(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 June 2014 (12.06.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/087248 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/IB2013/003164

(22) International Filing Date:
3 December 2013 (03.12.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/732,452	3 December 2012 (03.12.2012)	US
61/816,788	28 April 2013 (28.04.2013)	US
61/863,106	7 August 2013 (07.08.2013)	US
61/881,523	24 September 2013 (24.09.2013)	US
61/898,710	1 November 2013 (01.11.2013)	US

(71) Applicant: **NOVIMMUNE S.A.** [CH/CH]; 14 Ch. des Aulx, Plan-les-Ouates, CH-1228 Geneva (CH).

(72) Inventors: **MASTERNAK, Krzysztof**; Grand' Rue 15, CH-1146 Mollens (CH). **FISCHER, Nicolas**; 16, Ch. des Ouches, CH-1203 Geneva (CH). **ROUSSEAU, Francois**; 105 Impasse sous le Clos, F-74160 Collonges Sous Saleve (FR). **DHEILLY, Elie**; 14 Ch. des Aulx, Plan-les-Ouates, CH-1228 Geneva (CH). **KOSCO-VILBOIS, Marie**; Le Cret, F-74270 Minzier (FR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

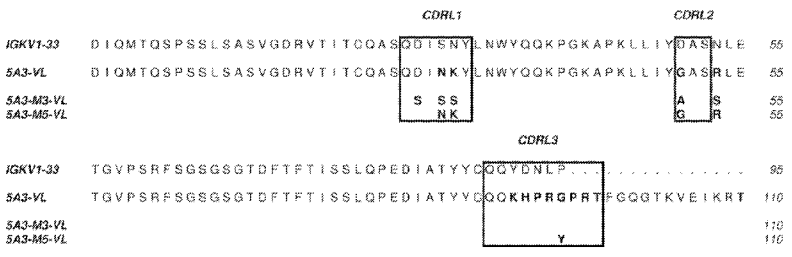
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: ANTI-CD47 ANTIBODIES AND METHODS OF USE THEREOF

FIGURE 1



(57) Abstract: The invention relates to monoclonal and/or monovalent antibodies that bind CD47. The invention relates to monoclonal and/or monovalent antibodies that bind CD19. The invention also relates to novel bispecific monoclonal antibodies carrying a different specificity for each binding site of the immunoglobulin molecule, where one of the binding sites is specific for CD47. The invention also relates to novel bispecific monoclonal antibodies carrying a different specificity for each binding site of the immunoglobulin molecule, where one of the binding sites is specific for CD19.

WO 2014/087248 A2

ANTI-CD47 ANTIBODIES AND METHODS OF USE THEREOF

Related Applications

[0001] This claims the benefit of U.S. Provisional Application No. 61/732452, filed December 3, 2012; U.S. Provisional Application No. 61/816788, filed April 28, 2013; U.S. Provisional Application No. 61/863106, filed August 7, 2013; U.S. Provisional Application No. 61/881523, filed September 24, 2013; and U.S. Provisional Application No. 61/898710, filed November 1, 2013; each of which is incorporated herein by reference in its entirety.

Field of the Invention

[0002] The invention relates to monoclonal and/or monovalent antibodies that bind CD47. The invention relates to monoclonal and/or monovalent antibodies that bind CD19. The invention also relates to novel bispecific monoclonal antibodies carrying a different specificity for each binding site of the immunoglobulin molecule, where one of the binding sites is specific for CD47. The invention also relates to novel bispecific monoclonal antibodies carrying a different specificity for each binding site of the immunoglobulin molecule, where one of the binding sites is specific for CD19.

Background of the Invention

[0003] CD47 or Integrin-Associated-Protein (IAP) is a ubiquitous 50 kDa transmembrane glycoprotein with multiple functions in cell-cell communication. It interacts with multiple ligands, such as integrins, SIRPα (Signal Regulatory Protein alpha), SIRPγ and thrombospondins (Oldenborg, P.A., CD47: A Cell Surface Glycoprotein Which Regulates Multiple Functions of Hematopoietic Cells in Health and Disease, ISRN Hematol. 2013; 2013:614619; Soto-Pantoja DR, et al., Therapeutic opportunities for targeting the ubiquitous cell surface receptor CD47 (2012), Expert Opin Ther Targets. 2013 Jan;17(1):89-103; Sick E, et al., CD47 Update: a multifaced actor in the tumor microenvironment of potential therapeutic interest, Br J Pharmacol. 2012 Dec;167(7):1415-30). In the context of the innate immune system, CD47 functions as a marker of self, transmitting an inhibitory "don't kill me" signal through binding to SIRPα expressed by myeloid cells, such as macrophages, neutrophils, and dendritic cells., The role of widespread expression of CD47 in the physiological situation is therefore to protect healthy

cells against the elimination by the innate immune system (Oldenborg PA, et al., CD47-Signal Regulatory Protein α (Sirpα) Regulates Fcγ and Complement Receptor–Mediated Phagocytosis, J Exp Med. 2001 Apr 2;193(7):855-62; Mattias Olsson, Role of the CD47/SIRPα-interaction in regulation of macrophage phagocytosis, Department of Integrative Medical Biology, Section for Histology and CellBiology, Umeå University,Umeå, Sweden, Thesis; Oldenborg PA., Role of CD47 in erythroid cells and in autoimmunity, Leuk Lymphoma. 2004 Jul;45(7):1319-27; Oldenborg PA, et al., Role of CD47 as a Marker of Self on Red Blood Cells., Science. 2000 Jun 16;288(5473):2051-4; Brown EJ, Frazier WA., integrin-associated protein (CD47) and its ligands., Trends Cell Biol. 2001 Mar;11(3):130-5).

[0004] Tumor cells hijack this immunosuppressive mechanism by overexpressing CD47, which efficiently helps them to escape immune surveillance and killing by innate immune cells. (Majeti R, Chet al., CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells, Cell. 2009 Jul 23;138(2):286-99; S. Jaiswal et al., CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis., Cell. 2009 Jul 23;138(2):271-85). CD47 expression is upregulated in most human cancers (e.g., NHL, AML, breast, colon, glioblastoma, glioma, ovarian, bladder and prostate cancers) and increased levels of CD47 expression clearly correlate with aggressive disease and poor survival. (Majeti R, et al., Cell. 2009 Jul 23;138(2):286-99; S. Jaiswal et al., Cell. 2009 Jul 23;138(2):271-85; Willingham SB, et al., The CD47-signal regulatory protein alpha (SIRPα) interaction is a therapeutic target for human solid tumors, Proc Natl Acad Sci U S A. 2012 Apr 24;109(17):6662-7; Chao MP, et al., Therapeutic antibody targeting of CD47 eliminates human acute lymphoblastic leukemia., Cancer Res. 2011 Feb 15;71(4):1374-84).

[0005] The widespread expression of CD47 in healthy tissues brings the question of treatment safety and efficacy: First, targeting CD47 with a neutralizing monoclonal antibody (Mab) could affect healthy cells, resulting in severe toxicities as shown in preclinical studies with mice and cynomolgus monkeys (Willingham SB, et al., Proc Natl Acad Sci U S A. 2012 Apr 24;109(17):6662-7; Weiskopf K, et al., Engineered SIRPα Variants as Immunotherapeutic Adjuvants to Anticancer Antibodies, Science. 2013 Jul 5;341(6141):88-91). Second, even if severe toxicities could be avoided or mitigated by using alternative formats (Weiskopf K, et al., Science. 2013 Jul 5;341(6141):88-91), broad expression of CD47 could still cause a rapid elimination of CD47-binding molecules

through target-mediated drug disposition resulting in poor pharmacokinetics and decreased efficacy.

[0006] Accordingly, there exists a need for antibodies and therapeutics that enable targeting of CD47 and overcome these obstacles.

Summary of the Invention

[0007] The invention provides monoclonal antibodies that bind CD47. These antibodies are collectively referred to herein as anti-CD47 monoclonal antibodies or anti-CD47 mAbs. Preferably, the monoclonal antibodies are specific for at least human CD47. In some embodiments, the monoclonal antibodies that recognize human CD47 are also cross-reactive for at least one other non-human CD47 protein, such as, by way of non-limiting example, non-human primate CD47, e.g., cynomolgus monkey CD47, and/or rodent CD47. In some embodiments, these anti-CD47 monoclonal antibodies inhibit the interaction between CD47 and signal-regulatory protein alpha (SIRPα). In some embodiments, these anti-CD47 monoclonal antibodies inhibit the interaction between human CD47 and human SIRPα. The invention also include antibodies that bind to the same epitope as an anti-CD47 monoclonal antibody disclosed herein and inhibits the interaction between CD47 and SIRPα, e.g., between human CD47 and human SIRPα.

[0008] The invention also provides monovalent antibodies and/or bispecific antibodies that include at least a first arm that is specific for CD47. Preferably, the monovalent antibodies and/or bispecific antibodies are specific for at least human CD47. In some embodiments, the monovalent antibodies and/or bispecific antibodies that recognize human CD47 are also cross-reactive for at least one other non-human CD47 protein, such as, by way of non-limiting example, non-human primate CD47, e.g., cynomolgus monkey CD47, and/or rodent CD47. In some embodiments, these anti-CD47 monovalent antibodies and/or anit-CD47 bispecific antibodies inhibit the interaction between CD47 and signal-regulatory protein alpha (SIRPα). In some embodiments, these anti-CD47 monovalent antibodies and/or anit-CD47 bispecific antibodies inhibit the interaction between human CD47 and human SIRPα. The invention also include antibodies that bind to the same epitope as an anti-CD47 monovalent and/or an anti-CD47 bispecific antibody disclosed herein and inhibits the interaction between CD47 and SIRPα, e.g., between human CD47 and human SIRPα.

[0009] The invention provides bispecific antibodies that recognize CD47 and a second target. The invention allows for the identification, production and purification of bispecific antibodies that are undistinguishable in sequence from standard antibodies and where one of the binding sites is specific for CD47 and the second binding site is specific for another target, for example a tumor-associated antigen (TAA). In some embodiments, the TAA is an antigen that is expressed on the cell surface of a cancer cell. In some embodiments, the cancer cell is selected from a lung cancer cell, a bronchial cancer cell, a prostate cancer cell, a breast cancer cell, a colorectal cancer cell, a pancreatic cancer cell, an ovarian, a leukemia cancer cell, a lymphoma cancer cell, an esophageal cancer cell, a liver cancer cell, a urinary and/or bladder cancer cell, a renal cancer cell, an oral cavity cancer cell, a pharyngeal cancer cell, a uterine cancer cell, and/or a melanoma cancer cell.

[0010] In some embodiments, suitable TAA, by way of non-limiting example, include CD20, HER2, HER3, EGFR, IGF1R, c-Met, PDGFR1, CD40, CD40L, CD30, CS1, CD70, glypican, mesothelin, PSMA, PSCA, MUC1, CA125, CEA, FRA, EpCAM, DR5, HGFR1, and/or 5T4.

[0011] CD47 (Cluster of Differentiation 47) functions as a "don't eat me" signal for phagocytic cells and is known to be over-expressed by many tumors (immune escape). CD47 interacts with SIRPα, which is expressed on phagocytic cells. CD47 down-regulates phagocytic activity. CD47 inhibits dendritic cell (DC) maturation and activation. CD47 has also been implicated in processes such as, for example, apoptosis, survival, proliferation, adhesion, migration, and regulation of angiogenesis, blood pressure, tissue perfusion, and/or platelet homeostasis.

[0012] CD47 has also been implicated in cancer. For example, CD47 is overexpressed in various hematological and solid malignancies. CD47 is a documented cancer stem cell/tumor initiating cell marker. It is thought that CD47 overexpression may help tumor cells to escape immune surveillance and killing by innate immune cells. High levels of CD47 are also associated with poor clinical outcome in cancers such as, for example, leukemias, lymphomas, breast cancer, colon cancer, ovarian cancer, bladder cancer, prostate cancer, and/or glioma. Thus, targeting CD47 would be useful in treating, delaying the progression of, or otherwise ameliorating a symptom of cancer.

[0013] As CD47 is ubiquitously expressed, it is a difficult target for a monoclonal antibody (mAb). Nevertheless, the antibodies that are specific for CD47 described herein are useful as monospecific antibodies and can be used for therapeutic intervention or as a

research or diagnostic reagent. Monospecific antibodies of the invention that bind CD47, as well as fragments of these monospecific antibodies that are immunologically active and still bind CD47, include the exemplary antibodies described herein, *e.g.*, the 5A3 antibody, the 5A3M4 antibody, the 5A3M3 antibody, the 5A3M5 antibody, the KE8 antibody, the KE8-P6H5 antibody (also referred to herein as KE8H5), the KE8-P3B2 antibody (also referred to herein as KE8B2), the KE8-P2A2 antibody (also referred to herein as KE8A25), the KE8F2 antibody, the KE8G2 antibody, the KE84G9 antibody, the KE81G9 antibody, the KE81A3 antibody, the KE8E8 antibody, the KE8G6 antibody, the KE8H3 antibody, the KE8C7 antibody, the KE8A4 antibody, the KE8A8 antibody, the KE8G11 antibody, the KE8B7 antibody, the KE8F1 antibody, the KE8C4 antibody, the KE8A3 antibody, the KE86G9 antibody, the KE8H6 antibody, the KA3 antibody, the KA3-P5G2 antibody (also referred to herein as KA3G2), the KA3-P1A3 antibody (also referred to herein as KA3A3), the KA3-P5C5 antibody (also referred to herein as KA3C5), the KA3H8 antibody, the KA3B2 antibody, the KA3A2 antibody, the KA3D3 antibody, the KA3H3 antibody, the KC4 antibody, the KC4-P1G11KC4-P4C11 antibody, the KC4-P6B1KC4-P4F4 antibody, and the KC4-P2E2 antibody (also referred to herein as KC4E2), the KC4 antibody, the KC4F4 antibody, the KC4A1 antibody, the KC4C11 antibody, the KC4E10 antibody, the KC4B1 antibody, the KC4C3 antibody, the KC4A4 antibody, the KC4G11 antibody, the KC4G9 antibody and fragments thereof.

[0014] The antibodies of the invention that bind CD47 and fragments thereof serve to modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with the functional activity of CD47. Functional activities of CD47 include, by way of non-limiting example, interaction with SIRPα. The antibodies are considered to completely modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with the CD47-SIRPα interaction when the level of CD47-SIRPα interaction in the presence of the antibody is decreased by at least 95%, *e.g.*, by 96%, 97%, 98%, 99% or 100% as compared to the level of CD47-SIRPα interaction in the absence of binding with an antibody described herein. The antibodies are considered to partially modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with the CD47-SIRPα interaction when the level of CD47-SIRPα interaction in the presence of the antibody is decreased by less than 95%, *e.g.*, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 85% or 90% as compared to the level of CD47-SIRPα interaction in the absence of binding with an antibody described herein.

[0015] The invention also provides bispecific antibodies in which at least one

binding site is specific for CD47. The bispecific antibodies of the invention target CD47 and a second antigen, *e.g.*, a tumor-associated antigen (TAA). In some embodiments, the bispecific antibody includes a functional Fc portion. The TAA-binding arm of the bispecific antibody targets the CD47 arm to the tumor cell or cancer stem cell. The CD47 arm blocks, inhibits or otherwise reduces the interaction between CD47 and SIRPα, thereby conveying an "eat me" signal to the phagocyte. In some embodiments, the TAA-binding arm of the bispecific antibody includes an anti-CD19 antibody sequence or antigen-binding fragment thereof.

[0016] In some embodiments, the bispecific antibody exhibits a "balanced" affinity for each of the two targets. In other embodiments, the bispecific antibody exhibits an "unbalanced" affinity for each of the two targets. For example, in an anti-CD47/CD19 bispecific antibody, the affinity of the anti-CD19 arm is increased. For example, in an anti-CD47/CD19 bispecific antibody, the affinity of the anti-CD47 arm is decreased. For example, in an anti-CD47/CD19 bispecific antibody, the affinity of the anti-CD19 arm is increased and the affinity of the anti-CD47 arm is decreased. These unbalanced affinity bispecific antibodies are useful, for example, to improve selectivity for a target cell or group of target cells.

[0017] In some embodiments, the affinity of the anti-CD19 arm is increased by at least 100 fold following affinity maturation. In some embodiments, the affinity of the anti-CD47 arm is decreased by at least 2 fold following affinity dematuration. For example, in some embodiments, the anti-CD47 arm exhibits an affinity for CD47 that is between about 2 fold and 100 fold lower following affinity dematuration.

[0018] The bispecific antibodies of the invention that include at least one anti-CD47 arm serve to modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with the functional activity of CD47. Functional activities of CD47 include, by way of non-limiting example, interaction with SIRPα. The bispecific antibodies are considered to completely modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with the CD47-SIRPα interaction when the level of CD47-SIRPα interaction in the presence of the bispecific antibody is decreased by at least 95%, *e.g.*, by 96%, 97%, 98%, 99% or 100% as compared to the level of CD47-SIRPα interaction in the absence of binding with a bispecific antibody described herein. The bispecific antibodies are considered to partially modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with the CD47-SIRPα interaction when the level of CD47-SIRPα interaction in the presence of the

bispecific antibody is decreased by less than 95%, *e.g.*, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 85% or 90% as compared to the level of CD47-SIRPα interaction in the absence of binding with a bispecific antibody described herein.

[0019] The anti-CD47 arms of the bispecific antibodies of the invention are useful with a number of arms that bind other antigens, *e.g.*, TAAs. Exemplary anti-CD47 arms, anti-CD47 monovalent antibodies and/or bispecific antibodies of the invention include the antibodies referred to herein as the 5A3 antibody, the 5A3M4 antibody, the 5A3M3 antibody, the 5A3M5 antibody, the KE8 antibody, the KE8-P6H5 antibody (also referred to herein as KE8H5), the KE8-P3B2 antibody (also referred to herein as KE8B2), the KE8-P2A2 antibody (also referred to herein as KE8A25), the KE8F2 antibody, the KE8G2 antibody, the KE84G9 antibody, the KE81G9 antibody, the KE81A3 antibody, the KE8E8 antibody, the KE8G6 antibody, the KE8H3 antibody, the KE8C7 antibody, the KE8A4 antibody, the KE8A8 antibody, the KE8G11 antibody, the KE8B7 antibody, the KE8F1 antibody, the KE8C4 antibody, the KE8A3 antibody, the KE86G9 antibody, the KE8H6 antibody, the KA3 antibody, the KA3-P5G2 antibody (also referred to herein as KA3G2), the KA3-P1A3 antibody (also referred to herein as KA3A3), the KA3-P5C5 antibody (also referred to herein as KA3C5), the KA3H8 antibody, the KA3B2 antibody, the KA3A2 antibody, the KA3D3 antibody, the KA3H3 antibody, the KC4 antibody, the KC4-P1G11KC4-P4C11 antibody, the KC4-P6B1KC4-P4F4 antibody, and the KC4-P2E2 antibody (also referred to herein as KC4E2), the KC4 antibody, the KC4F4 antibody, the KC4A1 antibody, the KC4C11 antibody, the KC4E10 antibody, the KC4B1 antibody, the KC4C3 antibody, the KC4A4 antibody, the KC4G11 antibody, the KC4G9 antibody and fragments thereof. In some embodiments, the TAA-binding arm of the bispecific antibody includes an anti-CD19 antibody sequence or antigen-binding fragment thereof.

[0020] The invention provides isolated bispecific antibodies having a first arm that includes a first amino acid sequence that binds CD47 and a second arm that includes a second amino acid sequence that does not bind CD47, wherein the bispecific antibody inhibits interaction between CD47 and signal-regulatory protein alpha (SIRPα). In some embodiments, the second amino acid sequence binds a tumor associated antigen (TAA). In some embodiments, the bispecific antibody inhibits interaction between human CD47 and human SIRPα.

[0021] In some embodiments, the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is at least ten times more potent than a

corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that includes the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein.

[0022] In some embodiments, the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is at least 100 times more potent than a corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that includes the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein.

[0023] In some embodiments, the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is at least 1,000 times more potent than a corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that includes the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein.

[0024] In some embodiments, the bispecific antibody includes a first arm that inhibits the interaction between human CD47 at the surface of cells and soluble human SIRPα with an IC50 greater than 5 nM in the assay described in Example 4 and in which the monovalent antibody 5A3M3 has an IC50 of approximately 13 nM.

[0025] In some embodiments, the bispecific antibody includes a first arm that is recovered at more than 80% after incubation at 37°C for 30 minutes in human whole blood at a concentration of 10 μg/ml as described in Example 15.

[0026] In some embodiments, the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is at least ten times, at least 100 times or at least 1,000 times more potent than a corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that includes the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein, and includes a first arm that inhibits the interaction between human CD47 at the surface of cells and soluble human SIRPα with an IC50 greater than 5 nM in the assay described in Example 4 and in which the monovalent antibody 5A3M3 has an IC50 of approximately 13 nM.

[0027] In some embodiments, the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is at least ten times, at least 100 times or at least 1,000 times more potent than a corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that

includes the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein, and includes a first arm that is recovered at more than 80% after incubation at 37°C for 30 minutes in human whole blood at a concentration of 10 μg/ml as described in Example 15.

[0028] In some embodiments, the TAA is CD19. In some embodiments, the second amino acid sequence does not bind a human protein.

[0029] In some embodiments, the first amino acid sequence includes a variable heavy chain complementarity determining region 1 (CDRH1) amino acid sequence of SEQ ID NO: 225, a variable heavy chain complementarity determining region 2 (CDRH2) amino acid sequence of SEQ ID NO: 226, a variable heavy chain complementarity determining region 3 (CDRH3) amino acid sequence of SEQ ID NO: 227, a variable light chain complementarity determining region 1 (CDRL1) amino acid sequence selected from SEQ ID NO: 228-241 and 262-272, a variable light chain complementarity determining region 2 (CDRL2) amino acid sequence selected from 242-245 and 273-280, and a variable light chain complementarity determining region 3 (CDRH3) amino acid sequence selected from 246-261 and 281.

[0030] In some embodiments, the first amino acid sequence includes a variable heavy chain amino acid sequence of SEQ ID NO: 114 and a variable light chain amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204 and 206.

[0031] In some embodiments, the bispecific antibody includes two copies of a single heavy chain polypeptide and a first light chain and a second light chain, wherein the first and second light chains are different.

[0032] In some embodiments, at least a portion of the first light chain is of the Kappa type and at least a portion of the second light chain is of the Lambda type. In some embodiments, the first light chain includes at least a Kappa constant region. In some embodiments, the first light chain further includes a Kappa variable region. In some embodiments, the first light chain further includes a Lambda variable region. In some embodiments, the second light chain includes at least a Lambda constant region. In some embodiments, the second light chain further includes a Lambda variable region. In some embodiments, the second light chain further includes a Kappa variable region. In some embodiments, the first light chain includes a Kappa constant region and a Kappa variable

region, and wherein the second light chain includes a Lambda constant region and a Lambda variable region.

[0033] In some embodiments, the constant and variable framework region sequences are human.

[0034] The invention also provides bispecific antibodies and/or monovalent antibodies that include at least a first arm that inhibits the interaction between human CD47 at the surface of cells and soluble human SIRPα with an IC50 greater than 5 nM in the assay described in Example 4 and in which the antibody 5A3M3 has an IC50 of approximately 13 nM.

[0035] The invention also provides bispecific antibodies and/or monovalent antibodies that include at least a first arm that is recovered at more than 80% after incubation at 37°C for 30 minutes in human whole blood at a concentration of 10 μg/ml as described in Example 15. In some embodiments, the bispecific antibody and/or monovalent antibody inhibits interaction between CD47 and signal-regulatory protein alpha (SIRPα). In some embodiments, the bispecific antibody and/or monovalent antibody inhibits interaction between human CD47 and human SIRPα.

[0036] The invention also provides isolated bispecific antibodies having a first arm that includes a first amino acid sequence that binds CD47 and a second arm that includes a second amino acid sequence that binds CD19, wherein the bispecific antibody inhibits interaction between CD47 and signal-regulatory protein alpha (SIRPα).

[0037] In some embodiments, the bispecific antibody inhibits interaction between human CD47 and human SIRPα. In some embodiments, the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is selected from the group consisting of at least ten times more potent, at least 100 times more potent and at least 1,000 times more potent than a corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that includes the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein.

[0038] In some embodiments, the first amino acid sequence includes a variable heavy chain complementarity determining region 1 (CDRH1) amino acid sequence of SEQ ID NO: 225, a variable heavy chain complementarity determining region 2 (CDRH2) amino acid sequence of SEQ ID NO: 226, a variable heavy chain complementarity determining region 3 (CDRH3) amino acid sequence of SEQ ID NO: 227, a variable light chain

complementarity determining region 1 (CDRL1) amino acid sequence selected from SEQ ID NO: 228-241 and 262-272, a variable light chain complementarity determining region 2 (CDRL2) amino acid sequence selected from 242-245 and 273-280, and a variable light chain complementarity determining region 3 (CDRH3) amino acid sequence selected from 246-261 and 281.

[0039] In some embodiments, the first amino acid sequence includes a variable heavy chain amino acid sequence of SEQ ID NO: 114 and a variable light chain amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204 and 206.

[0040] In some embodiments, the bispecific antibody includes two copies of a single heavy chain polypeptide and a first light chain and a second light chain, wherein the first and second light chains are different.

[0041] In some embodiments, at least a portion of the first light chain is of the Kappa type and at least a portion of the second light chain is of the Lambda type. In some embodiments, the first light chain includes at least a Kappa constant region. In some embodiments, the first light chain further includes a Kappa variable region. In some embodiments, the first light chain further includes a Lambda variable region. In some embodiments, the second light chain includes at least a Lambda constant region. In some embodiments, the second light chain further includes a Lambda variable region. In some embodiments, the second light chain further includes a Kappa variable region. In some embodiments, the first light chain includes a Kappa constant region and a Kappa variable region, and wherein the second light chain includes a Lambda constant region and a Lambda variable region.

[0042] In some embodiments, the constant and variable framework region sequences are human.

[0043] The invention also provides monovalent antibodies that bind CD47. These antibodies are collectively referred to herein as anti-CD47 monovalent antibodies or anti-CD47 monov mAbs. The monovalent antibodies of the invention include one arm that specific recognizes CD47, and a second arm referred to herein as a dummy arm. The dummy arm includes an amino acid sequence that does not bind or otherwise cross-react with a human protein. In some embodiments, the dummy arm includes an amino acid sequence that does not bind or otherwise cross-react with a human protein that is found in

whole blood. Those of ordinary skill in the art will appreciate that human proteins found in the blood are a proxy that represent all, or substantially all, antigens present in system circulation. In some embodiments, the dummy arm includes an amino acid sequence that does not bind or otherwise cross-react with a human protein that is found in solid tissue. Preferably, the monovalent antibodies are specific for at least human CD47. In some embodiments, the monovalent antibodies that recognize human CD47 are also cross-reactive for at least one other non-human CD47 protein, such as, by way of non-limiting example, non-human primate CD47, e.g., cynomolgus monkey CD47, and/or rodent CD47.

[0044] The anti-CD47 arms of the monovalent antibodies of the invention are useful with any dummy arm. Exemplary anti-CD47 arms of the monovalent antibodies of the invention include the antibodies referred to herein as the 5A3 antibody, the 5A3M4 antibody, the 5A3M3 antibody, the 5A3M5 antibody, the KE8 antibody, the KE8-P6H5 antibody (also referred to herein as KE8H5), the KE8-P3B2 antibody (also referred to herein as KE8B2), the KE8-P2A2 antibody (also referred to herein as KE8A25), the KE8F2 antibody, the KE8G2 antibody, the KE84G9 antibody, the KE81G9 antibody, the KE81A3 antibody, the KE8E8 antibody, the KE8G6 antibody, the KE8H3 antibody, the KE8C7 antibody, the KE8A4 antibody, the KE8A8 antibody, the KE8G11 antibody, the KE8B7 antibody, the KE8F1 antibody, the KE8C4 antibody, the KE8A3 antibody, the KE86G9 antibody, the KE8H6 antibody, the KA3 antibody, the KA3-P5G2 antibody (also referred to herein as KA3G2), the KA3-P1A3 antibody (also referred to herein as KA3A3), the KA3-P5C5 antibody (also referred to herein as KA3C5), the KA3H8 antibody, the KA3B2 antibody, the KA3A2 antibody, the KA3D3 antibody, the KA3H3 antibody, the KC4 antibody, the KC4-P1G11KC4-P4C11 antibody, the KC4-P6B1KC4-P4F4 antibody, and the KC4-P2E2 antibody (also referred to herein as KC4E2), the KC4 antibody, the KC4F4 antibody, the KC4A1 antibody, the KC4C11 antibody, the KC4E10 antibody, the KC4B1 antibody, the KC4C3 antibody, the KC4A4 antibody, the KC4G11 antibody, the KC4G9 antibody and fragments thereof. In some embodiments, the TAA-binding arm of the bispecific antibody includes an anti-CD19 antibody sequence or antigen-binding fragment thereof.

[0045] In some embodiments, the monovalent antibody inhibits interaction between human CD47 and human SIRPα.

[0046] In some embodiments, the anti-CD47 arm of the monovalent antibody includes a first amino acid sequence that includes a variable heavy chain complementarity

determining region 1 (CDRH1) amino acid sequence of SEQ ID NO: 225, a variable heavy chain complementarity determining region 2 (CDRH2) amino acid sequence of SEQ ID NO: 226, a variable heavy chain complementarity determining region 3 (CDRH3) amino acid sequence of SEQ ID NO: 227, a variable light chain complementarity determining region 1 (CDRL1) amino acid sequence selected from SEQ ID NO: 228-241 and 262-272, a variable light chain complementarity determining region 2 (CDRL2) amino acid sequence selected from 242-245 and 273-280, and a variable light chain complementarity determining region 3 (CDRH3) amino acid sequence selected from 246-261 and 281.

[0047] In some embodiments, the anti-CD47 arm of the monovalent antibody includes a first amino acid sequence that includes a variable heavy chain amino acid sequence of SEQ ID NO: 114 and a variable light chain amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204 and 206.

[0048] In some embodiments, the monovalent antibody includes two copies of a single heavy chain polypeptide and a first light chain and a second light chain, wherein the first and second light chains are different.

[0049] In some embodiments, at least a portion of the first light chain is of the Kappa type and at least a portion of the second light chain is of the Lambda type. In some embodiments, the first light chain includes at least a Kappa constant region. In some embodiments, the first light chain further includes a Kappa variable region. In some embodiments, the first light chain further includes a Lambda variable region. In some embodiments, the second light chain includes at least a Lambda constant region. In some embodiments, the second light chain further includes a Lambda variable region. In some embodiments, the second light chain further includes a Kappa variable region. In some embodiments, the first light chain includes a Kappa constant region and a Kappa variable region, and wherein the second light chain includes a Lambda constant region and a Lambda variable region.

[0050] In some embodiments, the constant and variable framework region sequences are human.

[0051] The bispecific antibodies of the invention are generated using any methods known in the art such as, by way of non-limiting example, the use of cross-linked fragments, quadromas, and/or any of a variety of recombinant formats such as, by way of

non-limiting examples, linked antibody fragments, forced heterodimers, and or recombinant formats based on single domains. Examples of Bispecific formats include but are not limited to bispecific IgG based on Fab arm exchange (Gramer et al., 2013 MAbs. 5(6)); the CrossMab format (Klein C et al., 2012 MAbs 4(6)); multiple formats based on forced heterodimerization approaches such as SEED technology (Davis JH et al., 2010 Protein Eng Des Sel. 23(4):195-202), electrostatic steering (Gunasekaran K et al., J Biol Chem. 2010 285(25):19637-46.) or knob-into-hole (Ridgway JB et al., Protein Eng. 1996 9(7):617-21.) or other sets of mutations preventing homodimer formation (Von Kreudenstein TS et al., 2013 MAbs. 5(5):646-54.); fragment based bispecific formats such as tandem scFv (such asBiTEs) (Wolf E et al., 2005 Drug Discov. Today 10(18):1237-44.); bispecific tetravalent antibodies (Pörtner LM et al., 2012 Cancer Immunol Immunother. 61(10):1869-75.); dual affinity retargeting molecules (Moore PA et al., 2011 Blood.117(17):4542-51), diabodies (Kontermann RE et al., Nat Biotechnol. 1997 15(7):629-31).

[0052] In some embodiments, the bispecific antibodies carry a different specificity in each combining site and including two copies of a single heavy chain polypeptide and a first light chain and a second light chain, wherein the first and second light chains are different.

[0053] In some antibodies, at least a first portion of the first light chain is of the Kappa type and at least a portion of the second light chain is of the Lambda type. In some antibodies, the first light chain includes at least a Kappa constant region. In some antibodies, the first light chain further includes a Kappa variable region. In some antibodies, the first light chain further includes a Lambda variable region. In some antibodies, the second light chain includes at least a Lambda constant region. In some antibodies, the second light chain further includes a Lambda variable region. In some antibodies, the second light chain further includes a Kappa variable region. In some antibodies, the first light chain includes a Kappa constant region and a Kappa variable region, and the second light chain includes a Lambda constant region and a Lambda variable region. In some embodiments, the constant and variable framework region sequences are human.

[0054] These anti-CD47 arms, monospecific anti-CD47 antibodies, monovalent anti-CD47 antibodies, and/or bispecific antibodies in which at least one binding site is specific for CD47 contain a variable heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 114 and a variable light chain amino acid sequence that is at least

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204 and 206.

