

CANNABINOID RECEPTOR TYPE 2 ANTIBODIES AND USES THEREOF**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Application No. 63/609,666 filed on December 13, 2023, U.S. Provisional Application No. 63/561,029 filed on March 4, 2024, U.S. Provisional Application No. 63/645,515 filed on May 10, 2024, U.S. Provisional Application No. 63/679,061 filed on August 2, 2024, and U.S. Provisional Application No. 63/716,676 filed on November 5, 2024, the contents of which are incorporated herein by reference in their entirety.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (185982000340SEQLIST.xml; Size: 291,969 bytes; and Date of Creation: December 11, 2024) is herein incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0003] This invention was made with government support under Project Numbers R43DK125191 and R44DK125191, awarded by the National Institutes of Health, Project Numbers R43CA241513 and R44CA241513 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD

[0004] The present invention relates to antibodies comprising an immunoglobulin single variable domain (ISVD) that specifically bind a cannabinoid receptor type 2 (CB2), and methods of making and using thereof.

BACKGROUND

[0005] In mammals, there are two G-protein coupled receptors that mediate the signaling of cannabinoids, which are found in both plants and animals. Cannabinoid Receptor 1 (CB1) is expressed most strongly in the neurons of the CNS and is primarily responsible for the psychotropic effects of cannabinoids on the body (*Nature*, 346: 561-564, 1990). CB2 is expressed predominantly in the spleen and hematopoietic cells, demonstrating a predominantly

peripheral localization for this receptor (*Nature*, 365: 61-65, 1993; and reviewed in *Pharmacol. Rev.* 58(3): 389-462, 2006).

[0006] CB2 agonists are effective in multiple models of acute and chronic pain resulting from chemical, mechanical and thermal pain stimuli (reviewed in *Pharmacol. Ther.* 95: 127-135 2002; *Pharmacol. Rev.* 58(3): 389-462, 2006). In chemotherapy-induced neuropathic pain (CIPN), it has been shown that CB2 activation suppresses paclitaxel-induced CIPN in rats (*J. Pharmacol. Exp. Ther.* 327: 584–591, 2008). Moreover, CB2 agonists suppressed CIPN due to all major classes of chemotherapeutic agents, including taxane (*i.e.*, paclitaxel-cited above), vinca alkaloid (*i.e.*, vincristine, *Br. J. Pharmacol.* 152:765-777, 2007) and platinum-derived (*i.e.*, cisplatin, *Mol Pain*, 8:71) anti-cancer agents. CB2 agonists have also shown to be an effective treatment of diabetic neuropathy in both rat (*Pharmacology*. 82(3):193-200, 2008) and mouse models (*Pain*. 2013 Jun;154(6):864-73; *Psychopharmacology* (Berl). 233(11):2209-2219, 2016), further supporting the use of CB2 agonists in the treatment of multiple pain indications.

[0007] CB2 activation has strong anti-inflammatory activity that is part of a natural negative feedback mechanism, where CB2 receptor is induced in injured or virally-infected cells in inflammatory settings (*Gastroenterology*. 129:437-453, 2005; *Am. J. Pathol.* 177:187-196, 2010; *Br. J. Pharmacol.* 151:1041-1048, 2007). CB2 activation subsequently represses secretion of multiple inflammatory factors and signals, including TNF α , IL-6, IL-8, CCL2 (reviewed in *Cell. Mol. Life Sci.* 73:4449-4470, 2016). Accordingly, CB2 agonists would be useful for the treatment of inflammatory conditions of the lung (*Biomed Res. Int.* 2014: 971750, 2014) atherosclerosis (*Eur. J. Pharmacol.* 649:285–292,2010), inflammatory bowel disease (*World J. Gastroenterol.* 22:9515–9524, 2016), and viral infection (*Virulence* 9:217–230, 2018).

[0008] CB2 receptor agonism also plays a role in mitigating fibrotic processes in multiple organs. For example, receptor agonist JWH-133 has been shown to reduce leukocyte infiltration and dermal thickening in bleomycin-induced experimental fibrosis (*Arthritis Rheum* 60:1129-1136, 2009) and alleviates bleomycin-induced pulmonary fibrosis in mice (*Oncotarget*. 8:103486-103498, 2017). The CB2 receptor has been identified as a potential target for the treatment of systemic sclerosis because it controls both skin fibroblast proliferation and the autoimmune reaction (*Am. J. Pathol.* 177: 187-196, 2010). In the liver, CB2 agonism in mouse models protect against liver fibrosis caused by carbon tetrachloride (CCl₄) (*Gastroenterology*. 128:742-755, 2005) and alcohol (*Hepatology*. 54:1217-1226, 2011), and enhance liver

regeneration after injury (*Hepatology*. 52:1046-1059, 2010). In addition to reducing inflammation, CB2 agonism reduces the proliferation and induces apoptosis of myofibroblasts, which secrete collagen, which forms the fibrotic lesions (*Gastroenterology*. 128:742-755, 2005). Therefore, CB2 may beneficially impact liver disease through multiple mechanisms, *i.e.*, inflammation and fibrosis.

[0009] There is need in the art for developing methods of using CB2 receptor agonists in safe and effective therapies and to reduce the risk of adverse events. CB2 small molecule agonists are rapidly cleared, can have significant CNS permeability, and are a high risk for drug metabolism effects. Even the most peripherally-restricted CB2 small molecules have 3-5% CNS penetrance (*Pain*. Apr 13, 2021). Most CB2 agonists exhibit some activity at CB1, and thus CNS-mediated side effects are a concern. For example, in a Phase II study of Olorinab – a CB2 small molecule agonist developed for Irritable Bowel Syndrome – ~20% of treated patients reported some degree of dizziness, somnolence, or other central signs of CB1 activation (*Higgins, et al 14th Congress of ECCO – Inflammatory Bowel Diseases; March 6-9, 2019; Copenhagen, Denmark*). Additionally, a compliance handicap is added by the short half-lives of small molecules, which imposes a need for multiple daily doses (*J. Behav. Med.* 31: 213–224, 2008). The antibodies described herein satisfy these needs in the art and provide related advantages as well.

[0010] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

BRIEF SUMMARY

[0011] The present application relates to anti-CB2 antibodies (hereinafter referred to as “CB2 antibodies”) comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, and methods of making and using thereof.

[0012] In one aspect, provided herein is a cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises a complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO:1, a CDR2 comprising the amino acid sequence of SEQ ID NO:2, and a CDR3 comprising the amino acid sequence of SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. Also provided is a CB2 antibody comprising an ISVD that specifically binds to a CB2, wherein the ISVD comprises a CDR1, a CDR2, and a CDR3 of an ISVD comprising the amino acid sequence of SEQ ID NO:201.

[0013] In some embodiments, the ISVD is a variable domain of the heavy chain of a heavy chain antibody (VHH). In some embodiments, the ISVD is camelid. In some embodiments, the ISVD is chimeric. In some embodiments, the ISVD is humanized.

[0014] In some embodiments, the ISVD comprises one or more amino acid residues selected from the group consisting of V5, Q39, Y58, G65, R71, A74, and L78 in one or more framework regions (FRs), wherein the amino acid numbering is according to Kabat. In some embodiments, the ISVD comprises amino acid residues V5, Q39, Y58 and G65 in one or more FRs.

[0015] In some embodiments, the ISVD comprises: an FR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:4-15; an FR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-30; an FR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:31-48 and 200; and an FR4 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:49-54. In some embodiments, the ISVD comprises: (i) an FR1 comprising the amino acid sequence of SEQ ID NO:14, an FR2 comprising the amino acid sequence of SEQ ID NO:29, an FR3 comprising the amino acid sequence of SEQ ID NO:43, and an FR4 comprising the amino acid sequence of SEQ ID NO:54; (ii) an FR1 comprising the amino acid sequence of SEQ ID NO:15, an FR2 comprising the amino acid sequence of SEQ ID NO:23, an FR3 comprising the amino acid sequence of SEQ ID NO:45, and an FR4 comprising the amino acid sequence of SEQ ID NO:54; or (iii) an FR1 comprising the amino acid sequence of SEQ ID NO:4, an FR2 comprising the amino acid sequence of SEQ ID NO:16, an FR3 comprising the amino acid sequence of SEQ ID NO:200, and an FR4 comprising the amino acid sequence of SEQ ID NO:49.

[0016] In some embodiments, the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:55-77 and 201, or a variant thereof having at least about 85% sequence identity to the amino acid sequence of any one of SEQ ID NOs:55-77 and 201. In some embodiments, the ISVD comprises the amino acid sequence of SEQ ID NO:200, 74 or 94.

[0017] In some embodiments, the CB2 antibody comprises an Fc region. In some embodiments, the antibody comprises an Fc region of an IgG1 or IgG4. In some embodiments, the antibody comprises a variant IgG4 Fc region exhibiting reduced effector function. In some embodiments, the Fc region comprises amino acid substitutions F234A and L235A, with numbering according to the EU index of Kabat. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO:130.

[0018] In some embodiments, the antibody comprises a hinge region. In some embodiments, the hinge region comprises the amino acid sequence of SEQ ID NO:131.

[0019] In some embodiments, the ISVD is fused to the Fc region via a peptide linker. In some embodiments, the peptide linker comprises the amino acid sequence of SEQ ID NO:132. In some embodiments, the antibody comprises a polypeptide chain comprising from the N-terminus to the C-terminus: the ISVD, a peptide linker, a hinge region, and an Fc region.

[0020] In some embodiments, the CB2 antibody comprises a polypeptide chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:78-95 and 202-203, or a variant thereof having at least about 85% sequence identity to the amino acid sequence of any one of SEQ ID NOs:78-95 and 202-203. In some embodiments, the CB2 antibody comprises a polypeptide chain comprising the amino acid sequence of SEQ ID NO:94. In some embodiments, the CB2 antibody comprises a polypeptide chain comprising the amino acid sequence of SEQ ID NO:203.

[0021] In some embodiments, the CB2 is human, mouse, rat or cynomolgus monkey CB2. In some embodiments, the CB2 is a human CB2.

[0022] In some embodiments, the CB2 antibody is a CB2 agonist. In some embodiments, the CB2 antibody does not agonize CB1. In some embodiments of the CB2 antibody: (i) the ISVD reduces forskolin-induced cyclic adenosine monophosphate (cAMP) level in HEK293 cells overexpressing human CB2 with a half maximal effective concentration (EC_{50}) that is less than 55 nM; and/or (ii) the ISVD reduces forskolin-induced cyclic adenosine monophosphate (cAMP) level in HEK293 cells overexpressing mouse CB2 with an EC_{50} that is less than 30 nM. In some embodiments, the ISVD does not specifically bind a cannabinoid receptor type 1 (CB1). In some embodiments, the CB2 antibody binds HEK293 cells overexpressing human CB2 with an EC_{50} that is less than 850 nM.

[0023] Further provided is an isolated nucleic acid encoding any one of the CB2 antibodies described above. Further provided is an expression vector comprising said nucleic acid. Further provided is a host cell comprising said nucleic acid or said expression vector.

[0024] Further provided is a method of producing any one of the CB2 antibodies described above, comprising culturing the host cell described above under conditions where the CB2 antibody is produced. In some embodiments, the method further comprises recovering the CB2 antibody produced by the host cell.

[0025] Further provided is a pharmaceutical composition comprising any one of the CB2 antibodies described above and a pharmaceutically acceptable carrier.

[0026] Further provided is a method of agonizing CB2 on a cell, comprising contacting the cell with an amount of any one of the CB2 antibodies described above that is sufficient for activating CB2 on the cell. In some embodiments, the method is *in vitro*. In some embodiments, the method is *in vivo*.

[0027] Further provided is a method of treating an individual in need thereof having a disease or condition, wherein agonizing CB2 ameliorates the disease or condition, comprising administering to the individual an effective amount of any one of the CB2 antibodies described above or the pharmaceutical composition described above. In some embodiments, the disease or condition is selected from the group consisting of chemotherapy induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy, respiratory infections, liver fibrosis, cold sensitivity, inflammatory bowel disease, and endometriosis. In some embodiments, the disease or condition is chemotherapy induced peripheral neuropathy (CIPN). In some embodiments, the CIPN is caused by a taxol drug. In some embodiments, the taxol drug is paclitaxel. In some embodiments, the disease or condition is a respiratory infection. In some embodiments, the respiratory infection is caused by a virus selected from the group consisting of influenza viruses and coronaviruses. In some embodiments, the respiratory infection is caused by SARS-CoV-2. In some embodiments, the respiratory infection is caused by H1N1 influenza. In some embodiments, the disease or condition is liver fibrosis. In some embodiments, the disease or condition is diabetic peripheral neuropathy.

[0028] Further provided is a method of treating a cancer in an individual in need thereof, comprising administering to the individual an effective amount of a chemotherapeutic agent, and an effective amount of any one of the CB2 antibodies described above.

[0029] Further provided is a method of reducing a cytokine release syndrome in an individual in need thereof, comprising administering to the individual an effective amount of any one of the CB2 antibodies described above. In some embodiments, the method decreases IL-16 and/or IL-8 level secreted by airway cells in the individual.

[0030] In some embodiments of any of the methods described above, the individual is a human.

[0031] Further provided is a kit comprising the CB2 antibody of any one of the CB2 antibodies described above or the pharmaceutical composition described above, and instructions for use.

[0032] Further provided is a cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises i) a complementarity determining region (CDR) 1 having the amino acid formula G-X1-X2-X3-S-I-X4-X5, wherein X1 is selected from D, S, or Q; X2 is selected from G, H, I, or K; X3 is selected from D, E, F, G, H, I, K, N, Q, R, S, T, V, W, or Y; X4 is selected from G, K, M, R, or Y; and X5 is selected from A or G; and ii) a CDR3 having the amino acid formula C1-C2-C3-I-K-C4-C5-C6-C7-C8-C9-C10-I-C11-C12-C13, wherein C1 is selected from F, H, I, K, L, R, S, T, V, or Y; wherein C2 is selected from A, E, F, G, I, L, Q, R, or V; wherein C3 is selected from A, F, G, I, K, L, N, or V; wherein C4 is selected from D, F, N, T, or Y; wherein C5 is selected from A, G, or R; wherein C6 is selected from R, S, or W; wherein C7 is selected from D, G, K, or R; wherein C8 is selected from D, I, L, Q, R, S, or T; wherein C9 is selected from F, L, or T; wherein C10 is selected from any D, E, H, or Q; wherein C11 is selected from K or N; wherein C12 is selected from A, F, G, H, I, K, L, N, P, R, S, V, T, or W; and wherein C13 is selected from A, D, F, G, H, T, or Y. In some embodiments, CDR2 is SEQ ID NO:2.

[0033] Further provided is a cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:248-288, CDR2 comprising an amino acid sequence of SEQ ID NO:2, and a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:289-329, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:205-212, 214-229, and 231-247, or a variant thereof having at least about 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs:205-212, 214-229, and 231-247. In some embodiments, the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NO:205, SEQ ID NO:212, SEQ ID NO:215, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:222, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:229, SEQ ID NO:240, and SEQ ID NO:241, or a variant thereof having at least about 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:205, SEQ ID NO:212, SEQ ID NO:215, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:222, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:229, SEQ ID NO:240, and SEQ ID NO:241.

[0034] In some embodiments, the ISVD is camelid. In some embodiments, the ISVD is chimeric. In some embodiments, the ISVD is humanized. In some embodiments, the antibody comprises an Fc region. In some embodiments, the antibody comprises an Fc region of an IgG1 or IgG4. In some embodiments, the antibody comprises a variant IgG4 Fc region exhibiting reduced effector function. In some embodiments, the antibody comprises a hinge region. In some embodiments, the CB2 is human, mouse, rat or cynomolgus monkey CB2. In some embodiments, the CB2 is a human CB2. In some embodiments, the CB2 antibody is a CB2 agonist. In some embodiments, the CB2 antibody does not agonize CB1.

[0035] Further provided is an isolated nucleic acid encoding any of the CB2 antibodies described above.

[0036] Further provided is an expression vector comprising a nucleic acid encoding any of the CB2 antibodies described above.

[0037] Further provided is a host cell comprising a nucleic acid encoding any of the CB2 antibodies described above or expression vector comprising said nucleic acids.

[0038] Further provided is a method of producing a CB2 antibody, comprising culturing any of the host cells described above under conditions where the CB2 antibody is produced. In some embodiments, the method further comprises recovering the CB2 antibody produced by the host cell.

