP of any one of claims 1-55, a V_H thereof, a V_L thereof, a light chain thereof, a heavy chain thereof or an antigen-binding portion thereof.

57. A vector comprising the polynucleotide of claim 56.

58. A host cell comprising the polynucleotide of claim 56 or the vector of claim 57.

59. A method of producing an ABP of any one of claims 1-55, comprising expressing the ABP in the host cell of claim 58 and isolating the expressed ABP.

60. A pharmaceutical composition comprising an ABP of any one of claims 1-55.

61. The pharmaceutical composition of claim 60, wherein the amount of the ABP in the pharmaceutical composition is sufficient to (a) increase effector T cell activity; (b) increase cytolytic T cell activity; (c) increase NK cell activity; (d) inhibit TIGIT-mediated signaling; (e) inhibit or block the binding of CD155 and or CD112 to TIGIT; or (f) any combination of (a) - (e), in a subject.

62. The pharmaceutical composition of any one of claims 60-61, further comprising an antibody that antagonizes PD-1 or blocks PD-L1 from interacting with PD-1.

63. The pharmaceutical composition of any one of claims 60-62 for use as a medicament.

64. The pharmaceutical composition of any one of claims 60-63 for use in the treatment of a cancer or a viral infection.

65. The pharmaceutical composition of claim 64 for use in the treatment of a cancer, wherein the cancer is selected from a solid tumor and a hematological tumor.

66. The pharmaceutical composition of any one of claims 60-65 for use as a medicament in the treatment of a disease or condition that was not responsive to a prior therapy.

67. The pharmaceutical composition of claim 66, wherein the prior therapy was a therapy comprising an agent that inhibits the interaction between PD-1 and PD-L1.

68. A method of treating or preventing a disease or condition in a subject in need thereof, comprising administering to the subject an effective amount of an ABP of any one of claims 1-55 or a pharmaceutical composition of any one of claims 60-67.

69. The method of claim 68, wherein the disease or condition is a cancer or viral infection.

70. The method of claim 69, wherein the disease or condition is a cancer, and the cancer is selected from a solid tumor and a hematological tumor.

71. A method of modulating an immune response in a subject in need thereof, comprising administering to the subject an effective amount of an ABP of any one of claims 1-55 or a pharmaceutical composition of any one of claims 60-67.

72. The method of any one of claims 68-71, further comprising administering one or more additional therapeutic agents to the subject.

73. The method of claim 72, wherein the additional therapeutic agent is selected from an agent that inhibits the interaction between PD-1 and PD-L1, a chemotherapy, an immunostimulatory agent, radiation, and combinations thereof.

74. The method of claim 73, wherein the additional therapeutic agent is an agent that inhibits the interaction between PD-1 and PD-L1, and wherein the agent that inhibits the interaction between PD-1 and PD-L1 is selected from an antibody, a peptidomimetic, a small molecule or a nucleic acid encoding such agent.

75. The method of claim 74, wherein the agent that inhibits the interaction between PD-1 and PD-L1 is selected from is selected from pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, BMS-936559, sulfamonomethoxine 1, and sulfamethizole 2.

76. The method of claim 73, wherein the additional therapeutic agent is an immunostimulatory agent selected from (a) an agent that blocks signaling of an inhibitory receptor of an immune cell or a ligand thereof or a nucleic acid encoding such agent; (b) an agonist to a stimulatory receptor of an immune cell or a nucleic acid encoding such agonist; (c) a cytokine or a nucleic acid encoding a cytokine; (d) an oncolytic virus or a nucleic acid encoding an oncolytic virus; (e) a T cell expressing a chimeric antigen receptor; (f) a bi- or multi-specific T cell directed antibody or a nucleic acid encoding such antibody; (g) an anti-TGF-ß antibody or a nucleic acid encoding such antibody; (h) a TGF-ß trap or a nucleic acid encoding such trap; (i) a vaccine to a cancer-associated antigen, including such antigen or a nucleic acid encoding such antigen and (j) combinations thereof.

77. The method of claim 76, wherein the additional therapeutic agent is an agent that blocks signaling of an inhibitory receptor of an immune cell or a ligand thereof or a nucleic acid encoding such agent, and the inhibitory receptor or ligand thereof is selected from CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, Tim3, neuritin, BTLA, CECAM-1, CECAM-5, VISTA, LAIR1, CD160, 2B4, TGF-R, KIR, and combinations thereof.

78. The method of claim 76, wherein the additional therapeutic agent is an agonist to a stimulatory receptor of an immune cell or a nucleic acid encoding such agonist, and the stimulatory receptor of an immune cell is selected from OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD28, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, CD83 ligand, and combinations thereof.