[0055] The invention provides monoclonal antibodies that bind CD47. For example, the invention provides monoclonal antibodies that inhibit the interaction between human CD47 at the surface of cells and soluble human SIRPα with an IC50 greater than 0.3 nM in the assay described in Example 4 and in which the antibody 5A3M3 has an IC50 of approximately 0.36 nM.

[0056] The invention also provides monoclonal antibodies that bind CD47 and are recovered at more than 80% after incubation at 37°C for 30 minutes in human whole blood at a concentration of 10 μg/ml as described in Example 15. In some embodiments, the monoclonal antibody inhibits interaction between CD47 and signal-regulatory protein alpha (SIRPα). In some embodiments, the monoclonal antibody inhibits interaction between human CD47 and human SIRPα.

[0057] The invention also provides anti-CD47 monoclonal antibodies that include a variable heavy chain complementarity determining region 1 (CDRH1) amino acid sequence of SEQ ID NO: 225, a variable heavy chain complementarity determining region 2 (CDRH2) amino acid sequence of SEQ ID NO: 226, a variable heavy chain complementarity determining region 3 (CDRH3) amino acid sequence of SEQ ID NO: 227, a variable light chain complementarity determining region 1 (CDRL1) amino acid sequence selected from SEQ ID NO: 228-241 and 262-272, a variable light chain complementarity determining region 2 (CDRL2) amino acid sequence selected from 242-245 and 273-280, and a variable light chain complementarity determining region 3 (CDRH3) amino acid sequence selected from 246-261 and 281.

[0058] In some embodiments, the anti-CD47 monoclonal antibody includes a variable heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 114. In some embodiments, the anti-CD47 monoclonal antibody includes a variable light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192,

194, 196, 198, 200, 202, 204 and 206. In some embodiments, the anti-CD47 monoclonal antibody includes a variable heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 114, and a variable light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204 and 206.

[0059] In some embodiments, the anti-CD47 monoclonal antibody includes a variable heavy chain amino acid sequence of SEQ ID NO: 114 and a variable light chain amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204 and 206.

[0060] In some embodiments, the anti-CD47 antibody includes a combination of a variable heavy chain sequence and a variable light chain sequence selected from the group consisting of the combinations shown in 5A3, 5A3M4, 5A3M3, 5A3M5, KE8, KE8F2, KE8G2, KE84G9, KE81G9, KE81A3, KE8E8, KE8G6, KE8H5, KE8A2, KE8H3, KE8C7, KE8B2, KE8A4, KE8A8, KE8G11, KE8B7, KE8F1, KE8C4, KE8A3, KE86G9, KE8H6, KA3, KA3H8, KA3A3, KA3C5, KA3B2, KA3A2, KA3D3, KA3G2, KA3H3, KC4, KC4E2, KC4F4, KC4A1, KC4C11, KC4E10, KC4B1, KC4C3, KC4A4, KC4G11, and KC4G9.

[0061] The invention provides monoclonal antibodies that bind CD19. These antibodies are collectively referred to herein as anti-CD19 monoclonal antibodies or anti-CD19 mAbs. Preferably, the monoclonal antibodies are specific for at least human CD19. In some embodiments, the monoclonal antibodies that recognize human CD19 are also cross-reactive for at least one other non-human CD19 protein, such as, by way of non-limiting example, non-human primate CD19, e.g., cynomolgus monkey CD19, and/or rodent CD19.

[0062] In some embodiments, the anti-CD19 monoclonal antibody includes a variable heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 114. In some embodiments, the anti-CD19 monoclonal antibody includes a variable light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

99% or more identical to an amino acid sequence selected from SEQ ID NO: 208, 210, 212, 214, 216, 218, and 220. In some embodiments, the anti-CD19 monoclonal antibody includes a variable heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 114, and a variable light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from SEQ ID NO: 208, 210, 212, 214, 216, 218, and 220.

[0063] In some embodiments, the anti-CD19 monoclonal antibody includes a variable heavy chain amino acid sequence of SEQ ID NO: 114 and a variable light chain amino acid sequence selected from SEQ ID NO: 208, 210, 212, 214, 216, 218, and 220.

[0064] The invention also provides monovalent antibodies that bind CD19. These antibodies are collectively referred to herein as anti-CD19 monovalent antibodies or anti-CD19 monov mAbs. The monovalent antibodies of the invention include one arm that specific recognizes CD19, and a second arm referred to herein as a dummy arm. The dummy arm includes an amino acid sequence that does not bind or otherwise cross-react with a human protein. In some embodiments, the dummy arm includes an amino acid sequence that does not bind or otherwise cross-react with a human protein that is found in whole blood. In some embodiments, the dummy arm includes an amino acid sequence that does not bind or otherwise cross-react with a human protein that is found in solid tissue. Preferably, the monovalent antibodies are specific for at least human CD19. In some embodiments, the monovalent antibodies that recognize human CD19 are also cross-reactive for at least one other non-human CD19 protein, such as, by way of non-limiting example, non-human primate CD19, e.g., cynomolgus monkey CD19, and/or rodent CD19.

[0065] The invention also provides bispecific antibodies that recognize CD19 and a second target. In some embodiments, the second target is an antigen known to be associated or otherwise implicated in autoimmune diseases and/or inflammatory diseases, such as, for example, B-cell mediated autoimmune diseases and/or inflammatory diseases, including by way of non-limiting example, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), idiopathic thrombocytopenic purpura (ITP), Waldenstrom's hypergammaglobulinaemia, Sjogren's syndrome, multiple sclerosis (MS), and/or lupus nephritis.

[0066] In some embodiments, suitable second targets include, by way of non-limiting example, CD20, CD22, CD40, BAFFR, CD5, CD32b, ICOSL, IL6R, and/or

IL21R.

[0067] The bispecific antibodies of the invention that recognize CD19 and a second target are generated using any methods known in the art such as, by way of non-limiting example, the use of cross-linked fragments, quadromas, and/or any of a variety of recombinant formats such as, by way of non-limiting examples, linked antibody fragments, forced heterodimers, and or recombinant formats based on single domains. The invention allows for the identification, production and purification of bispecific antibodies that are undistinguishable in sequence from standard antibodies and where one of the binding sites is specific for CD19 and the second binding site is specific for another target, for example a tumor-associated antigen (TAA). The unmodified nature of the antibodies of the invention provides them with favorable manufacturing and biochemical characteristics similar to standard monoclonal antibodies.

[0068] In some embodiments, the bispecific antibodies carry a different specificity in each combining site and including two copies of a single heavy chain polypeptide and a first light chain and a second light chain, wherein the first and second light chains are different.

[0069] In some antibodies, at least a first portion of the first light chain is of the Kappa type and at least a portion of the second light chain is of the Lambda type. In some antibodies, the first light chain includes at least a Kappa constant region. In some antibodies, the first light chain further includes a Kappa variable region. In some antibodies, the first light chain further includes a Lambda variable region. In some antibodies, the second light chain includes at least a Lambda constant region. In some antibodies, the second light chain further includes a Lambda variable region. In some antibodies, the second light chain further includes a Kappa variable region. In some antibodies, the first light chain includes a Kappa constant region and a Kappa variable region, and the second light chain includes a Lambda constant region and a Lambda variable region. In some embodiments, the constant and variable framework region sequences are human.

[0070] The monoclonal, monovalent and/or bispecific antibodies of the invention can be used for therapeutic intervention or as a research or diagnostic reagent. For example, the monoclonal, monovalent and/or bispecific antibodies of the invention are useful in methods of treating, preventing and/or delaying the progression of pathologies associated with aberrant CD47 and/or aberrant CD47-SIRPα expression and/or activity or alleviating a symptom associated with such pathologies, by administering an antibody of the invention to

a subject in which such treatment or prevention is desired. The subject to be treated is, *e.g.*, human. The monoclonal, monovalent and/or bispecific antibody is administered in an amount sufficient to treat, prevent, delay the progression or alleviate a symptom associated with the pathology.

[0071] In some embodiments, the monoclonal, monovalent and/or bispecific antibodies described herein are used in conjunction with one or more additional agents or a combination of additional agents. Suitable additional agents include current pharmaceutical and/or surgical therapies for an intended application, such as, for example, cancer, inflammation and/or autoimmune diseases. In some embodiments, the monoclonal, monovalent and/or bispecific antibodies can be used in conjunction with rituximab.

[0072] In some embodiments, the monoclonal, monovalent and/or bispecific antibodies and the additional agent are formulated into a single therapeutic composition, and the monoclonal, monovalent and/or bispecific antibody and additional agent are administered simultaneously. Alternatively, the ac monoclonal, monovalent and/or bispecific antibodies and additional agent are separate from each other, *e.g.*, each is formulated into a separate therapeutic composition, and the monoclonal, monovalent and/or bispecific antibody and the additional agent are administered simultaneously, or the monoclonal, monovalent and/or bispecific antibodies and the additional agent are administered at different times during a treatment regimen. For example, the monoclonal, monovalent and/or bispecific antibody is administered prior to the administration of the additional agent, the monoclonal, monovalent and/or bispecific antibody is administered subsequent to the administration of the additional agent, or the monoclonal, monovalent and/or bispecific antibody and the additional agent are administered in an alternating fashion. As described herein, the monoclonal, monovalent and/or bispecific antibody and additional agent are administered in single doses or in multiple doses.

[0073] Pathologies treated and/or prevented using the antibodies of the invention include, for example, cancer or any other disease or disorder associated with aberrant CD47 expression and/or activity.

[0074] The invention also provides methods of producing bispecific antibodies that exhibit an "unbalanced" affinity for each of the two targets. For example, in some embodiments of an anti-CD47/CD19 bispecific antibody, the affinity of the anti-CD19 arm is increased using affinity maturation. For example, in some embodiments of an anti-CD47/CD19 bispecific antibody, the affinity of the anti-CD47 arm is decreased using

affinity dematuration. For example, in some embodiments an anti-CD47/CD19 bispecific antibody, the affinity of the anti-CD19 arm is increased using affinity maturation, and the affinity of the anti-CD47 arm is decreased using affinity de-maturation. These unbalanced affinity bispecific antibodies are useful, for example, to improve selectivity for a target cell or group of target cells.

[0075] Pharmaceutical compositions according to the invention can include an antibody of the invention and a carrier. These pharmaceutical compositions can be included in kits, such as, for example, diagnostic kits.

Brief Description of the Drawings

[0076] Figure 1 is an illustration of the sequence alignment between the variable light chain (VL) sequence of the anti-CD47 antibody 5A3 (SEQ ID NO: 116) to its closest germline sequence (SEQ ID NO: 282), the human IGKV1-33 according to the IMGT nomenclature.

[0077] Figure 2 is a graph depicting the blocking potency of the 5A3-M3 and 5A3-M5 antibody variants as compared to the parental antibody 5A3 in a CD47/SIRPα binding assay.

[0078] Figure 3 is a graph depicting the specificity of various CD47 monoclonal antibodies (Mabs) as indicated by the binding of purified CD47 Mabs to CHO cells transfected with human CD47, assessed by flow cytometry (grey bars). CD47 MAbs did not bind to non-transfected CHO cells (black bars).

[0079] Figure 4 is a graph depicting binding to native CD47 and specificity of CD47 MAbs as shown by binding of purified CD47 Mabs to HEK293-P cells as assessed by flow cytometry (grey bars). Binding to HEK293-P cells stably transfected with hCD47-specific siRNA is significantly decreased (black bars).

[0080] Figure 5 is a graph depicting binding to native human CD47 and cross-reactivity with cynomolgus CD47. The binding of purified CD47 Mabs to human (light grey bars) and cynomolgus (dark grey bars) PBMC CD4+ T cells was evaluated.

[0081] Figure 6 is a graph depicting the potency of CD47 Mabs to block the CD47-SIRPα interaction, as tested in the CD47-SIRPα inhibition assay (competitive inhibition of the binding of recombinant soluble human SIRPα to hCD47-expressing CHO cells, as described in Example 4). IC50 values obtained in dose-response experiments are shown. CD47 Mabs are grouped by family and ranked from higher to lower potency. The

neutralizing activity of the antibodies of the present invention is compared to the commercially available CD47 antibody B6H12.

[0082] Figure 7 is an illustration depicting the hemagglutination activity of CD47 antibodies. Hemagglutination is evidenced as a clumped deposit of RBC, in the form of a crescent at the bottom around the inferior border of the well, whereas non-agglutinated are do not form aggregates and are distributed evenly over the well surface area. Figure 7 demonstrates that high-affinity CD47 Mabs of the 5A3, Ke8, and Ka3 families induce hemagglutination; in contrast to the other three families, Kc4 family antibodies tested in this experiment do not induce hemagglutination.

[0083] Figure 8 is a graph depicting dose-response curve for a FACS-binding assay done with Raji cells and the original anti-CD19 clone 1B7, clone D11 identified following the first affinity maturation round, and the final clone L7B7_c2, issued form the second affinity maturation round.

[0084] Figures 9A-9C are a series of graphs the ability of a CD47xCD19 BsAb to co-engage the two targets at the surface of cells. The graphs in Figures 9A-9C present FACS profiles generated with monovalent and bispecific antibodies binding to CD19-negative B-NHL cells (DS-1) and CD19-positive Burkitt lymphoma cells (Raji). All antibodies were human IgG1 format and were tested at four concentrations as indicated.

[0085] Figure 10 is a series of graphs depicting the SIRPα Blocking Activity of Monovalent and Bispecific Antibodies. Figure 10 demonstrates the co-engagement of CD19 and CD47 on the surface of the target cell, by showing that the neutralization of CD47-SIRPα interaction by CD47xCD19 BsAbs is CD19-dependent. The experiments were done in quadruplicates Mean and SEM are shown. Dose-response inhibition curves were fitted with GraphPad software.

[0086] Figures 11A-11C show ADCC dose-response curves generated with CD47xCD19 κλ bodies (black) or the corresponding CD47 monovalent antibodies (grey). ADCC with the CD19 Mab C2 is shown for comparison (dashed grey). The ADCC assay was performed with whole human PBMCs as effector cells and Calcein AM-stained Raji (Figure 11A, 11C) or Ramos (Figure 11B) as target cells (effector to target ratio: 50). Cytotoxicity was calculated from the degree of calcein release from target cells. The percentage of specific cell killing +/- SD is shown. The experiments were done in duplicates. Figures 11A-11B demonstrate the ability of CD47xCD19 BsAbs to kill CD19-positive cells in a CD19-dependent manner, as the corresponding CD47 monovalent

antibodies were much less efficient or not efficient at all. Figure 11C demonstrates that the efficacy of killing of Raji cells with CD47xCD19 antibodies was comparable to rituximab and much higher than with the CD19 Mab C2.

[0087] Figure 12 is a graph depicting the phagocytic activity of three of the CD47xCD19 κλ bodies of the present invention (black lines) compared to the corresponding CD47 monovalent antibodies (grey lines) in dose-response ADCP experiment. Phagocytosis with the CD47 Mab B6H12 (on human IgG1 background, dotted black line) and with the CD19 Mab C2 (dotted grey line) is shown for comparison. The ADCP experiment was performed with human macrophages differentiated from peripheral blood monocytes and Raji as target cells (effector: target ratio 1:5) Phagocytosis was assessed by FACS. The percentage of macrophages having phagocytosed at least one target cells is shown. CD47xCD19 κλ bodies phagocytose CD19-positive cells in a CD19-dependent manner analysis, as the corresponding CD47 monovalent antibodies were much less efficient or not efficient at all.

[0088] Figure 13 is a graph depicting the activity of various antibodies in a Raji B cell lymphoma xenograft in NOD/SCID mice. Antibody treatment started after the tumor graft has reached about 0.1 cm^3 and ended on D25. Treatment groups (n=5) were as indicated in the inset. Shown is the evolution of average tumor volume per treatment group +/- SD. Figure 13 shows that the efficacy of BsAB is similar to B6H12 or rituximab and that tumor eradication was CD19-dependent, as the corresponding monovalent was less efficacious.

[0089] Figure 14 is a graph depicting that high and moderate affinity CD47 antibodies are efficiently adsorbed on erythrocytes. In the case of BsAbs, this phenomenon is limited to molecules having a high affinity CD47 arms, such as 5A3.

Detailed Description

[0090] The invention provides monoclonal antibodies that bind CD47. These antibodies are collectively referred to herein as anti-CD47 monoclonal antibodies or anti-CD47 mAbs. Preferably, the monoclonal antibodies are specific for at least human CD47. In some embodiments, the monoclonal antibodies that recognize human CD47 are also cross-reactive for at least one other non-human CD47 protein, such as, by way of non-limiting example, non-human primate CD47, e.g., cynomolgus monkey CD47, and/or rodent CD47. In some embodiments, these anti-CD47 monoclonal antibodies inhibit the interaction

between CD47 and signal-regulatory protein alpha (SIRPα). In some embodiments, these anti-CD47 monoclonal antibodies inhibit the interaction between human CD47 and human SIRPα. The invention also include antibodies that bind to the same epitope as an anti-CD47 monoclonal antibody disclosed herein and inhibits the interaction between CD47 and SIRPα, e.g., between human CD47 and human SIRPα.

[0091] The invention also provides monovalent antibodies and/or bispecific antibodies that include at least a first arm that is specific for CD47. Preferably, the monovalent antibodies and/or bispecific antibodies are specific for at least human CD47. In some embodiments, the monovalent antibodies and/or bispecific antibodies that recognize human CD47 are also cross-reactive for at least one other non-human CD47 protein, such as, by way of non-limiting example, non-human primate CD47, e.g., cynomolgus monkey CD47, and/or rodent CD47. In some embodiments, these anti-CD47 monovalent antibodies and/or anit-CD47 bispecific antibodies inhibit the interaction between CD47 and signal-regulatory protein alpha (SIRPα). In some embodiments, these anti-CD47 monovalent antibodies and/or anit-CD47 bispecific antibodies inhibit the interaction between human CD47 and human SIRPα. The invention also include antibodies that bind to the same epitope as an anti-CD47 monovalent and/or an anti-CD47 bispecific antibody disclosed herein and inhibits the interaction between CD47 and SIRPα, e.g., between human CD47 and human SIRPα.

[0092] The bispecific antibodies of the invention allow for simultaneous binding of the two antibody arms to two antigens on the surface of the cell (termed co-engagement), which results in additive or synergistic increase of affinity due to avidity mechanism. As a consequence, co-engagement confers high selectivity towards cells expressing both antigens as compared to cells that express just one single antigen. In addition, the affinities of the two arms of a bispecific antibody to their respective targets can be set up in a way that binding to target cells is principally driven by one of the antibody arms. In some embodiments, the bispecific antibody includes a first arm that binds CD47 and a second arm that binds a tumor associated antigen (TAA), where the second arm binds to the TAA with high affinity, and the first arm binds to CD47 with low affinity, i.e., an affinity that is sufficient to inhibit CD47/SIRPα upon TAA co-engagement. This design allows the bispecific antibodies of the invention to preferentially inhibit CD47 in cancer versus normal cells. In the examples provided herein, a bispecific antibody with a first arm that binds CD47 with low affinity and a second arm that binds CD19 with high affinity (termed a

CD47xCD19 bispecific) allow preferential inhibition of CD47 in cancer versus normal cells. Besides the two antigen-binding arms, the CD47 x TAA bispecific antibody requires a functional Fc portion to recruit macrophages and/or other immune effector cells. A fully human bispecific IgG format (such as the κλ-body format described herein) is well suited for the generation of dual targeting CD47 x TAA bispecific antibodies. As shown in the examples provided herein, the ability of dual targeting bispecific antibodies to co-engage CD47 and CD19 results in a significant increase in the affinity of binding to CD19-positive cells and in CD19-dependent neutralization of the CD47-SIRPα interaction. This, in turn, translates into efficient and selective cancer cell killing mediated by the CD47xCD19 bispecific antibody, as demonstrated in the ADCC and ADCP experiments provided herein.

[0093] Exemplary anti-CD47 monoclonal, monospecific anti-CD47 antibodies, anti-CD47 monovalent antibodies, and/or bispecific antibodies of the invention in which at least one binding site is specific for CD47 include, for example, the 5A3 antibody, the 5A3M4 antibody, the 5A3M3 antibody, the 5A3M5 antibody, the KE8 antibody, the KE8-P6H5 antibody (also referred to herein as KE8H5), the KE8-P3B2 antibody (also referred to herein as KE8B2), the KE8-P2A2 antibody (also referred to herein as KE8A25), the KE8F2 antibody, the KE8G2 antibody, the KE84G9 antibody, the KE81G9 antibody, the KE81A3 antibody, the KE8E8 antibody, the KE8G6 antibody, the KE8H3 antibody, the KE8C7 antibody, the KE8A4 antibody, the KE8A8 antibody, the KE8G11 antibody, the KE8B7 antibody, the KE8F1 antibody, the KE8C4 antibody, the KE8A3 antibody, the KE86G9 antibody, the KE8H6 antibody, the KA3 antibody, the KA3-P5G2 antibody (also referred to herein as KA3G2), the KA3-P1A3 antibody (also referred to herein as KA3A3), the KA3-P5C5 antibody (also referred to herein as KA3C5), the KA3H8 antibody, the KA3B2 antibody, the KA3A2 antibody, the KA3D3 antibody, the KA3H3 antibody, the KC4 antibody, the KC4-P1G11KC4-P4C11 antibody, the KC4-P6B1KC4-P4F4 antibody, and the KC4-P2E2 antibody (also referred to herein as KC4E2), the KC4 antibody, the KC4F4 antibody, the KC4A1 antibody, the KC4C11 antibody, the KC4E10 antibody, the KC4B1 antibody, the KC4C3 antibody, the KC4A4 antibody, the KC4G11 antibody, and the KC4G9 antibody, as well as immunologically active and/or antigen-binding fragments thereof.

[0094] In some embodiments, exemplary anti-CD47 monoclonal, monospecific anti-CD47 antibodies, anti-CD47 monovalent antibodies, and/or bispecific antibodies of the invention include a combination of heavy chain and light chain complementarity

determining regions (CDRs) selected from the CDR sequences shown in Tables 1, 2 and 3, where the CDRs shown in Tables 1, 2 and 3 are defined according to the IMGT nomenclature.

[0095] In some embodiments, exemplary anti-CD47 monoclonal, monospecific anti-CD47 antibodies, anti-CD47 monovalent antibodies, and/or bispecific antibodies of the invention include the combination of heavy chain CDR sequences from Table 1 and two sets of light chain CDRs selected from the CDRL1, CDRL2 and CDRL3 sequences shown in Tables 2 and 3.

[0096] In some embodiments, exemplary anti-CD47 monoclonal, monospecific anti-CD47 antibodies, anti-CD47 monovalent antibodies, and/or bispecific antibodies of the invention include the combination of heavy chain CDR sequences from Table 1 and a first set of light chain CDRs selected from the CDRL1, CDRL2 and CDRL3 sequences shown in Table 2 and a second set of light chain CDRs selected from the CDRL1, CDRL2 and CDRL3 sequences shown in Table 3.

Table 1: Anti-CD47 Heavy Chain CDRs

CDRH1	CDRH2	CDRH3
GFTF----SSYA (SEQ ID NO:225)	ISGS--GGST (SEQ ID NO:226)	AKSYGAF----DY (SEQ ID NO:227)

Table 2: Anti-CD47 Kappa Light Chain CDRs

CDRL1	CDRL2	CDRL3
QDI------NKY (SEQ ID NO: 228)	AA-------S (SEQ ID NO: 242)	QQKHPRGP---RT (SEQ ID NO: 246)
QDI------NRY (SEQ ID NO: 229)	GA-------S (SEQ ID NO: 243)	QQFHKRAP---QT (SEQ ID NO: 247)
QNI------GKY (SEQ ID NO: 230)	NA-------S (SEQ ID NO: 244)	QQFHKRRP---QT (SEQ ID NO: 248)
QSI------ARY (SEQ ID NO: 231)	SA-------S (SEQ ID NO: 245)	QQFHKRSP---QT (SEQ ID NO: 249)
QSI------ASY (SEQ ID NO: 232)		QQKHPRAP---RT (SEQ ID NO: 250)
QSI------DKY (SEQ ID NO: 233)		QQKHPRSP---RT (SEQ ID NO: 251)

QSI------DRY (SEQ ID NO: 234)		QQKHPRYP---RT (SEQ ID NO: 252)
QSI------GKY (SEQ ID NO: 235)		QQKHPRNP---RT (SEQ ID NO: 253)
QSI------GRY (SEQ ID NO: 236)		QQMHPRAP---KT (SEQ ID NO: 254)
QSI------NRY (SEQ ID NO: 237)		QQMHPRGP---KT (SEQ ID NO: 255)
QSI------SKY (SEQ ID NO: 238)		QQMHPRSP---KT (SEQ ID NO: 256)
QSI------SRY (SEQ ID NO: 239)		QQRHPRAP---RT (SEQ ID NO: 257)
QSI------SSY (SEQ ID NO: 240)		QQRHKRSP---QT (SEQ ID NO: 258)
QSI------AKY (SEQ ID NO: 241)		QQRHPRGP---RT (SEQ ID NO: 259)
		QQRHPRGP---ST (SEQ ID NO: 260)
		QQRHPRGP---TT (SEQ ID NO: 261)

Table 3: Anti-CD47 Lambda Light Chain CDRs

CDRL1	CDRL2	CDRL3
SSDVG---GYNY (SEQ ID NO: 262)	EN-------S (SEQ ID NO: 273)	SSYDWWFRP--KV (SEQ ID NO: 281)
SSDVE---RKNY (SEQ ID NO: 263)	ES-------S (SEQ ID NO: 274)	
SSDVR---ANNY (SEQ ID NO: 264)	EV-------S (SEQ ID NO: 275)	
SSDVY---YNKY (SEQ ID NO: 265)	KD-------S (SEQ ID NO: 276)	
SSDVG---KANY (SEQ ID NO: 266)	KN-------S (SEQ ID NO: 277)	
SSDVR---GNNY (SEQ ID NO: 267)	KS-------S (SEQ ID NO: 278)	

SSDVS---ARNY (SEQ ID NO: 268)	KT-------S (SEQ ID NO: 279)	
SSDVN---SANY (SEQ ID NO: 269)	QD-------S (SEQ ID NO: 280)	
SSDVR---AANY (SEQ ID NO: 270)		
SSDVR---RANY (SEQ ID NO: 271)		
SSDVN---NTNY (SEQ ID NO: 272)		

[0097] Each of the exemplary anti-CD47, anti-CD19, monovalent and bispecific antibodies described herein include a common heavy chain (HC), one kappa chain or one lambda chain for anti-CD47 and anti-CD19 antibodies, one kappa and one lambda light chains (LC) for monovalent and bispecific antibodies, as shown in the amino acid and corresponding nucleic acid sequences listed below. Each of the exemplary anti-CD47, anti-CD19, monovalent and bispecific antibodies described below includes a common variable heavy domain (VH), one kappa variable light domain or one lambda variable light domain for anti-CD47 and anti-CD19 antibodies, one kappa and one lambda variable light domains (VL) for monovalent and bispecific antibodies, as shown in the amino acid and corresponding nucleic acid sequences listed below.

[0098] While antibody sequences below are provided herein as examples, it is to be understood that these sequences can be used to generate bispecific antibodies using any of a variety of art-recognized techniques. Examples of bispecific formats include but are not limited to bispecific IgG based on Fab arm exchange (Gramer et al., 2013 MAbs. 5(6)); the CrossMab format (Klein C et al., 2012 MAbs 4(6)); multiple formats based on forced heterodimerization approaches such as SEED technology (Davis JH et al., 2010 Protein Eng Des Sel. 23(4):195-202), electrostatic steering (Gunasekaran K et al., J Biol Chem. 2010 285(25):19637-46.) or knob-into-hole (Ridgway JB et al., Protein Eng. 1996 9(7):617-21.) or other sets of mutations preventing homodimer formation (Von Kreudenstein TS et al., 2013 MAbs. 5(5):646-54.); fragment based bispecific formats such as tandem scFv (such asBiTEs) (Wolf E et al., 2005 Drug Discov. Today 10(18):1237-44.); bispecific tetravalent antibodies (Pörtner LM et al., 2012 Cancer Immunol Immunother. 61(10):1869-75.); dual

affinity retargeting molecules (Moore PA et al., 2011 Blood.117(17):4542-51), diabodies (Kontermann RE et al., Nat Biotechnol. 1997 15(7):629-31).

[0099] The exemplary anti-CD47, anti-CD19, monovalent and bispecific antibodies include a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1.

>COMMON-HC-NT (SEQ ID NO: 1)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
CAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCT
GGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGG
TTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGG
ACACGGCCGTATATTACTGTGCGAAAAGTTATGGTGCTTTTGACTACTGGGGCCAGGGAACCCTGGT
CACAGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC
TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACAGTCTCGT
GGAACTCAGGAGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTA
CTCCCTCAGCAGCGTGGTGACTGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG
AATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACA
CATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACC
CAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
GGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCT
GAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATC
TCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTATACCCTGCCCCCATCTCGGGAGGAGATGA
CCAAGAACCAGGTCAGCCTGACTTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAACGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
TTCTTCCTCTATAGCAAGCTCACCGTGGACAAGTCCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT
CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTTAA

>COMMON-HC-AA (SEQ ID NO: 2)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[00100] The anti-CD47, anti-CD19, monovalent and bispecific antibodies include a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113.

>COMMON-VH-NT (SEQ ID NO: 113)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
CAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCT
GGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGG
TTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGG
ACACGGCCGTATATTACTGTGCGAAAAGTTATGGTGCTTTTGACTACTGGGGCCAGGGAACCCTGGT
CACAGTCTCGAGC

>COMMON-VH-AA (SEQ ID NO: 114)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSYGAFDYWGQGTLVTVSS

ANTI-CD47 ANTIBODIES

[00101] The 5A3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 4) encoded by the nucleic acid sequence shown in SEQ ID NO: 3.

>5A3-LC-NT (SEQ ID NO: 3)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTACGGTGCATCCAGGTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCT
GGGACAGATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGC
AGAAGCACCCCCGGGGGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>5A3-LC-AA (SEQ ID NO: 4)
DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYGASRLETGVPSRFSGSGS
GTDFTFTISSLQPEDIATYYCQQKHPRGPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00102] The 5A3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 116) encoded by the nucleic acid sequence shown in SEQ ID NO: 115.

>5A3-VL-NT (SEQ ID NO: 115)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTACGGTGCATCCAGGTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCT
GGGACAGATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGC
AGAAGCACCCCCGGGGGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>5A3-VL-AA (SEQ ID NO: 116)
DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYGASRLETGVPSRFSGSGS
GTDFTFTISSLQPEDIATYYCQQKHPRGPRTFGQGTKVEIK

[00103] The 5A3-M4 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 6) encoded by the nucleic acid sequence shown in SEQ ID NO: 5.

>5A3-M4-LC-NT (SEQ ID NO: 5)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTACGGTGCATCCAGGTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCT
GGGACAGATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGC
AGAAGCACCCCCGGAACCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC

CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>5A3-M4-LC-AA (SEQ ID NO: 6)
DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYGASRLETGVPSRFSGSGS
GTDFTFTISSLQPEDIATYYCQQKHPRNPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00104] The 5A3-M4 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 118) encoded by the nucleic acid sequence shown in SEQ ID NO: 117.

>5A3-M4-VL-NT (SEQ ID NO: 117)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTACGGTGCATCCAGGTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCT
GGGACAGATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGC
AGAAGCACCCCCGGAACCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>5A3-M4-VL-AA (SEQ ID NO: 118)
DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYGASRLETGVPSRFSGSGS
GTDFTFTISSLQPEDIATYYCQQKHPRNPRTFGQGTKVEIK

[00105] The 5A3-M3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 8) encoded by the nucleic acid sequence shown in SEQ ID NO: 7.

>5A3-M3-LC-NT (SEQ ID NO: 7)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGTCCATTAGTAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTACGCTGCATCCTCGTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCT
GGGACAGATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGC
AGAAGCACCCCCGGGGGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC

TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>5A3-M3-LC-AA (SEQ ID NO: 8)
DIQMTQSPSSLSASVGDRVTITCQASQSISSYLNWYQQKPGKAPKLLIYAASSLETGVPSRFSGSGS
GTDFTFTISSLQPEDIATYYCQQKHPRGPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00106] The 5A3-M3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 120) encoded by the nucleic acid sequence shown in SEQ ID NO: 119.

>5A3-M3-VL-NT (SEQ ID NO: 119)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGTCCATTAGTAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTACGCTGCATCCTCGTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCT
GGGACAGATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGC
AGAAGCACCCCCGGGGGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>5A3-M3-VL-AA (SEQ ID NO: 120)
DIQMTQSPSSLSASVGDRVTITCQASQSISSYLNWYQQKPGKAPKLLIYAASSLETGVPSRFSGSGS
GTDFTFTISSLQPEDIATYYCQQKHPRGPRTFGQGTKVEIK

[00107] The 5A3-M5 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 10) encoded by the nucleic acid sequence shown in SEQ ID NO: 9.

>5A3-M5-LC-NT (SEQ ID NO: 9)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA

GCTCCTGATCTACGGTGCATCCAGGTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCT
GGGACAGATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGC
AGAAGCACCCCCGGTACCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>5A3-M5-LC-AA(SEQ ID NO: 10)
DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYGASRLETGVPSRFSGSGS
GTDFTFTISSLQPEDIATYYCQQKHPRYPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00108] The 5A3-M5 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 122) encoded by the nucleic acid sequence shown in SEQ ID NO: 121.