[0039] Further provided is a pharmaceutical composition comprising any of the CB2 antibodies described above and a pharmaceutically acceptable carrier.

[0040] Further provided is a method of agonizing CB2 on a cell, comprising contacting the cell with an amount of any of the CB2 antibodies described above that is sufficient for activating CB2 on the cell. In some embodiments, the method is *in vitro*. In some embodiments, the method is *in vivo*.

[0041] Further provided is a method of treating an individual in need thereof having a disease or condition, wherein agonizing CB2 ameliorates the disease or condition, comprising administering to the individual an effective amount of a CB2 antibody. In some embodiments, the disease or condition is selected from the group consisting of chemotherapy induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy, respiratory infections, liver fibrosis, cold sensitivity, inflammatory bowel disease, and endometriosis. In some embodiments, the disease or condition is chemotherapy induced peripheral neuropathy (CIPN). In some

embodiments, the CIPN is caused by a taxol drug. In some embodiments, the taxol drug is paclitaxel.

[0042] Further provided is a method of treating a cancer in an individual in need thereof, comprising administering to the individual an effective amount of a chemotherapeutic agent, and an effective amount of a CB2 antibody. In some embodiments, the disease or condition is a respiratory infection. In some embodiments, the respiratory infection is caused by a virus selected from the group consisting of influenza viruses and coronaviruses. In some embodiments, the respiratory infection is caused by SARS-CoV-2. In some embodiments, the respiratory infection is caused by H1N1 influenza.

[0043] Further provided is a method of reducing a cytokine release syndrome in an individual in need thereof, comprising administering to the individual an effective amount of any of the CB2 antibodies described above. In some embodiments, the method decreases IL-16 and/or IL-8 level secreted by airway cells in the individual. In some embodiments, the disease or condition is liver fibrosis. In some embodiments, the disease or condition is diabetic peripheral neuropathy. In some embodiments, the individual is a human.

[0044] Further provided is a kit comprising any of the CB2 antibodies described above or a pharmaceutical composition comprising any CB2 antibodies described above and a pharmaceutically acceptable carrier, and instructions for use.

[0045] Further provided is a cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises a CDR3 having the amino acid formula C1-C2-C3-I-K-Y-G-S-G-C4-F-D-I-K-C5-C6, wherein C1 is selected from L, I, V, Y, or F; wherein C2 is selected from F, A, or V; wherein C3 is selected from A, I, or V; wherein C4 is selected from D or L; wherein C5 is selected from G, T, or V; and wherein C6 is selected from Y, A, or F, wherein the CDR3 is defined according to IMGT. In some embodiments, CDR1 is SEQ ID NO:248 and CDR2 is SEQ ID NO:2, wherein the CDR1 and CDR2 are defined according to IMGT.

[0046] Further provided is a cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises a CDR1 comprising an amino acid sequence of SEQ ID NO:248, CDR2 comprising an amino acid sequence of SEQ ID NO:2, and a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:345-359, wherein the CDR1, CDR2 and

CDR3 are defined according to IMGT. In some embodiments, the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:330-344, or a variant thereof having at least about 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs:330-344. In some embodiments, the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, and SEQ ID NO:344, or a variant thereof having at least about 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, and SEQ ID NO:344.

[0047] In some embodiments, the ISVD is camelid. In some embodiments, the ISVD is chimeric. In some embodiments, the ISVD is humanized. In some embodiments, the antibody comprises an Fc region. In some embodiments, the antibody comprises an Fc region of an IgG1 or IgG4.

[0048] In some embodiments, the antibody comprises a variant IgG4 Fc region exhibiting reduced effector function. In some embodiments, the antibody comprises a hinge region. In some embodiments, the CB2 is human, mouse, rat or cynomolgus monkey CB2. In some embodiments, the CB2 is a human CB2. In some embodiments, the CB2 antibody is a CB2 agonist. In some embodiments, the CB2 antibody does not agonize CB1.

[0049] Further provided is an isolated nucleic acid encoding any of the CB2 antibodies described above.

[0050] Further provided is an expression vector comprising any of the nucleic acids described above.

[0051] Further provided is a host cell comprising any of the nucleic acids described above or any of the expression vectors described above.

[0052] Further provided is a method of producing a CB2 antibody, comprising culturing any of the host cells described above under conditions where the CB2 antibody is produced. In some embodiments, the method further comprises recovering the CB2 antibody produced by the host cell.

[0053] Further provided is a pharmaceutical composition comprising any of the CB2 antibodies described above and a pharmaceutically acceptable carrier.

[0054] Further provided is a method of agonizing CB2 on a cell, comprising contacting the cell with an amount of any of the CB2 antibodies described above that is sufficient for activating CB2 on the cell. In some embodiments, the method is *in vitro*. In some embodiments, the method is *in vivo*.

[0055] Further provided is a method of treating an individual in need thereof having a disease or condition, wherein agonizing CB2 ameliorates the disease or condition, comprising administering to the individual an effective amount of any of the CB2 antibodies described above. In some embodiments, the disease or condition is selected from the group consisting of chemotherapy induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy, respiratory infections, liver fibrosis, cold sensitivity, inflammatory bowel disease, and endometriosis. In some embodiments, the disease or condition is chemotherapy induced peripheral neuropathy (CIPN). In some embodiments, the CIPN is caused by a taxol drug. In some embodiments, the taxol drug is paclitaxel.

[0056] Further provided is a method of treating a cancer in an individual in need thereof, comprising administering to the individual an effective amount of a chemotherapeutic agent, and an effective amount of any of the CB2 antibodies described above. In some embodiments, the disease or condition is a respiratory infection. In some embodiments, the respiratory infection is caused by a virus selected from the group consisting of influenza viruses and coronaviruses. In some embodiments, the respiratory infection is caused by SARS-CoV-2. In some embodiments, the respiratory infection is caused by H1N1 influenza.

[0057] Further provided is a method of reducing a cytokine release syndrome in an individual in need thereof, comprising administering to the individual an effective amount of any of the CB2 antibodies described above. In some embodiments, the method decreases IL-16 and/or IL-8 level secreted by airway cells in the individual. In some embodiments, the disease or condition is liver fibrosis. In some embodiments, the disease or condition is diabetic peripheral neuropathy. In some embodiments, the individual is a human.

[0058] Further provided is a kit comprising any of the CB2 antibodies described above or any of the pharmaceutical compositions described above, and instructions for use.

[0059] Further provided is a cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises: a CDR1 comprising the amino acid sequence of SEQ ID NO:248; a CDR2 comprising the amino acid sequence of SEQ ID NO:2; and a CDR3 having the amino acid formula C1-C2-C3-I-K-Y-G-S-G-C4-F-D-I-K-C5-C6, wherein C1 is selected from L, I, V, Y, or F; wherein C2 is selected from F, A, or V; wherein C3 is selected from A, I, or V; wherein C4 is selected from D or L; wherein C5 is selected from G, T, or V; and wherein C6 is selected from Y, A, or F, wherein the CDR1, CDR2, and CDR3 are defined according to IMGT. In some embodiments, the ISVD comprises: a CDR1 comprising the amino acid sequence of SEQ ID NO:248; a CDR2 comprising the amino acid sequence of SEQ ID NO:2; and a CDR3 comprising the amino acid sequence selected from the group consisting of SEQ ID NOS:345-359.

BRIEF DESCRIPTION OF THE DRAWINGS

[0060] **FIG. 1A** shows agonist activity (as EC₅₀) against cannabinoid receptors, as assessed by cAMP levels as percent of control. Agonist activity of negative control (“None”), CP55940, CP55940+SR144528, antibody designated AB101 (SEQ ID NO:55), AB101 + SR144528, or SR144528 is shown for human CB2 and agonist activity of negative control (“None”), CP55940, AB101, and negative control VHH are shown for human CB1.

[0061] **FIG. 1B** shows agonism of human and mouse CB2 by antibody designated AB101 (SEQ ID NO:55).

[0062] **FIG. 2A** shows activity of ABt140 (SEQ ID NO:94) or vehicle control in CIPN model mice (“CIPN”) or cremophor vehicle control mice (“Healthy”) as assessed by mechanical withdrawal thresholds.

[0063] **FIG. 2B** shows activity of Abt140 (SEQ ID NO:94) or vehicle control in CIPN model mice (“CIPN”) or cremophor vehicle control mice (“Healthy”) as assessed by cold allodynia.

[0064] **FIG. 3A** shows agonist activity of ABt140 (SEQ ID NO:94) and CP55940 against human CB2.

[0065] **FIG. 3B** shows agonist activity of ABt140 (SEQ ID NO:94) and a control antibody as assessed by inhibition of IL6 secretion from LPS-stimulated BEAS2B cells.

[0066] **FIG. 3C** shows agonist activity of ABt140 (SEQ ID NO:94) and a control antibody as assessed by inhibition of IL8 secretion from LPS-stimulated BEAS2B cells.

[0067] **FIG. 4A** shows effect of ABt140 (SEQ ID NO:94) in a mouse influenza model as assessed by improvement in clinical scores.

[0068] **FIG. 4B** shows effect of ABt140 (SEQ ID NO:94) in a mouse influenza model as assessed by 7-day survival.

[0069] **FIG. 4C** shows effect of ABt140 (SEQ ID NO:94) in a mouse influenza model as assessed by viral titer.

[0070] **FIGs. 5A-5B** show treatment of serum-starved RAW264.7 mouse macrophage cells with HU-308 (onternabenz), ABt281, ABt285, or ABt269 (1uM and 100nM) for 6 hours followed by either LPS (100ng/ml; **FIG. 5A**) or IL-4 (10ng/ml; **FIG. 5B**) for 12 hours. M1 and M2 macrophage gene expressions were measured by using RTPCR. Two-way ANOVA: * $p < 0.05$, *** $p = 0.0001$, **** $p < 0.0001$.

[0071] **FIG. 6** shows IL-6 secretion of RAW264.7 cells after treatment with CP-55,940 or the indicated antibodies, with (+) or without (-) LPS. IL-6 concentrations in the supernatant were measured using Perkin Elmer IL-6 LANCE Ultra TR-FRET kit, TRF1223C.

[0072] **FIG. 7** shows cAMP levels of RAW264.7 cells treated with NKH477 and HU308, ABt281, ABt285, or ABt269 as assessed by a luminescent cAMP kit (cAMP-Glo, Promega, V1501).

[0073] **FIGs. 8A-8B** shows activity of cremophor vehicle control, PBS control, AB269, or ABt281 in mechanical allodynia assay in mice for mechanical (**FIG. 8A**) and cold (**FIG. 8B**). N=6 mice. Data are mean $\pm$ SEM. B:pre-paclitaxel baseline. Pac:post-paclitaxel baseline. *** $P < .001$, CIPN+Ab (ABt281) versus CIPN+Control (ABt269) statistics analyzed using one way ANOVA followed by Bonferroni post hoc test.

[0074] **FIGs. 9A-9B** show activity of CIPN + control (ABt269) versus CIPN + Ab (ABt281) in mechanical and cold allodynia assay in CB2 knockout mice for mechanical (**FIG. 9A**) and cold (**FIG. 9B**). B:pre-paclitaxel baseline. Pac:post-paclitaxel baseline. CIPN+Ab (ABt281) versus CIPN+Control (ABt269) statistics analyzed using one way ANOVA followed by Bonferroni post hoc test.

[0075] **FIGs. 10A-10B** show activity of CIPN + control (ABt269) versus CIPN + Ab (ABt281) in mechanical and cold allodynia assay in mice for mechanical (**FIG. 10A**) and cold (**FIG. 10B**).

[0076] FIGs. 11A-11B show activity of CIPN + control (ABt269) versus CIPN + Ab (ABt281) in mechanical and cold allodynia assay in mice after treatment with AM1710 for mechanical (FIG. 11A) and cold (FIG. 11B).

[0077] FIGs 12A-12F shows the effect of the indicated treatments in human liver slice model (hPCLS) cells as assessed by secretion of collagen1a1 (Col1a1) into media as assessed by ELISA (FIG. 12A), and by mRNA expression levels for COL1A1 (FIG. 12B), ACTA2 (FIG. 12C), IL6 (FIG. 12D), IL10 (FIG. 12E), and TNF α (FIG. 12F). Two-way ANOVA; Dunnett's multiple comparison test; mean +/- standard deviation; *p<0.05, **p<0.005; ns=not significant.

[0078] FIGs. 13A-13B shows ERK phosphorylation induced by indicated agents in RAW264.7 cells as assessed by a TR-FRET pERK1/2 kit.

[0079] FIGs. 14A-14B show activity of ABt140 (SEQ ID NO:94), ABt281 (SEQ ID NO:202), ABt285 (SEQ ID NO:203), or vehicle control in CIPN model mice ("CIPN") or cremophor vehicle control mice ("Healthy") as assessed by mechanical thresholds (FIG. 14A) or cold allodynia (FIG. 14B) following initial injection and 2 subsequent reinjections.

[0080] FIG. 15 shows recruitment beta-arrestin2 induced by indicated agents in RAW264.7 cells as assessed by a HTRF beta-arrestin2 recruitment detection kit.

[0081] FIG. 16 shows RAW264.7 cells cultured and treated with HU308, CB2 agonist antibodies, or isotype control (ABt269).

[0082] FIG. 17 shows RAW264.7 cells cultured and treated with HU308, CB2 agonist antibodies, or isotype control (ABt269).

[0083] FIGs. 18A-18B show recruitment of beta-arrestin2 induced by indicated agents in RAW264.7 cells as assessed by a HTRF beta-arrestin2 recruitment detection kit.

[0084] FIG. 19 shows the positive hit rate (%) of antibodies created by the generative model compared to antibodies developed from functional maturation.

[0085] FIG. 20 shows the probability of truly active antibodies and created antibodies with higher activity compared to the seed antibody.

DETAILED DESCRIPTION

[0086] The present disclosure is based, at least in part, on the discovery of novel antibodies which specifically bind a cannabinoid receptor type 2 (CB2), which may be referred to synonymously as "anti-CB2 antibodies" or "CB2 antibodies," and antigen-binding fragments

thereof. The CB2 antibodies comprise at least an immunoglobulin single variable domain (ISVD) that specifically binds a CB2. The ISVD comprises a complementarity determining region 1 sequence (CDR1), a complementarity determining region 2 sequence (CDR2), and a complementarity determining region 3 sequence (CDR3). The ISVD may be a variable domain of the heavy chain of a heavy chain antibody (VHH). The ISVD may be, for example, a camelid, chimeric, or humanized ISVD. The ISVDs described herein may specifically bind CB2 (such as a human, cynomolgus, murine, and/or rat CB2), but have low or undetectable affinity for CB1 (such as a human, cynomolgus, murine, and/or rat CB1). The ISVDs described herein are selective agonists of CB2, which have no or undetectable agonist activity against CB1. In some embodiments, the anti-CB2 antibody comprises an Fc fragment (*e.g.*, a human IgG1 Fc, effectorless IgG1 Fc, IgG2 Fc, or IgG4 Fc). Also provided are pharmaceutical compositions comprising these antibodies, kits, and methods of treatment using the antibodies.

I. Definitions

[0087] The term “antibody” herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, 4-chain antibodies (such as IgG antibodies), heavy chain antibodies, and antibody fragments thereof so long as they exhibit the desired antigen-binding activity, *i.e.*, binding to CB2 (such as a human CB2, cynomolgus CB2, rat CB2, and/or a mouse CB2). The term “4-chain antibody” is used herein to refer to an antibody or antigen-binding fragment having two heavy chains and two light chains. The term “heavy chain antibody,” also known as “heavy chain-only antibody” or “HCAb” refers to a functional antibody, which comprises two heavy chains, but lacks two light chains usually found in 4-chain antibodies. Camelid animals (such as camels, llamas, or alpacas) are known to produce HCAbs.

[0088] As used herein, an “agonist” means an antibody stimulates a biological function and/or signaling of a target receptor. In the context of a CB2 agonist, the CB2 agonist is capable of activating the endocannabinoid signaling pathway through activation of CB2. CB2 agonism includes, but is not limited to, (a) stimulating or activating CB2 and (b) enhancing, increasing, promoting, inducing, or prolonging the activity, function, or presence of CB2 signaling or downstream signaling products.