79. The method of claim 76, wherein the additional therapeutic agent is a cytokine or a nucleic acid encoding a cytokine selected from IL-2, IL-5, IL-7, IL-12, IL-15, IL-21, and combinations thereof.

80. The method of claim 76, wherein the additional therapeutic agent is an oncolytic virus or a nucleic acid encoding an oncolytic virus selected from herpes simplex virus, vesicular stomatitis virus, adenovirus, Newcastle disease virus, vaccinia virus, a maraba virus, and combinations thereof.

81. The method of any one of claims 72-80, wherein the additional therapeutic agent is formulated in the same pharmaceutical composition as the ABP.

82. The method of any one of claims 72-80, wherein the additional therapeutic agent is formulated in a different pharmaceutical composition from the ABP.

83. The method of any one of claims 72-80 or 82, wherein the additional therapeutic agent is administered prior to administering the ABP.

84. The method of any one of claims 72-80 or 82, wherein the additional therapeutic agent is administered after administering the ABP.

85. The method of any one of claims 72-84, wherein the additional therapeutic agent is administered contemporaneously with the ABP.

86. The method of any one of claims 68-85, wherein the subject is a subject that has been treated with an agent that inhibits the interaction between PD-1 and PD-L1 prior to performing such method.

87. The method of any one of claims 68-86, wherein the disease or condition afflicting the subject was not responsive to a prior therapy.

88. The method of claim 87, wherein the prior therapy was a therapy comprising an agent that inhibits the interaction between PD-1 and PD-L1.

89. A kit comprising a pharmaceutical composition of any one of claims 60-61, and instructions for the use of such pharmaceutical composition.

90. The kit of claim 89, further comprising an additional pharmaceutical composition comprising an additional therapeutic agent and instructions for the use of such additional therapeutic agent.

91. The kit of claim 90, wherein the additional therapeutic agent is selected from an agent that inhibits the interaction between PD-1 and PD-L1, a chemotherapy, an immunostimulatory agent, radiation, and combinations thereof.

92. The kit of claim 91, wherein the additional therapeutic agent is an agent that inhibits the interaction between PD-1 and PD-L1, and wherein the agent inhibits the interaction between PD-1 and PD-L1 is selected from an antibody, a peptidomimetic, a small molecule or a nucleic acid encoding such agent.

93. The kit of claim 92, wherein the agent that inhibits the interaction between PD-1 and PD-L1 is selected from is selected from pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, BMS-936559, sulfamonomethoxine 1, and sulfamethizole 2.

94. The kit of claim 91, wherein the additional therapeutic agent is an immunostimulatory agent selected from (a) an agent that blocks signaling of an inhibitory receptor of an immune cell or a ligand thereof or a nucleic acid encoding such agent; (b) an agonist to a stimulatory receptor of an immune cell or a nucleic acid encoding such agonist; (c) a cytokine or a nucleic acid encoding a cytokine; (d) an oncolytic virus or a nucleic acid encoding an oncolytic virus; (e) a T cell expressing a chimeric antigen receptor; (f) a bi- or multi-specific T cell directed antibody or a nucleic acid encoding such antibody; (g) an anti-TGF-ß antibody or a nucleic acid encoding such antibody; (h) a TGF-ß trap or a nucleic acid encoding such trap; (i) a vaccine to a cancer-associated antigen, including such antigen or a nucleic acid encoding such antigen and (j) combinations thereof.

95. The kit of claim 94, wherein the additional therapeutic agent is an agent that blocks signaling of an inhibitory receptor of an immune cell or a ligand thereof or a nucleic acid encoding such agent, and the inhibitory receptor or ligand thereof is selected from CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, Tim3, neuritin, BTLA, CECAM-1, CECAM-5, VISTA, LAIR1, CD160, 2B4, TGF-R, KIR, and combinations thereof.

96. The kit of claim 94, wherein the additional therapeutic agent is an agonist to a stimulatory receptor of an immune cell or a nucleic acid encoding such agonist, and the stimulatory receptor of an immune cell is selected from OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD28, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, CD83 ligand, and combinations thereof.

97. The kit of claim 94, wherein the additional therapeutic agent is a cytokine or a nucleic acid encoding a cytokine selected from IL-2, IL-5, IL-7, IL-12, IL-15, IL-21, and combinations thereof.

98. The kit of claim 94, wherein the additional therapeutic agent is an oncolytic virus or a nucleic acid encoding an oncolytic virus selected from herpes simplex virus, vesicular stomatitis virus, adenovirus, Newcastle disease virus, vaccinia virus, a maraba virus, and combinations thereof.