>5A3-M5-VL-NT (SEQ ID NO: 121)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTACGGTGCATCCAGGTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCT
GGGACAGATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGC
AGAAGCACCCCCGGTACCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>5A3-M5-VL-AA(SEQ ID NO: 122)
DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYGASRLETGVPSRFSGSGS
GTDFTFTISSLQPEDIATYYCQQKHPRYPRTFGQGTKVEIK

[00109] The Ke8 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 12) encoded by the nucleic acid sequence shown in SEQ ID NO: 11.

>Ke8-LC-NT (SEQ ID NO: 11)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGTTCCACAAGCGGCGGCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8-LC-AA (SEQ ID NO: 12)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQFHKRRPQTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00110] The Ke8 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 124) encoded by the nucleic acid sequence shown in SEQ ID NO: 123.

>Ke8-VL-NT (SEQ ID NO: 123)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGTTCCACAAGCGGCGGCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8-VL-AA (SEQ ID NO: 124)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQFHKRRPQTFGQGTKVEIK

[00111] The Ke8H5 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 14) encoded by the nucleic acid sequence shown in SEQ ID NO: 13.

>KE8H5-LC-NT (SEQ ID NO: 13)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCGAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGTTCCATAAGCGTGCGCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8H5-LC-AA (SEQ ID NO: 14)
DIQMTQSPSSLSASVGDRVTITCRASQSIARYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQFHKRAPQTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00112] The Ke8H5 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 126) encoded by the nucleic acid sequence shown in SEQ ID NO: 125.

>KE8H5-VL-NT (SEQ ID NO: 125)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCGAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGTTCCATAAGCGTGCGCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8H5-VL-AA (SEQ ID NO: 126)
DIQMTQSPSSLSASVGDRVTITCRASQSIARYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQFHKRAPQTFGQGTKVEIK

[00113] The Ke8B2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 16) encoded by the nucleic acid sequence shown in SEQ ID NO: 15.

>KE8B2-LC-NT (SEQ ID NO: 15)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCACCCGCGTGCCCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8B2-LC-AA (SEQ ID NO: 16)
DIQMTQSPSSLSASVGDRVTITCRASQSIGKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRAPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00114] The Ke8B2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 128) encoded by the nucleic acid sequence shown in SEQ ID NO: 127.

>KE8B2-VL-NT (SEQ ID NO: 127)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT

GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCACCCGCGTGCCCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8B2-VL-AA (SEQ ID NO: 128)
DIQMTQSPSSLSASVGDRVTITCRASQSIGKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRAPRTFGQGTKVEIK

[00115] The Ke8A2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 18) encoded by the nucleic acid sequence shown in SEQ ID NO: 17.

>KE8A2-LC-NT (SEQ ID NO: 17)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGATAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCCCGTGGGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8A2-LC-AA (SEQ ID NO: 18)
DIQMTQSPSSLSASVGDRVTITCRASQSIDRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRGPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00116] The Ke8A2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 130) encoded by the nucleic acid sequence shown in SEQ ID NO: 129.

>KE8A2-VL-NT (SEQ ID NO: 129)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGATAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCCCGTGGGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8A2-VL-AA (SEQ ID NO: 130)
DIQMTQSPSSLSASVGDRVTITCRASQSIDRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRGPRTFGQGTKVEIK

[00117] The Ke8E8 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 20) encoded by the nucleic acid sequence shown in SEQ ID NO: 19.

>KE8E8-LC-NT (SEQ ID NO: 19)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCCCGTGGCCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8E8-LC-AA (SEQ ID NO: 20)
DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRGPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00118] The Ke8E8 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a

kappa variable light domain (SEQ ID NO: 132) encoded by the nucleic acid sequence shown in SEQ ID NO: 131.

>KE8E8-VL-NT (SEQ ID NO: 131)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCCCGTGGCCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8E8-VL-AA (SEQ ID NO: 132)
DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRGPRTFGQGTKVEIK

[00119] The Ke8H3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 22) encoded by the nucleic acid sequence shown in SEQ ID NO: 21.

>KE8H3-LC-NT (SEQ ID NO: 21)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAATAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCGCGTGGGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8H3-LC-AA (SEQ ID NO: 22)
DIQMTQSPSSLSASVGDRVTITCRASQSINRYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRGPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00120] The Ke8H3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 134) encoded by the nucleic acid sequence shown in SEQ ID NO: 133.

>KE8H3-VL-NT (SEQ ID NO: 133)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAATAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCGCGTGGGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8H3-VL-AA (SEQ ID NO: 134)
DIQMTQSPSSLSASVGDRVTITCRASQSINRYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRGPRTFGQGTKVEIK

[00121] The Ke8G6 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 24) encoded by the nucleic acid sequence shown in SEQ ID NO: 23.

>KE8G6-LC-NT (SEQ ID NO: 23)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGTAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTGCGCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8G6-LC-AA (SEQ ID NO: 24)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00122] The Ke8G6 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 136) encoded by the nucleic acid sequence shown in SEQ ID NO: 135.

>KE8G6-VL-NT (SEQ ID NO: 135)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGTAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTGCGCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8G6-VL-AA (SEQ ID NO: 136)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIK

[00123] The Ke8A3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 26) encoded by the nucleic acid sequence shown in SEQ ID NO: 25.

>KE8A3-LC-NT (SEQ ID NO: 25)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGTAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAGGCATCCCCGTGGGCCGAGCACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC

CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8A3-LC-AA (SEQ ID NO: 26)
DIQMTQSPSSLSASVGDRVTITCRVSQSISKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRGPSTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00124] The Ke8A3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 138) encoded by the nucleic acid sequence shown in SEQ ID NO: 137.

>KE8A3-VL-NT (SEQ ID NO: 137)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGTAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAGGCATCCCCGTGGGCCGAGCACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8A3-VL-AA (SEQ ID NO: 138)
DIQMTQSPSSLSASVGDRVTITCRVSQSISKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRGPSTFGQGTKVEIK

[00125] The Ke81A3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 28) encoded by the nucleic acid sequence shown in SEQ ID NO: 27.

>KE81A3-LC-NT (SEQ ID NO: 27)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAGGCATCCGCGTGCCCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC

TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE81A3-LC-AA (SEQ ID NO: 28)
DIQMTQSPSSLSASVGDRVTITCQASQDINRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRAPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00126] The Ke81A3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 140) encoded by the nucleic acid sequence shown in SEQ ID NO: 139.

>KE81A3-VL-NT (SEQ ID NO: 139)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAGGCATCCGCGTGCCCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE81A3-VL-AA (SEQ ID NO: 140)
DIQMTQSPSSLSASVGDRVTITCQASQDINRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRAPRTFGQGTKVEIK

[00127] The Ke8A8 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 30) encoded by the nucleic acid sequence shown in SEQ ID NO: 29.

>KE8A8-LC-NT (SEQ ID NO: 29)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA

GCTCCTGATCTATGCTGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTGCGCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8A8-LC-AA (SEQ ID NO: 30)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00128] The Ke8A8 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 142) encoded by the nucleic acid sequence shown in SEQ ID NO: 141.

>KE8A8-VL-NT (SEQ ID NO: 141)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTGCGCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8A8-VL-AA (SEQ ID NO: 142)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIK

[00129] The Ke8C7 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 32) encoded by the nucleic acid sequence shown in SEQ ID NO: 31.

>KE8C7-LC-NT (SEQ ID NO: 31)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGCGCCATCCGCGTGGCCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8C7-LC-AA (SEQ ID NO: 32)
DIQMTQSPSSLSASVGDRVTITCQASQDINRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRGPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00130] The Ke8C7 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 144) encoded by the nucleic acid sequence shown in SEQ ID NO: 143.

>KE8C7-VL-NT (SEQ ID NO: 143)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTAATAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGCGCCATCCGCGTGGCCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8C7-VL-AA (SEQ ID NO: 144)
DIQMTQSPSSLSASVGDRVTITCQASQDINRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRGPRTFGQGTKVEIK

[00131] The Ke8G2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 34) encoded by the nucleic acid sequence shown in SEQ ID NO: 33.

>KE8G2-LC-NT (SEQ ID NO: 33)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGTAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAACAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCCCGTGCGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8G2-LC-AA (SEQ ID NO: 34)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTINSLQPEDFATYYCQQKHPRAPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00132] The Ke8G2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 146) encoded by the nucleic acid sequence shown in SEQ ID NO: 145.

>KE8G2-VL-NT (SEQ ID NO: 145)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGTAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAACAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCCCGTGCGCCGAGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8G2-VL-AA (SEQ ID NO: 146)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTINSLQPEDFATYYCQQKHPRAPRTFGQGTKVEIK

[00133] The Ke81G9 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 36) encoded by the nucleic acid sequence shown in SEQ ID NO: 35.

>KE81G9-LC-NT (SEQ ID NO: 35)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGCGGCATAAGCGTTCCCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE81G9-LC-AA (SEQ ID NO: 36)
DIQMTQSPSSLSASVGDRVTITCRASQSIDKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHKRSPQTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00134] The Ke81G9 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 148) encoded by the nucleic acid sequence shown in SEQ ID NO: 147.

>KE81G9-VL-NT (SEQ ID NO: 147)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT

GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGCGGCATAAGCGTTCCCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE81G9-VL-AA (SEQ ID NO: 148)
DIQMTQSPSSLSASVGDRVTITCRASQSIDKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHKRSPQTFGQGTKVEIK

[00135] The Ke8F2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 38) encoded by the nucleic acid sequence shown in SEQ ID NO: 37.

>KE8F2-LC-NT (SEQ ID NO: 37)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCGCGTGCGCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8F2-LC-AA (SEQ ID NO: 38)
DIQMTQSPSSLSASVGDRVTITCRASQSIDKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRAPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00136] The Ke8F2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 150) encoded by the nucleic acid sequence shown in SEQ ID NO: 149.

>KE8F2-VL-NT (SEQ ID NO: 149)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCGCGTGCGCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8F2-VL-AA (SEQ ID NO: 150)
DIQMTQSPSSLSASVGDRVTITCRASQSIDKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRAPRTFGQGTKVEIK

[00137] The Ke8B7 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 40) encoded by the nucleic acid sequence shown in SEQ ID NO: 39.

>KE8B7-LC-NT (SEQ ID NO: 39)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGGAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTAGCCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8B7-LC-AA (SEQ ID NO: 40)
DIQMTQSPSSLSASVGDRVTITCRASQSIGKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRSPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00138] The Ke8B7 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a

kappa variable light domain (SEQ ID NO: 152) encoded by the nucleic acid sequence shown in SEQ ID NO: 151.

>KE8B7-VL-NT (SEQ ID NO: 151)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGGAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTAGCCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8B7-VL-AA (SEQ ID NO: 152)
DIQMTQSPSSLSASVGDRVTITCRASQSIGKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRSPKTFGQGTKVEIK

[00139] The Ke8C4 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 42) encoded by the nucleic acid sequence shown in SEQ ID NO: 41.

>KE8C4-LC-NT (SEQ ID NO: 41)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTGGGCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8C4-LC-AA (SEQ ID NO: 42)
DIQMTQSPSSLSASVGDRVTITCRASQSISRYLNWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRGPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00140] The Ke8C4 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 154) encoded by the nucleic acid sequence shown in SEQ ID NO: 153.

>KE8C4-VL-NT (SEQ ID NO: 153)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTGGGCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8C4-VL-AA (SEQ ID NO: 154)
DIQMTQSPSSLSASVGDRVTITCRASQSISRYLNWYQQKPGKAPKLLIYAASNLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRGPKTFGQGTKVEIK

[00141] The Ke8F1 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 44) encoded by the nucleic acid sequence shown in SEQ ID NO: 43.

>KE8F1-LC-NT (SEQ ID NO: 43)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCTTCTTATGTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCGGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGTTCCATAAGCGTCGGCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8F1-LC-AA (SEQ ID NO: 44)
DIQMTQSPSSLSASVGDRVTITCRASQSIASYVNWYQQKPGKAPKLLIYAASGLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQFHKRRPQTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00142] The Ke8F1 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 156) encoded by the nucleic acid sequence shown in SEQ ID NO: 155.

>KE8F1-VL-NT (SEQ ID NO: 155)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCTTCTTATGTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCGGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGTTCCATAAGCGTCGGCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8F1-VL-AA (SEQ ID NO: 156)
DIQMTQSPSSLSASVGDRVTITCRASQSIASYVNWYQQKPGKAPKLLIYAASGLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQFHKRRPQTFGQGTKVEIK

[00143] The Ke8G11 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 46) encoded by the nucleic acid sequence shown in SEQ ID NO: 45.

>KE8G11-LC-NT (SEQ ID NO: 45)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGGAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTGGGCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC

CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8G11-LC-AA (SEQ ID NO: 46)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRGPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00144] The Ke8G11 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 158) encoded by the nucleic acid sequence shown in SEQ ID NO: 157.

>KE8G11-VL-NT (SEQ ID NO: 157)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGGAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCGCGTGGGCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8G11-VL-AA (SEQ ID NO: 158)
DIQMTQSPSSLSASVGDRVTITCRASQSIGRYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRGPKTFGQGTKVEIK

[00145] The Ke8H6 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 48) encoded by the nucleic acid sequence shown in SEQ ID NO: 47.

>KE8H6-LC-NT (SEQ ID NO: 47)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATAATGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAGGCATCCGCGTGGGCCGCGCACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC

TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8H6-LC-AA (SEQ ID NO: 48)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYNASTLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRGPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00146] The Ke8H6 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 160) encoded by the nucleic acid sequence shown in SEQ ID NO: 159.

>KE8H6-VL-NT (SEQ ID NO: 159)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATAATGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAGGCATCCGCGTGGGCCGCGCACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8H6-VL-AA (SEQ ID NO: 160)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYNASTLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRGPRTFGQGTKVEIK

[00147] The Ke84G9 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 50) encoded by the nucleic acid sequence shown in SEQ ID NO: 49.

>KE84G9-LC-NT (SEQ ID NO: 49)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA

GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCGCGTAGCCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE84G9-LC-AA (SEQ ID NO: 50)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRSPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00148] The Ke84G9 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 162) encoded by the nucleic acid sequence shown in SEQ ID NO: 161.

>KE84G9-VL-NT (SEQ ID NO: 161)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAAGCATCCGCGTAGCCCGCGGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE84G9-VL-AA (SEQ ID NO: 162)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQKHPRSPRTFGQGTKVEIK

[00149] The Ke8A4 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 52) encoded by the nucleic acid sequence shown in SEQ ID NO: 51.

>KE8A4-LC-NT (SEQ ID NO: 51)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGTTCCATAAGCGTAGCCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE8A4-LC-AA (SEQ ID NO: 52)
DIQMTQSPSSLSASVGDRVTITCRASQSIAKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQFHKRSPQTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00150] The Ke8A4 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 164) encoded by the nucleic acid sequence shown in SEQ ID NO: 163.

>KE8A4-VL-NT (SEQ ID NO: 163)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGTTCCATAAGCGTAGCCCGCAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE8A4-VL-AA (SEQ ID NO: 164)
DIQMTQSPSSLSASVGDRVTITCRASQSIAKYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQFHKRSPQTFGQGTKVEIK

[00151] The Ke86G9 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 54) encoded by the nucleic acid sequence shown in SEQ ID NO: 53.

>KE86G9-LC-NT (SEQ ID NO: 53)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATAATGCATCCAATTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAGGCATCCGCGTGGGCCGACCACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KE86G9-LC-AA (SEQ ID NO: 54)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYNASNLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRGPTTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00152] The Ke86G9 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 166) encoded by the nucleic acid sequence shown in SEQ ID NO: 165.

>KE86G9-VL-NT (SEQ ID NO: 165)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATAATGCATCCAATTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGAGGCATCCGCGTGGGCCGACCACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KE86G9-VL-AA (SEQ ID NO: 166)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYNASNLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQRHPRGPTTFGQGTKVEIK

[00153] The Ka3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 56) encoded by the nucleic acid sequence shown in SEQ ID NO: 55.

>KA3-LC-NT (SEQ ID NO: 55)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCACCCGCGCGCCCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3-LC-AA (SEQ ID NO: 56)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00154] The Ka3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 168) encoded by the nucleic acid sequence shown in SEQ ID NO: 167.

>KA3-VL-NT (SEQ ID NO: 167)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT

GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCACCCGCGCGCCCCGAAGACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3-VL-AA (SEQ ID NO: 168)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIK

[00155] The Ka3A2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 58) encoded by the nucleic acid sequence shown in SEQ ID NO: 57.

>KA3A2-LC-NT (SEQ ID NO: 57)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCTCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3A2-LC-AA (SEQ ID NO: 58)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRSPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00156] The Ka3A2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 170) encoded by the nucleic acid sequence shown in SEQ ID NO: 169.

>KA3A2-VL-NT (SEQ ID NO: 169)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCTCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3A2-VL-AA (SEQ ID NO: 170)
DIQMTQSPSSLSASVGDRVTITCRASQSISKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRSPKTFGQGTKVEIK

[00157] The Ka3H3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 60) encoded by the nucleic acid sequence shown in SEQ ID NO: 59.

>KA3H3-LC-NT (SEQ ID NO: 59)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTGCTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCGCTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCTCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3H3-LC-AA (SEQ ID NO: 60)
DIQMTQSPSSLSASVGDRVTITCQASQDIAKYLNWYQQKPGKAPKLLIYAASALQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRSPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00158] The Ka3H3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a

kappa variable light domain (SEQ ID NO: 172) encoded by the nucleic acid sequence shown in SEQ ID NO: 171.

>KA3H3-VL-NT (SEQ ID NO: 171)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCAGGCGAGTCAGGACATTGCTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCGCTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCTCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3H3-VL-AA (SEQ ID NO: 172)
DIQMTQSPSSLSASVGDRVTITCQASQDIAKYLNWYQQKPGKAPKLLIYAASALQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRSPKTFGQGTKVEIK

[00159] The Ka3A3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 62) encoded by the nucleic acid sequence shown in SEQ ID NO: 61.

>KA3A3-LC-NT (SEQ ID NO: 61)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCTAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3A3-LC-AA (SEQ ID NO: 62)
DIQMTQSPSSLSASVGDRVTITCRASQSIASYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00160] The Ka3A3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 174) encoded by the nucleic acid sequence shown in SEQ ID NO: 173.

>KA3A3-VL-NT (SEQ ID NO: 173)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCTAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3A3-VL-AA (SEQ ID NO: 174)
DIQMTQSPSSLSASVGDRVTITCRASQSIASYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIK

[00161] The Ka3H8 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 64) encoded by the nucleic acid sequence shown in SEQ ID NO: 63.

>KA3H8-LC-NT (SEQ ID NO: 63)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCGAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCTCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3H8-LC-AA (SEQ ID NO: 64)
DIQMTQSPSSLSASVGDRVTITCRASQSIASYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRSPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00162] The Ka3H8 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 176) encoded by the nucleic acid sequence shown in SEQ ID NO: 175.

>KA3H8-VL-NT (SEQ ID NO: 175)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGCGAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCGGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCTCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3H8-VL-AA (SEQ ID NO: 176)
DIQMTQSPSSLSASVGDRVTITCRASQSIASYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRSPKTFGQGTKVEIK

[00163] The Ka3B2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 66) encoded by the nucleic acid sequence shown in SEQ ID NO: 65.

>KA3B2-LC-NT (SEQ ID NO: 65)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAACATTGGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATAGTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC

CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3B2-LC-AA (SEQ ID NO: 66)
DIQMTQSPSSLSASVGDRVTITCRASQNIGKYLNWYQQKPGKAPKLLIYSASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00164] The Ka3B2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 178) encoded by the nucleic acid sequence shown in SEQ ID NO: 177.

>KA3B2-VL-NT (SEQ ID NO: 177)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAACATTGGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATAGTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3B2-VL-AA (SEQ ID NO: 178)
DIQMTQSPSSLSASVGDRVTITCRASQNIGKYLNWYQQKPGKAPKLLIYSASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIK

[00165] The Ka3C5 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 68) encoded by the nucleic acid sequence shown in SEQ ID NO: 67.

>KA3C5-LC-NT (SEQ ID NO: 67)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATTCTGCATCCTCTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGCCCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC

TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3C5-LC-AA (SEQ ID NO: 68)
DIQMTQSPSSLSASVGDRVTITCRASQSISRYLNWYQQKPGKAPKLLIYSASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00166] The Ka3C5 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 180) encoded by the nucleic acid sequence shown in SEQ ID NO: 179.

>KA3C5-VL-NT (SEQ ID NO: 179)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTAGTAGGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATTCTGCATCCTCTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGCCCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3C5-VL-AA (SEQ ID NO: 180)
DIQMTQSPSSLSASVGDRVTITCRASQSISRYLNWYQQKPGKAPKLLIYSASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIK

[00167] The Ka3G2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 70) encoded by the nucleic acid sequence shown in SEQ ID NO: 69.

>KA3G2-LC-NT (SEQ ID NO: 69)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA

GCTCCTGATCTATGCTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGGGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3G2-LC-AA (SEQ ID NO: 70)
DIQMTQSPSSLSASVGDRVTITCRASQSIDKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRGPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00168] The Ka3G2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 182) encoded by the nucleic acid sequence shown in SEQ ID NO: 181.

>KA3G2-VL-NT (SEQ ID NO: 181)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGATAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGGGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3G2-VL-AA (SEQ ID NO: 182)
DIQMTQSPSSLSASVGDRVTITCRASQSIDKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRGPKTFGQGTKVEIK

[00169] The Ka3D3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a kappa light chain (SEQ ID NO: 72) encoded by the nucleic acid sequence shown in SEQ ID NO: 71.

>KA3D3-LC-NT (SEQ ID NO: 71)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGC
TGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG
TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>KA3D3-LC-AA (SEQ ID NO: 72)
DIQMTQSPSSLSASVGDRVTITCRASQSIGKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[00170] The Ka3D3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a kappa variable light domain (SEQ ID NO: 184) encoded by the nucleic acid sequence shown in SEQ ID NO: 183.

>KA3D3-VL-NT (SEQ ID NO: 183)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT
GCCGGGCAAGTCAGAGCATTGGTAAGTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGGTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGC
AGATGCATCCTCGCGCGCCGAAAACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>KA3D3-VL-AA (SEQ ID NO: 184)
DIQMTQSPSSLSASVGDRVTITCRASQSIGKYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQMHPRAPKTFGQGTKVEIK

[00171] The Kc4 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 74) encoded by the nucleic acid sequence shown in SEQ ID NO: 73.

>KC4-LC-NT (SEQ ID NO: 73)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTGGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGGTCAGTAATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4-LC-AA (SEQ ID NO: 74)
QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00172] The Kc4 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 186) encoded by the nucleic acid sequence shown in SEQ ID NO: 185.

>KC4-VL-NT (SEQ ID NO: 185)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTGGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGGTCAGTAATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4-VL-AA (SEQ ID NO: 186)
QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00173] The Kc4G11 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 76) encoded by the nucleic acid sequence shown in SEQ ID NO: 75.

>KC4G11-LC-NT (SEQ ID NO: 75)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTGGGAAGGCGAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGGATAGTGATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4G11-LC-AA (SEQ ID NO: 76)
QSALTQPASVSGSPGQSITISCTGTSSDVGKANYVSWYQQHPGKAPKLMIYKDSDRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00174] The Kc4G11 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 188) encoded by the nucleic acid sequence shown in SEQ ID NO: 187.

>KC4G11-VL-NT (SEQ ID NO: 187)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTGGGAAGGCGAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGGATAGTGATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC

AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4G11-VL-AA (SEQ ID NO: 188)
QSALTQPASVSGSPGQSITISCTGTSSDVGKANYVSWYQQHPGKAPKLMIYKDSDRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00175] The Kc4C11 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 78) encoded by the nucleic acid sequence shown in SEQ ID NO: 77.

>KC4C11-LC-NT (SEQ ID NO: 77)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGGGGGAATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGAATAGTAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4C11-LC-AA (SEQ ID NO: 78)
QSALTQPASVSGSPGQSITISCTGTSSDVRGNNYVSWYQQHPGKAPKLMIYENSKRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00176] The Kc4C11 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 190) encoded by the nucleic acid sequence shown in SEQ ID NO: 189.

>KC4C11-VL-NT (SEQ ID NO: 189)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGGGGGAATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGAATAGTAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4C11-VL-AA (SEQ ID NO: 190)
QSALTQPASVSGSPGQSITISCTGTSSDVRGNNYVSWYQQHPGKAPKLMIYENSKRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00177] The Kc4A1 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 80) encoded by the nucleic acid sequence shown in SEQ ID NO: 79.

>KC4A1-LC-NT (SEQ ID NO: 79)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGTGCGAGGAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGAGTAGTAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4A1-LC-AA (SEQ ID NO: 80)
QSALTQPASVSGSPGQSITISCTGTSSDVSARNYVSWYQQHPGKAPKLMIYESSKRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00178] The Kc4A1 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a

lambda variable light domain (SEQ ID NO: 192) encoded by the nucleic acid sequence shown in SEQ ID NO: 191.

>KC4A1-VL-NT (SEQ ID NO: 191)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGTGCGAGGAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGAGTAGTAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4A1-VL-AA (SEQ ID NO: 192)
QSALTQPASVSGSPGQSITISCTGTSSDVSARNYVSWYQQHPGKAPKLMIYESSKRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00179] The Kc4A4 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 82) encoded by the nucleic acid sequence shown in SEQ ID NO: 81.

>KC4A4-LC-NT (SEQ ID NO: 81)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTAGAACCAGCAGTGACGTTAATAATACTAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGACTAGTGGTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4A4-LC-AA (SEQ ID NO: 82)
QSALTQPASVSGSPGQSITISCTRTSSDVNNTNYVSWYQQHPGKAPKLMIYKTSGRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00180] The Kc4A4 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 194) encoded by the nucleic acid sequence shown in SEQ ID NO: 193.

>KC4A4-VL-NT (SEQ ID NO: 193)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTAGAACCAGCAGTGACGTTAATAATACTAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGACTAGTGGTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4A4-VL-AA (SEQ ID NO: 194)
QSALTQPASVSGSPGQSITISCTRTSSDVNNTNYVSWYQQHPGKAPKLMIYKTSGRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00181] The Kc4E10 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 84) encoded by the nucleic acid sequence shown in SEQ ID NO: 83.

>KC4E10-LC-NT (SEQ ID NO: 83)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAATTCTGCTAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGAGTAGTAGTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4E10-LC-AA (SEQ ID NO: 84)
QSALTQPASVSGSPGQSITISCTGTSSDVNSANYVSWYQQHPGKAPKLMIYKSSSRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00182] The Kc4E10 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 196) encoded by the nucleic acid sequence shown in SEQ ID NO: 195.

>KC4E10-VL-NT (SEQ ID NO: 195)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAATTCTGCTAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGAGTAGTAGTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4E10-VL-AA (SEQ ID NO: 196)
QSALTQPASVSGSPGQSITISCTGTSSDVNSANYVSWYQQHPGKAPKLMIYKSSSRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00183] The Kc4G9 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 86) encoded by the nucleic acid sequence shown in SEQ ID NO: 85.

>KC4G9-LC-NT (SEQ ID NO: 85)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCCGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTGAGAGGAAGAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGAATAGTACTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC

CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4G9-LC-AA (SEQ ID NO: 86)
QSALTQPASVSGSPGQSITISCTGTSSDVERKNYVSWYQQHPGKAPKLMIYKNSTRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00184] The Kc4G9 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 198) encoded by the nucleic acid sequence shown in SEQ ID NO: 197.

>KC4G9-VL-NT (SEQ ID NO: 197)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCCGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTGAGAGGAAGAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGAATAGTACTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4G9-VL-AA (SEQ ID NO: 198)
QSALTQPASVSGSPGQSITISCTGTSSDVERKNYVSWYQQHPGKAPKLMIYKNSTRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00185] The Kc4C3 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 88) encoded by the nucleic acid sequence shown in SEQ ID NO: 87.

>KC4C3-LC-NT (SEQ ID NO: 87)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGGGCGGCTAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGAATAGTACTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG

TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4C3-LC-AA (SEQ ID NO: 88)
QSALTQPASVSGSPGQSITISCTGTSSDVRAANYVSWYQQHPGKAPKLMIYKNSTRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00186] The Kc4C3 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 200) encoded by the nucleic acid sequence shown in SEQ ID NO: 199.

>KC4C3-VL-NT (SEQ ID NO: 199)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGGGCGGCTAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATAAGAATAGTACTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4C3-VL-AA (SEQ ID NO: 200)
QSALTQPASVSGSPGQSITISCTGTSSDVRAANYVSWYQQHPGKAPKLMIYKNSTRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00187] The Kc4F4 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 90) encoded by the nucleic acid sequence shown in SEQ ID NO: 89.

>KC4F4-LC-NT (SEQ ID NO: 89)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGGAGGGCTAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC

CCCCAAACTCATGATTTATCAGGATAGTAGTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4F4-LC-AA (SEQ ID NO: 90)
QSALTQPASVSGSPGQSITISCTGTSSDVRRANYVSWYQQHPGKAPKLMIYQDSSRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00188] The Kc4F4 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 202) encoded by the nucleic acid sequence shown in SEQ ID NO: 201.

>KC4F4-VL-NT (SEQ ID NO: 201)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGGAGGGCTAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATCAGGATAGTAGTCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4F4-VL-AA (SEQ ID NO: 202)
QSALTQPASVSGSPGQSITISCTGTSSDVRRANYVSWYQQHPGKAPKLMIYQDSSRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00189] The Kc4B1 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 92) encoded by the nucleic acid sequence shown in SEQ ID NO: 91.

>KC4B1-LC-NT (SEQ ID NO: 91)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGGGCTAATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGAGTAGTGCGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4B1-LC-AA (SEQ ID NO: 92)
QSALTQPASVSGSPGQSITISCTGTSSDVRANNYVSWYQQHPGKAPKLMIYESSARPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00190] The Kc4B1 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 204) encoded by the nucleic acid sequence shown in SEQ ID NO: 203.

>KC4B1-VL-NT (SEQ ID NO: 203)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTAGGGCTAATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGAGTAGTGCGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4B1-VL-AA (SEQ ID NO: 204)
QSALTQPASVSGSPGQSITISCTGTSSDVRANNYVSWYQQHPGKAPKLMIYESSARPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

[00191] The Kc4E2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 94) encoded by the nucleic acid sequence shown in SEQ ID NO: 93.

>KC4E2-LC-NT (SEQ ID NO: 93)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTTATTATAATAAGTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGAGTAGTAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGG
TCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATA
GCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGC
CAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACG
CATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>KC4E2-LC-AA (SEQ ID NO: 94)
QSALTQPASVSGSPGQSITISCTGTSSDVYYNKYVSWYQQHPGKAPKLMIYESSKRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS

[00192] The Kc4E2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 206) encoded by the nucleic acid sequence shown in SEQ ID NO: 205.

>KC4E2-VL-NT (SEQ ID NO: 205)
CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCA
CTGGAACCAGCAGTGACGTTTATTATAATAAGTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGC
CCCCAAACTCATGATTTATGAGAGTAGTAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCC
AAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACT
GCAGCTCATATGATTGGTGGTTCCGCCCCAAGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>KC4E2-VL-AA (SEQ ID NO: 206)
QSALTQPASVSGSPGQSITISCTGTSSDVYYNKYVSWYQQHPGKAPKLMIYESSKRPSGVSNRFSGS
KSGNTASLTISGLQAEDEADYYCSSYDWWFRPKVFGGGTKLTVL

ANTI-CD19 ANTIBODIES

[00193] The C2 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95.

>C2-LC-NT (SEQ ID NO: 95)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGAAGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTATGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACCTACGACCAGAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
AGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGC
GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTC
ACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>C2-LC-AA (SEQ ID NO: 96)
NFMLTQPHSVSESPGKTVTISCTRSSGSIEDKYVQWYQQRPGSSPTIVIYYDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDQSLYGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV
THEGSTVEKTVAPTECS

[00194] The C2 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

>C2-VL-NT (SEQ ID NO: 207)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGAAGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTATGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACCTACGACCAGAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
A

>C2-VL-AA (SEQ ID NO: 208)
NFMLTQPHSVSESPGKTVTISCTRSSGSIEDKYVQWYQQRPGSSPTIVIYYDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDQSLYGWVFGGGTKLTVL

[00195] The A6 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 98) encoded by the nucleic acid sequence shown in SEQ ID NO: 97.

>A6-LC-NT (SEQ ID NO: 97)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGGTGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTATGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACGTACGACGAGAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
AGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGC
GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTC
ACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>A6-LC-AA (SEQ ID NO: 98)
NFMLTQPHSVSESPGKTVTISCTRSSGSIGDKYVQWYQQRPGSSPTIVIYYDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDESLYGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV
THEGSTVEKTVAPTECS

[00196] The A6 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 210) encoded by the nucleic acid sequence shown in SEQ ID NO: 209.

>A6-VL-NT (SEQ ID NO: 209)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGGTGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTATGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACGTACGACGAGAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
A

>A6-VL-AA (SEQ ID NO: 210)
NFMLTQPHSVSESPGKTVTISCTRSSGSIGDKYVQWYQQRPGSSPTIVIYYDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDESLYGWVFGGGTKLTVL

[00197] The C6 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 100) encoded by the nucleic acid sequence shown in SEQ ID NO: 99.