[0089] The term “immunoglobulin single variable domain” (also referred to as “ISV” or “ISVD”) is generally used to refer to immunoglobulin variable domains (which may be heavy

chain or light chain domains, including VH, VHH or VL domains) that can form a functional antigen-binding site without interaction with another variable domain (*e.g.*, without a VH/VL interaction as is required between the VH and VL domains of a 4-chain monoclonal antibody). Examples of ISVDs include Nanobodies (including a VHH, a humanized VHH and/or a camelized VHS such as camelized human VHS), shark IgNAR domains, single-domain antibodies (or dAbs) that are VH domains or that are derived from a VH domain, single-domain antibodies (or dAbs) that are VL domains or that are derived from a VL domain. ISVDs that are based on and/or derived from heavy chain variable domains (such as VH or VHH domains) are generally preferred. In some embodiments, an ISVD is a Nanobody. The term “Nanobody” is generally as defined in WO 2008/020079 or WO 2009/138519, and thus in a specific aspect generally denotes a VHH, a humanized VHH or a camelized VH (such as a camelized human VH) or generally a sequence optimized VHH (such as, *e.g.*, optimized for chemical stability and/or solubility, maximum overlap with known human framework regions and maximum expression).

[0090] “Antibody fragments” comprise a portion of an antibody, preferably the antigen binding or variable region of the antibody. Examples of antibody fragments include VHHs, single-domain antibodies, Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (see U.S. Patent No. 5,641,870, Example 2; Zapata *et al.*, Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. The term “constant domain” refers to the portion of an immunoglobulin molecule having a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable domain, which contains the antigen-binding site. The constant domain contains the C_H1, C_H2 and C_H3 domains (collectively, C_H) of the heavy chain and the C_HL (or C_L) domain of the light chain.

[0091] The term “Fc region” or “fragment crystallizable region” herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy-chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly

engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue. Suitable native-sequence Fc regions for use in the antibodies described herein include human IgG1, IgG2 (IgG2A, IgG2B), IgG3 and IgG4.

[0092] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (*e.g.*, isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present application may be made by a variety of techniques, including, for example, the hybridoma method (*e.g.*, Kohler and Milstein., *Nature*, 256:495-97 (1975); Hongo *et al.*, *Hybridoma*, 14 (3): 253-260 (1995), Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling *et al.*, in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981)), recombinant DNA methods (*see, e.g.*, U.S. Pat. No. 4,816,567), phage-display technologies (*see, e.g.*, Clackson *et al.*, *Nature*, 352: 624-628 (1991); Marks *et al.*, *J. Mol. Biol.* 222: 581-597 (1992); Sidhu *et al.*, *J. Mol. Biol.* 338(2): 299-310 (2004); Lee *et al.*, *J. Mol. Biol.* 340(5): 1073-1093 (2004); Fellouse, *Proc. Natl. Acad. Sci. USA* 101(34): 12467-12472 (2004); and Lee *et al.*, *J. Immunol. Methods* 284(1-2): 119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (*see, e.g.*, WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits *et al.*, *Proc. Natl. Acad. Sci. USA* 90: 2551 (1993);

Jakobovits *et al.*, *Nature* 362: 255-258 (1993); Bruggemann *et al.*, *Year in Immunol.* 7:33 (1993); U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks *et al.*, *Bio/Technology* 10: 779-783 (1992); Lonberg *et al.*, *Nature* 368: 856-859 (1994); Morrison, *Nature* 368: 812-813 (1994); Fishwild *et al.*, *Nature Biotechnol.* 14: 845-851 (1996); Neuberger, *Nature Biotechnol.* 14: 826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.* 13: 65-93 (1995).

[0093] The term “variable region” or “variable domain” refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (*See, e.g., Kindt et al. Kuby Immunology*, 6th ed., W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. *See, e.g., Portolano et al., J. Immunol.* 150:880-887 (1993); Clarkson *et al.*, *Nature* 352:624-628 (1991).

[0094] The term “hypervariable region” or “HVR” as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence (“complementarity determining regions” or “CDRs”) and/or form structurally defined loops (“hypervariable loops”) and/or contain the antigen-contacting residues (“antigen contacts”). Generally, 4-chain antibodies and antigen-binding antibody fragments thereof comprise six HVRs: three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). Generally, heavy-chain antibodies comprise three HVRs (HVR1, HVR2, HVR3).

[0095] A number of HVR delineations are in use and are encompassed herein. Exemplary HVRs for 4-chain antibodies and antigen-binding antibody fragments thereof herein include: (a) hypervariable loops occurring at amino acid residues 26-32 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987)); (b) CDRs occurring at amino acid residues 24-34 (L1), 50-56 (L2), 89-97 (L3), 31-35b (H1), 50-65 (H2), and 95-102 (H3) (Kabat *et al., Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991)); (c) antigen contacts occurring at amino acid residues 27c-36 (L1), 46-55 (L2), 89-96 (L3), 30-35b (H1), 47-58 (H2),

and 93-101 (H3) (MacCallum *et al. J. Mol. Biol.* 262: 732-745 (1996)); and (d) combinations of (a), (b), and/or (c), including HVR amino acid residues 46-56 (L2), 47-56 (L2), 48-56 (L2), 49-56 (L2), 26-35 (H1), 26-35b (H1), 49-65 (H2), 93-102 (H3), and 94-102 (H3).

[0096] Unless otherwise indicated, HVR residues and other residues in the variable domain (*e.g.*, framework, “FR,” residues) are numbered herein according to Kabat *et al.*, *supra*.

[0097] The amino acid residues of a single-domain antibody (such as VHH) can be numbered according to the general numbering for V_H domains given by Kabat *et al.* (“Sequence of proteins of immunological interest”, US Public Health Services, NIH Bethesda, Md., Publication No. 91), as applied to VHH domains from Camelids in the article of Riechmann and Muyldermans, J. Immunol. Methods 2000 Jun. 23; 240 (1-2): 185-195. According to this numbering, FR1 of a VHH comprises the amino acid residues at positions 1-30, CDR1 of a VHH comprises the amino acid residues at positions 31-35, FR2 of a VHH comprises the amino acids at positions 36-49, CDR2 of a VHH comprises the amino acid residues at positions 50-65, FR3 of a VHH comprises the amino acid residues at positions 66-94, CDR3 of a VHH comprises the amino acid residues at positions 95-102, and FR4 of a VHH comprises the amino acid residues at positions 103-113. In this respect, it should be noted that—as is well known in the art for V_H domains and for VHH domains—the total number of amino acid residues in each of the CDRs may vary and may not correspond to the total number of amino acid residues indicated by the Kabat numbering (that is, one or more positions according to the Kabat numbering may not be occupied in the actual sequence, or the actual sequence may contain more amino acid residues than the number allowed for by the Kabat numbering).

[0098] “Framework” or “FR” residues are those variable-domain residues other than the HVR residues as herein defined.

[0099] The term “chimeric” antibody refers to an antibody in which a portion of the heavy and/or light chain is identical to or derived from a particular source or species, while the remainder of the heavy and/or light chain is identical to or derived from a different source or species.

[0100] “Humanized” antibodies are antibodies that contain minimal sequence derived from the non-human antibody. Generally, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as camelid, mouse,

rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In certain aspects, a “humanized” antibody refers to a chimeric antibody comprising amino acid residues from non-human (*e.g.*, camelid) CDRs and amino acid residues from human FRs. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. For further details, see Jones *et al.*, *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

[0101] An “affinity-matured” antibody is one with one or more alterations in one or more CDRs thereof that result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody that does not possess those alteration(s). In some embodiments, an affinity-matured antibody has nanomolar or even picomolar affinities for the target antigen. Affinity-matured antibodies are produced by procedures known in the art. For example, random mutagenesis of CDR and/or framework residues is described by, for example: Barbas *et al.* *Proc Nat. Acad. Sci. USA* 91:3809-3813 (1994); Schier *et al.* *Gene* 169:147-155 (1995); Yelton *et al.* *J. Immunol.* 155:1994-2004 (1995); Jackson *et al.*, *J. Immunol.* 154(7):3310-9 (1995); and Hawkins *et al.*, *J. Mol. Biol.* 226:889-896 (1992).

[0102] “Percent (%) amino acid sequence identity” or “homology” with respect to the polypeptide and antibody sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the polypeptide being compared, after aligning the sequences considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid

sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0103] The term “specific binding” or “specifically binds” or is “specific for” a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a K_D for the target of at least about 10^{-4} M, alternatively at least about 10^{-5} M, alternatively at least about 10^{-6} M, alternatively at least about 10^{-7} M, alternatively at least about 10^{-8} M, alternatively at least about 10^{-9} M, alternatively at least about 10^{-10} M, alternatively at least about 10^{-11} M, alternatively at least about 10^{-12} M, or greater. In some embodiments, the term “specific binding” refers to binding where a molecule binds a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. K_D can be determined by methods known in the art, such as ELISA, surface plasmon resonance (SPR), fluorescence activated cell sorting (FACS) analysis, or radioimmunoprecipitation (RIA). Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target.

[0104] As used herein, “treatment,” “treating,” or “treat” are defined as an approach for obtaining beneficial or desired results including clinical results. For purposes of this application, beneficial or desired clinical results include, but are not limited to, one or more of the following: alleviating one or more symptoms resulting from a disease, diminishing the extent of a disease, stabilizing a disease (*e.g.*, preventing or delaying the worsening of a disease), preventing or delaying the spread (*e.g.*, metastasis) of a disease, preventing or delaying the recurrence of a disease, delay or slowing the progression of a disease, ameliorating a disease state, providing a remission (partial

or total) of a disease, decreasing the dose of one or more other medications required to treat a disease, delaying the progression of a disease, increasing or improving the quality of life, increasing weight gain, and/or prolonging survival. Also encompassed by “treatment” is a reduction of pathological consequence of a disease. The methods herein contemplate any one or more of these aspects of treatment. With respect to treatment of pain, such methods refer to reduction of pain. Reduction of pain includes, but is not limited to, reducing or ameliorating the generation of, sensation of, perception of, and/or effects of pain and/or its other symptoms; reducing the risk of occurrence of pain in a subject; impeding the initiation of pain; relieving pain, *i.e.*, causing regression of the pain and/or relieving one or more symptoms of pain; alleviating pain; lessening of pain; limiting pain; reducing pain including duration and/or intensity of pain; mitigating pain; blocking pain; and inhibiting the propagation of pain.

[0105] As used herein, the term “effective amount” or “therapeutically effective amount” of a substance (such as a CB2 antibody, construct, or composition) is at least the minimum concentration required to bring about a measurable improvement or prevention of a particular disorder or to achieve particular desired result or results. An effective amount herein may vary according to factors such as the disease state, the age, sex, and weight of the patient, and the ability of the substance to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects (*i.e.*, a therapeutic index). An effective amount can be administered in one or more administrations. As is understood in the clinical context, an effective amount may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable results may be or is achieved.

[0106] An “individual” or “subject” is a mammal. Mammals include, but are not limited to, domesticated animals (*e.g.*, cows, sheep, cats, dogs, and horses), primates (*e.g.*, humans and non-human primates such as rhesus and cynomolgus monkeys), rabbits, and rodents (*e.g.*, mice and rats). In some embodiments, the individual or subject is a human.

[0107] “Antibody effector functions” refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody,

and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.*, B cell receptors); and B cell activation. “Reduced or minimized” antibody effector function means that which is reduced by at least 50% (alternatively 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%) from the wild type or unmodified antibody. The determination of antibody effector function is readily determinable and measurable by one of ordinary skill in the art. In a preferred embodiment, the antibody effector functions of complement binding, complement dependent cytotoxicity and antibody dependent cytotoxicity are affected. In some embodiments, effector function is eliminated through a mutation in the constant region that eliminated glycosylation, *e.g.*, “effectorless mutation.” In one aspect, the effectorless mutation is an N297A or DANA mutation (D265A+N297A) in the C_H2 region. Shields *et al.*, *J. Biol. Chem.* 276 (9): 6591-6604 (2001). Alternatively, additional mutations resulting in reduced or eliminated effector function include: K322A and L234A/L235A (LALA). Alternatively, mutations resulting in reduced or eliminated effector function include: F234A and L235A (FALA) according to EU index. Alternatively, mutations resulting in reduced or eliminated effector function include: L234A, L235A, and P329G (LALAPG) according to EU index. Alternatively, mutations resulting in reduced or eliminated effector function include: M252Y, S254T, and T256E, (YTE) according to EU index. Alternatively, effector function can be reduced or eliminated through production techniques, such as expression in host cells that do not glycosylate (*e.g.*, *E. coli.*) or in which result in an altered glycosylation pattern that is ineffective or less effective at promoting effector function (*e.g.*, Shinkawa *et al.*, *J. Biol. Chem.* 278(5): 3466-3473 (2003).

[0108] As used herein, by “pharmaceutically acceptable” or “pharmacologically compatible” is meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0109] Half maximal effective concentration (EC_{50}) is a measure of the effectiveness of a substance (such as an antibody) which induces a specific biological or biochemical function. It indicates how much of a particular drug or other substance (such as an antibody) is needed to achieve a response halfway between the baseline and maximum after a specified exposure time in a given biological process. The values are typically expressed as molar concentration. EC_{50} is comparable to an “ IC_{50} ” for an antagonist drug or other substance. EC_{50} or IC_{50} can be measured by bioassays such as inhibition of ligand binding by FACS analysis (competition binding assay), cell based cytokine release assay, or amplified luminescent proximity homogeneous assay (AlphaLISA).

[0110] An “isolated” nucleic acid molecule encoding a construct, antibody, or antigen-binding fragment thereof described herein is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the environment in which it was produced. Preferably, the isolated nucleic acid is free of association with all components associated with the production environment. The isolated nucleic acid molecules encoding the polypeptides and antibodies described herein is in a form other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from nucleic acid encoding the polypeptides and antibodies described herein existing naturally in cells. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0111] The term “control sequences” refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

[0112] Nucleic acid is “operably linked” when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding

sequence if it is positioned so as to facilitate translation. Generally, “operably linked” means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

[0113] The term “vector,” as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as “expression vectors.”

[0114] The term “transfected” or “transformed” or “transduced” as used herein refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A “transfected” or “transformed” or “transduced” cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

[0115] The terms “host cell,” “host cell line,” and “host cell culture” are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include “transformants” and “transformed cells,” which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0116] The term “pharmaceutical formulation” or “pharmaceutical composition” refers to a preparation that is in such form as to permit the biological activity of the active ingredient to be effective, and that contains no additional components that are unacceptably toxic to a subject to which the formulation would be administered. Such formulations are sterile. A “sterile” formulation is aseptic or free from all living microorganisms and their spores.

[0117] Reference to “about” a value or parameter herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to “about”

a value or parameter herein includes (and describes) aspects that are directed to that value or parameter *per se*. For example, description referring to “about X” includes description of “X”.

[0118] It is understood that aspects and embodiments of the present application include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

[0119] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise.

[0120] The term “and/or” as used herein a phrase such as “A and/or B” is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term “and/or” as used herein a phrase such as “A, B, and/or C” is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

II. Anti-CB2 antibodies

[0121] Described herein, in various embodiments, are antibodies which specifically bind CB2 (*i.e.*, “anti-CB2 antibodies,” “CB2 antibodies,” “antibodies targeting CB2”). The CB2 antibodies described herein may comprise three CDRs from an immunoglobulin single variable domain (ISVD), or comprise an ISVD, or may be ISVDs. For instance, in some embodiments, the CB2 antibody described herein comprises a binding domain comprising three CDRs from an ISVD taught herein, *e.g.*, such as listed in **Table 1**. In the embodiments below, the structure and functionality of CB2 antibodies are presented in a modular fashion as anti-CB2 ISVDs. The recitation of an anti-CB2 ISVD alone is not intended to be limiting in scope, and encompasses, in a non-limiting fashion, CB2 antibodies which include, in whole or in part, three CDRs from an anti-CB2 ISVD or an anti-CB2 ISVD (*e.g.*, CDRs as shown in **Table 1**).

[0122] The CB2 antibodies described herein comprise an anti-CB2 ISVD. In some embodiments, the anti-CB2 ISVD specifically recognizes human CB2. In some embodiments, the anti-CB2 ISVD does not specifically recognize a CB1, such as a human CB1. In some embodiments, the anti-CB2 ISVD does not agonize a CB1, such as a human CB1. In some embodiments, the anti-CB2 ISVD specifically recognizes an epitope within human CB2. In some embodiments, the CB2 antibody comprises an ISVD that is a variable domain of the heavy chain of a heavy chain antibody (VHH). In some embodiments, the CB2 antibody comprises an ISVD and is a camelid. In some embodiments, the CB2 antibody comprises an ISVD that is chimeric. In some

embodiments, the CB2 antibody comprises an ISVD that is humanized. In some embodiments, the CB2 antibody comprises an ISVD that is partially humanized.

[0123] In some embodiments, the ISVD comprises a CDR1, CDR2, and/or CDR3 of an ISVD comprising the amino acid sequence of SEQ ID NO:55. In some embodiments, the ISVD comprises a CDR1, CDR2, and/or CDR3 of an ISVD comprising the amino acid sequence of SEQ ID NO:55, wherein the CDR1, CDR2, and CDR3 are defined according to IMGT (for explanation of IMGT, *see* Lefranc *et al.*, *Dev. Comparat. Immunol.* 27:55-77, 2003 and Ruiz *et al.*, *Nucleic Acids Res.* 29(1):207-9, 2001). In some embodiments, the CB2 antibody comprises an ISVD that comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:1. In some embodiments, the CB2 antibody comprises an ISVD that comprises a CDR2 comprising the amino acid sequence of SEQ ID NO:2. In some embodiments, the CB2 antibody comprises an ISVD that comprises a CDR3 comprising the amino acid sequence of SEQ ID NO:3. In some embodiments, the ISVD comprises a CDR1, CDR2, and/or CDR3 of an ISVD comprising the amino acid sequence of SEQ ID NO:55, wherein the CDR1, CDR2, and CDR3 are defined according to Kabat. In some embodiments, the ISVD comprises a CDR1, CDR2, and/or CDR3 of an ISVD comprising the amino acid sequence of SEQ ID NO:55, wherein the CDR1, CDR2, and CDR3 are defined according to Chothia.

[0124] In some embodiments, provided herein is a CB2 antibody comprising an ISVD that specifically binds a CB2, wherein the ISVD comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:1, a CDR1 comprising the amino acid sequence of SEQ ID NO:2, a CDR1 comprising the amino acid sequence of SEQ ID NO:3, wherein the CDR1, CDR2, and CDR3 are defined according to IMGT.

[0125] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:96 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:103 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0126] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:96 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:204 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0127] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:97 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:104 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0128] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:98 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:105 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0129] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:98 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:106 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0130] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:110 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:107 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0131] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:98 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:108 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0132] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:100 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:109 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0133] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:101 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:110 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0134] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:98 defined according to Kabat, a CDR2

comprising the amino acid sequence of SEQ ID NO:111 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0135] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:101 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:112 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0136] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:98 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:113 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0137] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:98 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:115 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0138] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:98 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:116 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0139] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:98 defined according to Kabat, a CDR2 comprising the amino acid sequence of SEQ ID NO:117 defined according to Kabat, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Kabat.

[0140] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:118 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0141] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:119 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0142] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:120 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0143] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:121 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0144] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:122 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0145] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:123 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0146] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:124 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0147] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:125 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0148] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:126 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0149] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2

comprising the amino acid sequence of SEQ ID NO:127 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0150] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:102 defined according to Chothia, a CDR2 comprising the amino acid sequence of SEQ ID NO:128 defined according to Chothia, and a CDR3 comprising the amino acid sequence of SEQ ID NO:129 defined according to Chothia.

[0151] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:345 defined according to IMGT.

[0152] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:346 defined according to IMGT.

[0153] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:347 defined according to IMGT.

[0154] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:348 defined according to IMGT.

[0155] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:349 defined according to IMGT.

[0156] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:350 defined according to IMGT.

[0157] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:351 defined according to IMGT.

[0158] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:352 defined according to IMGT.

[0159] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:353 defined according to IMGT.

[0160] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:354 defined according to IMGT.

[0161] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:355 defined according to IMGT.

[0162] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:356 defined according to IMGT.

[0163] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:357 defined according to IMGT.

[0164] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2

comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:358 defined according to IMGT.

[0165] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1 comprising the amino acid sequence of SEQ ID NO:248 defined according to IMGT, a CDR2 comprising the amino acid sequence of SEQ ID NO:2 defined according to IMGT, and a CDR3 comprising the amino acid sequence of SEQ ID NO:359 defined according to IMGT.

[0166] In some embodiments, the CB2 antibody comprises an ISVD comprising a CDR1, a CDR2, and a CDR3 of an antibody designated AB101, ABt107, ABt108, ABt109, ABt110, ABt111, ABt112, ABt113, ABt114, ABt115, ABt116, ABt117, ABt118, ABt119, ABt120, ABt121, ABt124, ABt247, ABt250, ABt251, ABt252, ABt253, ABt254, ABt105, ABt125, ABt126, ABt127, ABt128, ABt129, ABt130, ABt131, ABt132, ABt133, ABt134, ABt135, ABt136, ABt137, ABt138, ABt139, ABt140, ABt143, ABt276, ABt281, ABt285, ABhit_0426, ABhit_0427, ABhit_0428, ABhit_0429, ABhit_0430, ABhit_0431, ABhit_0432, ABhit_0433, ABhit_0434, ABhit_0435, ABhit_0436, ABhit_0437, ABhit_0438, ABhit_0439, or ABhit_0440 as defined in **Table 1**, below.

[0167] The sequences of the CDRs of the exemplary CB2 antibodies noted herein are provided in **Table 1**, below, and defined according to IMGT, Kabat, or Chothia. In some aspects of the teachings provided herein, the antibodies may be referenced with a leading zero (*e.g.*

ABt285=ABt0285). A skilled person in the art would readily appreciate that the CB2 antibodies comprising CDRs or variable domain sequences derived from the antibodies described herein, but wherein the CDRs or variable domain sequences are predicted using algorithms other than one of the IMGT, Kabat, or Chothia systems, are within the scope of the present invention.

Table 1. CB2 antibody sequences and CDRs (according to IMGT, Kabat, or Chothia).			
Antibody	CDR1	CDR2	CDR3
AB101 (SEQ ID NO:55)	GSIFSIMA (SEQ ID NO:1; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT)
	IMAMA (SEQ ID NO:96; Kabat)	GIDTGGGTYYAESVK G (SEQ ID NO:103; Kabat)	AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)

	GSIFSI (SEQ ID NO:102; Chothia)	GIDTGGGTY (SEQ ID NO:118; Chothia)	
ABt107 (SEQ ID NO:56)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAIG (SEQ ID NO:97; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) CIDTGGGTYADSVK G (SEQ ID NO:104; Kabat) CIDTGGGTY (SEQ ID NO:119; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt108 (SEQ ID NO:57)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTNYADSVK G (SEQ ID NO:105; Kabat) AIDTGGGTN (SEQ ID NO:120; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt109 (SEQ ID NO:58)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYADSVK G (SEQ ID NO:106; Kabat) AIDTGGGTY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)

ABt110 (SEQ ID NO:59)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMR (SEQ ID NO:99; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) CIDTGGGTNYADSVK A (SEQ ID NO:107; Kabat) CIDTGGGTN (SEQ ID NO:122; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt111 (SEQ ID NO:60)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYYADSVK G (SEQ ID NO:106; Kabat) AIDTGGGTYY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt112 (SEQ ID NO:61)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) TIDTGGGTYYADSVK G (SEQ ID NO:108; Kabat) TIDTGGGTYY (SEQ ID NO:123; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt113 (SEQ ID NO:62)	GSIFSIMA (SEQ ID NO:1; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT)

	IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	AIDTGGGTTYADSVK G (SEQ ID NO:106; Kabat) AIDTGGGTY (SEQ ID NO:121; Chothia)	AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt114 (SEQ ID NO:63)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTNYADSVK G (SEQ ID NO:105; Kabat) AIDTGGGTN (SEQ ID NO:120; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt115 (SEQ ID NO:64)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAIG (SEQ ID NO:97; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) CIDTGGGTTYADSVK G (SEQ ID NO:104; Kabat) CIDTGGGTY (SEQ ID NO:119; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt116 (SEQ ID NO:65)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMD (SEQ ID NO:100; Kabat)	IDTGGGT (SEQ ID NO:2; IMGT) GIDTGGGTNYADSVK G (SEQ ID NO:109; Kabat)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)

	GSIFSI (SEQ ID NO:102; Chothia)	GIDTGGGTN (SEQ ID NO:124; Chothia)	
ABt117 (SEQ ID NO:66)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMS (SEQ ID NO:101; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) DIDTGGGTYYADSVK G (SEQ ID NO:110; Kabat) DIDTGGGTYY (SEQ ID NO:125; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt118 (SEQ ID NO:67)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) TIDTGGGTYYADSVK G (SEQ ID NO:108; Kabat) TIDTGGGTYY (SEQ ID NO:123; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt119 (SEQ ID NO:68)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYYPDSVE G (SEQ ID NO:111; Kabat) AIDTGGGTYY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)

ABt120 (SEQ ID NO:69)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMS (SEQ ID NO:101; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) GIDTGGGTRYAGSVK G (SEQ ID NO:112; Kabat) GIDTGGGTR (SEQ ID NO:126; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt121 (SEQ ID NO:70)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTIYGDSVKD (SEQ ID NO:113; Kabat) AIDTGGGTI (SEQ ID NO:127; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt124 (SEQ ID NO:71)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTHYADSVK G (SEQ ID NO:114; Kabat) AIDTGGGTH (SEQ ID NO:128; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt247 (SEQ ID NO:72)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTIYGDSVKD (SEQ ID NO:113; Kabat)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT)

	GSIFSI (SEQ ID NO:102; Chothia)	AIDTGGGTI (SEQ ID NO:127; Chothia)	AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt250 (SEQ ID NO:73)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYYGDSVK G (SEQ ID NO:115; Kabat) AIDTGGGTY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt251 (SEQ ID NO:74)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYYGDSVK G (SEQ ID NO:115; Kabat) AIDTGGGTY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt252 (SEQ ID NO:75)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTIYGDSVKG (SEQ ID NO:116; Kabat) AIDTGGGTI (SEQ ID NO:127; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)

ABt253 (SEQ ID NO:76)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYYGDSVK D (SEQ ID NO:117; Kabat) AIDTGGGTYY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt254 (SEQ ID NO:77)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYYGDSVK G (SEQ ID NO:115; Kabat) AIDTGGGTYY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt105 (SEQ ID NO:78)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) GIDTGGGTYYAESVK G (SEQ ID NO:103; Kabat) GIDTGGGTYY (SEQ ID NO:118; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt125 (SEQ ID NO:79)	GSIFSIMA (SEQ ID NO:1; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT)

	IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	GIDTGGGTYAESVK G (SEQ ID NO:103; Kabat) GIDTGGGTY (SEQ ID NO:118; Chothia)	AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt126 (SEQ ID NO:80)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAIG (SEQ ID NO:97; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) CIDTGGGTYADSVK G (SEQ ID NO:104; Kabat) CIDTGGGTY (SEQ ID NO:119; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt127 (SEQ ID NO:81)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTNYADSVK G (SEQ ID NO:105; Kabat) AIDTGGGTN (SEQ ID NO:120; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt128 (SEQ ID NO:82)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYADSVK G (SEQ ID NO:106; Kabat)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)

	GSIFSI (SEQ ID NO:102; Chothia)	AIDTGGGTY (SEQ ID NO:121; Chothia)	
ABt129 (SEQ ID NO:83)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMR (SEQ ID NO:99; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) CIDTGGGTNYADSVK A (SEQ ID NO:107; Kabat) CIDTGGGTN (SEQ ID NO:122; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt130 (SEQ ID NO:84)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYYADSVK G (SEQ ID NO:106; Kabat) AIDTGGGTY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt131 (SEQ ID NO:85)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) TIDTGGGTYYADSVK G (SEQ ID NO:108; Kabat) TIDTGGGTY (SEQ ID NO:123; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)

ABt132 (SEQ ID NO:86)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYADSVK G (SEQ ID NO:106; Kabat) AIDTGGGTY (SEQ ID NO:121; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt133 (SEQ ID NO:87)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTNYADSVK G (SEQ ID NO:105; Kabat) AIDTGGGTN (SEQ ID NO:120; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt134 (SEQ ID NO:88)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAIG (SEQ ID NO:97; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) CIDTGGGTYADSVK G (SEQ ID NO:104; Kabat) CIDTGGGTY (SEQ ID NO:119; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt135 (SEQ ID NO:89)	GSIFSIMA (SEQ ID NO:1; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT)

	IMAMD (SEQ ID NO:100; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	GIDTGGGTNYADSVK G (SEQ ID NO:109; Kabat) GIDTGGGTN (SEQ ID NO:124; Chothia)	AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt136 (SEQ ID NO:90)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMS (SEQ ID NO:101; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) DIDTGGGTYYADSVK G (SEQ ID NO:110; Kabat) DIDTGGGTYY (SEQ ID NO:125; Chothia)	SGAIKYGSGRFDIKNY (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt137 (SEQ ID NO:91)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) TIDTGGGTYYADSVK G (SEQ ID NO:108; Kabat) TIDTGGGTYY (SEQ ID NO:123; Chothia)	SGAIKYGSGRFDIKNY (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt138 (SEQ ID NO:92)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTYYPDSVE G (SEQ ID NO:111; Kabat)	SGAIKYGSGRFDIKNY (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)

	GSIFSI (SEQ ID NO:102; Chothia)	AIDTGGGTY (SEQ ID NO:121; Chothia)	
ABt139 (SEQ ID NO:93)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMS (SEQ ID NO:101; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) GIDTGGGTRYAGSVK G (SEQ ID NO:112; Kabat) GIDTGGGTR (SEQ ID NO:126; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt140 (SEQ ID NO:94)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTIYGDSVKD (SEQ ID NO:113; Kabat) AIDTGGGTI (SEQ ID NO:127; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt143 (SEQ ID NO:95)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMG (SEQ ID NO:98; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) AIDTGGGTHYADSVK G (SEQ ID NO:114; Kabat) AIDTGGGTH (SEQ ID NO:128; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt276 (SEQ ID NO:201)	GSIFSIMA (SEQ ID NO:1; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT)

	IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	GIDTGGGTYADSVK G (SEQ ID NO:204; Kabat) GIDTGGGTY (SEQ ID NO:118; Chothia)	AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt281 (SEQ ID NO:202)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) GIDTGGGTYAESVK G (SEQ ID NO:103; Kabat) GIDTGGGTY (SEQ ID NO:118; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABt285 (SEQ ID NO:203)	GSIFSIMA (SEQ ID NO:1; IMGT) IMAMA (SEQ ID NO:96; Kabat) GSIFSI (SEQ ID NO:102; Chothia)	IDTGGGT (SEQ ID NO:2; IMGT) GIDTGGGTYADSVK G (SEQ ID NO:204; Kabat) GIDTGGGTY (SEQ ID NO:118; Chothia)	SGAIKYGSGRFDIKN Y (SEQ ID NO:3; IMGT) AIKYGSGRFDIKNY (SEQ ID NO:129; Kabat/Chothia)
ABhit_0426 (SEQ ID NO:330)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	VVIKYGSGDFDIKTY (SEQ ID NO:345; IMGT)
ABhit_0427 (SEQ ID NO:331)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	YVVIKYGSGDFDIKV Y (SEQ ID NO:346; IMGT)

ABhit_0428 (SEQ ID NO:332)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	LFIKYGSGDFDIKTY (SEQ ID NO:347; IMGT)
ABhit_0429 (SEQ ID NO:333)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	IVIKYGSGDFDIKTY (SEQ ID NO:348; IMGT)
ABhit_0430 (SEQ ID NO:334)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	LVIKYGSGDFDIKTY (SEQ ID NO:349; IMGT)
ABhit_0431 (SEQ ID NO:335)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	LFAIKYGSGDFDIKT Y (SEQ ID NO:350; IMGT)
ABhit_0432 (SEQ ID NO:336)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	FVAIKYGSGDFDIKV Y (SEQ ID NO:351; IMGT)
ABhit_0433 (SEQ ID NO:337)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	FVVIKYGSGDFDIKV Y (SEQ ID NO:352; IMGT)
ABhit_0434 (SEQ ID NO:338)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	LVVIKYGSGDFDIKT Y (SEQ ID NO:353; IMGT)
ABhit_0435 (SEQ ID NO:339)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	YAIKYGSGDFDIKV Y (SEQ ID NO:354; IMGT)
ABhit_0436 (SEQ ID NO:340)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	IAIKYGSGDFDIKTY (SEQ ID NO:355; IMGT)
ABhit_0437 (SEQ ID NO:341)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	LFAIKYGSGDFDIKTF (SEQ ID NO:356; IMGT)