>C6-LC-NT (SEQ ID NO: 99)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCAATGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTTTGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACCTACGACACCAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
AGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGC
GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTC
ACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>C6-LC-AA (SEQ ID NO: 100)
NFMLTQPHSVSESPGKTVTISCTRSSGSINDKYVQWYQQRPGSSPTIVIYFDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDTSLYGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV
THEGSTVEKTVAPTECS

[00198] The C6 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 212) encoded by the nucleic acid sequence shown in SEQ ID NO: 211.

>C6-VL-NT (SEQ ID NO: 211)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCAATGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTTTGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACCTACGACACCAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
A

>C6-VL-AA (SEQ ID NO: 212)
NFMLTQPHSVSESPGKTVTISCTRSSGSINDKYVQWYQQRPGSSPTIVIYFDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDTSLYGWVFGGGTKLTVL

[00199] The C9 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 102) encoded by the nucleic acid sequence shown in SEQ ID NO: 101.

>C9-LC-NT (SEQ ID NO: 101)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGCTGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTATGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACCTACGACGAGAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
AGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAG

ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGC
GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTC
ACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>C9-LC-AA (SEQ ID NO: 102)
NFMLTQPHSVSESPGKTVTISCTRSSGSIADKYVQWYQQRPGSSPTIVIYYDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDESLYGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV
THEGSTVEKTVAPTECS

[00200] The C9 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 214) encoded by the nucleic acid sequence shown in SEQ ID NO: 213.

>C9-VL-NT (SEQ ID NO: 213)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGCTGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTATGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACCTACGACGAGAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
A

>C9-VL-AA (SEQ ID NO: 214)
NFMLTQPHSVSESPGKTVTISCTRSSGSIADKYVQWYQQRPGSSPTIVIYYDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDESLYGWVFGGGTKLTVL

[00201] The B11 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 104) encoded by the nucleic acid sequence shown in SEQ ID NO: 103.

>B11-LC-NT (SEQ ID NO: 103)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGAAGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTATGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC

GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACCTACGACAACAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
AGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGC
GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTC
ACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>B11-LC-AA (SEQ ID NO: 104)
NFMLTQPHSVSESPGKTVTISCTRSSGSIEDKYVQWYQQRPGSSPTIVIYYDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDNSLYGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV
THEGSTVEKTVAPTECS

[00202] The B11 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 216) encoded by the nucleic acid sequence shown in SEQ ID NO: 215.

>B11-VL-NT (SEQ ID NO: 215)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGAAGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCATTGTGATCTATTATGATAACGAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGACCTACGACAACAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
A

>B11-VL-AA (SEQ ID NO: 216)
NFMLTQPHSVSESPGKTVTISCTRSSGSIEDKYVQWYQQRPGSSPTIVIYYDNERPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQTYDNSLYGWVFGGGTKLTVL

[00203] The D11 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105.

>D11-LC-NT (SEQ ID NO: 105)

AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCAGCATCGATGATAAGTTTGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCACTGTGATCTATTATGATAACATTAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGTCCTATGACGCGAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
AGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGC
GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTC
ACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>D11-LC-AA (SEQ ID NO: 106)

NFMLTQPHSVSESPGKTVTISCTRSSGSIDDKFVQWYQQRPGSSPTTVIYYDNIRPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQSYDASLYGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV
THEGSTVEKTVAPTECS

[00204] The D11 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

>D11-VL-NT (SEQ ID NO: 217)

AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCAGCATCGATGATAAGTTTGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCACTGTGATCTATTATGATAACATTAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGTCCTATGACGCGAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
A

>D11-VL-AA (SEQ ID NO: 218)

NFMLTQPHSVSESPGKTVTISCTRSSGSIDDKFVQWYQQRPGSSPTTVIYYDNIRPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQSYDASLYGWVFGGGTKLTVL

[00205] The B7 antibody includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1 and includes a lambda light chain (SEQ ID NO: 108) encoded by the nucleic acid sequence shown in SEQ ID NO: 107.

>B7-LC-NT (SEQ ID NO: 107)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGCGGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCACTGTGATCTATGAGGATAACCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGTCCTATGACAGCAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
AGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGC
GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTC
ACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>B7-LC-AA (SEQ ID NO: 108)
NFMLTQPHSVSESPGKTVTISCTRSSGSIADKYVQWYQQRPGSSPTTVIYEDNQRPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQSYDSSLYGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV
THEGSTVEKTVAPTECS

[00206] The B7 antibody includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113 and includes a lambda variable light domain (SEQ ID NO: 220) encoded by the nucleic acid sequence shown in SEQ ID NO: 219.

>B7-VL-NT (SEQ ID NO: 219)
AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATCTCCTGCA
CCCGCAGCAGTGGCTCTATCGCGGATAAGTATGTGCAGTGGTACCAGCAGCGCCCGGGCAGTTCCCC
CACCACTGTGATCTATGAGGATAACCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGGCTCCATC
GACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGACTGAAGACTGAGGACGAGGCTGACTACT
ACTGTCAGTCCTATGACAGCAGCCTGTATGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCT
A

>B7-VL-AA (SEQ ID NO: 220)
NFMLTQPHSVSESPGKTVTISCTRSSGSIADKYVQWYQQRPGSSPTTVIYEDNQRPSGVPDRFSGSI
DSSSNSASLTISGLKTEDEADYYCQSYDSSLYGWVFGGGTKLTVL

DUMMY LIGHT CHAINS

[00207] The Dummy light chain 1 (SEQ ID NO: 110) is encoded by the nucleic acid sequence shown in SEQ ID NO: 109.

>DUMMY-LC1-NT (SEQ ID NO: 109)
CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCACCATCTCCTGCT
CTGGAAGCAGCTCCAATATTGAGACTGGTTCTGTATCCTGGTACCAGCAGCTCCCAGGAACAGCCCC
CAAACTCCTCATTTATGACAATAATAAGCGACCCTCAGGGATTCCTGACCGATTCTCTGGCTCCAAG
TCTGGCACGTCAGCCACCCTGGGCATCACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCG
GAACATGGGATGACAGCCTGCCTGGATGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCA
GCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCC
ACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTTGGAAAGCAGATAGCA
GCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAG
CAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAA

>DUMMY-LC1-AA (SEQ ID NO: 110)
QSVLTQPPSVSAAPGQKVTISCSGSSSNIETGSVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSK
SGTSATLGITGLQTGDEADYYCGTWDDSLPGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKA
TLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS

[00208] The Dummy variable light domain 1 (SEQ ID NO: 222) is encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

>DUMMY-VL1-NT (SEQ ID NO: 221)
CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCACCATCTCCTGCT
CTGGAAGCAGCTCCAATATTGAGACTGGTTCTGTATCCTGGTACCAGCAGCTCCCAGGAACAGCCCC
CAAACTCCTCATTTATGACAATAATAAGCGACCCTCAGGGATTCCTGACCGATTCTCTGGCTCCAAG

TCTGGCACGTCAGCCACCCTGGGCATCACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCG
GAACATGGGATGACAGCCTGCCTGGATGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA

>DUMMY-VL1-AA (SEQ ID NO: 222)
QSVLTQPPSVSAAPGQKVTISCSGSSSNIETGSVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSK
SGTSATLGITGLQTGDEADYYCGTWDDSLPGWVFGGGTKLTVL

[00209] The Dummy light chain 2 (SEQ ID NO: 112) is encoded by the nucleic acid sequence shown in SEQ ID NO: 111.

>DUMMY-LC2-NT (SEQ ID NO: 111)
GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCCACCCTCTCCT
GCAGGGCCAGTCAGACGGTTAAGAATAATTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAG
GCTCCTCATCTATGGTGCATCCACCAGGGCCACTGGTATCCCAGCCAGGTTCAGTGGCAGTGGGTCT
GGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTCTGAAGATTTTGCAGTTTATTACTGTCAGC
AGTATAACAACTGGTTGCCCATCAACCCCTATACCTTCGGCCAAGGGACCAAGGTGGAAATCAAACG
TACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCC
TCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACG
CCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCT
CAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACC
CATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

>DUMMY-LC2-AA (SEQ ID NO: 112)
EIVMTQSPATLSVSPGERATLSCRASQTVKNNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGS
GTEFTLTISSLQSEDFAVYYCQQYNNWLPINPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVT
HQGLSSPVTKSFNRGEC

[00210] The Dummy variable light domain 2 (SEQ ID NO: 224) is encoded by the nucleic acid sequence shown in SEQ ID NO: 223.

>DUMMY-VL2-NT (SEQ ID NO: 223)
GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCCACCCTCTCCT
GCAGGGCCAGTCAGACGGTTAAGAATAATTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAG
GCTCCTCATCTATGGTGCATCCACCAGGGCCACTGGTATCCCAGCCAGGTTCAGTGGCAGTGGGTCT

GGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTCTGAAGATTTTGCAGTTTATTACTGTCAGC
AGTATAACAACTGGTTGCCCATCAACCCCTATACCTTCGGCCAAGGGACCAAGGTGGAAATCAAA

>DUMMY-VL2-AA (SEQ ID NO: 224)
EIVMTQSPATLSVSPGERATLSCRASQTVKNNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGS
GTEFTLTISSLQSEDFAVYYCQQYNNWLPINPYTFGQGTKVEIK

MONOVALENT ANTIBODIES

[00211] In some embodiments, the monovalent antibody 5A3 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 4) encoded by the nucleic acid sequence shown in SEQ ID NO: 3 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody 5A3 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 116) encoded by the nucleic acid sequence shown in SEQ ID NO: 115 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00212] In some embodiments, the monovalent antibody 5A3-M3 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 8) encoded by the nucleic acid sequence shown in SEQ ID NO: 7 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody 5A3-M3 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 120) encoded by the nucleic acid sequence shown in SEQ ID NO: 119 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00213] In some embodiments, the monovalent antibody 5A3-M5 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 10) encoded by the nucleic acid sequence shown in SEQ ID NO: 9 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the

nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody 5A3-M5 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 122) encoded by the nucleic acid sequence shown in SEQ ID NO: 121 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00214] In some embodiments, the monovalent antibody Ke8 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 12) encoded by the nucleic acid sequence shown in SEQ ID NO: 11 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ke8 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 124) encoded by the nucleic acid sequence shown in SEQ ID NO: 123 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00215] In some embodiments, the monovalent antibody Ke8A2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 18) encoded by the nucleic acid sequence shown in SEQ ID NO: 17 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ke8A2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 130) encoded by the nucleic acid sequence shown in SEQ ID NO: 129 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00216] In some embodiments, the monovalent antibody Ke8B2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 16) encoded by the nucleic acid sequence shown in SEQ ID NO: 15 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ke8B2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ

ID NO: 128) encoded by the nucleic acid sequence shown in SEQ ID NO: 127 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00217] In some embodiments, the monovalent antibody Ke8G11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 46) encoded by the nucleic acid sequence shown in SEQ ID NO: 45 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ke8G11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 158) encoded by the nucleic acid sequence shown in SEQ ID NO: 157 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00218] In some embodiments, the monovalent antibody Ke8C4 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 42) encoded by the nucleic acid sequence shown in SEQ ID NO: 41 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ke8C4 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 154) encoded by the nucleic acid sequence shown in SEQ ID NO: 153 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00219] In some embodiments, the monovalent antibody Ke8A3 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 26) encoded by the nucleic acid sequence shown in SEQ ID NO: 25 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ke8A3 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 138) encoded by the nucleic acid sequence shown in SEQ ID NO: 137 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00220] In some embodiments, the monovalent antibody Ka3 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 56) encoded by the nucleic acid sequence shown in SEQ ID NO: 55 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ka3 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 168) encoded by the nucleic acid sequence shown in SEQ ID NO: 167 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00221] In some embodiments, the monovalent antibody Ka3A3 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 62) encoded by the nucleic acid sequence shown in SEQ ID NO: 61 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ka3A3 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 174) encoded by the nucleic acid sequence shown in SEQ ID NO: 173 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00222] In some embodiments, the monovalent antibody Ka3G2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 70) encoded by the nucleic acid sequence shown in SEQ ID NO: 69 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ka3G2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 182) encoded by the nucleic acid sequence shown in SEQ ID NO: 181 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00223] In some embodiments, the monovalent antibody Ka3H3 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 60) encoded by the nucleic acid sequence shown

in SEQ ID NO: 59 and a lambda dummy light chain 1 (SEQ ID NO: 110) encoded by the nucleic acid sequence shown in SEQ ID NO: 109. In some embodiments, the monovalent antibody Ka3H3 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 172) encoded by the nucleic acid sequence shown in SEQ ID NO: 171 and a lambda dummy variable light domain 1 (SEQ ID NO: 222) encoded by the nucleic acid sequence shown in SEQ ID NO: 221.

[00224] In some embodiments, the monovalent antibody C2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa dummy light chain 2 (SEQ ID NO: 112) encoded by the nucleic acid sequence shown in SEQ ID NO: 111 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the monovalent antibody C2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa dummy variable light domain 2 (SEQ ID NO: 224) encoded by the nucleic acid sequence shown in SEQ ID NO: 223 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

BISPECIFIC ANTIBODIES

[00225] In some embodiments, the bispecific antibody 5A3xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 4) encoded by the nucleic acid sequence shown in SEQ ID NO: 3 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody 5A3xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 116) encoded by the nucleic acid sequence shown in SEQ ID NO: 115 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00226] In some embodiments, the bispecific antibody 5A3-M3xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 8) encoded by the nucleic acid sequence shown

in SEQ ID NO: 7 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody 5A3-M3xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 120) encoded by the nucleic acid sequence shown in SEQ ID NO: 119 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00227] In some embodiments, the bispecific antibody 5A3-M3xC2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 8) encoded by the nucleic acid sequence shown in SEQ ID NO: 7 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the bispecific antibody 5A3-M3xC2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 120) encoded by the nucleic acid sequence shown in SEQ ID NO: 119 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

[00228] In some embodiments, the bispecific antibody 5A3-M5xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 10) encoded by the nucleic acid sequence shown in SEQ ID NO: 9 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody 5A3-M5xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 122) encoded by the nucleic acid sequence shown in SEQ ID NO: 121 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00229] In some embodiments, the bispecific antibody 5A3-M5xC2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 10) encoded by the nucleic acid sequence shown in SEQ ID NO: 9 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the bispecific antibody 5A3-M5xC2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the

nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 122) encoded by the nucleic acid sequence shown in SEQ ID NO: 121 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

[00230] In some embodiments, the bispecific antibody Ke8xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 12) encoded by the nucleic acid sequence shown in SEQ ID NO: 11 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ke8xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 124) encoded by the nucleic acid sequence shown in SEQ ID NO: 123 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00231] In some embodiments, the bispecific antibody Ke8xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 12) encoded by the nucleic acid sequence shown in SEQ ID NO: 11 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ke8xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 124) encoded by the nucleic acid sequence shown in SEQ ID NO: 123 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00232] In some embodiments, the bispecific antibody Ke8A2xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 18) encoded by the nucleic acid sequence shown in SEQ ID NO: 17 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ke8A2xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 130) encoded by the nucleic acid sequence shown in SEQ ID

NO: 129 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00233] In some embodiments, the bispecific antibody Ke8B2xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 16) encoded by the nucleic acid sequence shown in SEQ ID NO: 15 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ke8B2xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 128) encoded by the nucleic acid sequence shown in SEQ ID NO: 127 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00234] In some embodiments, the bispecific antibody Ke8G11xC2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 46) encoded by the nucleic acid sequence shown in SEQ ID NO: 45 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the bispecific antibody Ke8GxC2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 158) encoded by the nucleic acid sequence shown in SEQ ID NO: 157 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

[00235] In some embodiments, the bispecific antibody Ke8C4xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 42) encoded by the nucleic acid sequence shown in SEQ ID NO: 41 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ke8C4xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 154) encoded by the nucleic acid sequence shown in SEQ ID NO: 153 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00236] In some embodiments, the bispecific antibody Ke8C4xC2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 42) encoded by the nucleic acid sequence shown in SEQ ID NO: 41 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the bispecific antibody Ke8C4xC2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 154) encoded by the nucleic acid sequence shown in SEQ ID NO: 153 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

[00237] In some embodiments, the bispecific antibody Ke8A3xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 26) encoded by the nucleic acid sequence shown in SEQ ID NO: 25 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ke8A3xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 138) encoded by the nucleic acid sequence shown in SEQ ID NO: 137 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00238] In some embodiments, the bispecific antibody Ke8A3xC2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 26) encoded by the nucleic acid sequence shown in SEQ ID NO: 25 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the bispecific antibody Ke8A3xC2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 138) encoded by the nucleic acid sequence shown in SEQ ID NO: 137 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

[00239] In some embodiments, the bispecific antibody Ka3xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 56) encoded by the nucleic acid sequence shown

in SEQ ID NO: 55 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ka3xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 168) encoded by the nucleic acid sequence shown in SEQ ID NO: 167and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00240] In some embodiments, the bispecific antibody Ka3xC2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 56) encoded by the nucleic acid sequence shown in SEQ ID NO: 55 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the bispecific antibody Ka3xC2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 168) encoded by the nucleic acid sequence shown in SEQ ID NO: 167 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

[00241] In some embodiments, the bispecific antibody Ka3A3xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 62) encoded by the nucleic acid sequence shown in SEQ ID NO: 61 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ka3A3xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 174) encoded by the nucleic acid sequence shown in SEQ ID NO: 173 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00242] In some embodiments, the bispecific antibody Ka3G2xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 70) encoded by the nucleic acid sequence shown in SEQ ID NO: 69 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ka3G2xD11 includes a common variable heavy domain (SEQ ID NO: 114)

encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 182) encoded by the nucleic acid sequence shown in SEQ ID NO: 181 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00243] In some embodiments, the bispecific antibody Ka3G2xC2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 70) encoded by the nucleic acid sequence shown in SEQ ID NO: 69 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the bispecific antibody Ka3G2xC2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 182) encoded by the nucleic acid sequence shown in SEQ ID NO: 181 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

[00244] In some embodiments, the bispecific antibody Ka3H3xD11 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 60) encoded by the nucleic acid sequence shown in SEQ ID NO: 59 and a lambda light chain (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 105. In some embodiments, the bispecific antibody Ka3H3xD11 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 172) encoded by the nucleic acid sequence shown in SEQ ID NO: 171 and a lambda variable light domain (SEQ ID NO: 218) encoded by the nucleic acid sequence shown in SEQ ID NO: 217.

[00245] In some embodiments, the bispecific antibody Ka3H3xC2 includes a common heavy chain (SEQ ID NO: 2) encoded by the nucleic acid sequence shown in SEQ ID NO: 1, a kappa light chain (SEQ ID NO: 60) encoded by the nucleic acid sequence shown in SEQ ID NO: 59 and a lambda light chain (SEQ ID NO: 96) encoded by the nucleic acid sequence shown in SEQ ID NO: 95. In some embodiments, the bispecific antibody Ka3H3xC2 includes a common variable heavy domain (SEQ ID NO: 114) encoded by the nucleic acid sequence shown in SEQ ID NO: 113, a kappa variable light domain (SEQ ID NO: 172) encoded by the nucleic acid sequence shown in SEQ ID

NO: 171 and a lambda variable light domain (SEQ ID NO: 208) encoded by the nucleic acid sequence shown in SEQ ID NO: 207.

Definitions:

[00246] Unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well-known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (*e.g.,* electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. *See e.g.,* Sambrook *et al.* Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[00247] As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[00248] As used herein, the term "antibody" refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. By "specifically bind" or "immunoreacts with" or "immunospecifically bind" is meant that the antibody reacts with one or more antigenic determinants of the desired antigen and does not react with other polypeptides or binds at much lower affinity ($K_d > 10^{-6}$). Antibodies

include, but are not limited to, polyclonal, monoclonal, chimeric, dAb (domain antibody), single chain, F_{ab}, $F_{ab'}$ and $F_{(ab')2}$ fragments, scFvs, and an F_{ab} expression library.

[00249] The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. In general, antibody molecules obtained from humans relate to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG_1, IgG_2, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain.

[00250] The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

[00251] The term "antigen-binding site," or "binding portion" refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains, referred to as "hypervariable regions," are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus, the term "FR" refers to amino acid sequences which are naturally found between, and adjacent to, hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." The assignment of amino acids to each domain is in accordance with the definitions of Kabat Sequences of

Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk J. Mol. Biol. 196:901-917 (1987), Chothia *et al.* Nature 342:878-883 (1989).

[00252] As used herein, the term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin, an scFv, or a T-cell receptor. The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. For example, antibodies may be raised against N-terminal or C-terminal peptides of a polypeptide. An antibody is the to specifically bind an antigen when the dissociation constant is ≤ 1 μM; *e.g.*, ≤ 100 nM, preferably ≤ 10 nM and more preferably ≤ 1 nM.

[00253] As used herein, the terms "immunological binding," and "immunological binding properties" refer to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. (*See* Nature 361:186-87 (1993)). The ratio of K_{off} /K_{on} enables the cancellation of all parameters not related to affinity, and is equal to the dissociation constant K_d. (*See, generally*, Davies et al. (1990) Annual Rev Biochem 59:439-473). An antibody of the present invention is the to specifically bind to its target, when the equilibrium binding constant (K_d) is ≤ 1 μM, *e.g.*, $\leq$ 100 nM, preferably ≤ 10 nM, and more preferably ≤ 1 nM, as measured by assays such as radioligand binding assays or similar assays known to those skilled in the art.

[00254] The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which

by virtue of its origin the "isolated polynucleotide" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence. Polynucleotides in accordance with the invention include the nucleic acid molecules encoding the heavy chain immunoglobulin molecules, and nucleic acid molecules encoding the light chain immunoglobulin molecules described herein.

[00255] The term "isolated protein" referred to herein means a protein of cDNA, recombinant RNA, or synthetic origin or some combination thereof, which by virtue of its origin, or source of derivation, the "isolated protein" (1) is not associated with proteins found in nature, (2) is free of other proteins from the same source, *e.g.,* free of marine proteins, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

[00256] The term "polypeptide" is used herein as a generic term to refer to native protein, fragments, or analogs of a polypeptide sequence. Hence, native protein fragments, and analogs are species of the polypeptide genus. Polypeptides in accordance with the invention comprise the heavy chain immunoglobulin molecules, and the light chain immunoglobulin molecules described herein, as well as antibody molecules formed by combinations comprising the heavy chain immunoglobulin molecules with light chain immunoglobulin molecules, such as kappa light chain immunoglobulin molecules, and vice versa, as well as fragments and analogs thereof.

[00257] The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory or otherwise is naturally-occurring.

[00258] The term "operably linked" as used herein refers to positions of components so described are in a relationship permitting them to function in their intended manner. A control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences.

[00259] The term "control sequence" as used herein refers to polynucleotide sequences which are necessary to effect the expression and processing of coding sequences to which they are ligated. The nature of such control sequences differs depending upon the host organism in prokaryotes, such control sequences generally include promoter, ribosomal

binding site, and transcription termination sequence in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. The term "polynucleotide" as referred to herein means a polymeric boron of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA.

[00260] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. *See* Immunology - A Synthesis (2nd Edition, E.S. Golub and D.R. Gren, Eds., Sinauer Associates, Sunderland Mass. (1991)). Stereoisomers (*e.g.,* D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α-, α-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4 hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε -N-acetyllysine, O-phosphoserine, N- acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (*e.g.,* 4- hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[00261] As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80 percent sequence identity, preferably at least 90 percent sequence identity, more preferably at least 95 percent sequence identity, and most preferably at least 99 percent sequence identity.

[00262] Preferably, residue positions which are not identical differ by conservative amino acid substitutions.

[00263] Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine; a group of amino acids having amide- containing side chains is asparagine and glutamine; a group of amino acids having

aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side chains is lysine, arginine, and histidine; and a group of amino acids having sulfur- containing side chains is cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine valine, glutamic- aspartic, and asparagine-glutamine.

[00264] As discussed herein, minor variations in the amino acid sequences of antibodies or immunoglobulin molecules are contemplated as being encompassed by the present invention, providing that the variations in the amino acid sequence maintain at least 75%, more preferably at least 80%, 90%, 95%, and most preferably 99%. In particular, conservative amino acid replacements are contemplated. Conservative replacements are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids are generally divided into families: (1) acidic amino acids are aspartate, glutamate; (2) basic amino acids are lysine, arginine, histidine; (3) non-polar amino acids are alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, and (4) uncharged polar amino acids are glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. The hydrophilic amino acids include arginine, asparagine, aspartate, glutamine, glutamate, histidine, lysine, serine, and threonine. The hydrophobic amino acids include alanine, cysteine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, tyrosine and valine. Other families of amino acids include (i) serine and threonine, which are the aliphatic-hydroxy family; (ii) asparagine and glutamine, which are the amide containing family; (iii) alanine, valine, leucine and isoleucine, which are the aliphatic family; and (iv) phenylalanine, tryptophan, and tyrosine, which are the aromatic family. For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the binding or properties of the resulting molecule, especially if the replacement does not involve an amino acid within a framework site. Whether an amino acid change results in a functional peptide can readily be determined by assaying the specific activity of the polypeptide derivative. Assays are described in detail herein. Fragments or analogs of antibodies or immunoglobulin molecules can be readily prepared by those of ordinary skill in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data

to public or proprietary sequence databases. Preferably, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. Bowie *et al.* Science 253:164 (1991). Thus, the foregoing examples demonstrate that those of skill in the art can recognize sequence motifs and structural conformations that may be used to define structural and functional domains in accordance with the invention.

[00265] Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (4) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various muteins of a sequence other than the naturally-occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally- occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (*e.g.,* a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in Proteins, Structures and Molecular Principles (Creighton, Ed., W. H. Freeman and Company, New York (1984)); Introduction to Protein Structure (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et at. Nature 354:105 (1991).

[00266] As used herein, the terms "label" or "labeled" refers to incorporation of a detectable marker, *e.g.,* by incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (*e.g.,* streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or calorimetric methods). In certain situations, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.,* ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent labels (*e.g.,* FITC, rhodamine, lanthanide phosphors), enzymatic labels (*e.g.,* horseradish peroxidase, p-galactosidase, luciferase, alkaline phosphatase), chemiluminescent, biotinyl

groups, predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance. The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient.

[00267] Other chemistry terms herein are used according to conventional usage in the art, as exemplified by The McGraw-Hill Dictionary of Chemical Terms (Parker, S., Ed., McGraw-Hill, San Francisco (1985)).

[00268] As used herein, "substantially pure" means an object species is the predominant species present (*i.e.,* on a molar basis it is more abundant than any other individual species in the composition), and preferably a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species present.

[00269] Generally, a substantially pure composition will comprise more than about 80 percent of all macromolecular species present in the composition, more preferably more than about 85%, 90%, 95%, and 99%. Most preferably, the object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

[00270] The term patient includes human and veterinary subjects.

Antibodies

[00271] Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a given target, such as, for example, CD47, a tumor associated antigen or other target, or against derivatives, fragments, analogs homologs or orthologs thereof. (*See*, *for example,* Antibodies: A Laboratory Manual, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference).

[00272] Antibodies are purified by well-known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify

the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

[00273] In some embodiments, the antibodies of the invention are monoclonal antibodies. Monoclonal antibodies are generated, for example, by using the procedures set forth in the Examples provided herein. Antibodies are also generated, *e.g.*, by immunizing BALB/c mice with combinations of cell transfectants expressing high levels of a given target on their surface. Hybridomas resulting from myeloma/B cell fusions are then screened for reactivity to the selected target.

[00274] Monoclonal antibodies are prepared, for example, using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized *in vitro*.

[00275] The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental 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.

[00276] Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell

Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of monoclonal antibodies. (*See* Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63)).

[00277] The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980). Moreover, in therapeutic applications of monoclonal antibodies, it is important to identify antibodies having a high degree of specificity and a high binding affinity for the target antigen.

[00278] After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. (*See* Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown *in vivo* as ascites in a mammal.

[00279] The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

[00280] Monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can 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 murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce

immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (*see* U.S. Patent No. 4,816,567; Morrison, Nature 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

[00281] Monoclonal antibodies of the invention include humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization is performed, *e.g.*, by following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539). In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies also comprise, *e.g.*, residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody includes substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also includes at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)).

[00282] Fully human antibodies are antibody molecules in which the entire sequence of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein.

Monoclonal antibodies can be prepared by using trioma technique; the human B-cell hybridoma technique (*see* Kozbor, et al., 1983 Immunol Today 4: 72); and the EBV hybridoma technique to produce monoclonal antibodies (*see* Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Monoclonal antibodies may be utilized and may be produced by using human hybridomas (*see* Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus *in vitro* (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

[00283] In addition, human antibodies can also be produced using additional techniques, including phage display libraries. (*See* Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al., Bio/Technology 10, 779-783 (1992); Lonberg et al., Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild et al, Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); and Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

[00284] Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (*See* PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. An example of such a nonhuman animal is a mouse termed the Xenomouse™ as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B cells which

secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv (scFv) molecules.

[00285] An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method, which includes deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

[00286] One method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. This method includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

[00287] In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen and a correlative method for selecting an antibody that binds specifically to the relevant epitope with high affinity are disclosed in PCT publication WO 99/53049.

[00288] The antibody can be expressed by a vector containing a DNA segment encoding the single chain antibody described above.

[00289] These can include vectors, liposomes, naked DNA, adjuvant-assisted DNA. gene gun, catheters, *etc*. Vectors include chemical conjugates such as described in WO 93/64701, which has targeting moiety (*e.g.,* a ligand to a cellular surface receptor), and a nucleic acid binding moiety (*e.g.,* polylysine), viral vector (*e.g.,* a DNA or RNA viral vector), fusion proteins such as described in PCT/US 95/02140 (WO 95/22618) which is a

fusion protein containing a target moiety (*e.g.,* an antibody specific for a target cell) and a nucleic acid binding moiety (*e.g.,* a protamine), plasmids, phage, etc. The vectors can be chromosomal, non-chromosomal or synthetic.

[00290] Preferred vectors include viral vectors, fusion proteins and chemical conjugates. Retroviral vectors include moloney murine leukemia viruses. DNA viral vectors are preferred. These vectors include pox vectors such as orthopox or avipox vectors, herpesvirus vectors such as a herpes simplex I virus (HSV) vector (*see* Geller, A. I. et al., J. Neurochem, 64:487 (1995); Lim, F., et al., in DNA Cloning: Mammalian Systems, D. Glover, Ed. (Oxford Univ. Press, Oxford England) (1995); Geller, A. I. et al., Proc Natl. Acad. Sci.: U.S.A. 90:7603 (1993); Geller, A. I., et al., Proc Natl. Acad. Sci USA 87:1149 (1990), Adenovirus Vectors (*see* LeGal LaSalle et al., Science, 259:988 (1993); Davidson, et al., Nat. Genet 3:219 (1993); Yang, et al., J. Virol. 69:2004 (1995) and Adeno-associated Virus Vectors (*see* Kaplitt, M. G. et al., Nat. Genet. 8:148 (1994).

[00291] Pox viral vectors introduce the gene into the cells cytoplasm. Avipox virus vectors result in only a short term expression of the nucleic acid. Adenovirus vectors, adeno-associated virus vectors and herpes simplex virus (HSV) vectors are preferred for introducing the nucleic acid into neural cells. The adenovirus vector results in a shorter term expression (about 2 months) than adeno-associated virus (about 4 months), which in turn is shorter than HSV vectors. The particular vector chosen will depend upon the target cell and the condition being treated. The introduction can be by standard techniques, *e.g.,* infection, transfection, transduction or transformation. Examples of modes of gene transfer include *e.g.*, naked DNA, $CaPO_4$ precipitation, DEAE dextran, electroporation, protoplast fusion, lipofection, cell microinjection, and viral vectors.

[00292] The vector can be employed to target essentially any desired target cell. For example, stereotaxic injection can be used to direct the vectors (*e.g.,* adenovirus, HSV) to a desired location. Additionally, the particles can be delivered by intracerebroventricular (icv) infusion using a minipump infusion system, such as a SynchroMed Infusion System. A method based on bulk flow, termed convection, has also proven effective at delivering large molecules to extended areas of the brain and may be useful in delivering the vector to the target cell. (*See* Bobo et al., Proc. Natl. Acad. Sci. USA 91:2076-2080 (1994); Morrison et al., Am. J. Physiol. 266:292-305 (1994)). Other methods that can be used include catheters, intravenous, parenteral, intraperitoneal and subcutaneous injection, and oral or other known routes of administration.

[00293] Bispecific antibodies are antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for a target such as CD47 or any fragment thereof. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

[00294] Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

[00295] Bispecific and/or monovalent antibodies of the invention can be made using any of a variety of art-recognized techniques, including those disclosed in co-pending application WO 2012/023053, filed August 16, 2011, the contents of which are hereby incorporated by reference in their entirety. The methods described in WO 2012/023053 generate bispecific antibodies that are identical in structure to a human immunoglobulin. This type of molecule is composed of two copies of a unique heavy chain polypeptide, a first light chain variable region fused to a constant Kappa domain and second light chain variable region fused to a constant Lambda domain. Each combining site displays a different antigen specificity to which both the heavy and light chain contribute. The light chain variable regions can be of the Lambda or Kappa family and are preferably fused to a Lambda and Kappa constant domains, respectively. This is preferred in order to avoid the generation of non-natural polypeptide junctions. However it is also possible to obtain bispecific antibodies of the invention by fusing a Kappa light chain variable domain to a constant Lambda domain for a first specificity and fusing a Lambda light chain variable domain to a constant Kappa domain for the second specificity. The bispecific antibodies described in WO 2012/023053 are referred to as IgGκλ antibodies or "κλ bodies," a new fully human bispecific IgG format. This κλ-body format allows the affinity purification of a bispecific antibody that is undistinguishable from a standard IgG molecule with characteristics that are undistinguishable from a standard monoclonal antibody and, therefore, favorable as compared to previous formats.

[00296] An essential step of the method is the identification of two antibody Fv regions (each composed by a variable light chain and variable heavy chain domain) having different antigen specificities that share the same heavy chain variable domain. Numerous methods have been described for the generation of monoclonal antibodies and fragments thereof. (*See*, *e.g.,* Antibodies: A Laboratory Manual, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Fully human antibodies are antibody molecules in which the sequence of both the light chain and the heavy chain, including the CDRs 1 and 2, arise from human genes. The CDR3 region can be of human origin or designed by synthetic means. Such antibodies are termed "human antibodies", or "fully human antibodies" herein. Human monoclonal antibodies can be prepared by using the trioma technique; the human B-cell hybridoma technique (*see* Kozbor, et al., 1983 Immunol Today 4: 72); and the EBV hybridoma technique to produce human monoclonal antibodies (*see* Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized and may be produced by using human hybridomas (*see* Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus *in vitro* (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

[00297] Monoclonal antibodies are generated, *e.g.*, by immunizing an animal with a target antigen or an immunogenic fragment, derivative or variant thereof. Alternatively, the animal is immunized with cells transfected with a vector containing a nucleic acid molecule encoding the target antigen, such that the target antigen is expressed and associated with the surface of the transfected cells. A variety of techniques are well-known in the art for producing xenogenic non-human animals. For example, see U.S. Pat. No. 6,075,181 and No. 6,150,584, which is hereby incorporated by reference in its entirety.

[00298] Alternatively, the antibodies are obtained by screening a library that contains antibody or antigen binding domain sequences for binding to the target antigen. This library is prepared, *e.g.*, in bacteriophage as protein or peptide fusions to a bacteriophage coat protein that is expressed on the surface of assembled phage particles and the encoding DNA sequences contained within the phage particles (*i.e.*, "phage displayed library").

[00299] Hybridomas resulting from myeloma/B cell fusions are then screened for reactivity to the target antigen. Monoclonal antibodies are prepared, for example, using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495

(1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized *in vitro*.

[00300] Although not strictly impossible, the serendipitous identification of different antibodies having the same heavy chain variable domain but directed against different antigens is highly unlikely. Indeed, in most cases the heavy chain contributes largely to the antigen binding surface and is also the most variable in sequence. In particular the CDR3 on the heavy chain is the most diverse CDR in sequence, length and structure. Thus, two antibodies specific for different antigens will almost invariably carry different heavy chain variable domains.

[00301] The methods disclosed in co-pending application WO 2012/023053 overcomes this limitation and greatly facilitates the isolation of antibodies having the same heavy chain variable domain by the use of antibody libraries in which the heavy chain variable domain is the same for all the library members and thus the diversity is confined to the light chain variable domain. Such libraries are described, for example, in co-pending applications WO 2010/135558 and WO 2011/084255, each of which is hereby incorporated by reference in its entirety. However, as the light chain variable domain is expressed in conjunction with the heavy variable domain, both domains can contribute to antigen binding. To further facilitate the process, antibody libraries containing the same heavy chain variable domain and either a diversity of Lambda variable light chains or Kappa variable light chains can be used in parallel for *in vitro* selection of antibodies against different antigens. This approach enables the identification of two antibodies having a common heavy chain but one carrying a Lambda light chain variable domain and the other a Kappa light chain variable domain that can be used as building blocks for the generation of a bispecific antibody in the full immunoglobulin format of the invention. The bispecific antibodies of the invention can be of different Isotypes and their Fc portion can be modified in order to alter the bind properties to different Fc receptors and in this way modify the effectors functions of the antibody as well as it pharmacokinetic properties. Numerous methods for the modification of the Fc portion have been described and are applicable to antibodies of the invention. (see for example Strohl, WR Curr Opin Biotechnol 2009 (6):685-91; U.S. Pat. No. 6,528,624; PCT/US2009/0191199 filed Jan 9, 2009). The methods of the invention can also be used to generate bispecific antibodies and antibody mixtures in

a F(ab')2 format that lacks the Fc portion.

[00302] The common heavy chain and two different light chains are co-expressed into a single cell to allow for the assembly of a bispecific antibody of the invention. If all the polypeptides get expressed at the same level and get assembled equally well to form an immunoglobulin molecule then the ratio of monospecific (same light chains) and bispecific (two different light chains) should be 50%. However, it is likely that different light chains are expressed at different levels and/or do not assemble with the same efficiency. Therefore, a means to modulate the relative expression of the different polypeptides is used to compensate for their intrinsic expression characteristics or different propensities to assemble with the common heavy chain. This modulation can be achieved via promoter strength, the use of internal ribosome entry sites (IRES) featuring different efficiencies or other types of regulatory elements that can act at transcriptional or translational levels as well as acting on mRNA stability. Different promoters of different strength could include CMV (Immediate-early Cytomegalovirus virus promoter); EF1-1α (Human elongation factor 1α-subunit promoter); Ubc (Human ubiquitin C promoter); SV40 (Simian virus 40 promoter). Different IRES have also been described from mammalian and viral origin. (See *e.g.*, Hellen CU and Sarnow P. Genes Dev 2001 **15**: 1593–612). These IRES can greatly differ in their length and ribosome recruiting efficiency. Furthermore, it is possible to further tune the activity by introducing multiple copies of an IRES (Stephen et al. 2000 Proc Natl Acad Sci USA 97: 1536-1541). The modulation of the expression can also be achieved by multiple sequential transfections of cells to increase the copy number of individual genes expressing one or the other light chain and thus modify their relative expressions. The Examples provided herein demonstrate that controlling the relative expression of the different chains is critical for maximizing the assembly and overall yield of the bispecific antibody.

[00303] The co-expression of the heavy chain and two light chains generates a mixture of three different antibodies into the cell culture supernatant: two monospecific bivalent antibodies and one bispecific bivalent antibody. The latter has to be purified from the mixture to obtain the molecule of interest. The method described herein greatly facilitates this purification procedure by the use of affinity chromatography media that specifically interact with the Kappa or Lambda light chain constant domains such as the CaptureSelect Fab Kappa and CaptureSelect Fab Lambda affinity matrices (BAC BV, Holland). This multi-step affinity chromatography purification approach is efficient and

generally applicable to antibodies of the invention. This is in sharp contrast to specific purification methods that have to be developed and optimized for each bispecific antibodies derived from quadromas or other cell lines expressing antibody mixtures. Indeed, if the biochemical characteristics of the different antibodies in the mixtures are similar, their separation using standard chromatography technique such as ion exchange chromatography can be challenging or not possible at all.

[00304] Other suitable purification methods include those disclosed in co-pending application PCT/IB2012/003028, filed on October 19, 2012, published as WO2013/088259, the contents of which are hereby incorporated by reference in their entirety.

[00305] In other embodiments of producing bispecific antibodies, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

[00306] According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface includes at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (*e.g.,* tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (*e.g.,* alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

[00307] Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

[00308] Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., J. Immunol. 152:5368 (1994).

[00309] Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., J. Immunol. 147:60 (1991).

[00310] Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (*e.g.,* CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

[00311] Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (*see* U.S. Patent No. 4,676,980), and for treatment of HIV infection (*see* WO

91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

[00312] It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer and/or other diseases and disorders associated with aberrant CD47 expression and/or activity. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). (*See* Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992)). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. (*See* Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989)).

[00313] The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

[00314] Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

[00315] Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as

glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. (*See* WO94/11026).

[00316] Those of ordinary skill in the art will recognize that a large variety of possible moieties can be coupled to the resultant antibodies of the invention. (*See, for example*, "Conjugate Vaccines", Contributions to Microbiology and Immunology, J. M. Cruse and R. E. Lewis, Jr (eds), Carger Press, New York, (1989), the entire contents of which are incorporated herein by reference).

[00317] Coupling may be accomplished by any chemical reaction that will bind the two molecules so long as the antibody and the other moiety retain their respective activities. This linkage can include many chemical mechanisms, for instance covalent binding, affinity binding, intercalation, coordinate binding and complexation. The preferred binding is, however, covalent binding. Covalent binding can be achieved either by direct condensation of existing side chains or by the incorporation of external bridging molecules. Many bivalent or polyvalent linking agents are useful in coupling protein molecules, such as the antibodies of the present invention, to other molecules. For example, representative coupling agents can include organic compounds such as thioesters, carbodiimides, succinimide esters, diisocyanates, glutaraldehyde, diazobenzenes and hexamethylene diamines. This listing is not intended to be exhaustive of the various classes of coupling agents known in the art but, rather, is exemplary of the more common coupling agents. (*See* Killen and Lindstrom, Jour. Immun. 133:1335-2549 (1984); Jansen et al., Immunological Reviews 62:185-216 (1982); and Vitetta et al., Science 238:1098 (1987).

[00318] Preferred linkers are described in the literature. (*See, for example*, Ramakrishnan, S. et al., Cancer Res. 44:201-208 (1984) describing use of MBS (M-maleimidobenzoyl-N-hydroxysuccinimide ester). *See also*, U.S. Patent No. 5,030,719, describing use of halogenated acetyl hydrazide derivative coupled to an antibody by way of an oligopeptide linker. Particularly preferred linkers include: (i) EDC (1-ethyl-3-(3-dimethylamino-propyl) carbodiimide hydrochloride; (ii) SMPT (4-succinimidyloxycarbonyl-alpha-methyl-alpha-(2-pridyl-dithio)-toluene (Pierce Chem. Co.,

Cat. (21558G); (iii) SPDP (succinimidyl-6 [3-(2-pyridyldithio) propionamido]hexanoate (Pierce Chem. Co., Cat #21651G); (iv) Sulfo-LC-SPDP (sulfosuccinimidyl 6 [3-(2-pyridyldithio)-propianamide] hexanoate (Pierce Chem. Co. Cat. #2165-G); and (v) sulfo-NHS (N-hydroxysulfo-succinimide: Pierce Chem. Co., Cat. #24510) conjugated to EDC.

[00319] The linkers described above contain components that have different attributes, thus leading to conjugates with differing physio-chemical properties. For example, sulfo-NHS esters of alkyl carboxylates are more stable than sulfo-NHS esters of aromatic carboxylates. NHS-ester containing linkers are less soluble than sulfo-NHS esters. Further, the linker SMPT contains a sterically hindered disulfide bond, and can form conjugates with increased stability. Disulfide linkages, are in general, less stable than other linkages because the disulfide linkage is cleaved *in vitro*, resulting in less conjugate available. Sulfo-NHS, in particular, can enhance the stability of carbodimide couplings. Carbodimide couplings (such as EDC) when used in conjunction with sulfo-NHS, forms esters that are more resistant to hydrolysis than the carbodimide coupling reaction alone.

[00320] The antibodies disclosed herein can also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang et al., Proc. Natl Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

[00321] Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction.

Use of anti-CD47 antibodies

[00322] It will be appreciated that administration of therapeutic entities in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, PA (1975)), particularly Chapter 87 by Blaug, Seymour,

therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as Lipofectin™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in treatments and therapies in accordance with the present invention, provided that the active ingredient in the formulation is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. *See* also Baldrick P. "Pharmaceutical excipient development: the need for preclinical guidance." Regul. Toxicol Pharmacol. 32(2):210-8 (2000), Wang W. "Lyophilization and development of solid protein pharmaceuticals." Int. J. Pharm. 203(1-2):1-60 (2000), Charman WN "Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts." J Pharm Sci. 89(8):967-78 (2000), Powell *et al.* "Compendium of excipients for parenteral formulations" PDA J Pharm Sci Technol. 52:238-311 (1998) and the citations therein for additional information related to formulations, excipients and carriers well known to pharmaceutical chemists.

[00323] Therapeutic formulations of the invention, which include an antibody of the invention, are used to treat or alleviate a symptom associated with a cancer, such as, by way of non-limiting example, leukemias, lymphomas, breast cancer, colon cancer, ovarian cancer, bladder cancer, prostate cancer, glioma, lung & bronchial cancer, colorectal cancer, pancreatic cancer, esophageal cancer, liver cancer, urinary bladder cancer, kidney and renal pelvis cancer, oral cavity & pharynx cancer, uterine corpus cancer, and/or melanoma The present invention also provides methods of treating or alleviating a symptom associated with a cancer. A therapeutic regimen is carried out by identifying a subject, *e.g.*, a human patient suffering from (or at risk of developing) a cancer, using standard methods.

[00324] Efficaciousness of treatment is determined in association with any known method for diagnosing or treating the particular immune-related disorder. Alleviation of one or more symptoms of the immune-related disorder indicates that the antibody confers a clinical benefit.

[00325] Methods for the screening of antibodies that possess the desired specificity include, but are not limited to, enzyme linked immunosorbent assay (ELISA) and other immunologically mediated techniques known within the art.

[00326] Antibodies directed against a target such as CD47, a tumor associated antigen or other antigen (or a fragment thereof) may be used in methods known within the

art relating to the localization and/or quantitation of these targets, *e.g.*, for use in measuring levels of these targets within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies specific any of these targets, or derivative, fragment, analog or homolog thereof, that contain the antibody derived antigen binding domain, are utilized as pharmacologically active compounds (referred to hereinafter as "Therapeutics").

[00327] An antibody of the invention can be used to isolate a particular target using standard techniques, such as immunoaffinity, chromatography or immunoprecipitation. Antibodies of the invention (or a fragment thereof) can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

[00328] Antibodies of the invention, including polyclonal, monoclonal, humanized and fully human antibodies, may be used as therapeutic agents. Such agents will generally be employed to treat or prevent a disease or pathology associated with aberrant expression or activation of a given target in a subject. An antibody preparation, preferably one having high specificity and high affinity for its target antigen, is administered to the subject and will generally have an effect due to its binding with the target. Administration of the antibody may abrogate or inhibit or interfere with the signaling function of the target. Administration of the antibody may abrogate or inhibit or interfere with the binding of the target with an endogenous ligand to which it naturally binds. For example, the antibody binds to the target and neutralizes or otherwise inhibits the interaction between CD47 and SIRPα.

[00329] A therapeutically effective amount of an antibody of the invention relates generally to the amount needed to achieve a therapeutic objective. As noted above, this may be a binding interaction between the antibody and its target antigen that, in certain cases, interferes with the functioning of the target. The amount required to be administered will furthermore depend on the binding affinity of the antibody for its specific antigen, and will also depend on the rate at which an administered antibody is depleted from the free volume other subject to which it is administered. Common ranges for therapeutically effective dosing of an antibody or antibody fragment of the invention may be, by way of nonlimiting example, from about 0.1 mg/kg body weight to about 50 mg/kg body weight. Common dosing frequencies may range, for example, from twice daily to once a week.

[00330] Antibodies or a fragment thereof of the invention can be administered for the treatment of a variety of diseases and disorders in the form of pharmaceutical compositions. Principles and considerations involved in preparing such compositions, as well as guidance in the choice of components are provided, for example, in Remington: The Science And Practice Of Pharmacy 19th ed. (Alfonso R. Gennaro, et al., editors) Mack Pub. Co., Easton, Pa.: 1995; Drug Absorption Enhancement: Concepts, Possibilities, Limitations, And Trends, Harwood Academic Publishers, Langhorne, Pa., 1994; and Peptide And Protein Drug Delivery (Advances In Parenteral Sciences, Vol. 4), 1991, M. Dekker, New York.

[00331] Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. (*See*, *e.g.*, Marasco et al., Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993)). The formulation can also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition can comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[00332] The active ingredients can also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate)

microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions.

[00333] The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

[00334] Sustained-release preparations can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT ™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods.

[00335] An antibody according to the invention can be used as an agent for detecting the presence of a given target (or a protein fragment thereof) in a sample. In some embodiments, the antibody contains a detectable label. Antibodies are polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, F_{ab}, scFv, or $F_{(ab)2}$) is used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. Included within the usage of the term "biological sample", therefore, is blood and a fraction or component of blood including blood serum, blood plasma, or lymph. That is, the detection method of the invention can be used to detect an analyte mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of an analyte mRNA include Northern hybridizations and *in situ*

hybridizations. *In vitro* techniques for detection of an analyte protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. *In vitro* techniques for detection of an analyte genomic DNA include Southern hybridizations. Procedures for conducting immunoassays are described, for example in "ELISA: Theory and Practice: Methods in Molecular Biology", Vol. 42, J. R. Crowther (Ed.) Human Press, Totowa, NJ, 1995; "Immunoassay", E. Diamandis and T. Christopoulus, Academic Press, Inc., San Diego, CA, 1996; and "Practice and Theory of Enzyme Immunoassays", P. Tijssen, Elsevier Science Publishers, Amsterdam, 1985. Furthermore, *in vivo* techniques for detection of an analyte protein include introducing into a subject a labeled anti-analyte protein antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

Pharmaceutical compositions

[00336] The antibodies of the invention (also referred to herein as "active compounds"), and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the antibody and a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[00337] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation),

transdermal (*i.e.,* topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00338] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00339] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally,

dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00340] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00341] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[00342] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00343] The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00344] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[00345] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[00346] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[00347] The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

EXAMPLE 1: Cloning, Expression and Purification of Human CD47

[00348] *Cloning.* The sequence corresponding to the extracellular domain of human CD47 (hCD47), was amplified from human cDNA by polymerase chain reaction (PCR) using specific oligonucleotides. The amplification production was gel-purified and cloned into the pEAK8 mammalian expression vector (Edge Biosystems, Gaithersburg, MD). The vector was further modified to introduce an Avitag™ (Avidity, Denver CO) and an hexa-

histidine tag at the C-terminus allowing for single site biotinylation of the protein and purification by IMAC (Immobilized Metal Ion Affinity Chromatography). The constructs were verified by DNA sequencing.

[00349] *Expression*. The plasmid was then transfected into mammalian cells using a liposome based transfection reagent such as TransIT-LT1 (Mirus, Madison, WI). The transfection step requires only small quantities of DNA and cells, typically $2x10^5$ cells and 2 μg of plasmid DNA per well and the transfection carried out in a 6-well plate. Although different mammalian cell lines can be used, in the examples given below, transformed human embryo kidney monolayer epithelial cells (PEAK cells) were transfected. These cells stably express the EBNA-1 gene, further supporting the episomal replication process, are semi-adherent and can be grown under standard conditions cell culture incubator (5% CO2; 37 °C in DMEM medium supplemented with 10% fetal calf serum). After 24h, cells were placed under selective conditions by adding medium containing 0.5–2 μg/mL puromycin, as cells harboring the episomal vector are resistant to this antibiotic.

[00350] Two to three weeks after transfection, were used to seed Tri-flasks or disposable CELLine bioreactors for the production step. The CELLine is a two compartment bioreactor that can be used in a standard cell culture incubator. The smaller compartment (15 ml) contains the cells and is separated from a larger (one liter) medium containing compartment by a semi-permeable membrane with a cut-off size of 10 kDa (Bruce et al. 2002, McDonald et al. 2005). This system allows for the diffusion of nutrients, gazes and metabolic waste products, while retaining cells and secreted proteins in the smaller compartment. The culture was maintained for 7–10 days before harvest of the supernatant. As the medium contains serum, the cells maintain good viability and several production runs can be generated using the same cells and containers.

[00351] *Purification*. After harvest, the cell culture supernatants were clarified by centrifugation and filtered through a 0.22 μm membrane. The supernatant from Tri-flasks were concentrated 20–40 times using a concentration device such as a SartoFlow 200 (Sartorius) with a membrane having an appropriate cut-off size to retain the protein of interest. This step was not required using the CELLline bioreactor due to the low volume recovered from the cell compartment. In addition, the concentration step increases the concentration of both the protein of interest and high molecular weight contaminants such as bovine serum albumin or immunoglobulins. In contrast, the supernatant retrieved from the cell compartment of the CELLine bioreactor contains concentrated recombinant protein

and reduced levels of contaminants as they cannot cross the 10 kDa membrane separating the two chambers of the reactor. This increased recombinant protein to contaminant ratio greatly enhances the efficiency of purification using IMAC. The concentrated supernatant was then supplemented with 100 mM imidazole and loaded on Ni–NTA affinity chromatography resin (Qiagen). The relatively high concentration of imidazole minimizes binding of contaminants to the resin. After washing of the column, proteins are eluted at a flow rate of 2 mL/min using a 30 mL imidazole gradient (20–400 mM imidazole) on an ÄKTA Prime chromatography system (Amersham Pharmacia Biotech). The elution gradient further improves the purity of the recombinant protein but can be replaced by a step elution approach if a chromatography system is not available. The eluted fractions can be analyzed by SDS-PAGE or ELISA to determine their content in recombinant protein. The fractions of interest are pooled and desalted on PD-10 columns (GE Healthcare) equilibrated with phosphate buffered saline or another appropriate buffer. The desalted proteins can then be quantified using various techniques and their purity analyzed by SDS-PAGE. Recombinant CD47 was biotinylated in vitro using biotin ligase (Avidity, Denver CO) according to manufacturer's instructions. After desalting the biotinylation level was evaluated by pull-down assays using streptavidin magnetic beads and SDS-PAGE analysis.

EXAMPLE 2: Cloning, Expression and Purification of Human CD19

[00352] *Cloning.* The sequence corresponding to the extracellular domain of human CD19 (hCD419), was amplified from human cDNA by polymerase chain reaction (PCR) using specific oligonucleotides. The amplification production was gel-purified and cloned into the pEAK8 mammalian expression vector (Edge Biosystems, Gaithersburg, MD). The vector was further modified to introduce an Avitag™ (Avidity, Denver CO) and an hexa-histidine tag at the C-terminus allowing for single site biotinylation of the protein and purification by IMAC (Immobilized Metal Ion Affinity Chromatography). The constructs were verified by DNA sequencing.

[00353] *Expression and Purification.* The expression, purification and biotinylation of soluble hCD19 were performed as described in Example 1.

EXAMPLE 3: Phage display selection using human scFv libraries containing fixed variable heavy chain

[00354] General procedures for construction and handling of human scFv libraries displayed on M13 bacteriophage are described in Vaughan et al., (Nat. Biotech. 1996, 14:309-314), hereby incorporated by reference in its entirety. The libraries used for selection and screening encode scFv that all share the same VH domain and are solely diversified in the VL domain. Methods for the generation of fixed VH libraries and their use for the identification and assembly of bispecific antibodies are described in US 2012/0184716 and WO 2012/023053, each of which is hereby incorporated by reference in its entirety. The procedures to identify scFv binding to hCD19 or hCD47 are described below.

[00355] *Liquid phase selections.* Aliquots of scFv phage libraries (10^{12} Pfu) were blocked with PBS containing 3% (w/v) skimmed milk for one hour at room temperature on a rotary mixer. Blocked phage was then deselected on streptavidin magnetic beads (Dynal M-280) for one hour at room temperature on a rotary mixer. Deselected phage was then incubated with in vivo biotinylated hCD19 or hCD47 (100 nM) for two hours at room temperature on a rotary mixer. Beads were captured using a magnetic stand followed by four washes with PBS/0.1% Tween 20 and 3 washes with PBS. Beads were then directly added to 10 ml of exponentially growing TG1 cells and incubated for one hour at 37 °C with slow shaking (100 rpm). An aliquot of the infected TG1 was serial diluted to titer the selection output. The remaining infected TG1 were spun at 3000 rpm for 15 minutes and re-suspended in 0.5 ml 2xTY-AG (2xTY media containing 100 µg/ml ampicillin and 2% glucose) and spread on 2xTYAG agar Bioassay plates. After overnight incubation at 30 °C 10 ml of 2xTYAG was added to the plates and the cells were scraped form the surface and transferred to a 50 ml polypropylene tube. 2xTYAG containing 50% glycerol was added to the cell suspension to obtain a final concentration of 17% glycerol. Aliquots of the selection round were kept at –80 °C.

[00356] *Phage rescue.* 100 µl of cell suspension obtained from previous selection rounds were added to 20 ml of 2xTYAG and grown at 37 °C with agitation (240 rpm) until an OD_{600} of 0.3 to 0.5 was reached. The culture was then super-infected with 3.3 x 10^{10} MK13K07 helper phage and incubated for one hour at 37 °C (150 rpm). The medium was then changed by centrifuging the cells at 2000 rpm for 10 minutes, removing the medium

and resuspending the pellet in 20 ml of 2xTY-AK (100 µg/ml ampicillin; 50 µg/ml kanamycin). The culture was then grown overnight at 30 °C (240 rpm). The next day, the phage containing supernatant was used for the next round of selection.

[00357] *Cell surface selections.* Phage containing supernatants were blocked with PBS containing 3% (w/v) skimmed milk for one hour at room temperature on a rotary mixer. Blocked phage was then deselected for one hour on Jukat T cells that do not express CD19 and that had been previously blocked with PBS containing 2% (w/v) skimmed milk. Deselected phage was then incubated with $2x10^7$ Raji cells expressing CD19 for one hour at room temperature with gentle shaking. Cells were then pelleted and washed ten times with PBS. Bound phage was eluted by adding directly 10 ml of exponentially growing TG1 to the T75 flask and incubating for one hour at 37 °C with slow shaking. An aliquot of the infected TG1 was serial diluted to titer the selection output. Infected TG1 were spun at 3000 rpm for 15 minutes and re-suspended in 0.5 ml 2xTY-AG (2xTY media containing 100 µg/ml ampicillin and 2% glucose) and spread on 2xTYAG agar Bioassay plates. After overnight incubation at 30°C 10 ml of 2xTYAG was added to the plates and the cells were scraped form the surface and transferred to a 50 ml polypropylene tube. 2xTYAG containing 50% glycerol was added to the cell suspension to obtain a final concentration of 17% glycerol. Aliquots of the selection round were kept at –80°C.

[00358] *scFv periplasmic preparation for binding and functional tests.* Individual clones were inoculated into a deep well microtiter plate containing 0.9 ml of 2xTYAG media (0.1% glucose) per well and grown at 37 °C for 5-6h (250 rpm). 100µl per well of 0.2 mM IPTG in 2xTY medium were then added to give a final concentration of 0.02 mM IPTG. Plates were then incubated overnight at 30 °C with shaking at 250 rpm. The deep-well plates were centrifuged at 2,500 rpm for 10 min and the supernatant carefully removed. The pellets were re-suspended in 150 µl TES buffer (50 mM Tris / HCl (pH 8), 1 mM EDTA (pH 8), 20% sucrose, complemented with Complete protease inhibitor, Roche). A hypotonic shock was produced by adding 150 µl of diluted TES buffer (1:5 TES:water dilution) and incubation on ice for 30 min. Plates were then centrifuged at 4000 rpm for 10 minutes to remove cells and debris. The supernatants were carefully transferred into another microtiter plate and kept on ice for immediate testing in functional assays or binding assays.

[00359] *Phage clone sequencing.* Single clones were placed in a microtiter plate containing 150µl of 2xTYAG media (2% glucose) per well and grown at 30 °C (120 rpm) overnight. The next day 5 µl of culture was transferred into another plate containing 45 µl

of dH_2O and mixed. The plate was then frozen at –20 °C. After thawing, 1 µl of this suspension was used for PCR amplification using standard PCR protocols with primer specific for pNDS1: mycseq, 5'-CTCTTCTGAGATGAGTTTTTG-3' (SEQ ID NO: 283) and gene3leader, 5'-TTATTATTCGCAATTCCTTTAGTTGTTCCT-3' (SEQ ID NO: 284). The PCR reactions were purified in 96 well format using the Montage PCRµ96 system (Millipore). 5 µl of the eluted DNA was sequencing using the mycseq and gene3leader primers.

EXAMPLE 4: Screening for scFv binding to hCD47 and scFv inhibiting SIRPα interaction

[00360] *Binding*: Screening of scFv for binding to hCD47 was tested in a homogenous assay using FMAT technology. The following reagents were mixed in each well of a 384 optical plate (Costar): 30µl of a streptavidin polystyrene bead suspension (Spherotech; 3000 beads/well) coated with biotinylated hCD47 or a control biotinylated protein (NusA); 60µl of scFv periplasmic preparation; 10µl of detection buffer (PBS containing anti-cmyc antibody at 5 µg/mL; anti-mouse Fc AlexaFluor 647 diluted 1:200). After mixing at 450 rpm for 5 minutes, the 384 well plates were incubated at room temperature and read after 1 and 3 hours on an FMAT 8200 Cellular Detection System (Applied Biosystems). Each scFv sample was tested in duplicate against hCD47 and NusA. Clones expressing scFv giving a specific signal for hCD47 and not NusA were selected for further analysis.

[00361] *Inhibition of CD47-SIRPα interaction*: ScFv were also screened for their capacity to inhibit the interaction between CD47 and SIRPα in a bead based homogenous assay using FMAT technology. Protein A polystyrene beads (Spherotech) are incubated with 5 µg/mL of goat anti-human lgG Fcy specific (Jackson lmmunoresearch). After washing of the beads 5 µg/mL SIRPα-Fc (R&D Systems) was added so that the fusion protein can be captured at the bead surface. After blocking with PBS; 2% Tropix l-block (Applied Biosystems), 30µl of the beads suspension (3000 beads/well) coated were added to each well of a 384 optical plate (Costar). In a separate 96 well plate 120µl of scFv periplasmic preparation were mixed with 24µl of biotinylated hCD47 (300ng/ml) and incubated for 50 minutes at room temperature so that the scFv can bind to hCD47. After incubation, 24µl of Streptavidin Cy5 (1 µg/ml; Invitrogen) are added to the mix and 70µl of

this final mix are added to the 30µl of beads in each well of the 384 well plate. After 3 hours of incubation at room temperature, the plate is then read on an FMAT 8200 Cellular Detection System (Applied Biosystems). Controls well containing no scFv or an irrelevant scFv not binding to CD47 were included in each plate so that clones expressing scFv leading to a reduction of the SIRPα-CD47 signal measured in controls were selected for further analysis.

[00362] Alternatively a cell based assay monitoring the interaction of soluble SIRPα with hCD47 expressed at the surface of stably transfected Chinese hamster ovary (CHO) cell line was also used for screening of candidates. 20 µl of PBS-BSA 2% azide 0.1% containing 3000 CHO expressing hCD47 cells were added to each well of a 384 optical plate (Costar). 50 µl of a twofold dilution of the scFv periplasmic preparation was then added to the well and incubated at room temperature for 30 minutes to allow the scFv to bind to CD47 on cells. After incubation 30 µl of PBS 2% BSA azide 0.1% containing 10ng/ml of SIRPα-Fc (R&D systems) and Anti hIgG-Fc FMAT Blue coupled antibody (diluted 1:2000) were added and further incubated for 3 hours before reading on an FMAT 8200 Cellular Detection System (Applied Biosystems).

EXAMPLE 5: Screening for scFv binding to hCD19

[00363] Screening of scFv for binding to recombinant hCD19 was tested in a homogenous assay using FMAT technology as described in Example 4.

[00364] Screening was also performed on Raji cells for binding to the native form of hCD19. To each well of a 384 optical plate (Costar) 30 µl of PBS-BSA 2% azide 0.1% containing 3000 Raji cells (a human B cell line expressing CD19) or Jurkat cells (a human T cell line that do not express CD19) were added. Then, 30 µl of a twofold dilution of the scFv periplasmic preparation, 30 µl of PBS-BSA2% and 10 30 µl of 10X detection buffer (Qiagen Antibody pentaHis AF647 diluted 1:700 in PBS-BSA2%). After mixing at 450 rpm for 5 minutes, the 384 well plates were incubated at room temperature and read after 1 and 3 hours on an FMAT 8200 Cellular Detection System (Applied Biosystems). Clones expressing scFv giving a specific signal for Raji and not Jurkat cells were selected for further analysis.

EXAMPLE 6: Fixed VH candidates reformatting into IgG and transient expression in mammalian cells

[00365] After screening, scFv candidates against hCD19 or hCD47 were reformatted into IgG and expressed by transient transfection into PEAK cells. The VH and VL sequences of selected scFv were amplified with specific oligonucleotides and cloned into an expression vector containing the heavy and light chain constant regions and the constructions were verified by sequencing. The expression vectors were transfected into mammalian cells using the Fugene 6 Transfection Reagent (Roche, Basel, Switzerland). Briefly, Peak cells were cultured in 6-well plates at a concentration of 6 x 10^5 cells per well in 2 ml culture media containing fetal bovine serum. The expression vectors encoding the candidate VH and VL sequences were co-transfected into the cells using the Fugene 6 Transfection Reagent according to manufacturer's instructions. One day following transfection, the culture media was aspirated, and 3 ml of fresh serum-free media was added to cells and cultured for three days at 37 °C. Following three days culture period, the supernatant was harvested for IgG purified on protein G-Sepharose 4B fast flow columns (Sigma, St. Louis, MO) according to manufacturer's instructions. Briefly, supernatants from transfected cells were incubated overnight at 4 °C with ImmunoPure (G) IgG binding buffer (Pierce, Rockford IL). Samples were then passed over Protein G-Sepharose 4B fast flow columns and the IgG consequently purified using elution buffer. The eluted IgG fraction was then dialyzed against PBS and the IgG content quantified by absorption at 280 nm. Purity and IgG integrity were verified by SDS-PAGE.