ABhit_0438 (SEQ ID NO:342)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	LFAIKYGSGLFDIKTY (SEQ ID NO:357; IMGT)
ABhit_0439 (SEQ ID NO:343)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	LFAIKYGSGDFDIKT A (SEQ ID NO:358; IMGT)
ABhit_0440 (SEQ ID NO:344)	GSIFSIMG (SEQ ID NO:248; IMGT)	IDTGGGT (SEQ ID NO:2; IMGT)	LFAIKYGSGDFDIKG Y (SEQ ID NO:359; IMGT)

[0168] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:1, or a variant thereof comprising up to 3 (such as any of 1, 2, or 3) amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO:2, or a variant thereof comprising up to 3 (such as any of 1, 2, or 3) amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO:3, or a variant thereof comprising up to 3 (such as any of 1, 2, or 3) amino acid substitutions, wherein the CDR1, CDR2, and CDR3 are defined according to IMGT. In some embodiments, the CB2 antibody comprises an ISVD having 1, 2, or 3 amino acid substitutions in any one of the CDR1 sequences (*e.g.*, SEQ ID NO:1) described herein. In some embodiments, the ISVD comprises 1, 2, or 3 amino acid substitution at positions 27, 28, 29, 31, 32 or 33 with respect to SEQ ID NO:1, wherein the amino acid numbering is according to IMGT. In some embodiments, the CB2 antibody comprises an ISVD having 1, 2, or 3 amino acid substitutions in any one of the CDR3 sequences (*e.g.*, SEQ ID NO:3) described herein. In some embodiments, the ISVD comprises an A or P at position 15, F or W at position 52, A or S at position 54, A or G at position 55, S or W at position 103, and/or S or W at position 118, wherein the amino acid numbering is according to IMGT. In some embodiments, the CB2 antibody comprises an ISVD having 0, 1, 2, or 3 amino acid substitutions at one or more of IMGT positions selected from positions 15, 52, 54, 55, 103, and 118, wherein a substitution at position 15, if present, is A or P, a substitution at position 52, if present, is F or W, a substitution at position 54, if present, is A or S, a substitution at position 55, if present, is A or G, a substitution at position 103, if present, is S or W, and a substitution at position 118, if present, is

S or W; 0, 1, 2, or 3 substitutions in any one of the CDR3 sequences (*e.g.*, SEQ ID NO:3), wherein none of the substitutions, if present are to C or M; and 0, 1, 2, or 3 amino acid substitutions at positions 27, 28, 29, 31, 32, or 33 with respect to SEQ ID NO:1 defined according to IMGT, wherein none of the substitutions, if present, are to C or M.

[0169] In some embodiments, the CB2 antibody comprises a binding domain that specifically binds a CB2, wherein the binding domain comprises a CDR3 having the amino acid formula C1-C2-C3-I-K-Y-G-S-G-C4-F-D-I-K-C5-C6, wherein C1 is selected from L, I, V, Y, or F; wherein C2 is selected from F, A, or V; wherein C3 is selected from A, I, or V; wherein C4 is selected from D or L; wherein C5 is selected from G, T, or V; and wherein C6 is selected from Y, A, or F. In some embodiments, the CB2 antibody comprises a CDR1 of SEQ ID NO:248. In some embodiments, the CB2 antibody comprises a CDR2 of SEQ ID NO:2.

[0170] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2, wherein the ISVD comprises a CDR3 having the amino acid formula C1-C2-C3-I-K-Y-G-S-G-C4-F-D-I-K-C5-C6, wherein C1 is selected from L, I, V, Y, or F; wherein C2 is selected from F, A, or V; wherein C3 is selected from A, I, or V; wherein C4 is selected from D or L; wherein C5 is selected from G, T, or V; and wherein C6 is selected from Y, A, or F. In some embodiments, the CB2 antibody comprises a CDR1 of SEQ ID NO:248. In some embodiments, the CB2 antibody comprises a CDR2 of SEQ ID NO:2.

[0171] In some embodiments, the CB2 antibody comprises a binding domain that specifically binds a CB2, wherein the binding domain comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:248; a CDR2 comprising the amino acid sequence of SEQ ID NO:2; and a CDR3 having the amino acid formula C1-C2-C3-I-K-Y-G-S-G-C4-F-D-I-K-C5-C6, wherein C1 is selected from L, I, V, Y, or F; wherein C2 is selected from F, A, or V; wherein C3 is selected from A, I, or V; wherein C4 is selected from D or L; wherein C5 is selected from G, T, or V; and wherein C6 is selected from Y, A, or F, wherein the CDR1, CDR2, and CDR3 are defined according to IMGT. In some embodiments, the ISVD comprises: a CDR1 comprising the amino acid sequence of SEQ ID NO:248; a CDR2 comprising the amino acid sequence of SEQ ID NO:2; and a CDR3 comprising the amino acid sequence selected from the group consisting of SEQ ID NOS:345-359.

[0172] In some embodiments, provided is a CB2 antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises: a CDR1

comprising the amino acid sequence of SEQ ID NO:248; a CDR2 comprising the amino acid sequence of SEQ ID NO:2; and a CDR3 having the amino acid formula C1-C2-C3-I-K-Y-G-S-G-C4-F-D-I-K-C5-C6, wherein C1 is selected from L, I, V, Y, or F; wherein C2 is selected from F, A, or V; wherein C3 is selected from A, I, or V; wherein C4 is selected from D or L; wherein C5 is selected from G, T, or V; and wherein C6 is selected from Y, A, or F, wherein the CDR1, CDR2, and CDR3 are defined according to IMGT. In some embodiments, the ISVD comprises: a CDR1 comprising the amino acid sequence of SEQ ID NO:248; a CDR2 comprising the amino acid sequence of SEQ ID NO:2; and a CDR3 comprising the amino acid sequence selected from the group consisting of SEQ ID NOS:345-359.

[0173] The CB2 antibodies described herein comprise an ISVD comprising four framework regions (FRs). The CB2 antibodies described herein may comprise any suitable sequences for the framework regions. In some embodiments, the ISVD comprises a framework region 1 (FR1) of any one of SEQ ID NOS: 4-15. In some embodiments, the ISVD comprises a FR2 of any one of SEQ ID NOS:16-30. In some embodiments, the ISVD comprises a FR3 of any one of SEQ ID NOS: 31-48. In some embodiments, the ISVD comprises a FR4 of any one of SEQ ID NOS: 49-54. In some embodiments, the ISVD comprises a FR3 of SEQ ID NO:200. In some embodiments, the FR1, FR2, FR3 and FR4 are defined according to IMGT.

[0174] In some embodiments, the ISVD comprises a framework region 1 (FR1) of any one of SEQ ID NOS:4-15, or a variant thereof comprising up to 5 (such as any of about 1, 2, 3, 4, or 5) amino acid substitutions. In some embodiments, the ISVD comprises a FR2 of any one of SEQ ID NOS:16-30, or a variant thereof comprising up to 5 (such as any of about 1, 2, 3, 4, or 5) amino acid substitutions. In some embodiments, the ISVD comprises a FR3 of any one of SEQ ID NOS:31-48, or a variant thereof comprising up to 5 (such as any of about 1, 2, 3, 4, or 5) amino acid substitutions. In some embodiments, the ISVD comprises a FR3 of SEQ ID NO:200, or a variant thereof comprising up to 5 (such as any of about 1, 2, 3, 4, or 5) amino acid substitutions. In some embodiments, the ISVD comprises a FR4 of any one of SEQ ID NOS:49-54, or a variant thereof comprising up to 5 (such as any of about 1, 2, 3, 4, or 5) amino acid substitutions. In some embodiments, the FR1, FR2, FR3 and FR4 are defined according to IMGT.

[0175] In some embodiments, the ISVD comprises a framework 1 region (FR1) of any one of SEQ ID NOS:4-15, a FR2 of any one of SEQ ID NOS:16-30, a FR3 of any one of SEQ ID

NOs:31-48, and a FR4 of any one of SEQ ID NOs:49-54. In some embodiments, the ISVD comprises a framework 1 region (FR1) of any one of SEQ ID NOs:4-15, a FR2 of any one of SEQ ID NOs:16-30, a FR3 of SEQ ID NO:200, and a FR4 of any one of SEQ ID NOs:49-54. In some embodiments, the ISVD comprises a FR1 of any one of SEQ ID NOs:4-15 or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of any one of SEQ ID NOs:16-30, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of any one of SEQ ID NOs:31-48 or 200, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; and a FR4 of any one of SEQ ID NOs:49-54, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions.

[0176] In some embodiments, the CB2 antibody comprises an ISVD comprising a FR1, a FR2, a FR3, and a FR4 of an antibody designated ABt101, ABt107, ABt108, ABt109, ABt110, ABt111, ABt112, ABt113, ABt114, ABt115, ABt116, ABt117, ABt118, ABt119, ABt120, ABt121, ABt124, ABt247, ABt250, ABt251, ABt252, ABt253, ABt254, ABt105, ABt125, ABt126, ABt127, ABt128, ABt129, ABt130, ABt131, ABt132, ABt133, ABt134, ABt135, ABt136, ABt137, ABt138, ABt139, ABt140, ABt143, ABt276, ABt281, or ABt285 as defined in **Table 2**, below.

[0177] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a FR1 of SEQ ID NO:4, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of SEQ ID NO:16, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of SEQ ID NO:31, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; and a FR4 of SEQ ID NO:49, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions, wherein FR1, FR2, FR3, and FR4 are according to IMGT.

[0178] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a FR1 of SEQ ID NO:4, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of SEQ ID NO:16, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of SEQ ID NO:200, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; and a FR4 of SEQ ID NO:49, or a variant thereof comprising up to 5 (such as any

of 1, 2, 3, 4, or 5) amino acid substitutions, wherein FR1, FR2, FR3, and FR4 are according to IMGT.

[0179] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a FR1 of SEQ ID NO:14, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of SEQ ID NO:29, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of SEQ ID NO:43, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; and a FR4 of SEQ ID NO:54, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions, wherein FR1, FR2, FR3, and FR4 are according to IMGT.

[0180] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a FR1 of SEQ ID NO:15, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of SEQ ID NO:23, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of SEQ ID NO:45, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; and a FR4 of SEQ ID NO:54, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions, wherein FR1, FR2, FR3, and FR4 are according to IMGT.

[0181] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a FR1 of SEQ ID NO:15, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of SEQ ID NO:23, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of SEQ ID NO:45, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; and a FR4 of SEQ ID NO:54, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions, wherein FR1, FR2, FR3, and FR4 are according to IMGT.

[0182] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a FR1 of SEQ ID NO:15, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of SEQ ID NO:23, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of SEQ ID NO:46, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid

substitutions; and a FR4 of SEQ ID NO:54, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions, wherein FR1, FR2, FR3, and FR4 are according to IMGT.

[0183] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a FR1 of SEQ ID NO:15, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of SEQ ID NO:29, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of SEQ ID NO:47, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; and a FR4 of SEQ ID NO:54, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions, wherein FR1, FR2, FR3, and FR4 are according to IMGT.

[0184] In some embodiments, the CB2 antibody comprises an ISVD that specifically binds a CB2 and comprises a FR1 of SEQ ID NO:15, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR2 of SEQ ID NO:29, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; a FR3 of SEQ ID NO:45, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions; and a FR4 of SEQ ID NO:54, or a variant thereof comprising up to 5 (such as any of 1, 2, 3, 4, or 5) amino acid substitutions, wherein FR1, FR2, FR3, and FR4 are according to IMGT.

[0185] In some embodiments, the CB2 antibody comprises an ISVD comprising a FR1, a FR2, a FR3, and a FR4, wherein the ISVD comprises one or more amino acid residues selected from the group consisting of V5, Q44, Y66, G74, R80, A83, and L87 in one or more of the framework regions, wherein amino acid numbering is according to IMGT.

[0186] In some embodiments, the framework regions of the CB2 antibody comprises one or more amino acid substitutions selected from the group consisting of: (1) at amino acid position 5 (*e.g.*, substitution to V); (2) at amino acid position 44 (*e.g.*, substitution to Q); (3) at amino acid position 66 (*e.g.*, substitution to Y); (4) at amino acid position 74 (*e.g.*, substitution to G); (5) at amino acid position 80 (*e.g.*, substitution to R); (6) at amino acid position 83 (*e.g.*, substitution to A); and (7) at amino acid position 87 (*e.g.*, substitution to L), wherein amino acid positions are according to IMGT numbering. In some embodiments, the CB2 antibody comprises one or more amino acid substitutions in the framework regions, wherein the one or more amino acid

substitutions comprise M5V, wherein amino acid positions are according to IMGT numbering. In some embodiments, the CB2 antibody comprises one or more amino acid substitutions in the framework regions, wherein the one or more amino acid substitutions comprise M5V, R44Q, and I66Y, wherein amino acid positions are according to IMGT numbering. In some embodiments, the CB2 antibody comprises one or more amino acid substitutions in the framework regions, wherein the one or more amino acid substitutions comprise M5V, R44Q, I66Y, and D65G, wherein amino acid positions are according to IMGT numbering. In some embodiments, the CB2 antibody comprises one or more amino acid substitutions in the framework regions, wherein the one or more amino acid substitutions comprise M5V, R44Q, and D65G, wherein amino acid positions are according to IMGT numbering. In some embodiments, the CB2 antibody comprises one or more amino acid substitutions in the framework regions, wherein the one or more amino acid substitutions comprise M5V and I66Y, wherein amino acid positions are according to IMGT numbering. In some embodiments, the CB2 antibody comprises one or more amino acid substitutions in the framework regions, wherein the one or more amino acid substitutions comprise M5V, I66Y, and D74G, wherein amino acid positions are according to IMGT numbering. In some embodiments, the CB2 antibody comprises one or more amino acid substitutions in the framework regions, wherein the one or more amino acid substitutions comprise N80R, S83A, and A87L, wherein amino acid positions are according to IMGT numbering. In some embodiments, the CB2 antibody comprises a CDR1 according to SEQ ID NO:1, a CDR2 according to SEQ ID NO:2, a CDR3 according to SEQ ID NO:3, and comprises a framework region comprising the amino acid V at position 5, wherein amino acid numbering is according to IMGT. In some embodiments, the CB2 antibody comprises a CDR1 according to SEQ ID NO:1, a CDR2 according to SEQ ID NO:2, a CDR3 according to SEQ ID NO:3, and comprises a framework region comprising the amino acids V at position 5, Q at position 44, and Y at position 66, wherein amino acid numbering is according to IMGT. In some embodiments, the CB2 antibody comprises a CDR1 according to SEQ ID NO:1, a CDR2 according to SEQ ID NO:2, a CDR3 according to SEQ ID NO:3, and comprises a framework region comprising the amino acids V at position 5, Q at position 44, Y at position 66, and G at position 74, wherein amino acid numbering is according to IMGT. In some embodiments, the CB2 antibody comprises a CDR1 according to SEQ ID NO:1, a CDR2 according to SEQ ID NO:2, a CDR3 according to SEQ ID NO:3, and comprises a framework region comprising the amino acids V at

position 5, Q at position 44, and G at position 74, wherein amino acid numbering is according to IMGT. In some embodiments, the CB2 antibody comprises a CDR1 according to SEQ ID NO:1, a CDR2 according to SEQ ID NO:2, a CDR3 according to SEQ ID NO:3, and comprises a framework region comprising the amino acids V at position 5 and Y at position 66, wherein amino acid numbering is according to IMGT. In some embodiments, the CB2 antibody comprises a CDR1 according to SEQ ID NO:1, a CDR2 according to SEQ ID NO:2, a CDR3 according to SEQ ID NO:3, and comprises a framework region comprising the amino acids V at position 5, Y at position 66, and G at position 74, wherein amino acid numbering is according to IMGT. In some embodiments, the CB2 antibody comprises a CDR1 according to SEQ ID NO:1, a CDR2 according to SEQ ID NO:2, a CDR3 according to SEQ ID NO:3, and comprises a framework region comprising the amino acids R at position 80, A at position 83, and L at position 87, wherein amino acid numbering is according to IMGT.

Table 2. CB2 antibody sequences and framework regions.