EXAMPLE 7: Affinity modulation of anti-hCD47 antibodies

(a) Antibodies Ka3, Ke8, Kc4

[00366] Three antibodies identified during the screening process described in the Examples above were shown to be specific for human CD47 and able to block the interaction between CD47 and SIRPα were selected for affinity maturation in order to increase their affinity and potency. All these antibodies share the same variable heavy chain but have different variable light chains. Ka3 and Ke8 contain a kappa light chain (IGVK1-39 according to the IMGT nomenclature) whereas Kc4 contains a lambda light chain (IGVL2-14). Several phage libraries displaying scFv variants were generated by introducing diversity into the CDR1, CDR2 and CDR3 of the variable light chain region while the

heavy chain variable region was kept unmodified. One library of $9x10^7$ transformants covering a theoretical diversity of $7x10^5$ was generated for Ka3; two libraries of $2x10^8$ transformants each, partially covering a theoretical diversity of $2.4x10^9$ were generated for Ke8 and one library of $3.6 x10^7$ transformants covering a theoretical diversity of $2.6x10^5$ was generated for Kc4. These libraries were used for phage display selections as described in Example 3 except that the selection stringency was increased between rounds by reducing the concentration of hCD47 between different rounds: 10 nM and 1 nM of hCD47 were used in the first and second round of selection, respectively. The selected variants were screened for the capacity to inhibit the interaction between hCD47 and SIRPα using the assay described in Example 4. Positive clones were then reformatted as IgG and characterized as described in the following Examples. These affinity maturation efforts lead to the identification of the following anti-VD47 antibodies:

- Ke8H6; Ke86G9; Ke8A3; Ke8C4; Ke8F1; Ke8B7; Ke8G11; Ke8A8; Ke8A4; Ke8B2; Ke8C7; Ke8H3; Ke8A2; Ke8H5; Ke8G6; Ke8E8; Ke81A3; Ke81G9; Ke84G9; Ke8G2; Ke8F2
- Ka3G2; Ka3D3; Ka3A2; Ka3B2; Ka3C5; Ka3A3; Ka3H8; Ka3H3
- Kc4E2; Kc4F4; Kc4A1; Kc4C11; Kc4E10; Kc4B1; Kc4C3; Kc4A4; Kc4G11; Kc4G9

(b) 5A3 antibody engineering for affinity modulation

[00367] The VL sequence of anti-CD47 5A3 antibody was engineered to decrease its affinity toward its target. The 5A3-VL sequence was aligned to its closest germline sequence, the human IGKV1-33 according to the IMGT nomenclature (Fig. 1). Using this alignment, several residues were identified in the CDRL1 and CDRL2 of 5A3 VL which are not conserved with the germline sequence. Some of these amino acids were mutated in order to alter the binding affinity of the antibody. Residues of the 5A3 CDRL3 were also changed to modulate antibody binding while at the same time targeting the same epitope on CD47. These different strategies led to the identification of the 5A3-M3 and 5A3-M5 candidates.

[00368] These variants were first tested in a CD47/SIRPα binding assay to determine their blocking potency compared to the parental 5A3 antibody (Figure 2). The 5A3-M3 and

5A3-M5 are both less potent at inhibiting the interaction between CD47 and SIRPα than 5A3 with 5A3-M5 showing the weakest inhibition potency profile.

[00369] The affinity of these variants for human CD47 was then evaluated by surface plasmon resonance technology. The K_D of the 5A3, 5A3-M3 and 5A3-M5 antibodies are about 2.36E-08, 5.60E-08 and 2.84E-06 M, respectively. These data confirmed that the 5A3 variants are binding to CD47 with a lower affinity compared to the parental antibody and that the 5A3-M5 has the weakest affinity for human CD47 while the 5A3-M3 has an intermediate affinity.

EXAMPLE 8: Characterization of CD47 Antibodies

Binding of CD47 Antibodies to huCD47-transfected CHO cells

[00370] The specificity of CD47 monoclonal antibodies (Mabs) was shown by flow cytometry using CHO cells stably transfected with human CD47 (CHO-huCD47 cells). Non-transfected CHO cells were used as control. In brief, purified CD47 Mabs were incubated with CHO-huCD47 cells at a final concentration of 10 µg/ml for 30 minutes. After two washes, bound CD47 antibodies were detected using a Cy-5 conjugated anti-human Fc secondary antibody (BD biosciences). Figure 3 shows a significant binding of CD47 MAbs to hu-CD47 transfected CHO cells, but no binding (or background-level binding) to non-transfected CHO cells, thus demonstrating the specificity of CD47 MAbs of the present invention.

Binding of CD47 Antibodies to HEK293-P cells

[00371] The specificity of CD47 Mabs was further confirmed in an experiment using HEK293-P cells with a siRNA mediated CD47 gene knock-down. The HEK293-P cells (Peak cells) were derived from human embryonic kidney cells and expresses low to moderate levels of CD47. A CD47-deficient variant of Peak cells has been generated by stably transfecting them with siRNA specific to the CD47 gene. Cell surface expression of CD47 antigen is reduced in these CD47 knock-down PEAK cells by more than 85% (data not shown). Figure 4 demonstrates the binding of selected CD47 MAbs to non-transfected Peak cells and to CD47 knock-down Peak cells. Binding of CD47 Mabs to CD47 siRNA-transfected Peak cells is significantly reduced, thus confirming their antigen specificity.

Cross-reactivity of CD47 Antibodies with cynomolgus CD47; Binding of CD47 Antibodies to human and cynomolgus CD4+ T cells

[00372] The ability of CD47 monoclonal antibodies of the present invention to cross-react with native cynomolgus monkey CD47 was tested by flow cytometry. Binding of CD47 antibodies to cynomolgus CD4-positive T lymphocytes present in peripheral blood mononuclear cells (PBMCs) was compared to the binding to the corresponding human cell population. In brief, cynomolgus peripheral blood mononuclear cells (PBMCs) were obtained from Ricerca Biosciences. Human PBMCs were isolated from a buffy coat using CPT ficoll tubes (Beckton and Dickinson). For flow cytometry analysis, PBMCs were pre-incubated with FcgR Blocking Reagent, (Miltenyi Biotech.) for 20 minutes in order to block Fc gamma receptors before addition of CD47 antibodies (final concentration of 0.005 mg/ml). After an incubation period of 30 minutes cells were washed and reacted with PE-conjugated anti human CD4 antibody (clone L200, BD Pharmingen diluted 1/100) and FMAT Blue-conjugated goat-anti human Fc antibody (Jackson Immuno Research, 109-005-098). The MFI for CD47 binding (FL4) was then determined by flow cytometry in the CD4+ positive population (gated on FL2). As shown in Figure 5, CD47 monoclonal antibodies of the present invention bind to native human CD47 and cross-react with cynomolgus CD47.

SIRPα Blocking Activity of CD47 antibodies

[00373] The SIRPα blocking activity of CD47 was determined in the CD47-SIRPα competitive binding assay. Dose-response experiments with CD47 Mabs allowed determining an IC50 value for each of the CD47 MAbs of the present invention. In brief, human CD47 transfected CHO cells were incubated with His-tagged soluble human SIRPα (final concentration, 200ng/ml) and increasing concentrations of CD47 Mab (3.3 pM to 330 nM, in quadruplicates) The detection of bound SIRPα was as described in example 4. Figure 6 shows the potency of CD47 Mabs to block the CD47-SIRPα interaction, represented by IC50 values. CD47 Mabs are grouped by family and ranked from higher to lower potency. Their neutralizing activity was compared to the commercially available CD47 antibody B6H12. It is apparent from figure 6 that the neutralizing potencies of CD47 Mabs of the present invention vary over a wide range.

Hemagglutination Activity of CD47 Antibodies

[00374] Figure 7 demonstrates that high-affinity CD47 Mabs of the 5A3, Ke8, and Ka3 families induce hemagglutination; in contrast to the other three families, Kc4 family antibodies tested in this experiment do not seem to induce hemagglutination even the one binding strongly to CD47 and inhibiting potently the CD47-SIRPα interaction.

[00375] CD47 MAbs were tested for their ability to induce homotypic clustering of erythrocytes (hemagglutination). 10 microliters of human whole blood was diluted in 40 microliters of antibody solution in PBS at different concentrations (range: 0.003 microg/ml to 50 microg/ml final Mab concentration) in flat-bottom 96 well plates. The blood-antibody mix was incubated O/N at 37°C without shaking. At the end of the incubation, the plates were agitated manually, tilted at about 30°C, and let to rest for about 10 minutes.

[00376] Evidence of hemagglutination is demonstrated by the formation of a clumped deposit, in the form of a crescent at the bottom around the inferior border of the well. All but the lowest affinity CD47 antibodies of the 5A3, Ke8, and Ka3 families (specifically, 5A3M5, Ke8A3, Ka3A3) caused hemagglutination. In contrast, he CD47 antibodies of the Kc4 family did not cause hemagglutination, even the higher affinity ones (Kc4E2, Kc4F4).

EXAMPLE 9: CD19 antibody affinity maturation

(a) Antibody B7

[00377] Amongst the antibodies identified during the screening process described in the Examples above B7 was selected for affinity maturation in order to increase its affinity for hCD19. Candidate B7 contains a lambda light chain (IGLV6-57) and several phage libraries displaying scFv variants were generated by introducing diversity into the CDR1, CDR2 and CDR3 of the variable light chain region while the heavy chain variable region was kept unmodified. Different diversification strategies were used to generate 20 libraries comprising a total of $2x10^9$ transformants partially covering a theoretical diversity of $4x10^{12}$.

(b) Antibody L7B7_D11

[00378] Antibody D11 was identified during the affinity maturation of B7 described above and binds to hCD19 with a higher affinity than the parental antibody B7. This antibody was selected for a second round of affinity maturation of its light chain. A total of 6 libraries comprising $2.8x10^9$ transformants partially covering a theoretical diversity of

$4x10^9$ were generated and used for phage display selections as described above except that 1nM of hCD19 was used for each round of selection. This second round of affinity maturation lead to the identification of the following antibodies with and improved binding to CD19: L7B7_C2; L7B7_A6; L7B7_B11; L7B7_C6 and L7B7_C9

EXAMPLE 10: Expression and purification of bispecific antibodies carrying a Lambda and a Kappa light chain.

[00379] The simultaneous expression of one heavy chain and two lights chain in the same cell can lead to the assembly of three different antibodies. Simultaneous expression can be achieved in different ways such as that the transfection of multiple vectors expressing one of the chains to be co-expressed or by using vectors that drive multiple gene expression. A vector pNovi κHλ was previously generated to allow for the co-expression of one heavy chain, one Kappa light chain and one Lambda light chain as described in US 2012/0184716 and WO 2012/023053, each of which is hereby incorporated by reference in its entirety. The expression of the three genes is driven by human cytomegalovirus promoters (hCMV) and the vector also contains a glutamine synthetase gene (GS) that enables the selection and establishment of stable cell lines. The VH and VL gene of the anti-hCD19 IgGλ or the anti-hCD47 IgGκ were cloned in the vector pNovi κHλ, for transient expression in mammalian cells. Peak cells were cultured in 6-well plates at a concentration of 6 x 10^5 cells per well in 2 ml culture media containing fetal bovine serum. 2 μg of plasmid DNA was transfected into the cells using TransIT-LT1 transfection reagent (Mirus) according to manufacturer's instructions. Antibody concentration in the serum-containing supernatant of transfected cells was measured at several time points during the production using the Bio-Layer Interferometry (BLI) technology. An OctetRED96 instrument and Protein A biosensors were used for quantitation (Pall, Basel, Switzerland). 200 μL of supernatant were used to determine IgG concentration; biosensors were pre-conditioned and regenerated using 10 mM glycine pH 1.7 and IgG calibrators diluted in conditioned PEAK cell medium were prepared for standard curve generation. Concentrations were determined using the dose response 5PL weighted Y standard curve equation and an initial slope binding rate equation. According to antibody concentration, supernatants were harvested 7 to 10 days after transfection and clarified by centrifugation at 1300 g for 10 min. The purification process was composed of three affinity steps. First, the CaptureSelect™ IgG-

CH1 affinity matrix (Life Technologies, Zug, Switzerland) was washed with PBS and then added in the clarified supernatant. After incubation overnight at +4°C, supernatants were centrifuged at 1000 g for 10 min, flow through was stored and resin washed twice with PBS. Then, the resin was transferred on spin columns and a solution containing 50 mM glycine at pH 2.7 was used for elution. Several elution fractions were generated, pooled and desalted against PBS using 50 kDa Amicon® Ultra Centrifugal filter units (Merck KGaA, Darmstadt, Germany). The final product, containing total human IgGs from the supernatant, was quantified using a Nanodrop spectrophotometer (NanoDrop Technologies, Wilmington, DE) and incubated for 15 min at RT and 20 rpm with the appropriate volume of CaptureSelect™ LC-kappa (Hu) affinity matrix (Life Technologies, Zug, Switzerland). Incubation, resin recovery, elution and desalting steps were performed as described previously. The last affinity purification step was performed using the CaptureSelect™ LC-lambda (Hu) affinity matrix (Life Technologies, Zug, Switzerland) applying the same process as for the two previous purifications. The final product was quantified using the Nanodrop. Purified bispecific antibodies were analyzed by electrophoresis in denaturing and reducing conditions. The Agilent 2100 Bioanalyzer was used with the Protein 80 kit as described by the manufacturer (Agilent Technologies, Santa Clara, CA, USA). 4 µL of purified samples were mixed with sample buffer supplemented with dithiothréitol (DTT; Sigma Aldrich, St. Louis, MO). Samples were heated at 95°C for 5 min and then loaded on the chip. All samples were tested for endotoxin contamination using the Limulus Amebocyte Lysate test (LAL; Charles River Laboratories, Wilmington, MA).

EXAMPLE 11: Characterization of Monovalent and Bispecific Antibodies.

[00380] Dual-targeting bispecific antibodies bind to two different antigens on the surface of the same cell. Simultaneous binding of the two antibody arms to two antigens on the surface of the cell (termed co-engagement) results in additive or synergistic increase of affinity due to avidity mechanism. As a consequence, co-engagement confers high selectivity towards cells expressing both antigens as compared to cells that express just one single antigen. In addition, the affinities of the two arms of a bispecific antibody to their respective targets can be set up in a way that binding to target cells is principally driven by one of the antibody arms. For instance, a dual targeting κλ-body composed of one arm binding with high affinity to a tumor associated antigen (TAA), for example CD19, and a

second arm binding with lower affinity to CD47 -- but sufficient to inhibit CD47/SIRPα upon TAA co-engagement -- should allow preferential inhibition of CD47 in cancer versus normal cells. The experiments described below (Figures 9 to 13) compare the binding affinity, the CD47-SIRPα neutralization potency, and the tumor cell killing activity of CD47xCD19 bispecific κλ-body and the corresponding monovalent antibody, i.e., having the same CD47-binding arm plus a "dummy" non-binding arm.

Binding of Monovalent and Bispecific Antibodies to B cell lines

[00381] To demonstrate that binding of CD47xCD19 κλ bodies to target cells is CD19 dependent, a series of FACS experiments comparing the binding of CD47xCD19 κλ bodies to their monovalent counterparts were performed. Two types of cells were used, a CD19-positive Burkitt lymphoma cell line Raji (expressing about 65,000 CD47 molecules per cell) and the CD19-negative B-NHL cell line DS-1 (expressing about 150,000 CD47 molecules per cell) as a control. Figures 9A-9C demonstrate that a CD47xCD19 κλ body co-engages the two targets at the surface of Raji cells. This is shown by (i) increased affinity to Raji cells as compared to DS-1 cells and (ii) increased affinity of the CD47xCD19 κλ body as compared to the CD47 monovalent antibody, observed with Raji cells—but not with DS-1 cells. A comparison of FACS profiles generated with the binding of CD19 monovalent antibody, the CD47 monovalent antibody, and the CD47xCD19 κλ body to Raji cells clearly demonstrates that binding of the CD47xCD19 κλ to target cells is principally driven by the CD19 arm.

SIRPα Blocking Activity of Monovalent and Bispecific Antibodies

[00382] Another series of experiments provides a further proof of co-engagement of CD19 and CD47 on the surface of the target cell by showing that the neutralization of CD47-SIRPα interaction by CD47xCD19 κλ bodies is CD19-dependent. In this experiment, the activity of CD47xCD19 κλ bodies and the corresponding monovalent antibodies was tested in the CD47-SIRPα inhibition assay as described in Example 4. Figure 10 shows that CD47xCD19 κλ bodies inhibited the CD47-SIRPα interaction in Raji cells with a significantly higher potency than the corresponding CD47 monovalent antibodies. Efficient neutralization of CD47-SIRPα interaction required CD19 co-engagement. IC50 values obtained with CD47xCD19 BsAbs are 20 to 1000x lower than the values obtained with the corresponding CD47 monovalent antibody (see Table 4).

Table 4: IC50 values of CD47 monovalent and bispecific antibodies

	IC50 CD47-SIRPα Assay (Raji)		
CD47 Arm	**CD47Xcd19 BsAb [nM]**	**CD47 Monovalent [nM]**	**Monovalent/BsAb ratio**
5A3M3	0.031	13	419
5A3M4	0.36	400	1111
Ke8G11	0.066	1.2	18
Ke8C4	0.12	13	108
Ke8A3	1.1	>500	>500
Ka3G2	0.11	5.1	46
Ka3	0.32	6.7	21
Ka3H3	0.71	44	62

EXAMPLE 12: ADCC MEDIATED by Bispecific Antibodies is CD19-dependent.

[00383] The ability of dual targeting κλ-bodies to co-engage CD47 and CD19 results in a significant increase in the affinity of binding to CD19-positive cells and in CD19-dependent neutralization of the CD47-SIRPα interaction. This, in turn, translates into efficient and selective cancer cell killing mediated by CD47xCD19 κλ body, as demonstrated in ADCC and ADCP experiments described in this and the following example.

[00384] ADCC assays were performed with unfractionated human PBMC and Raji or Ramos B cell lymphoma target cells. Dose-response experiments shown in Figure 11 demonstrate that CD47xCD19 κλ bodies provided herein kill B cell lymphoma cells in a more efficient way than the corresponding CD47 monovalent antibodies. Efficient ADCC is therefore dependent on CD19 co-engagement. Figure 11C shows that the efficacy of ADCC with CD47xCD19 κλ bodies is comparable to rituximab and that it is significantly higher than with the CD19 Mab C2.

EXAMPLE 13: ADCP Mediated by Bispecific Antibodies is CD19-dependent

[00385] Figure 12 demonstrates that CD47xCD19 BsAbs provided herein phagocytose CD19-positive cells in a CD19-dependent manner, as the corresponding CD47 monovalent antibodies are much less efficient (if any).

[00386] ADCP experiments were performed with human macrophages differentiated from peripheral blood monocytes and Raji as target cells. Macrophages were co-incubated with CFSE-labeled Raji cells (effector: target ratio 1:5) for 2.5 hours at 37°C in the presence of increasing concentrations of bispecific or monovalent antibody. At the end of the incubation period, biotinylated anti- human CD14 antibody and Strep-Cy5 were added to label the macrophages. The cells were then washed and subjected to FACS analysis. Phagocytosis was evidenced by double-positive events.

[00387] Dose-response experiments shown in Figure 12 demonstrate that CD47xCD19 κλ bodies are more potent than the corresponding CD47 monovalent antibodies. Efficient ADCC is therefore dependent on CD19 co-engagement. CD19 co-engagement by the bispecific antibody drives efficacy. What is more, the experiments shown in Figure 12 confirm that blocking CD47 is necessary to elicit efficient ADCP, as the CD19 Mab C2, which binds target cells with high affinity, does not induce significant phagocytosis.

EXAMPLE 14: in vivo Antitumor Activity of Bispecific Antibodies

[00388] The anti-tumor activity of a CD47xCD19 κλ body was evaluated in a Raji model of lymphoma. 2.10^6 Raji cells were implanted subcutaneously in NOD/SCID mice. Tumor volumes were measured 3 times per week. After the tumor graft reached $0.1cm^3$, mice were randomized into 5 groups (5 mice per group) and the antibody treatment was initiated. This experiment compared the effect of CD47xCD19 κλ-body Ka3xD11 to the effect of Ka3 monovalent antibody, and two positive control Mabs, the CD47 Mab B6H12 and rituximab. Antibody was injected i.p. three times per week until the end of the experiment (d25). Rituximab was administered at 200µg per mouse per injection. All the other antibodies were administered at 400µg per mouse per injection.

[00389] As shown in Figure 13 the efficacy of the CD47xCD19 κλ-body Ka3xD11 is similar to B6H12 known to bind strongly to CD47, block CD47-SIRPα interaction and to suppress tumor growth in this lymphoma model. Of note, the efficacy of the CD47xCD19 κλ-body was also comparable to the efficacy of rituximab. The monovalent CD47 antibody was clearly less efficacious than the CD47xCD19 bispecific κλ-body demonstrating that tumor eradication is CD19-dependent.

EXAMPLE 15: CD47 Antibody Binding to Erythrocytes

[00390] With more than 5 billion cells per ml of blood, and 25,000 CD47 molecules per cell, erythrocytes represent potentially the major antigen sink for CD47-binding antibodies. To assess the effect of erythrocyte adsorption, CD47 antibodies were incubated with whole blood. Following incubation, the fraction of CD47 antibodies remaining in the plasma was determined by ELISA.

[00391] In brief, 200 µl of whole blood containing an anti-coagulant was mixed with 20 µl of antibody (110 µl/ml in PBS) and incubated for 30 minutes at 37°C with shaking. The plasma was then separated from the cells by centrifugation, and the concentration of unbound antibody determined by ELISA. For each antibody tested, the results obtained were compared to the control, that is the same antibody spiked directly into plasma, and normalized against non-binding IgGs tested in parallel.

[00392] Figure 14 demonstrates that high and moderate affinity CD47 antibodies are efficiently adsorbed on erythrocytes. However, in the case of BsAbs, this phenomenon is limited to molecules having a high affinity CD47 arms, such as 5A3. This suggests that, in general, BsAbs are less prone to erythrocyte adsorption and TMDD than CD47 Mabs.

Other Embodiments

[00393] While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. An isolated bispecific antibody comprising a first arm that comprises a first amino acid sequence that binds CD47 and a second arm that comprises a second amino acid sequence that does not bind CD47, wherein the bispecific antibody inhibits interaction between CD47 and signal-regulatory protein alpha (SIRPα).

2. The isolated bispecific antibody of claim 1, wherein the second amino acid sequence binds a tumor associated antigen (TAA).

3. The isolated bispecific antibody of claim 2, wherein the bispecific antibody inhibits interaction between human CD47 and human SIRPα.

4. The isolated bispecific antibody of claim 3, wherein the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is at least ten times more potent than a corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that comprises the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein.

5. The isolated bispecific antibody of claim 3, wherein the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is at least 100 times more potent than a corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that comprises the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein.

6. The isolated bispecific antibody of claim 3, wherein the bispecific antibody inhibits interaction between human CD47 and human SIRPα at a level that is at least 1,000 times more potent than a corresponding level of inhibition of human CD47/human SIRPα interaction exhibited by a monovalent anti-CD47 antibody that comprises the first amino acid sequence that binds CD47 and a second amino acid sequence that does not bind a human protein.

7. The isolated bispecific antibody of any one of claims 1 to 6, wherein the first arm comprises an amino acid sequence that inhibits the interaction between human CD47 at the

surface of cells and soluble human SIRPα with an IC50 greater than 5 nM in the assay described in Example 4 and in which the monovalent antibody 5A3M3 has an IC50 of approximately 13 nM.

8. The isolated bispecific antibody of any one of claims 1 to 6, wherein the first arm comprises an amino acid sequence that is recovered at more than 80% after incubation at 37°C for 30 minutes in human whole blood at a concentration of 10 μg/ml as described in Example 15.

9. The isolated bispecific antibody of claim 2, wherein the TAA is CD19.

10. The isolated bispecific antibody of claim 1, wherein the second amino acid sequence does not bind a human protein.

11. The isolated bispecific antibody of claim 1, wherein the first amino acid sequence comprises a variable heavy chain complementarity determining region 1 (CDRH1) amino acid sequence of SEQ ID NO: 225, a variable heavy chain complementarity determining region 2 (CDRH2) amino acid sequence of SEQ ID NO: 226, a variable heavy chain complementarity determining region 3 (CDRH3) amino acid sequence of SEQ ID NO: 227, a variable light chain complementarity determining region 1 (CDRL1) amino acid sequence selected from SEQ ID NO: 228-241 and 262-272, a variable light chain complementarity determining region 2 (CDRL2) amino acid sequence selected from 242-245 and 273-280, and a variable light chain complementarity determining region 3 (CDRH3) amino acid sequence selected from 246-261 and 281.

12. The isolated bispecific antibody of claim 1, wherein the first amino acid sequence comprises a variable heavy chain amino acid sequence of SEQ ID NO: 114 and a variable light chain amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204 and 206.

13. The isolated bispecific antibody of claim 1, wherein the bispecific antibody comprises two copies of a single heavy chain polypeptide and a first light chain and a second light chain, wherein the first and second light chains are different.

14. The isolated bispecific antibody of claim 13, wherein at least a portion of the first light chain is of the Kappa type and at least a portion of the second light chain is of the Lambda type.

15. The isolated bispecific antibody of claim 14, wherein the first light chain comprises at least a Kappa constant region.

16. The isolated bispecific antibody of claim 15, wherein the first light chain further comprises a Kappa variable region.

17. The isolated bispecific antibody of claim 15, wherein the first light chain further comprises a Lambda variable region.

18. The isolated bispecific antibody of claim 14, wherein the second light chain comprises at least a Lambda constant region.

19. The isolated bispecific antibody of claim 18, wherein the second light chain further comprises a Lambda variable region.

20. The isolated bispecific antibody of claim 18, wherein the second light chain further comprises a Kappa variable region.

21. The isolated bispecific antibody of claim 14, wherein the first light chain comprises a Kappa constant region and a Kappa variable region, and wherein the second light chain comprises a Lambda constant region and a Lambda variable region.

22. The isolated bispecific antibody of claim 1, wherein the constant and variable framework region sequences are human.

23. An isolated monovalent or bispecific antibody comprising a first arm that binds to human CD47 and is recovered at more than 80% after incubation at 37°C for 30 minutes in human whole blood at a concentration of 10 μg/ml as described in Example 15.

24. The isolated monovalent or bispecific antibody of claim 23, wherein the antibody inhibits interaction between human CD47 and human SIRPα.

25. An isolated monoclonal antibody comprising an amino acid sequence that binds to human CD47 and is recovered at more than 80% after incubation at 37°C for 30 minutes in human whole blood at a concentration of 10 μg/ml as described in Example 15.

26. The isolated monoclonal antibody of claim 25, wherein the antibody inhibits interaction between human CD47 and human SIRPα.

27. An isolated monoclonal antibody comprising an amino acid sequence that binds CD47 and inhibits the interaction between human CD47 at the surface of cells and soluble human SIRPα with an IC50 greater than 0.3 nM in the assay described in Example 4 and in which the antibody 5A3M3 has an IC50 of approximately 0.36 nM.

28. An isolated monoclonal antibody that binds CD47 and comprises a combination of a variable heavy chain comprising a variable heavy chain complementarity determining region 1 (CDRH1) amino acid sequence of SEQ ID NO: 225, a variable heavy chain complementarity determining region 2 (CDRH2) amino acid sequence of SEQ ID NO: 226, a variable heavy chain complementarity determining region 3 (CDRH3) amino acid sequence of SEQ ID NO: 227, a variable light chain complementarity determining region 1 (CDRL1) amino acid sequence selected from SEQ ID NO: 228-241 and 262-272, a variable light chain complementarity determining region 2 (CDRL2) amino acid sequence selected from 242-245 and 273-280, and a variable light chain complementarity determining region 3 (CDRH3) amino acid sequence selected from 246-261 and 281.

29. The isolated monoclonal antibody of claim 28 further comprising a combination of a variable heavy chain amino acid sequence of SEQ ID NO: 114 and a variable light chain amino acid sequence selected from SEQ ID NO: 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204 and 206.

FIGURE 1

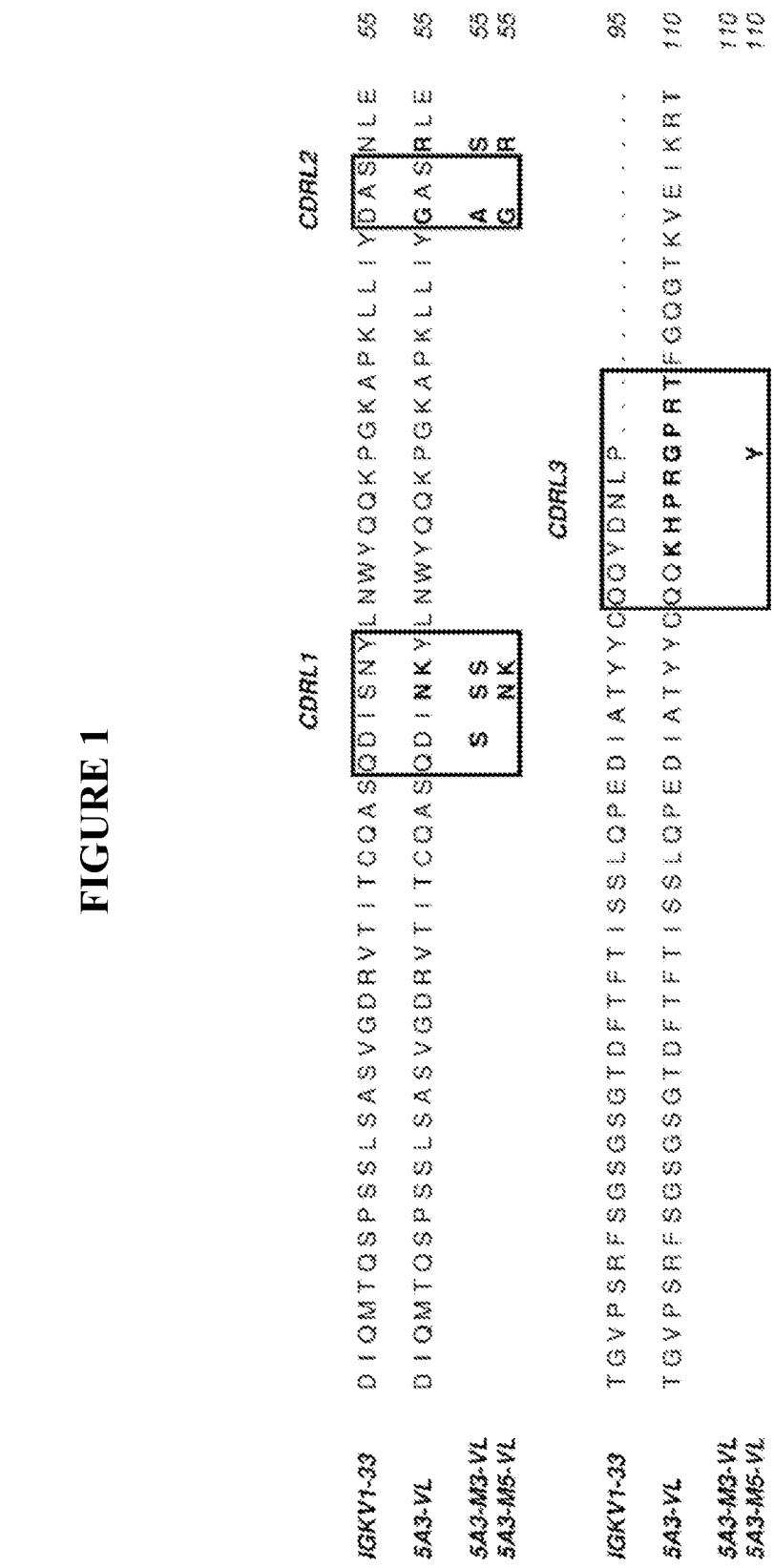

CDRL1
CDRL2
CDRL3
IGKV1-33 DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLE 55
5A3-VL DIQMTQSPSSLSASVGDRVTITCQASQDINKYLNWYQQKPGKAPKLLIYGASRLE 55
5A3-M3-VL SS NK A S 55
5A3-M5-VL SS NK G R 55
IGKV1-33 TGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQYDNLP..... 95
5A3-VL TGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQKHPRGPRT FGQGTKVEIKRT 110
5A3-M3-VL Y 110
5A3-M5-VL Y 110

FIGURE 2

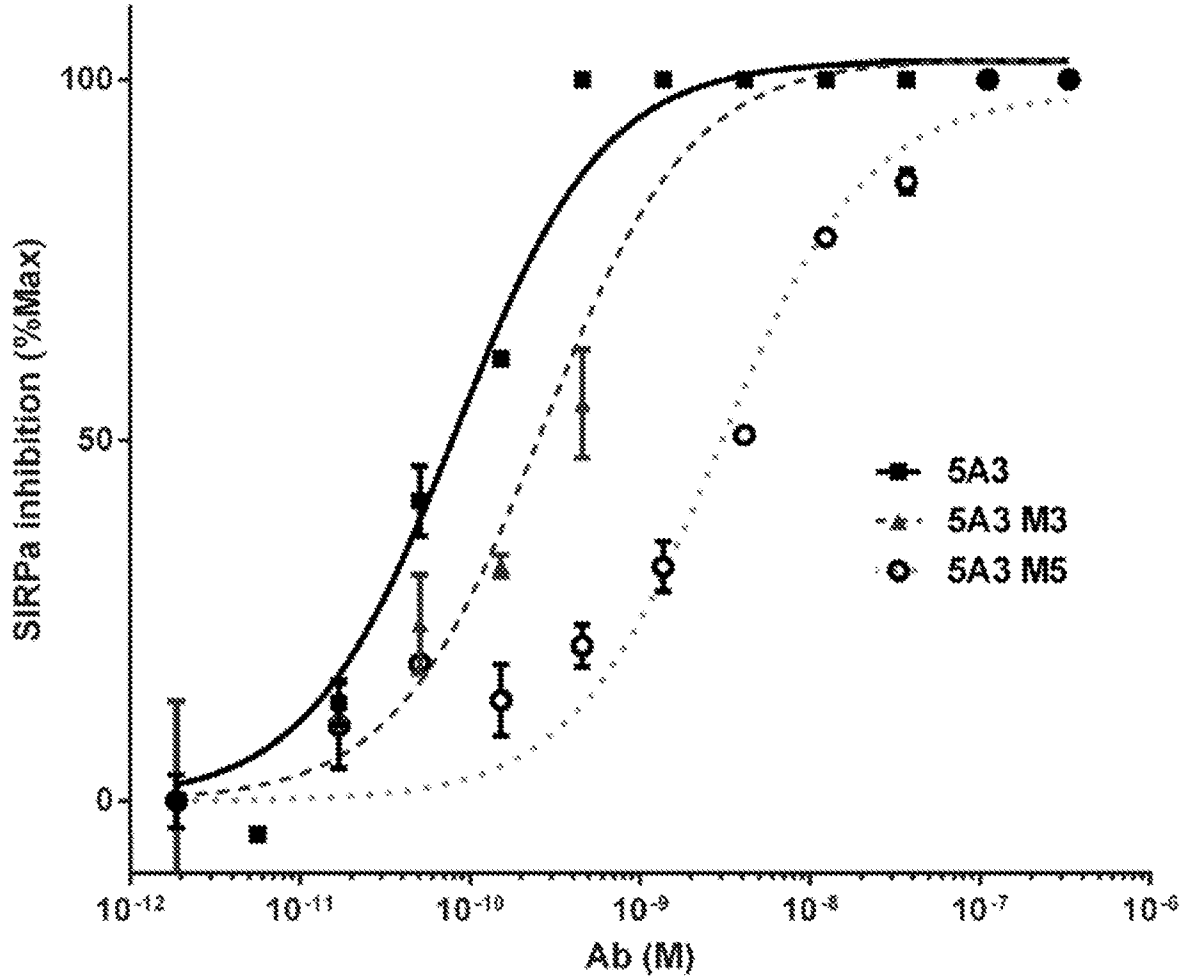

100
50
0
SIRPa inhibition (%Max)
10-12
10-11
10-10
10-9
10-8
10-7
10-6
Ab (M)
5A3
5A3 M3
5A3 M5

FIGURE 3

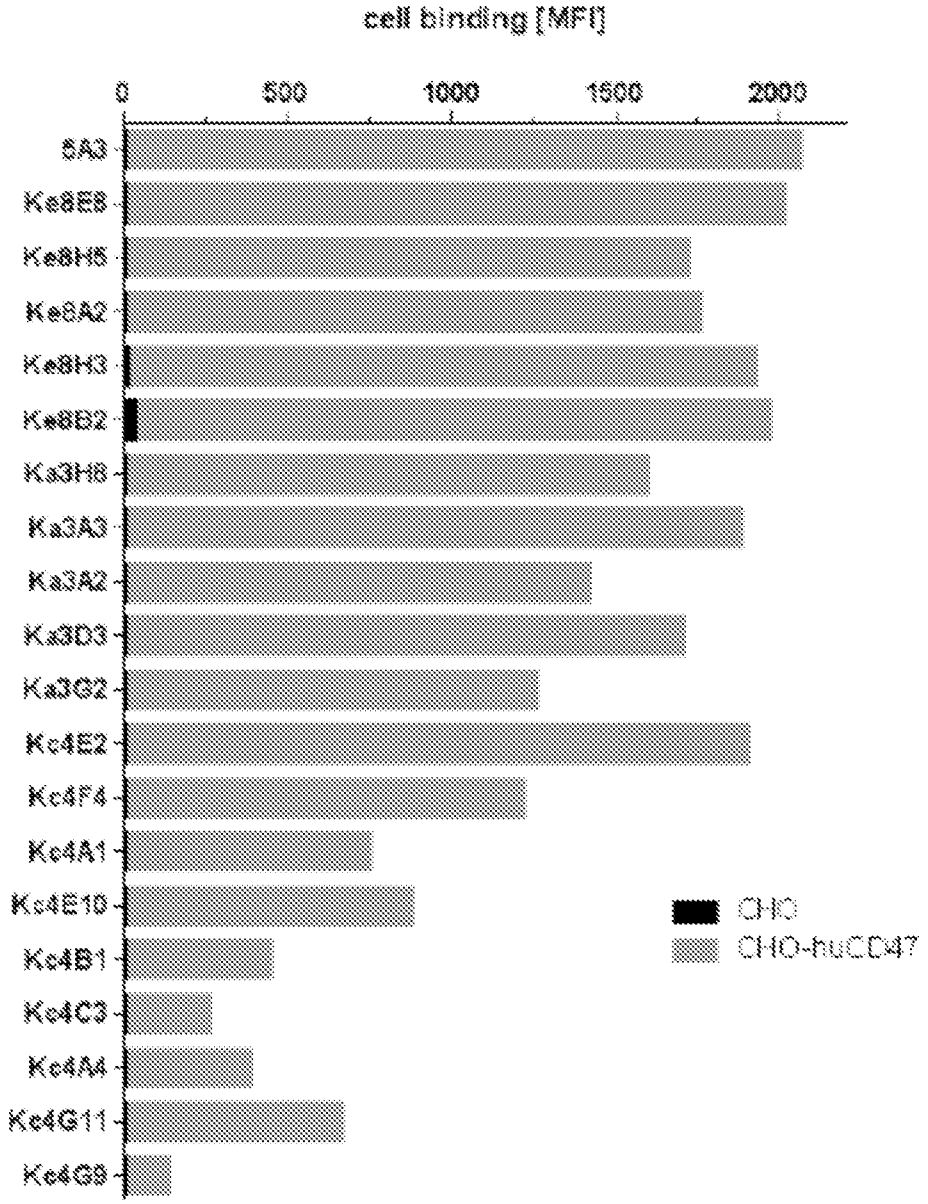

cell binding [MFI]
0
500
1000
1500
2000
5A3
Ke8E8
Ke8H5
Ke8A2
Ke8H3
Ke8B2
Ka3H8
Ka3A3
Ka3A2
Ka3D3
Ka3G2
Kc4E2
Kc4F4
Kc4A1
Kc4E10
Kc4B1
Kc4C3
Kc4A4
Kc4G11
Kc4G9
CHO
CHO-huCD47

FIGURE 4

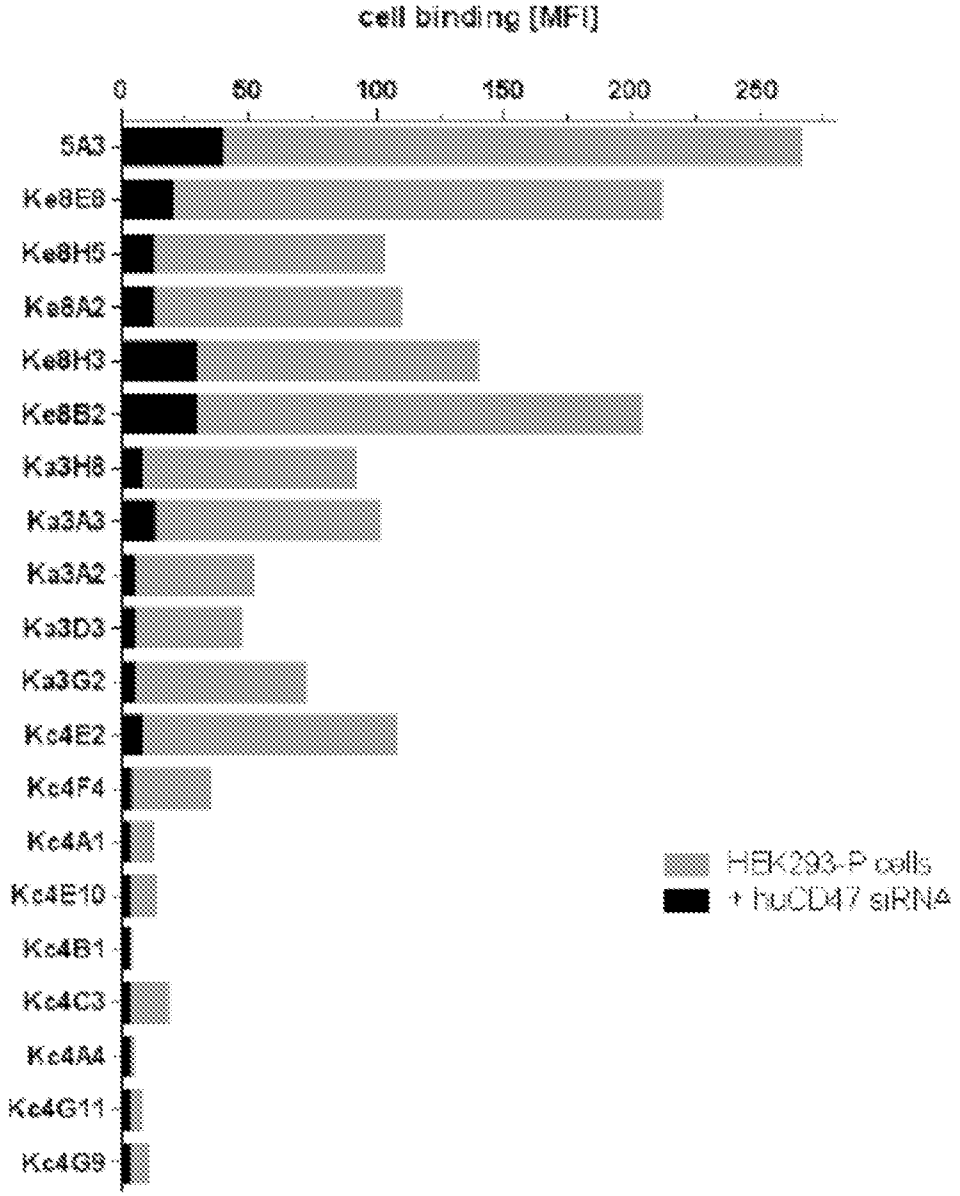

cell binding [MFI]
0
50
100
150
200
250
5A3
Ke8E8
Ke8H5
Ke8A2
Ke8H3
Ke8B2
Ka3H8
Ka3A3
Ka3A2
Ka3D3
Ka3G2
Kc4E2
Kc4F4
Kc4A1
Kc4E10
Kc4B1
Kc4C3
Kc4A4
Kc4G11
Kc4G9
HEK293-F cells
+ huCD47 siRNA

FIGURE 5

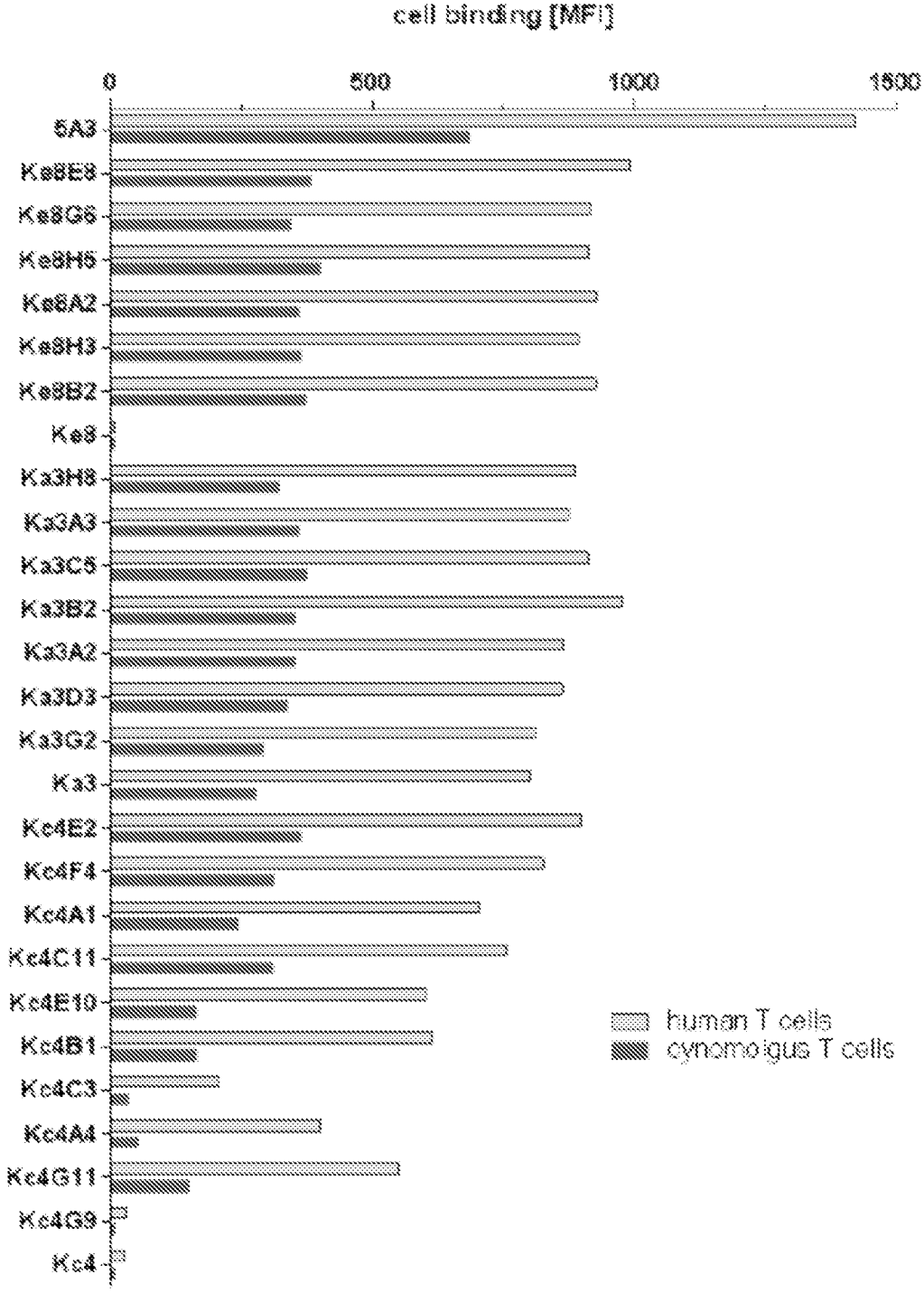

cell binding [MFI]
0
500
1000
1500
5A3
Ke8E8
Ke8G6
Ke8H5
Ke8A2
Ke8H3
Ke8B2
Ke8
Ka3H8
Ka3A3
Ka3C6
Ka3B2
Ka3A2
Ka3D3
Ka3G2
Ka3
Kc4E2
Kc4F4
Kc4A1
Kc4C11
Kc4E10
Kc4B1
Kc4C3
Kc4A4
Kc4G11
Kc4G9
Kc4
human T cells
cynomolgus T cells

FIGURE 6

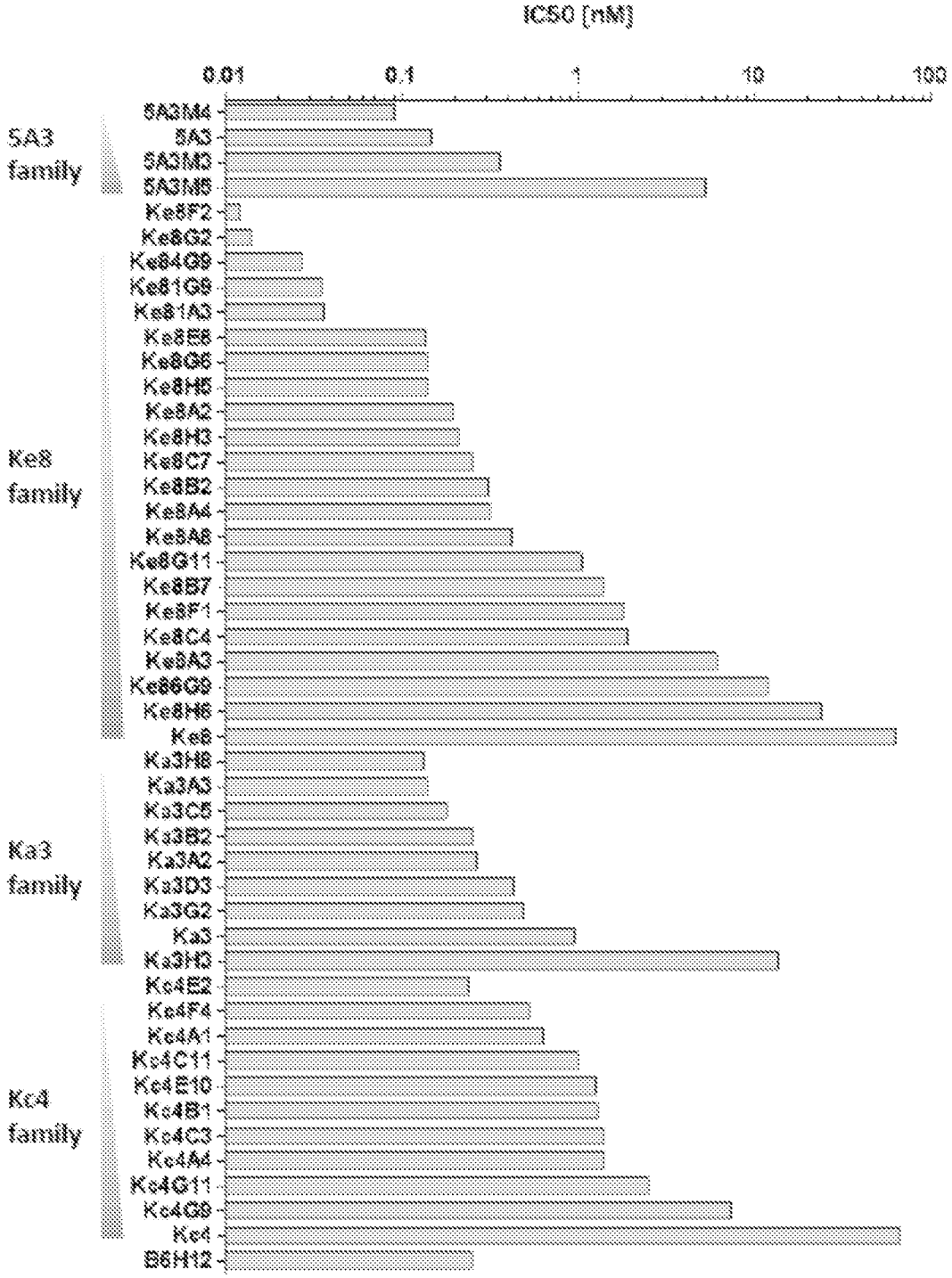

IC50 [nM]
0.01
0.1
1
10
100
5A3 family
Ke8 family
Ka3 family
Kc4 family
5A3M4
5A3
5A3M3
5A3M5
Ke8F2
Ke8G2
Ke84G9
Ke81G9
Ke81A3
Ke8E8
Ke8G6
Ke8H5
Ke8A2
Ke8H3
Ke8C7
Ke8B2
Ke8A4
Ke8A8
Ke8G11
Ke8B7
Ke8F1
Ke8C4
Ke8A3
Ke86G9
Ke8H6
Ke8
Ka3H8
Ka3A3
Ka3C5
Ka3B2
Ka3A2
Ka3D3
Ka3G2
Ka3
Ka3H3
Kc4E2
Kc4F4
Kc4A1
Kc4C11
Kc4E10
Kc4B1
Kc4C3
Kc4A4
Kc4G11
Kc4G9
Kc4
B6H12

FIGURE 7

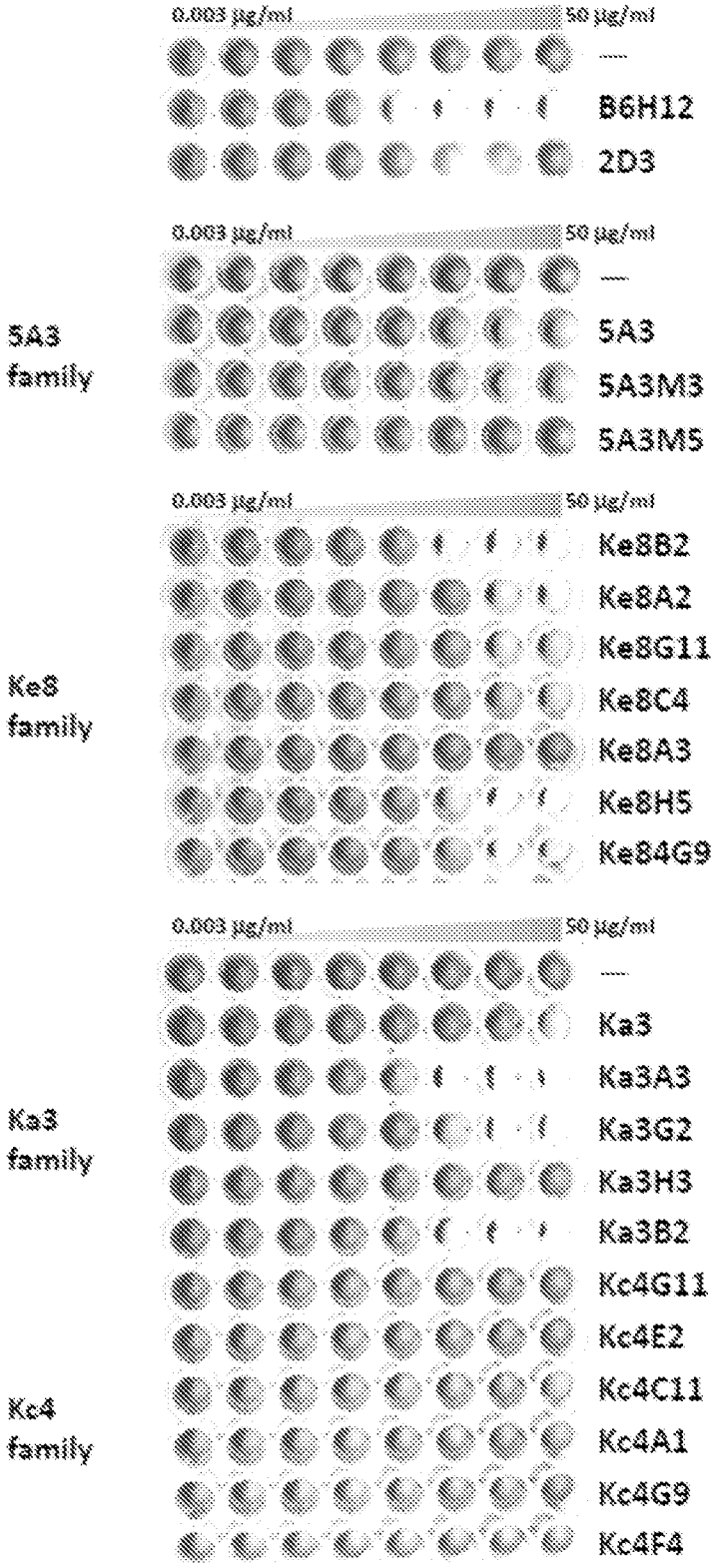

0.003 µg/ml
50 µg/ml
—
B6H12
2D3
0.003 µg/ml
50 µg/ml
—
5A3
family
5A3
5A3M3
5A3M5
0.003 µg/ml
50 µg/ml
Ke8
family
Ke8B2
Ke8A2
Ke8G11
Ke8C4
Ke8A3
Ke8H5
Ke84G9
0.003 µg/ml
50 µg/ml
—
Ka3
family
Ka3
Ka3A3
Ka3G2
Ka3H3
Ka3B2
Kc4
family
Kc4G11
Kc4E2
Kc4C11
Kc4A1
Kc4G9
Kc4F4

FIGURE 8

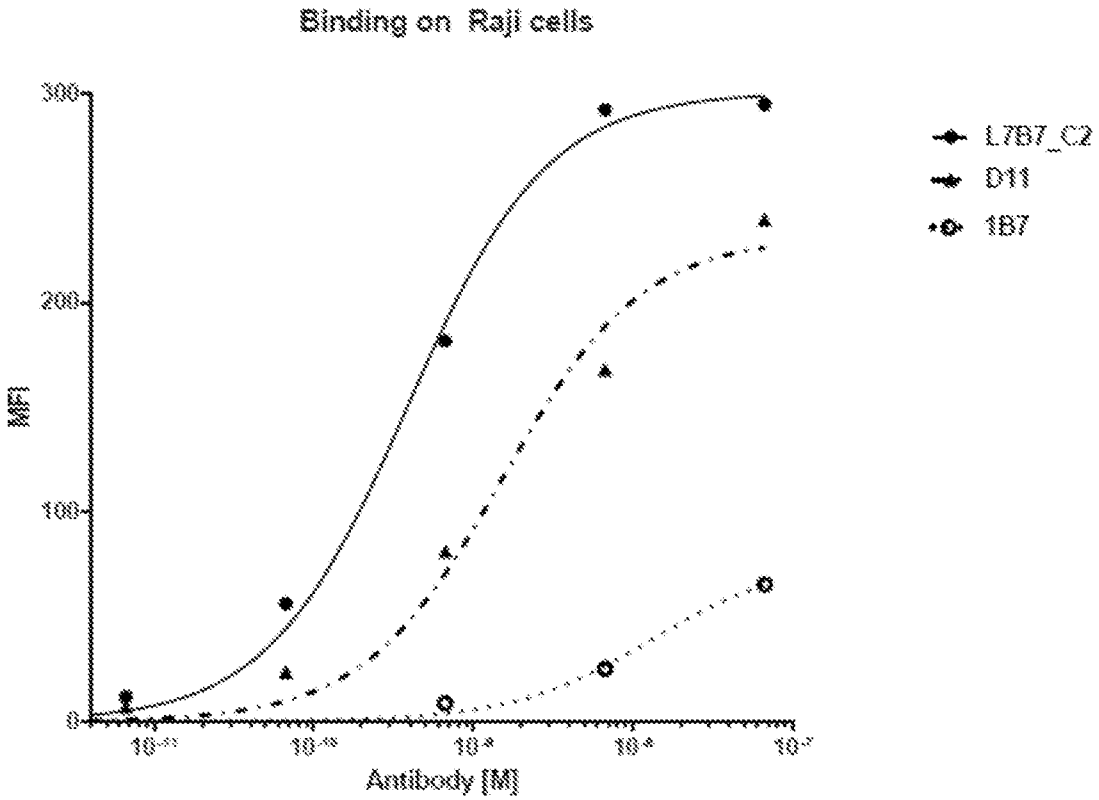

Binding on Raji cells
300
200
100
0
MFI
Antibody [M]
L7B7_C2
D11
1B7

FIGURE 9A

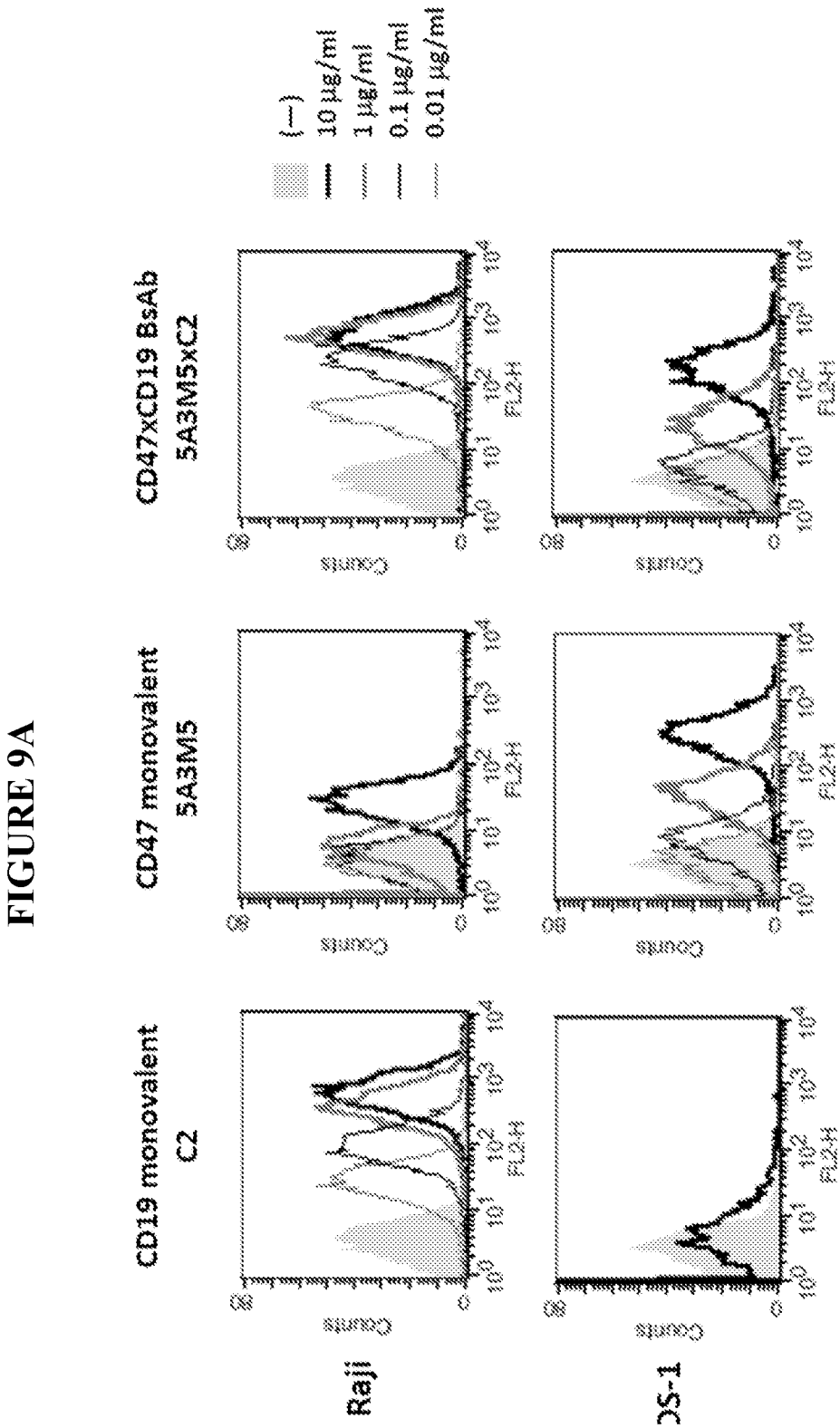

CD19 monovalent C2
CD47 monovalent 5A3M5
CD47xCD19 BsAb 5A3M5xC2
(—)
10 µg/ml
1 µg/ml
0.1 µg/ml
0.01 µg/ml
Raji
JS-1
Counts
FL2-H

FIGURE 9B

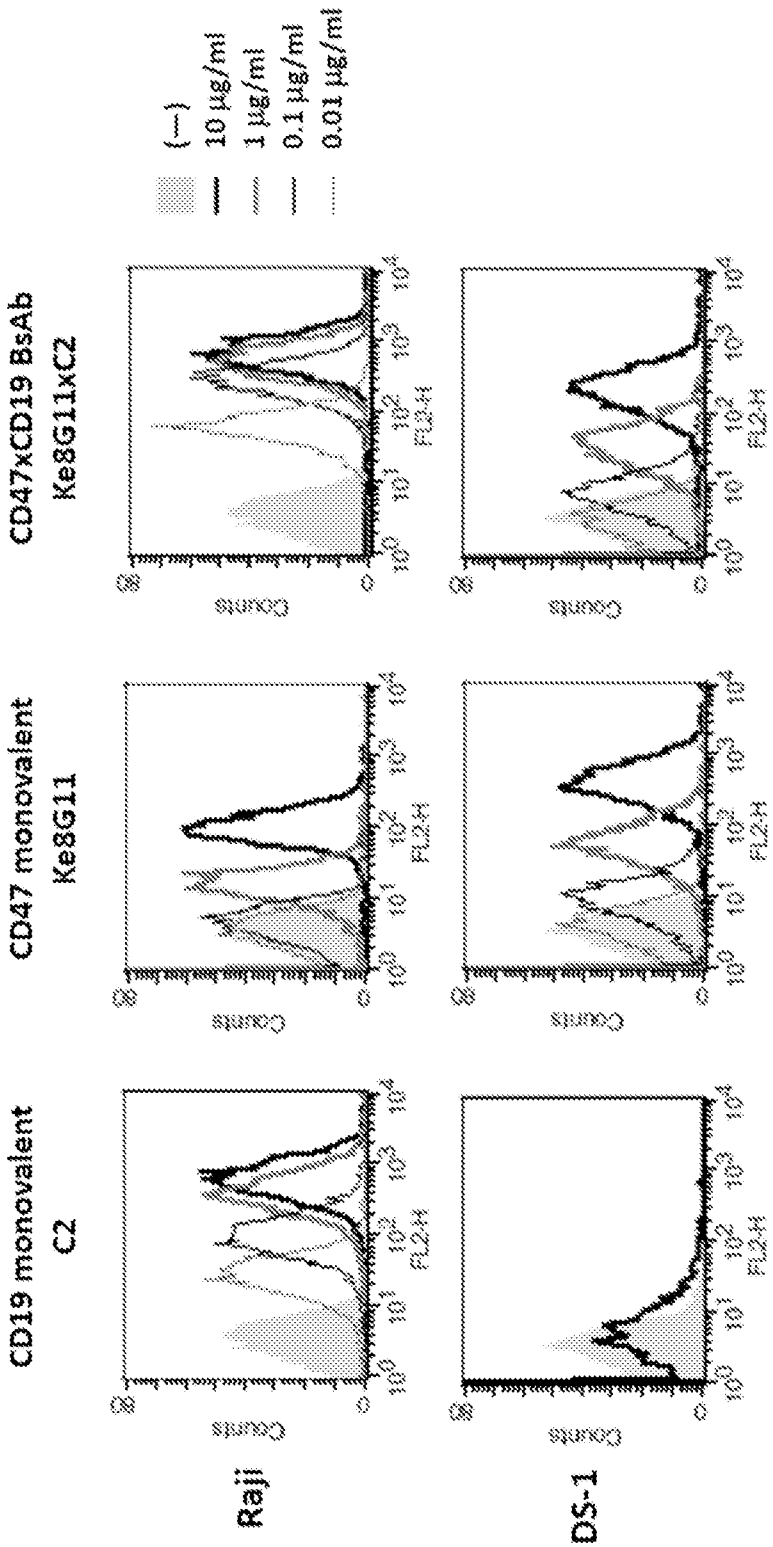

CD19 monovalent C2
CD47 monovalent Ke8G11
CD47xCD19 BsAb Ke8G11xC2
(—)
10 µg/ml
1 µg/ml
0.1 µg/ml
0.01 µg/ml
Raji
DS-1
Counts
FL2-H