Antibody	FR1	FR2	FR3	FR4
AB101 (SEQ ID NO:55)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	MAWYRQAPG KEREWVSG (SEQ ID NO:16)	YYAESVKGRFTISNDN SKNTAYLQMNSLKPE DTAVYYC (SEQ ID NO:31)	WGQGTQVT VSS (SEQ ID NO:49)
ABt107 (SEQ ID NO:56)	QVQLVESGGGL VQPGGSLRLSCA AS (SEQ ID NO:5)	IGWFRQAPGK EREGVSC (SEQ ID NO:17)	YYADSVKGRFTISRDN AKNTVYLMNSLKPE DTAVYYC (SEQ ID NO:32)	YCAGTQVT VSS (SEQ ID NO:50)
ABt108 (SEQ ID NO:57)	QVQLVESGGGL VQAGGSLRLSCA AS (SEQ ID NO:6)	MGWYRQAPG KERELVAA (SEQ ID NO:18)	NYADSVKGRFTISRDN AKNTVYLMNSLKPE DTAVYYC (SEQ ID NO:33)	YCNGTQVT VSS (SEQ ID NO:51)
ABt109 (SEQ ID NO:58)	QVQLVESGGGL VQAGGSLRHSC AAS (SEQ ID NO:7)	MGWYRQAPG KERELVAA (SEQ ID NO:18)	YYADSVKGQFTISRDN NAKNTLYLMNSLKPE GDTAVYYC (SEQ ID NO:34)	WGQGTQVT VSS (SEQ ID NO:49)

ABt110 (SEQ ID NO:59)	QVQLVESVGGL VQDGGSLRLSCA AS (SEQ ID NO:8)	MRWFRQAPGK EREWVSC (SEQ ID NO:19)	NYADSVKARFTISRDN AKNTLYLQMNSLKPE DTAVYYC (SEQ ID NO:35)	WGQGTQVT VSS (SEQ ID NO:49)
ABt111 (SEQ ID NO:60)	QVQLVESGGGL VQAGGSLRLSCA AS (SEQ ID NO:6)	MAWFRQAPGK EREFVAA (SEQ ID NO:20)	YYADSVKGRFTISRDN AKNTVFLQMNSLKPE DTAVYYC (SEQ ID NO:36)	WGQGTQVT VSS (SEQ ID NO:49)
ABt112 (SEQ ID NO:61)	QVQLQESGGGL VQAGGSLRLSCA AS (SEQ ID NO:9)	MGWYRQAPG KEREFVAT (SEQ ID NO:21)	YYADSVKGRFTISRDN AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:32)	WGQGTQVT VSS (SEQ ID NO:49)
ABt113 (SEQ ID NO:62)	QVQLVESGGGL AQAGGSLRLSCA AS (SEQ ID NO:10)	MAWFRQPPGK EREFVAA (SEQ ID NO:22)	YYADSVKGRFTISRDN AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:32)	WGQGTQVT VSS (SEQ ID NO:49)
ABt114 (SEQ ID NO:63)	QVQLVESGGGL VQAGGSLRLSCA AS (SEQ ID NO:6)	MGWFRQAPGK EREFVAA (SEQ ID NO:23)	NYADSVKGRFTISRDN SKNTQYLQMNSLKPE DTAVYYC (SEQ ID NO:37)	WGQGTQVT VSS (SEQ ID NO:49)
ABt115 (SEQ ID NO:64)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	IGWFRQAPGK EREGVSC (SEQ ID NO:17)	YYADSVKGRFTISRDN AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:32)	YGKGTQVT VSS (SEQ ID NO:52)
ABt116 (SEQ ID NO:65)	DVQLVESGGGL VQPGGSLRLSCA YS (SEQ ID NO:11)	MDWYRQAPG KERELVAG (SEQ ID NO:24)	NYADSVKGRFTISRDS AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:38)	WGQGTQVT VSS (SEQ ID NO:49)
ABt117 (SEQ ID NO:66)	QVQLVESGGGL VQPGGSLRLSCA AS (SEQ ID NO:5)	MSWVRQAPGK GLEWVSD (SEQ ID NO:25)	YYADSVKGRFTISRDN AKNTLYLQMNSLKPE	WGQGTQVT VSS (SEQ ID NO:49)

			DTAVYYC (SEQ ID NO:39)	
ABt118 (SEQ ID NO:67)	QVQLQESGGGL VQPGGSLRLSCA AS (SEQ ID NO:12)	MGWYRQAPG KEHELVAT (SEQ ID NO:26)	YYADSVKGRFTISRDN AKNTLYLQMNSLKPE DTAMYYC (SEQ ID NO:40)	WGQGTQVT VSS (SEQ ID NO:49)
ABt119 (SEQ ID NO:68)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	MGWFRQAPGK GRELVAA (SEQ ID NO:27)	YYPDSVEGRFTISRDN AKRMVYLQMNSLRA EDTAVYYC (SEQ ID NO:41)	WGQGTQVT VSS (SEQ ID NO:49)
ABt120 (SEQ ID NO:69)	EVQLVESGGGLV QTGGSLRLSCAA S (SEQ ID NO:13)	MSWVRQAPGK GLEWVSG (SEQ ID NO:28)	RYAGSVKGRFTISRDN AKNMLYLQMNSLKPE DTAVYYC (SEQ ID NO:42)	RGQGTQVT VSS (SEQ ID NO:53)
ABt121 (SEQ ID NO:70)	EVQLMESGGGL VQAGGSLRLSCA AS (SEQ ID NO:14)	MGWFRRAPGK EREFVAA (SEQ ID NO:29)	IYGDSVKDRFTISRDN AKNTLYLQMNSLKPE DTAVYTC (SEQ ID NO:43)	SGQGTQVT VSS (SEQ ID NO:54)
ABt124 (SEQ ID NO:71)	QVQLVESGGGL VQAGGSLRLSCA AS (SEQ ID NO:6)	MGWFRQAPGK ERESVAA (SEQ ID NO:30)	HYADSVKGRFTISRDN SKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:44)	WGQGTQVT VSS (SEQ ID NO:49)
ABt247 (SEQ ID NO:72)	EVQLVESGGGLV QAGGSLRLSCAA S (SEQ ID NO:15)	MGWFRRAPGK EREFVAA (SEQ ID NO:29)	IYGDSVKDRFTISRDN AKNTLYLQMNSLKPE DTAVYTC (SEQ ID NO:43)	SGQGTQVT VSS (SEQ ID NO:54)
ABt250 (SEQ ID NO:73)	EVQLVESGGGLV QAGGSLRLSCAA S (SEQ ID NO:15)	MGWFRQAPGK EREFVAA (SEQ ID NO:23)	YYGDSVKGRFTISRDN AKNTLYLQMNSLKPE DTAVYTC (SEQ ID NO:45)	SGQGTQVT VSS (SEQ ID NO:54)

ABt251 (SEQ ID NO:74)	EVQLVESGGGLV QAGGSLRLSCAA S (SEQ ID NO:15)	MGWFRQAPGK EREFVAA (SEQ ID NO:23)	YYGDSVKGRFTISRDN AKNTLYLQMNSLKPE DTAVYTC (SEQ ID NO:45)	SGQGTQVT VSS (SEQ ID NO:54)
ABt252 (SEQ ID NO:75)	EVQLVESGGGLV QAGGSLRLSCAA S (SEQ ID NO:15)	MGWFRQAPGK EREFVAA (SEQ ID NO:23)	IYGDSVKGRFTISRDN AKNTLYLQMNSLKPE DTAVYTC (SEQ ID NO:46)	SGQGTQVT VSS (SEQ ID NO:54)
ABt253 (SEQ ID NO:76)	EVQLVESGGGLV QAGGSLRLSCAA S (SEQ ID NO:15)	MGWFRRAPGK EREFVAA (SEQ ID NO:29)	YYGDSVKDRFTISRDN AKNTLYLQMNSLKPE DTAVYTC (SEQ ID NO:47)	SGQGTQVT VSS (SEQ ID NO:54)
ABt254 (SEQ ID NO:77)	EVQLVESGGGLV QAGGSLRLSCAA S (SEQ ID NO:15)	MGWFRRAPGK EREFVAA (SEQ ID NO:29)	YYGDSVKGRFTISRDN AKNTLYLQMNSLKPE DTAVYTC (SEQ ID NO:45)	SGQGTQVT VSS (SEQ ID NO:54)
ABt105 (SEQ ID NO:78)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	MAWYRQAPG KEREWVSG (SEQ ID NO:16)	YYAESVKGRFTISNDN SKNTAYLQMNSLKPE DTAVYYC (SEQ ID NO:31)	WGQGTQVT VSS (SEQ ID NO:49)
ABt125 (SEQ ID NO:79)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	MAWYRQAPG KEREWVSG (SEQ ID NO:16)	YYAESVKGRFTISRDN AKNTLYLQMNSLKPE DTAVYYC (SEQ ID NO:48)	WGQGTQVT VSS (SEQ ID NO:49)
ABt126 (SEQ ID NO:80)	QVQLVESGGGL VQPGGSLRLSCA AS (SEQ ID NO:5)	IGWFRQAPGK EREGVSC (SEQ ID NO:17)	YYADSVKGRFTISRDN AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:32)	YCAGTQVT VSS (SEQ ID NO:50)
ABt127 (SEQ ID NO:81)	QVQLVESGGGL VQAGGSLRLSCA AS (SEQ ID NO:6)	MGWYRQAPG KERELVAA (SEQ ID NO:18)	NYADSVKGRFTISRDN AKNTVYLQMNSLKPE	YCNGTQVT VSS (SEQ ID NO:51)

			DTAVYYC (SEQ ID NO:33)	
ABt128 (SEQ ID NO:82)	QVQLVESGGGL VQAGGSLRHSC AAS (SEQ ID NO:7)	MGWYRQAPG KERELVAA (SEQ ID NO:18)	YYADSVKGQFTISRD NAKNTLYLQMNSLKPE GDTAVYYC (SEQ ID NO:34)	WGQGTQVT VSS (SEQ ID NO:49)
ABt129 (SEQ ID NO:83)	QVQLVESVGGGL VQDGGSLRLSCA AS (SEQ ID NO:8)	MRWFRQAPGK EREWVSC (SEQ ID NO:19)	NYADSVKARFTISRDN AKNTLYLQMNSLKPE DTAVYYC (SEQ ID NO:35)	WGQGTQVT VSS (SEQ ID NO:49)
ABt130 (SEQ ID NO:84)	QVQLVESGGGL VQAGGSLRLSCA AS (SEQ ID NO:6)	MAWFRQAPGK EREFVAA (SEQ ID NO:20)	YYADSVKGRFTISRDN AKNTVFLQMNSLKPE DTAVYYC (SEQ ID NO:36)	WGQGTQVT VSS (SEQ ID NO:49)
ABt131 (SEQ ID NO:85)	QVQLQESGGGL VQAGGSLRLSCA AS (SEQ ID NO:9)	MGWYRQAPG KEREFVAT (SEQ ID NO:21)	YYADSVKGRFTISRDN AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:32)	WGQGTQVT VSS (SEQ ID NO:49)
ABt132 (SEQ ID NO:86)	QVQLVESGGGL AQAGGSLRLSCA AS (SEQ ID NO:10)	MAWFRQPPGK EREFVAA (SEQ ID NO:22)	YYADSVKGRFTISRDN AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:32)	WGQGTQVT VSS (SEQ ID NO:49)
ABt133 (SEQ ID NO:87)	QVQLVESGGGL VQAGGSLRLSCA AS (SEQ ID NO:6)	MGWFRQAPGK EREFVAA (SEQ ID NO:23)	NYADSVKGRFTISRDN SKNTQYLQMNSLKPE DTAVYYC (SEQ ID NO:37)	WGQGTQVT VSS (SEQ ID NO:49)
ABt134 (SEQ ID NO:88)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	IGWFRQAPGK EREGVSC (SEQ ID NO:17)	YYADSVKGRFTISRDN AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:32)	YGKGTQVT VSS (SEQ ID NO:52)

ABt135 (SEQ ID NO:89)	DVQLVESGGGL VQPGGSLRLSCA YS (SEQ ID NO:11)	MDWYRQAPG KERELVAG (SEQ ID NO:24)	NYADSVKGRFTISRDS AKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:38)	WGQGTQVT VSS (SEQ ID NO:49)
ABt136 (SEQ ID NO:90)	QVQLVESGGGL VQPGGSLRLSCA AS (SEQ ID NO:5)	MSWVRQAPGK GLEWVSD (SEQ ID NO:25)	YYADSVKGRFTISRDN AKNTLYLQMNSLKPE DTAVYYC (SEQ ID NO:39)	WGQGTQVT VSS (SEQ ID NO:49)
ABt137 (SEQ ID NO:91)	QVQLQESGGGL VQPGGSLRLSCA AS (SEQ ID NO:12)	MGWYRQAPG KEHELVAT (SEQ ID NO:26)	YYADSVKGRFTISRDN AKNTLYLQMNSLKPE DTAMYCYC (SEQ ID NO:40)	WGQGTQVT VSS (SEQ ID NO:49)
ABt138 (SEQ ID NO:92)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	MGWFRQAPGK GRELVAA (SEQ ID NO:27)	YYPDSVEGRFTISRDN AKRMVYLQMNSLRA EDTAVYYC (SEQ ID NO:41)	WGQGTQVT VSS (SEQ ID NO:49)
ABt139 (SEQ ID NO:93)	EVQLVESGGGLV QTGGSLRLSCAA S (SEQ ID NO:13)	MSWVRQAPGK GLEWVSG (SEQ ID NO:28)	RYAGSVKGRFTISRDN AKNMLYLQMNSLKPE DTAVYYC (SEQ ID NO:42)	RGQGTQVT VSS (SEQ ID NO:53)
ABt140 (SEQ ID NO:94)	EVQLMESGGGL VQAGGSLRLSCA AS (SEQ ID NO:14)	MGWFRRAPGK EREFVAA (SEQ ID NO:29)	IYGDSVKDRFTISRDN AKNTLYLQMNSLKPE DTAVYTC (SEQ ID NO:43)	SGQGTQVT VSS (SEQ ID NO:54)
ABt143 (SEQ ID NO:95)	QVQLVESGGGL VQAGGSLRLSCA AS (SEQ ID NO:6)	MGWFRQAPGK ERESVAA (SEQ ID NO:30)	HYADSVKGRFTISRDN SKNTVYLQMNSLKPE DTAVYYC (SEQ ID NO:44)	WGQGTQVT VSS (SEQ ID NO:49)
ABt276 (SEQ ID NO:201)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	MAWYRQAPG KEREWVSG (SEQ ID NO:16)	YYADSVKGRFTISRDN SKNTLYLQMNSLKPE	WGQGTQVT VSS (SEQ ID NO:49)

			DTAVYYC (SEQ ID NO:200)	
ABt281 (SEQ ID NO:202)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	MAWYRQAPG KEREWVSG (SEQ ID NO:16)	YYAESVKGRFTISNDN SKNTAYLQMNSLKPE DTAVYYC (SEQ ID NO:31)	WGQGTQVT VSS (SEQ ID NO:49)
ABt285 (SEQ ID NO:203)	EVQLVESGGGLV QPGGSLRLSCAA S (SEQ ID NO:4)	MAWYRQAPG KEREWVSG (SEQ ID NO:16)	YYADSVKGRFTISRDN SKNTLYLQMNSLKPE DTAVYYC (SEQ ID NO:200)	WGQGTQVT VSS (SEQ ID NO:49)

[0187] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:55, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:55.

[0188] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:201, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:201.

[0189] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:56, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:56.

[0190] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:57, or a variant

thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:57.

[0191] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:58, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:58.

[0192] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:59, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:59.

[0193] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:60, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:60.

[0194] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:61, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:61.

[0195] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:62, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least

89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:62

[0196] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:63, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:63.

[0197] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:64, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:64.

[0198] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:65, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:65.

[0199] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:66, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:66.

[0200] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:67, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:67.

[0201] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:68, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:68.

[0202] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:69, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:69.

[0203] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:70.

[0204] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:330.

[0205] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:331.

[0206] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:332.

[0207] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:333.

[0208] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:334.

[0209] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:335.

[0210] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:336.

[0211] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:337.

[0212] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:338.

[0213] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:339.

[0214] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:340.

[0215] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:341.

[0216] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:342.

[0217] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:343.

[0218] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:70, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:344.

[0219] In some embodiments, the CB2 antibody comprises the sequence of amino acids of the CB2 antibody designated ABt101, ABt107, ABt108, ABt109, ABt110, ABt111, ABt112, ABt113, ABt114, ABt115, ABt116, ABt117, ABt118, ABt119, ABt120, ABt121, ABt124, ABt247, ABt250, ABt251, ABt252, ABt253, ABt254, ABt105, ABt125, ABt126, ABt127, ABt128, ABt129, ABt130, ABt131, ABt132, ABt133, ABt134, ABt135, ABt136, ABt137, ABt138, ABt139, ABt140, ABt143, ABt276, ABt281, ABt285, ABhit_0426, ABhit_0427, ABhit_0428, ABhit_0429, ABhit_0430, ABhit_0431, ABhit_0432, ABhit_0433, ABhit_0434, ABhit_0435, ABhit_0436, ABhit_0437, ABhit_0438, ABhit_0439, or ABhit_0440 as defined in **Table 3**, below.

Table 3. CB2 antibody sequences.	
Antibody	Sequence

AB101 (SEQ ID NO:55)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMAWYRQAPGKEREWVSGI DTGGGTYYAESVKGRFTISNDNSKNTAYLQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt107 (SEQ ID NO:56)	QVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAIGWFRQAPGKEREGVSCIDT GGGTYYADSVKGRFTISRDNAKNTVYLYQMNSLKPEDTAVYYCSGAIKYGS RFDIKNYYCAGTQVTVSS
ABt108 (SEQ ID NO:57)	QVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWYRQAPGKERELVAAI DTGGGTNYADSVKGRFTISRDNAKNTVYLYQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYYCNGTQVTVSS
ABt109 (SEQ ID NO:58)	QVQLVESGGGLVQAGGSLRHSCAASGSIFSIMAMGWYRQAPGKERELVAAI DTGGGTYYADSVKGQFTISRDNAKNTLYLYQMNSLKPEDTAVYYCSGAIKY GSGRFDIKNYWGQGTQVTVSS
ABt110 (SEQ ID NO:59)	QVQLVESVGGGLVQDGGSLRLSCAASGSIFSIMAMRWFRQAPGKEREWVSCI DTGGGTNYADSVKARFTISRDNAKNTLYLYQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt111 (SEQ ID NO:60)	QVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMAWFRQAPGKEREFVAAI DTGGGTYYADSVKGRFTISRDNAKNTVFLQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt112 (SEQ ID NO:61)	QVQLQESGGGLVQAGGSLRLSCAASGSIFSIMAMGWYRQAPGKEREFVATI DTGGGTYYADSVKGRFTISRDNAKNTVYLYQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt113 (SEQ ID NO:62)	QVQLVESGGGLAQAGGSLRLSCAASGSIFSIMAMAWFRQPPGKEREFVAID TGGGTYYADSVKGRFTISRDNAKNTVYLYQMNSLKPEDTAVYYCSGAIKYGS GRFDIKNYWGQGTQVTVSS
ABt114 (SEQ ID NO:63)	QVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRQAPGKEREFVAAI DTGGGTNYADSVKGRFTISRDNKNTQYLYQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt115 (SEQ ID NO:64)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAIGWFRQAPGKEREGVSCIDT GGGTYYADSVKGRFTISRDNAKNTVYLYQMNSLKPEDTAVYYCSGAIKYGS RFDIKNYYGKGTQVTVSS
ABt116 (SEQ ID NO:65)	DVQLVESGGGLVQPGGSLRLSCAYSGSIFSIMAMDWYRQAPGKERELVAGI DTGGGTNYADSVKGRFTISRDSAKNTVYLYQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt117 (SEQ ID NO:66)	QVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMSWVRQAPGKGLEWVSDI DTGGGTYYADSVKGRFTISRDNAKNTLYLYQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt118 (SEQ ID NO:67)	QVQLQESGGGLVQPGGSLRLSCAASGSIFSIMAMGWYRQAPGKEHELVATI DTGGGTYYADSVKGRFTISRDNAKNTLYLYQMNSLKPEDTAMYYCSGAIKY GSGRFDIKNYWGQGTQVTVSS
ABt119 (SEQ ID NO:68)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMGWFRQAPGKGRELVAID TGGGTYYPDSVEGRFTISRDNAKRMVYLYQMNSLRAEDTAVYYCSGAIKYGS GRFDIKNYWGQGTQVTVSS
ABt120 (SEQ ID NO:69)	EVQLVESGGGLVQTGGSLRLSCAASGSIFSIMAMSWVRQAPGKGLEWVSGI DTGGGTRYAGSVKGRFTISRDNAKNMLYLYQMYSKLPEDTAVYYCSGAIKY GSGRFDIKNYRGQGTQVTVSS

ABt121 (SEQ ID NO:70)	EVQLMESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRRAPGKEREFVAAI DTGGGTIYGDSVKDRFTISRDNKNTLYLQMNSLKPEDTAVYTCSGAIKYGS GRFDIKNYSGQGTQVTVSS
ABt124 (SEQ ID NO:71)	QVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRQAPGKERESVAAI DTGGGTHYADSVKGRFTISRDNKNTVYLYQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt247 (SEQ ID NO:72)	EVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRRAPGKEREFVAAID TGGGTIYGDSVKDRFTISRDNKNTLYLQMNSLKPEDTAVYTCSGAIKYGS RFDIKNYSGQGTQVTVSS
ABt250 (SEQ ID NO:73)	EVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRQAPGKEREFVAAID TGGGTYYGDSVKGRFTISRDNKNTLYLQMNSLKPEDTAVYTCSGAIKYGS GRFDIKNYSGQGTQVTVSS
ABt251 (SEQ ID NO:74)	EVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRQAPGKEREFVAAID TGGGTYYGDSVKGRFTISRDNKNTLYLQMNSLKPEDTAVYTCSGAIKYGS GRFDIKNYSGQGTQVTVSS
ABt252 (SEQ ID NO:75)	EVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRQAPGKEREFVAAID TGGGTIYGDSVKGRFTISRDNKNTLYLQMNSLKPEDTAVYTCSGAIKYGS RFDIKNYSGQGTQVTVSS
ABt253 (SEQ ID NO:76)	EVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRRAPGKEREFVAAID TGGGTYYGDSVKDRFTISRDNKNTLYLQMNSLKPEDTAVYTCSGAIKYGS GRFDIKNYSGQGTQVTVSS
ABt254 (SEQ ID NO:77)	EVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRRAPGKEREFVAAID TGGGTYYGDSVKGRFTISRDNKNTLYLQMNSLKPEDTAVYTCSGAIKYGS GRFDIKNYSGQGTQVTVSS
ABt105 (SEQ ID NO:78)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMAWYRQAPGKEREWVSGI DTGGGTYYAESVKGRFTISNDNSKNTAYLQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK LSLSLG
ABt125 (SEQ ID NO:79)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMAWYRQAPGKEREWVSGI DTGGGTYYAESVKGRFTISRDNKNTLYLQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK LSLSLG
ABt126 (SEQ ID NO:80)	QVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAIGWFRQAPGKEREGVSCIDT GGGTYYADSVKGRFTISRDNKNTVYLYQMNSLKPEDTAVYYCSGAIKYGS RFDIKNYYCAGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCAPEAA GGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKS LSLSLG

ABt127 (SEQ ID NO:81)	QVQLVESGGGLVQAGGSLRLSCAASGSISSIMAMGWYRQAPGKERELVAAI DTGGGTNYADSVKGRFTISRDNANKNTVYLMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYCNGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK SLSLSLG
ABt128 (SEQ ID NO:82)	QVQLVESGGGLVQAGGSLRHSCAASGSISSIMAMGWYRQAPGKERELVAAI DTGGGTYYADSVKGQFTISRDNANKNTLYLMNSLKPEDTAVYYCSGAIKYG GSGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLG
ABt129 (SEQ ID NO:83)	QVQLVESVGGGLVQDGGSLRLSCAASGSISSIMAMRWFRQAPGKEREWVSCI DTGGGTNYADSVKARFTISRDNANKNTLYLMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK SLSLSLG
ABt130 (SEQ ID NO:84)	QVQLVESGGGLVQAGGSLRLSCAASGSISSIMAMAWFRQAPGKEREFVAAI DTGGGTYYADSVKGRFTISRDNANKNTVFLQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK SLSLSLG
ABt131 (SEQ ID NO:85)	QVQLQESGGGLVQAGGSLRLSCAASGSISSIMAMGWYRQAPGKEREFVATI DTGGGTYYADSVKGRFTISRDNANKNTVYLMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK SLSLSLG
ABt132 (SEQ ID NO:86)	QVQLVESGGGLAQAGGSLRLSCAASGSISSIMAMAWFRQPPGKEREFVAID TGGGTYYADSVKGRFTISRDNANKNTVYLMNSLKPEDTAVYYCSGAIKYGS GRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK SLSLSLG

ABt133 (SEQ ID NO:87)	QVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRQAPGKEREFVAAI DTGGGTNYADSVKGRFTISRDN SKNTQYLQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGSGGGGSGGGGSAESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQK SLSLSLG
ABt134 (SEQ ID NO:88)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAIGWFRQAPGKEREGVSCIDT GGGTYYADSVKGRFTISRDN AKNTVY LQMNSLKPEDTAVYYCSGAIKYGSG RFDIKNYGKGTQVTVSSGGGSGGGGSGGGGSAESKYGPPCPPCPAPEA GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKS LSLSLG
ABt135 (SEQ ID NO:89)	DVQLVESGGGLVQPGGSLRLSCAYSGSIFSIMAMDWYRQAPGKERELVAGI DTGGGTNYADSVKGRFTISRDS AKNTVY LQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGSGGGGSGGGGSAESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQK SLSLSLG
ABt136 (SEQ ID NO:90)	QVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMSWVRQAPGKGLEWVSDI DTGGGTYYADSVKGRFTISRDN AKNTLY LQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGSGGGGSGGGGSAESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQK SLSLSLG
ABt137 (SEQ ID NO:91)	QVQLQESGGGLVQPGGSLRLSCAASGSIFSIMAMGWYRQAPGKEHELVATI DTGGGTYYADSVKGRFTISRDN AKNTLY LQMNSLKPEDTAMYYCSGAIKY GSGRFDIKNYWGQGTQVTVSSGGGSGGGGSGGGGSAESKYGPPCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYT QKSLSLSLG
ABt138 (SEQ ID NO:92)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMGWFRQAPGKGRELVAID TGGGTYYPDSVEGRFTISRDN AKRMVY LQMNSLRAEDTAVYYCSGAIKYGS GRFDIKNYWGQGTQVTVSSGGGSGGGGSGGGGSAESKYGPPCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQK SLSLSLG

ABt139 (SEQ ID NO:93)	EVQLVESGGGLVQTGGSLRLSCAASGSIFSIMAMSWVRQAPGKGLEWVSGI DTGGGTRYAGSVKGRFTISRDNAMNMLYLQMYSLKPEDTAVYYCSGAIKY GSGRFDIKNYRGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK SLSLSLG
ABt140 (SEQ ID NO:94)	EVQLMESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRAPGKEREVFAAI DTGGGTIYGDSVKDRFTISRDNAMNTLYLQMNSLKPEDTAVYTCSGAIKYG GRFDIKNYSGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK SLSLSLG
ABt143 (SEQ ID NO:95)	QVQLVESGGGLVQAGGSLRLSCAASGSIFSIMAMGWFRQAPGKERESVAAI DTGGGTHYADSVKGRFTISRDNAMNTVYLQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSAESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQK SLSLSLG
ABt276 (SEQ ID NO:201)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMAWYRQAPGKEREWVSGI DTGGGTYYADSVKGRFTISRDNAMNTLYLQMNSLKPEDTAVYYCSGAIKYG SGRFDIKNYWGQGTQVTVSS
ABt281 (SEQ ID NO:202)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMAWYRQAPGKEREW VSGIDTGGGTYYAESVKGRFTISNDNSKNTAYLQMNSLKPEDTAVYY CSGAIKYGSGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSD HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYS KLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK
ABt285 (SEQ ID NO:203)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMAMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDNAMNTLYLQMNSLKPEDTAVYY CSGAIKYGSGRFDIKNYWGQGTQVTVSSGGGGSGGGGSGGGGSEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSD HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYS KLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK
ABhit_0426 (SEQ ID NO:330)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDNAMNTLYLQMNSLKPEDTAVYY CVVIKYGSGDFDIKTYSGQGTQVTVSS

ABhit_0427 (SEQ ID NO:331)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CYVVIKYGSGDFDIKVYSGQGTQVTVSS
ABhit_0428 (SEQ ID NO:332)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CLFIHKYGSGDFDIKTYSGQGTQVTVSS
ABhit_0429 (SEQ ID NO:333)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CIVIIKYGSGDFDIKTYSGQGTQVTVSS
ABhit_0430 (SEQ ID NO:334)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CLVIIKYGSGDFDIKTYSGQGTQVTVSS
ABhit_0431 (SEQ ID NO:335)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CLFAIKYGSGDFDIKTYSGQGTQVTVSS
ABhit_0432 (SEQ ID NO:336)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CFVAIKYGSGDFDIKVYSGQGTQVTVSS
ABhit_0433 (SEQ ID NO:337)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CFVVIKYGSGDFDIKVYSGQGTQVTVSS
ABhit_0434 (SEQ ID NO:338)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CLVVIKYGSGDFDIKTYSGQGTQVTVSS
ABhit_0435 (SEQ ID NO:339)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CYAIIKYGSGDFDIKVYSGQGTQVTVSS
ABhit_0436 (SEQ ID NO:340)	EVQLVESGGGLVQPGGSLRLSCAASGSISSIMGMAWYRQAPGKEREW VSGIDTGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CIAIIKYGSGDFDIKTYSGQGTQVTVSS

ABhit_0437 (SEQ ID NO:341)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMGMAWYRQAPGKEREW VSGIDTGGGTTYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CLFAIKYGS GDFDIKTFSGQGTQVTVSS
ABhit_0438 (SEQ ID NO:342)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMGMAWYRQAPGKEREW VSGIDTGGGTTYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CLFAIKYGS GLFDIKTYS GQGTQVTVSS
ABhit_0439 (SEQ ID NO:343)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMGMAWYRQAPGKEREW VSGIDTGGGTTYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CLFAIKYGS GDFDIKTAS GQGTQVTVSS
ABhit_0440 (SEQ ID NO:344)	EVQLVESGGGLVQPGGSLRLSCAASGSIFSIMGMAWYRQAPGKEREW VSGIDTGGGTTYADSVKGRFTISRDN SKNTLYLQMNSLKPEDTAVYY CLFAIKYGS GDFDIKGYSGQGTQVTVSS

[0220] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:71, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:71.

[0221] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:72, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:72.

[0222] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:73, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:73.

[0223] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:74, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:74.

[0224] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:75, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:75.

[0225] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:76, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:76.

[0226] In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2, wherein the ISVD comprises an amino acid sequence of SEQ ID NO:77, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:77.

[0227] The CB2 antibodies described herein, in some embodiments, comprise an Fc region. In some embodiments, the CB2 antibody comprises an Fc region of an IgG1, IgG2, IgG3, or IgG4, or a variant thereof. In some embodiments, the CB2 antibody comprises an Fc region of an IgG1. In some embodiments, the CB2 antibody comprises an Fc region of an IgG4. In some embodiments, the CB2 antibody comprises an Fc variant that exhibits reduced effector function. In some embodiments, the reduced effector function reduces ADCC activity. In some embodiments, the antibody comprises an IgG1 Fc region exhibiting reduced effector function. In

some embodiments, the antibody comprises a variant IgG1 Fc region comprising one or more variant amino acids. In some embodiments, the one or more variant amino acids of the variant IgG Fc regions described herein may be an addition, a substitution, or a deletion. Such variant IgG1 Fc regions are relative to a conserved Fc sequence, *e.g.*, a conserved human Fc sequence.

[0228] In some embodiments, the antibody comprises an IgG1 Fc region exhibiting reduced effector function, wherein the Fc region comprises the amino acid substitutions L234A and L235A, with numbering according to the EU index of Kabat. In some embodiments, the antibody comprises an IgG4 Fc region exhibiting reduced effector function. In some embodiments, the antibody comprises an IgG4 Fc region exhibiting reduced effector function, wherein the Fc region comprises the amino acid substitutions F234A/L235A (FALA), with numbering according to the EU index of Kabat. In some embodiments, the variant IgG1 Fc region comprises the amino acid substitutions selected from the group consisting of (1) LALA, (2) YTE, and (3) LALAPG. In some embodiments, the variant IgG1 Fc region comprises the LALAPG variants. In some embodiments, the variant IgG1 Fc region comprises the LALAPG variants and the YTE variants. In some embodiments, the variant IgG1 Fc region comprises the LALA variants and the YTE variants. The LALAPG variants are known as L234A, L235A, P329G, wherein the residues are numbered according to the EU index. The LALA variants are known as L234A and L235A, wherein the residues are numbered according to the EU index. The YTE variants are known as M252Y, S254T, and T256E, wherein the residues are numbered according to the EU index.