FIGURE 9C

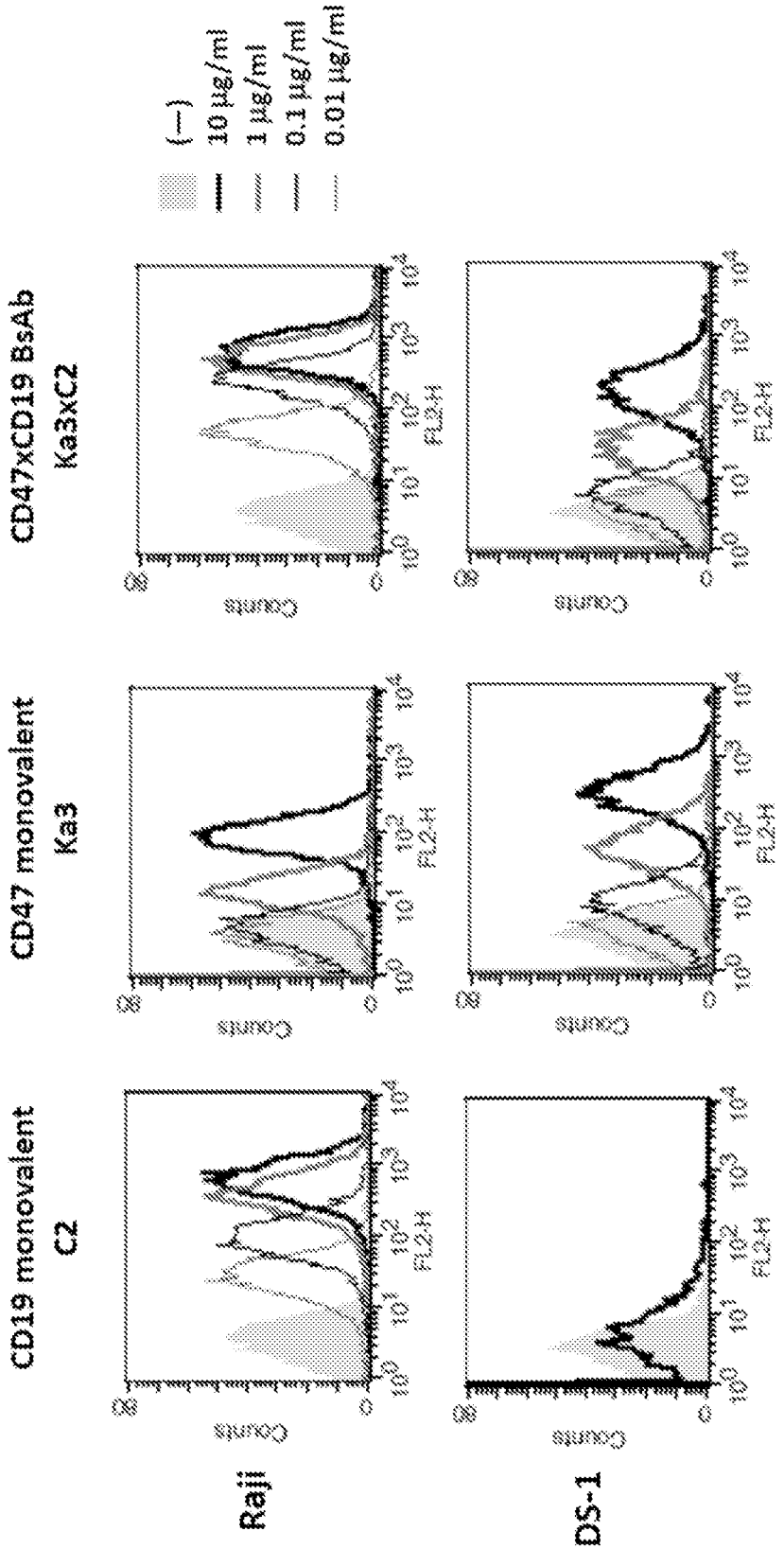

CD19 monovalent
C2
CD47 monovalent
Ka3
CD47xCD19 BsAb
Ka3xC2
(—)
10 µg/ml
1 µg/ml
0.1 µg/ml
0.01 µg/ml
Raji
DS-1
Counts
FL2-H

FIGURE 10

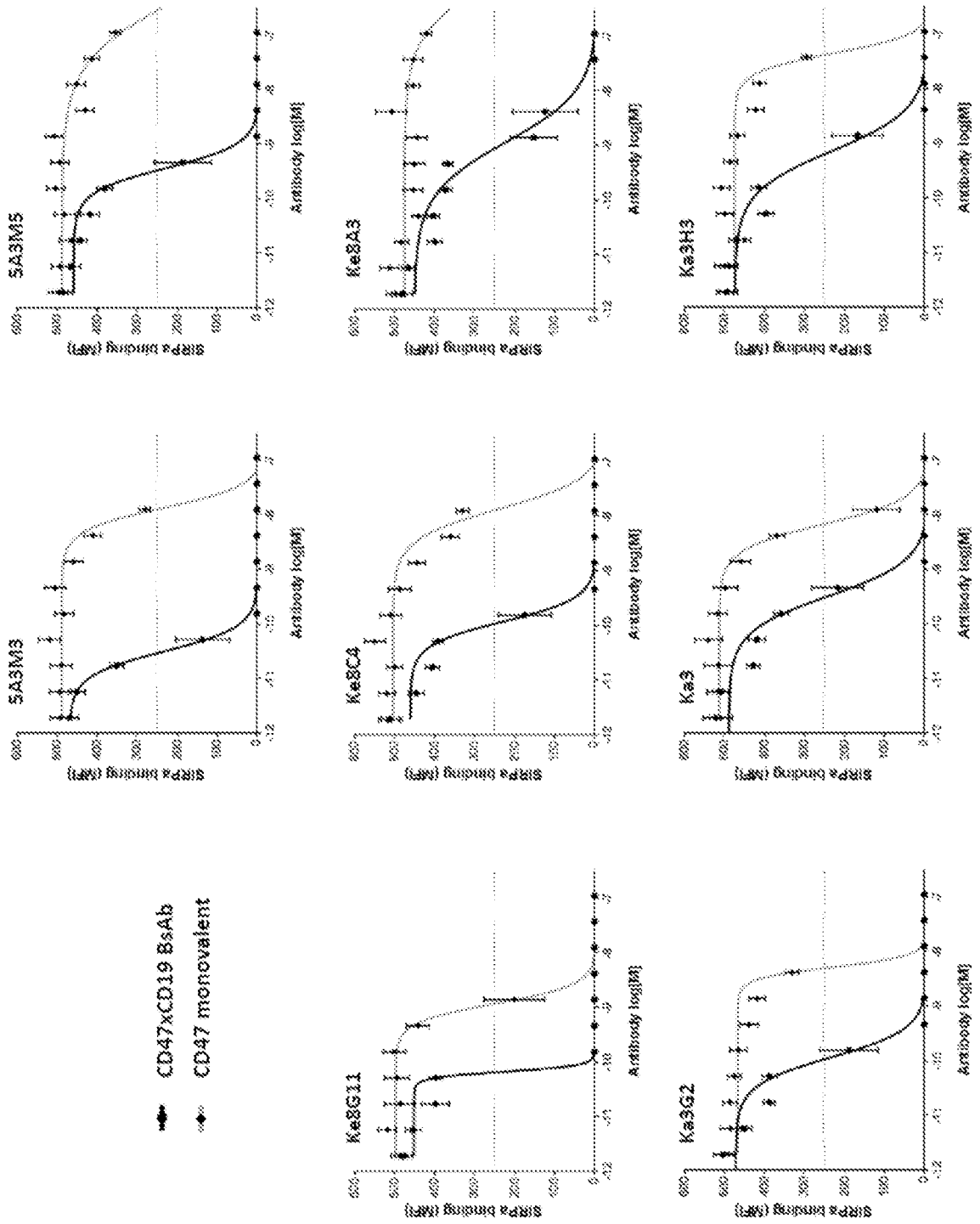

CD47xCD19 BsAb
CD47 monovalent
5A3M5
5A3M3
Ke8A3
Ke8C4
Ka3H3
Ka3
Ke8G11
Ka3G2
SIRPa binding (MFI)
Antibody log[M]

FIGURE 11A

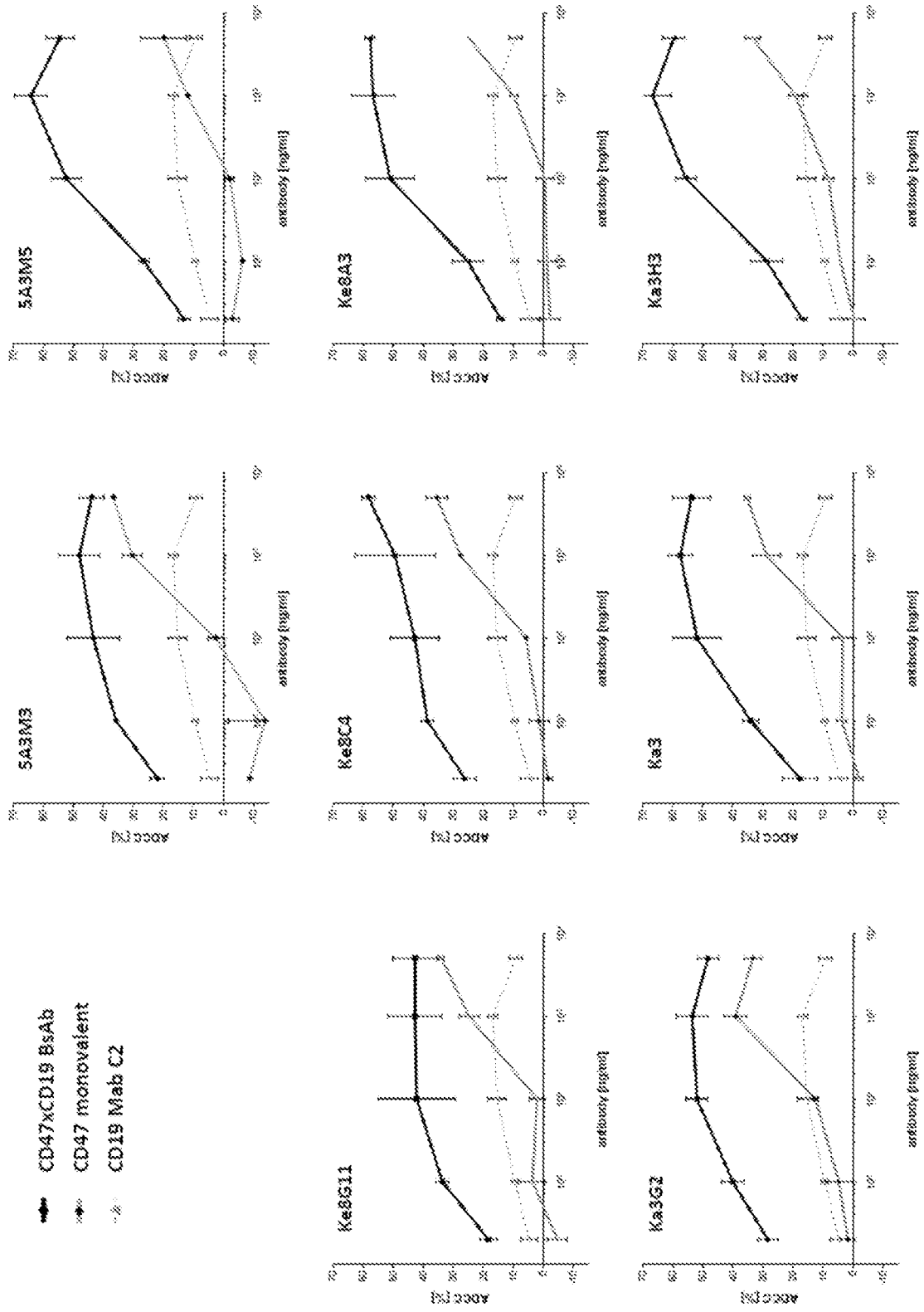

CD47xCD19 BsAb
CD47 monovalent
CD19 Mab C2
5A3M5
Ka6A3
Ka3H3
5A3M3
Ka6C4
Ka3
Ka6G11
Ka3G2
ADCC (%)
antibody (ng/ml)

FIGURE 11B

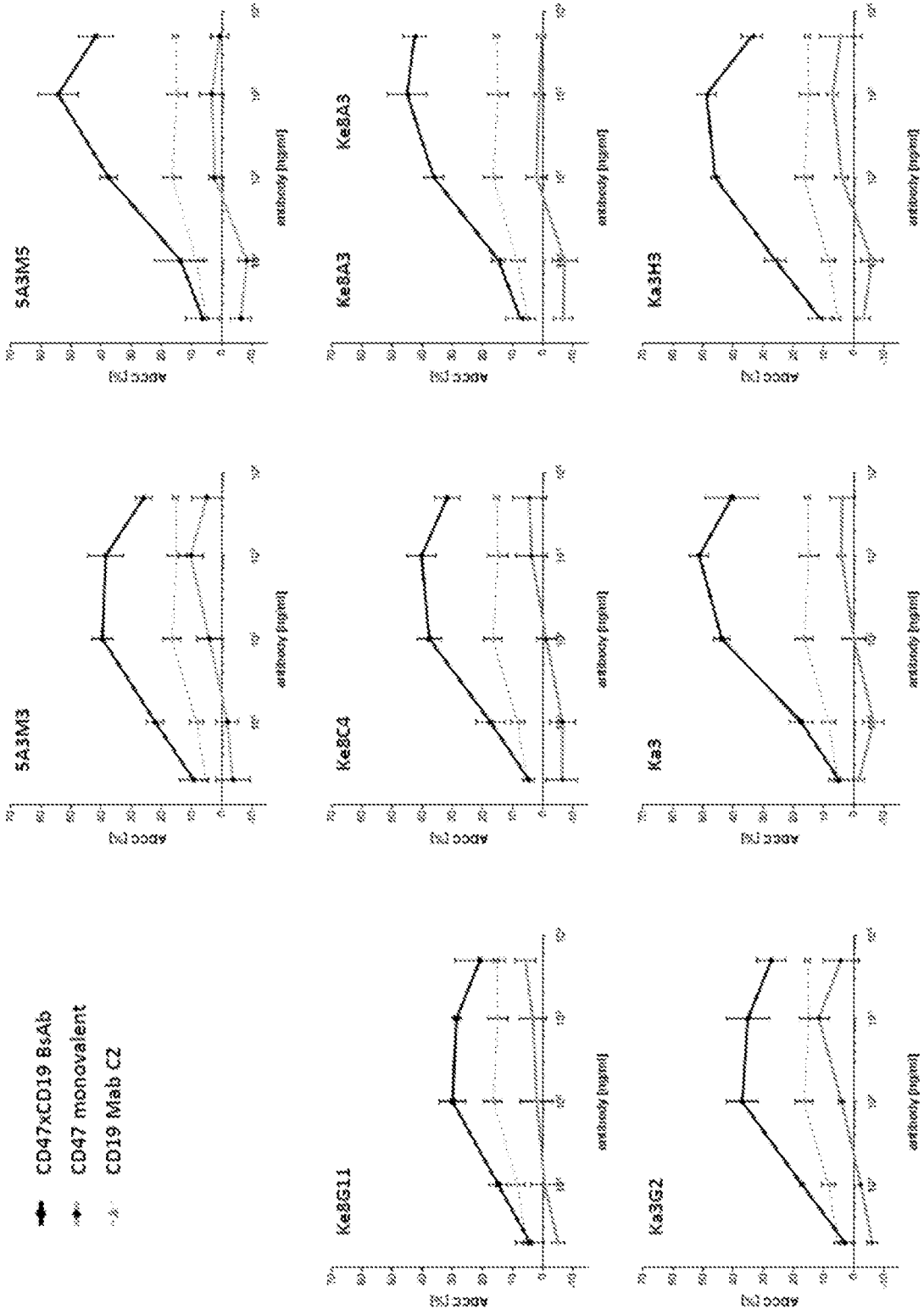

CD47xCD19 BsAb
CD47 monovalent
CD19 Mab C2
5A3M5
5A3M3
Ke8A3
Ke8A3
Ka3H3
Ke8C4
Ka3
Ke8G11
Ka3G2
ADCC (%)
antibody (ng/ml)

FIGURE 11C

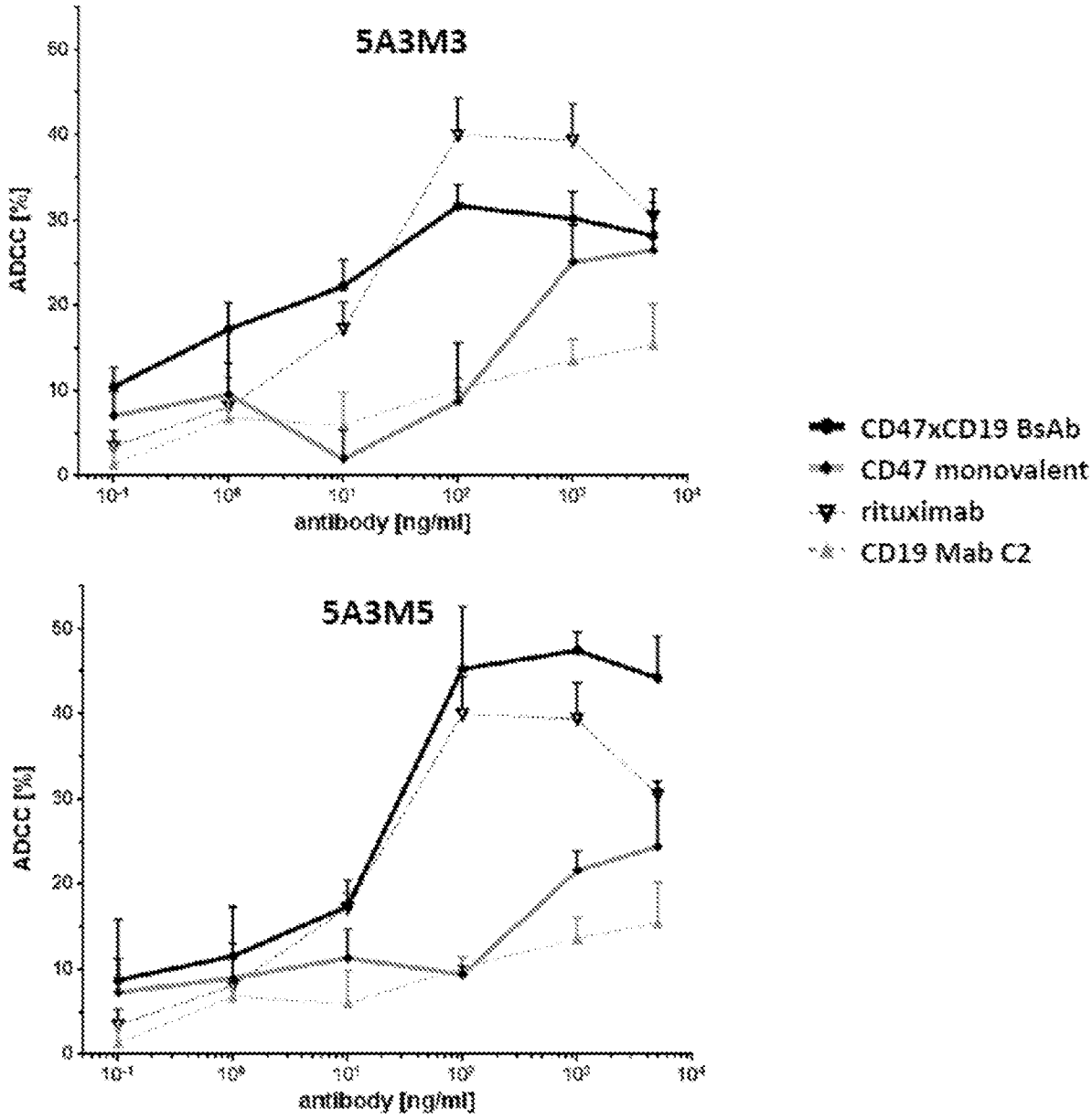

5A3M3
ADCC [%]
antibody [ng/ml]
5A3M5
ADCC [%]
antibody [ng/ml]
CD47xCD19 BsAb
CD47 monovalent
rituximab
CD19 Mab C2

FIGURE 12

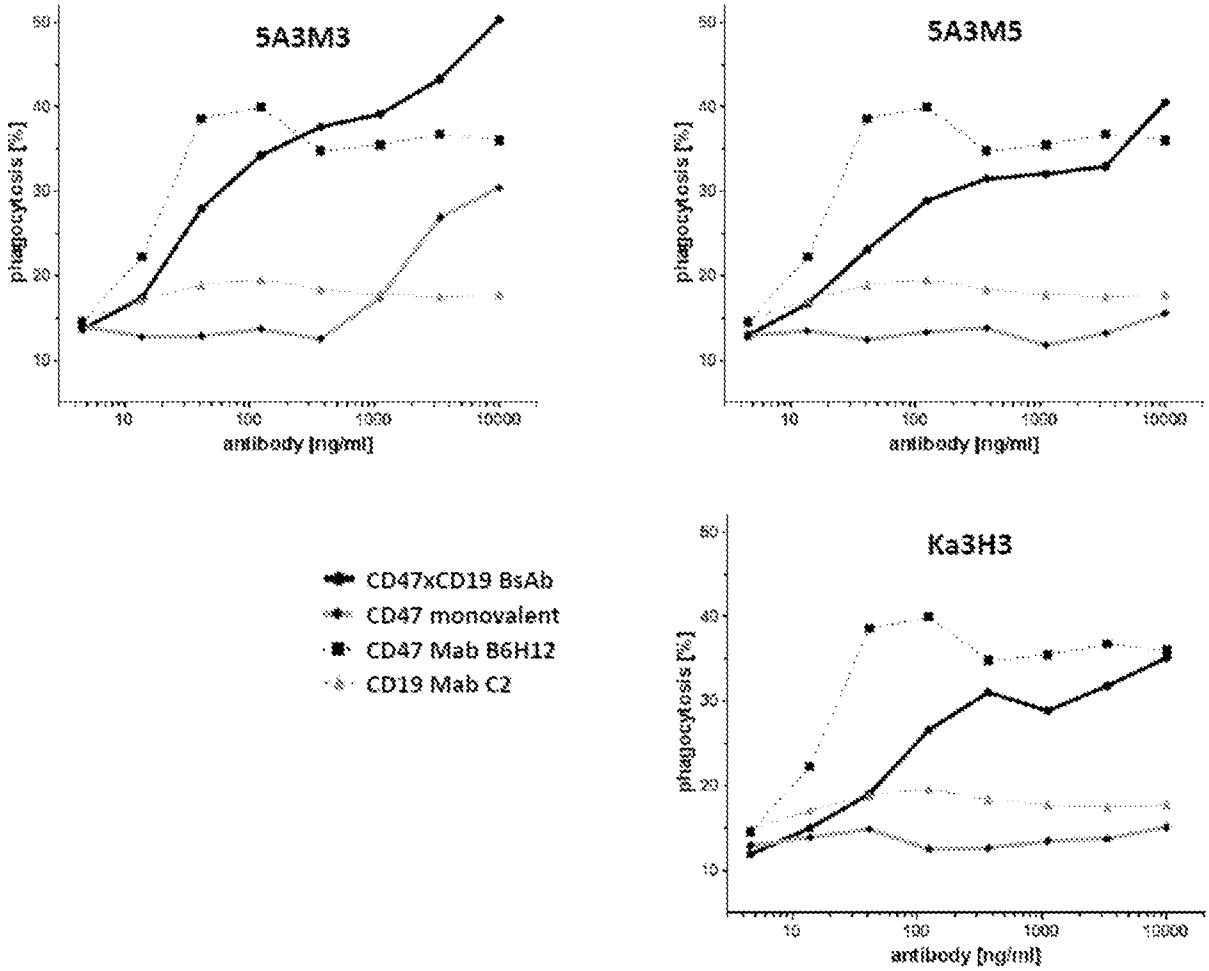

5A3M3
5A3M5
Ka3H3
phagocytosis [%]
antibody [ng/ml]
CD47xCD19 BsAb
CD47 monovalent
CD47 Mab B6H12
CD19 Mab C2

FIGURE 13

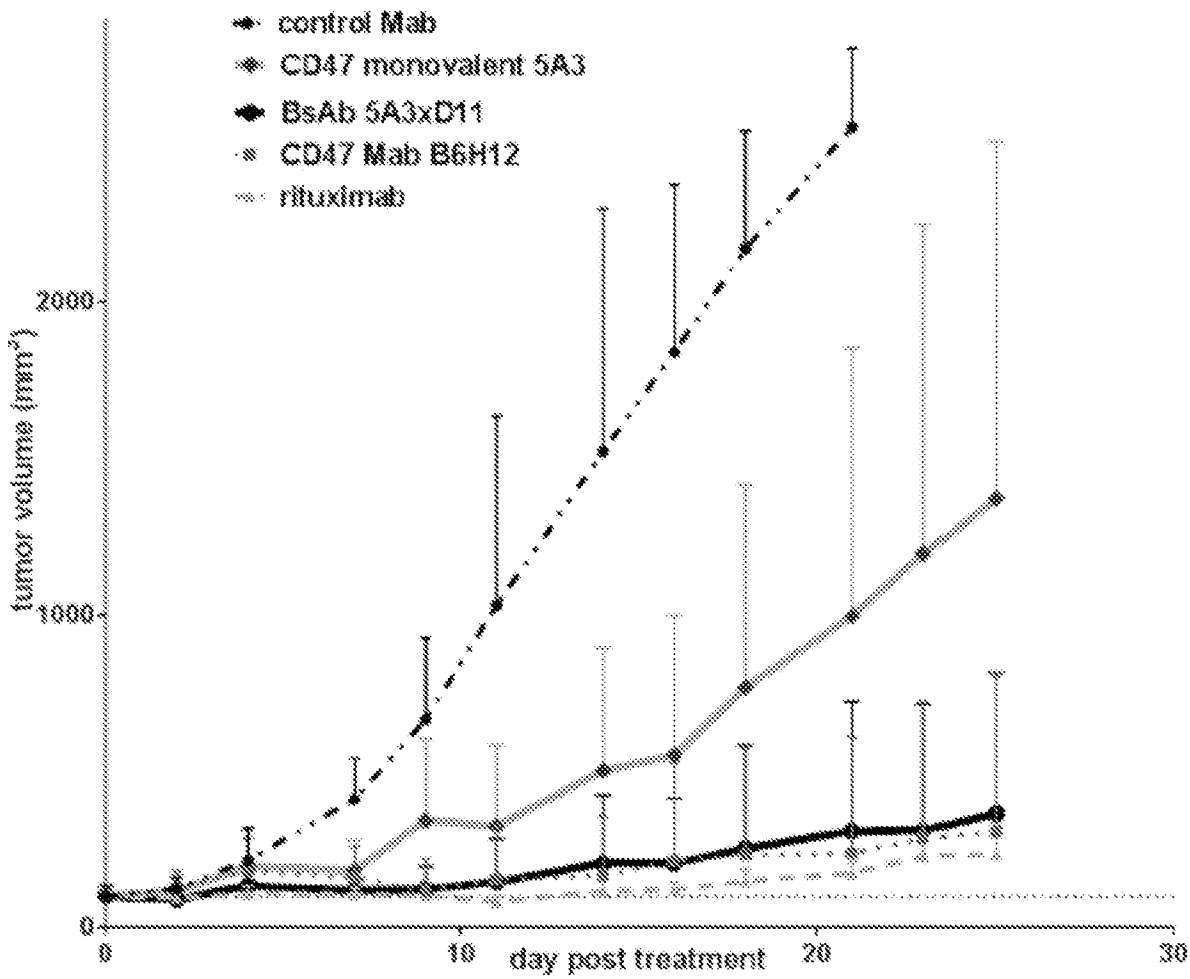
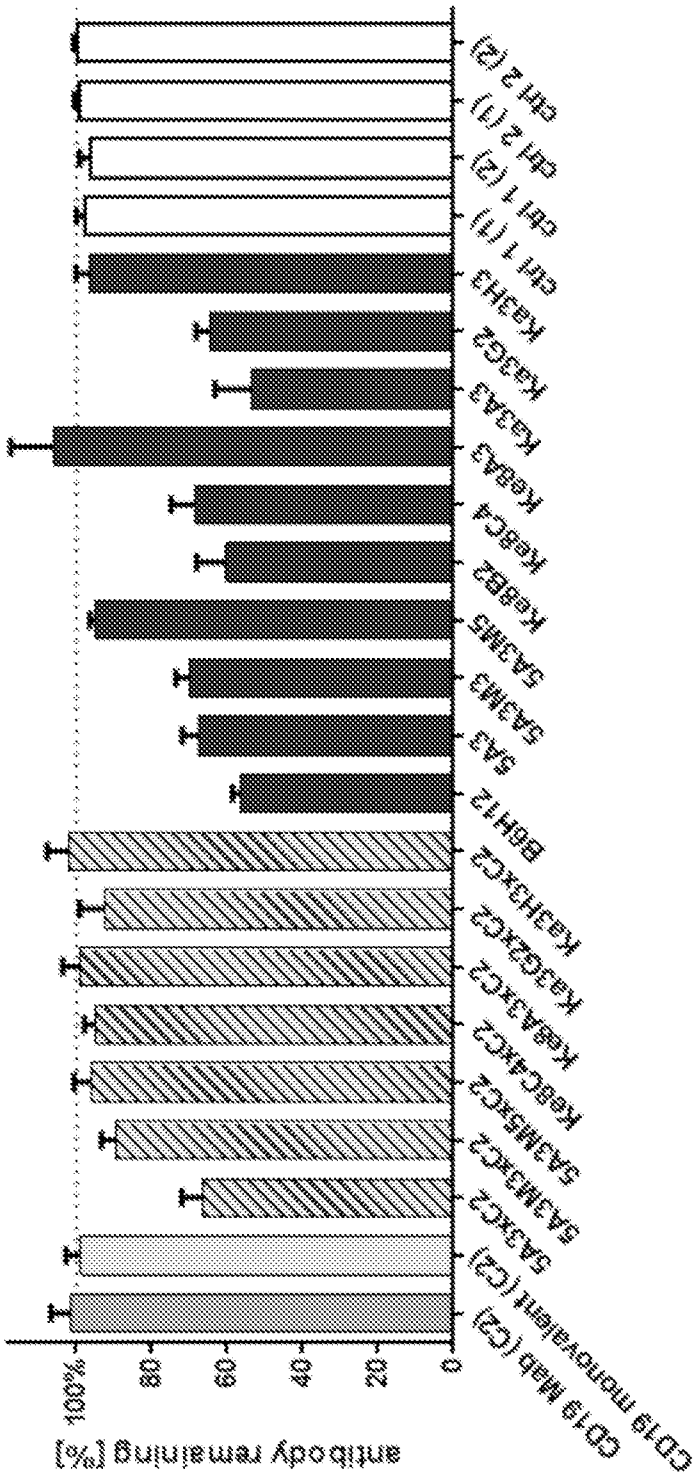

control Mab
CD47 monovalent 5A3
BsAb 5A3xD11
CD47 Mab B6H12
rituximab
tumor volume (mm³)
2000
1000
0
0
10
20
30
day post treatment

FIGURE 14


antibody remaining [%]
100%
80
60
40
20
0
CD19 Mab (C2)
CD19 monovalent (C2)
5A3xC2
5A3H3xC2
5A3M5xC2
KeBC4xC2
KeBA3xC2
Ka3G2xC2
Ka3H3xC2
B6H12
5A3
5A3M3
5A3M5
KeBB2
KeBC4
KeBA3
Ka3A3
Ka3C2
Ka3H3
cdr 1 (1)
cdr 1 (2)
cdr 2 (1)
cdr 2 (2)