[0229] In some embodiments, the CB2 antibody comprises an Fc region, wherein the Fc region comprises the amino acid sequence of SEQ ID NO:130. In some embodiments, the CB2 antibody comprises an Fc region, wherein the Fc region comprises the amino acid sequence of SEQ ID NO:363. In some embodiments, the CB2 antibody comprises an Fc region, wherein the Fc region comprises the amino acid sequence of SEQ ID NO:364. In some embodiments, the CB2 antibody comprises an Fc region, wherein the Fc region comprises the amino acid sequence of SEQ ID NO:365. In some embodiments, the CB2 antibody further comprises a hinge region. In some embodiments, the hinge region comprises the amino acid sequence of SEQ ID NO:131. In some embodiments, the ISVD is fused to the Fc region via a peptide linker. In some embodiments, the peptide linker comprises the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:132). In some embodiments, the CB2 antibody comprises a polypeptide chain comprising from the N-terminus to the C-terminus: the ISVD, a peptide linker, a hinge region, and an Fc region. In some

embodiments, the CB2 antibody does not comprise an Fc region. An exemplary hinge is provided:

AESKYGPPCPPCP (SEQ ID NO:131)

[0230] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:78, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:78.

[0231] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:79, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:79.

[0232] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:80, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:80.

[0233] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:81, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:81.

[0234] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:82, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:82.

[0235] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:83, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:83.

[0236] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:84, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:84.

[0237] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:85, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:85.

[0238] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:86, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:86.

[0239] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:87, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:87.

[0240] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:88, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:88.

[0241] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:89, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:89.

[0242] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:90, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:90.

[0243] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:91, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:91.

[0244] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:92, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:92.

[0245] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:93, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:93.

[0246] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:94, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:94.

[0247] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:95, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:95.

[0248] In some embodiments, the CB2 antibody described herein comprises a CB2 antibody that specifically binds to CB2 competitively with any one of the other CB2 antibodies described herein. In some embodiments, competitive binding may be determined using an ELISA assay. In some embodiments, the CB2 antibody specifically binds to a CB2 competitively with a CB2 antibody comprising a CDR1 of SEQ ID NO:1, a CDR2 of SEQ ID NO:2, and a CDR3 of SEQ ID NO:3. In some embodiments, the CB2 antibody specifically binds to a CB2 competitively with a CB2 antibody comprising the amino acid sequence of any one of SEQ ID NOs:55-95. In some embodiments, the CB2 antibody specifically binds to a CB2 competitively with a CB2 antibody according to the CB2 antibodies of **Table 1**. In some embodiments, the K_D of the binding between the competing CB2 antibodies and CB2 is about 10^{-7} M to about 10^{-12} M (such as about 10^{-8} M to about 10^{-12} M, or about 10^{-9} M to about 10^{-11} M). In some embodiments, the CB2 antibody cross-reacts with a CB2 from a non-human mammal. In some embodiments, the competing CB2 antibody is a camelid, chimeric, human, partially humanized, or fully humanized.

[0249] In some embodiments, the CB2 antibody described herein comprises a CB2 antibody that has undergone functional maturation. In some embodiments, the CB2 antibody comprises a CDR1 having the amino acid formula G-X1-X2-X3-S-I-X4-X5, wherein X1 is selected from D, S, or Q; X2 is selected from G, H, I, or K; X3 is selected from D, E, F, G, H, I, K, N, Q, R, S, T, V, W, or Y; X4 is selected from G, K, M, R, or Y; and X5 is selected from A or G. In some embodiments, the antibody comprises CDR2 and CDR3 defined herein. In some embodiments, CDR2 is SEQ ID NO:2, according to IMGT. In some embodiments, the CB2 antibody comprises a binding domain that specifically binds a CB2, wherein the binding domain comprises a CDR1 having the amino acid formula G-X1-X2-X3-S-I-X4-X5, wherein X1 is selected from D, S, or Q; X2 is selected from G, H, I, or K; X3 is selected from D, E, F, G, H, I, K, N, Q, R, S, T, V, W, or Y; X4 is selected from G, K, M, R, or Y; and X5 is selected from A or G. In some embodiments, the antibody comprises CDR2 and CDR3 defined herein. In some embodiments, CDR2 is SEQ ID NO:2, according to IMGT.

[0250] In some embodiments, the CB2 antibody comprises a CDR3 having the amino acid formula C1-C2-C3-I-K-C4-C5-C6-C7-C8-C9-C10-I-C11-C12-C13, wherein C1 is selected from

F, H, I, K, L, R, S, T, V, or Y; wherein C2 is selected from A, E, F, G, I, L, Q, R, or V; wherein C3 is selected from A, F, G, I, K, L, N, or V; wherein C4 is selected from D, F, N, T, or Y; wherein C5 is selected from A, G, or R; wherein C6 is selected from R, S, or W; wherein C7 is selected from D, G, K, or R; wherein C8 is selected from D, I, L, Q, R, S, or T; wherein C9 is selected from F, L, or T; wherein C10 is selected from any D, E, H, or Q; wherein C11 is selected from K or N; wherein C12 is selected from A, F, G, H, I, K, L, N, P, R, S, V, T, or W; and wherein C13 is selected from A, D, F, G, H, T, or Y. In some embodiments, the antibody comprises CDR1 and CDR2 defined herein. In some embodiments, CDR2 is SEQ ID NO:2, according to IMGT. In some embodiments, the CB2 antibody comprises a binding domain that specifically binds a CB2, wherein the binding domain comprises a CDR3 having the amino acid formula C1-C2-C3-I-K-C4-C5-C6-C7-C8-C9-C10-I-C11-C12-C13, wherein C1 is selected from F, H, I, K, L, R, S, T, V, or Y; wherein C2 is selected from A, E, F, G, I, L, Q, R, or V; wherein C3 is selected from A, F, G, I, K, L, N, or V; wherein C4 is selected from D, F, N, T, or Y; wherein C5 is selected from A, G, or R; wherein C6 is selected from R, S, or W; wherein C7 is selected from D, G, K, or R; wherein C8 is selected from D, I, L, Q, R, S, or T; wherein C9 is selected from F, L, or T; wherein C10 is selected from any D, E, H, or Q; wherein C11 is selected from K or N; wherein C12 is selected from A, F, G, H, I, K, L, N, P, R, S, V, T, or W; and wherein C13 is selected from A, D, F, G, H, T, or Y. In some embodiments, the antibody comprises CDR1 and CDR2 defined herein. In some embodiments, CDR2 is SEQ ID NO:2, according to IMGT.

[0251] In some embodiments, the CB2 antibody comprises a CDR1 having the amino acid formula G-X1-X2-X3-S-I-X4-X5, wherein X1 is selected from D, S, or Q; X2 is selected from G, H, I, or K; X3 is selected from D, E, F, G, H, I, K, N, Q, R, S, T, V, W, or Y; X4 is selected from G, K, M, R, or Y; and X5 is selected from A or G. In some embodiments, the CB2 antibody comprises a CDR3 having the amino acid formula C1-C2-C3-I-K-C4-C5-C6-C7-C8-C9-C10-I-C11-C12-C13, wherein C1 is selected from F, H, I, K, L, R, S, T, V, or Y; wherein C2 is selected from A, E, F, G, I, L, Q, R, or V; wherein C3 is selected from A, F, G, I, K, L, N, or V; wherein C4 is selected from D, F, N, T, or Y; wherein C5 is selected from A, G, or R; wherein C6 is selected from R, S, or W; wherein C7 is selected from D, G, K, or R; wherein C8 is selected from D, I, L, Q, R, S, or T; wherein C9 is selected from F, L, or T; wherein C10 is selected from any D, E, H, or Q; wherein C11 is selected from K or N; wherein C12 is selected

from A, F, G, H, I, K, L, N, P, R, S, V, T, or W; and wherein C13 is selected from A, D, F, G, H, T, or Y. In some embodiments, CDR2 is a CDR defined herein. In some embodiments, CDR2 is SEQ ID NO:2, according to IMGT. In some embodiments, the CB2 antibody comprises a binding domain that specifically binds a CB2, wherein the binding domain comprises a CDR1 having the amino acid formula G-X1-X2-X3-S-I-X4-X5, wherein X1 is selected from D, S, or Q; X2 is selected from G, H, I, or K; X3 is selected from D, E, F, G, H, I, K, N, Q, R, S, T, V, W, or Y; X4 is selected from G, K, M, R, or Y; and X5 is selected from A or G. In some embodiments, the CB2 antibody comprises a CDR3 having the amino acid formula C1-C2-C3-I-K-C4-C5-C6-C7-C8-C9-C10-I-C11-C12-C13, wherein C1 is selected from F, H, I, K, L, R, S, T, V, or Y; wherein C2 is selected from A, E, F, G, I, L, Q, R, or V; wherein C3 is selected from A, F, G, I, K, L, N, or V; wherein C4 is selected from D, F, N, T, or Y; wherein C5 is selected from A, G, or R; wherein C6 is selected from R, S, or W; wherein C7 is selected from D, G, K, or R; wherein C8 is selected from D, I, L, Q, R, S, or T; wherein C9 is selected from F, L, or T; wherein C10 is selected from any D, E, H, or Q; wherein C11 is selected from K or N; wherein C12 is selected from A, F, G, H, I, K, L, N, P, R, S, V, T, or W; and wherein C13 is selected from A, D, F, G, H, T, or Y. In some embodiments, CDR2 is a CDR defined herein. In some embodiments, CDR2 is SEQ ID NO:2, according to IMGT.

[0252] In some embodiments, provided is a CB2 antibody comprising a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:248-288, a CDR2 comprising an amino acid sequence of SEQ ID NO:2, and a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:289-329, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, CDR1, CDR3, and CDR3 are a set as provided according to **Table 4**.

[0253] In some embodiments, the CB2 antibody comprises the sequence of amino acids of one of a CB2 antibody designated ABhit_0231, ABhit_0232, ABhit_0233, ABhit_0234, ABhit_0235, ABhit_0236, ABhit_0238, ABhit_0239, ABhit_0241, ABhit_0242, ABhit_0243, ABhit_0244, ABhit_0245, ABhit_0246, ABhit_0247, ABhit_0248, ABhit_0249, ABhit_0250, ABhit_0251, ABhit_0252, ABhit_0253, ABhit_0254, ABhit_0255, ABhit_0256, ABhit_0258, ABhit_0259, ABhit_0260, ABhit_0261, ABhit_0262, ABhit_0263, ABhit_0264, ABhit_0266, ABhit_0267, ABhit_0268, ABhit_0269, ABhit_0270, ABhit_0271, ABhit_0272, ABhit_0320, ABhit_0321, or ABhit_0322, as defined in **Table 4** below. In some embodiments, provided is a

CB2 antibody comprising the CDR sequences of one of ABhit_0231, ABhit_0232, ABhit_0233, ABhit_0234, ABhit_0235, ABhit_0236, ABhit_0238, ABhit_0239, ABhit_0241, ABhit_0242, ABhit_0243, ABhit_0244, ABhit_0245, ABhit_0246, ABhit_0247, ABhit_0248, ABhit_0249, ABhit_0250, ABhit_0251, ABhit_0252, ABhit_0253, ABhit_0254, ABhit_0255, ABhit_0256, ABhit_0258, ABhit_0259, ABhit_0260, ABhit_0261, ABhit_0262, ABhit_0263, ABhit_0264, ABhit_0266, ABhit_0267, ABhit_0268, ABhit_0269, ABhit_0270, ABhit_0271, ABhit_0272, ABhit_0320, ABhit_0321, or ABhit_0322, as defined in **Table 4** below.

Table 4. Functionally matured CB2 antibody sequences; CDRs according to IMGT				
Antibody	Sequence	CDR1	CDR2	CDR3
ABhit_0231 (SEQ ID NO:205)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIM GMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSVVIKYGSGDFDIK AYSGQGTQVTVSS	GSIFSIMG (SEQ ID NO:248)	IDTGGGT (SEQ ID NO:2)	SVIIKYGS GDFDIKAY (SEQ ID NO:289)
ABhit_0232 (SEQ ID NO:206)	EVQLVESGGGLVQPG GSLRLSCAASGSISIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCIGAIKYGSGRFDIK LYSGQGTQVTVSS	GSISIMA (SEQ ID NO:249)	IDTGGGT (SEQ ID NO:2)	IGAIKYGS GRFDIKLY (SEQ ID NO:290)
ABhit_0233 (SEQ ID NO:207)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIG AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSGFIKYGSDRFDIK TYSQGTQVTVSS	GSIFSIGA (SEQ ID NO:250)	IDTGGGT (SEQ ID NO:2)	SGFIKYGS DRFDIKTY (SEQ ID NO:291)
ABhit_0234 (SEQ ID NO:208)	EVQLVESGGGLVQPG GSLRLSCAASGSISIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCLVAIKYGSFTDI KNYSQGTQVTVSS	GSISIMA (SEQ ID NO:251)	IDTGGGT (SEQ ID NO:2)	LVAIKYGS GFTDIKNY (SEQ ID NO:292)

ABhit_0235 (SEQ ID NO:209)	EVQLVESGGGLVQPG GSLRLSCAASGSIRSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCIGAIFYGSGIFDIK NYSQGQGTQVTVSS	GSIRSIMA (SEQ ID NO:252)	IDTGGGT (SEQ ID NO:2)	IGAIFYGSGI FDIKNY (SEQ ID NO:293)
ABhit_0236 (SEQ ID NO:210)	EVQLVESGGGLVQPG GSLRLSCAASGSIVSIM GMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCLGAIFYGSGRFDI KLYSGQGTQVTVSS	GSIVSIMG (SEQ ID NO:253)	IDTGGGT (SEQ ID NO:2)	LGAIFYGSG RFDIKLY (SEQ ID NO:294)
ABhit_0238 (SEQ ID NO:211)	EVQLVESGGGLVQPG GSLRLSCAASGSIKSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCHGAIFYGSGRFDI KVYSGQGTQVTVSS	GSIKSIMA (SEQ ID NO:254)	IDTGGGT (SEQ ID NO:2)	HGAIFYGSG RFDIKVY (SEQ ID NO:295)
ABhit_0239 (SEQ ID NO:212)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIG AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSGKIIFYGSGRFDI KTYSGQGTQVTVSS	GSIFSIGA (SEQ ID NO:255)	IDTGGGT (SEQ ID NO:2)	SGKIIFYGSG RFDIKTY (SEQ ID NO:296)
ABhit_0241 (SEQ ID NO:214)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIIK AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSGIIIFYGSGRTDIK WYSGQGTQVTVSS	GSIFSIIKA (SEQ ID NO:256)	IDTGGGT (SEQ ID NO:2)	SGIIIFYGSGR TDIKWY (SEQ ID NO:297)
ABhit_0242 (SEQ ID NO:215)	EVQLVESGGGLVQPG GSLRLSCAASGSIHSIY AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV	GSIHSIYA (SEQ ID NO:257)	IDTGGGT (SEQ ID NO:2)	HGAIFYGSG DFDIKVY (SEQ ID NO:298)

	YYCHGAIKYGSGDFDI KVYSGQGTQVTVSS			
ABhit_0243 (SEQ ID NO:216)	EVQLVESGGGLVQPG GSLRLSCAAPGSIFSIM GMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSVVIKYGSGDFDIK AYSGQGTQVTVSS	GSIFSIMG (SEQ ID NO:258)	IDTGGGT (SEQ ID NO:2)	SVIIKYGSGD FDIKAY (SEQ ID NO:299)
ABhit_0244 (SEQ ID NO:217)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIG AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSGIIKYGSGRFDIK TYSGQGTQVTVSS	GSIFSIGA (SEQ ID NO:259)	IDTGGGT (SEQ ID NO:2)	SGIIKYGSGR FDIKTY (SEQ ID NO:300)
ABhit_0245 (SEQ ID NO:218)	EVQLVESGGGLVQPG GSLRLSCAASGSKFSIG AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSGIIKYGSGRFDIK HYWGQGTQVTVSS	GSKFSIGA (SEQ ID NO:260)	IDTGGGT (SEQ ID NO:2)	SGIIKYGSGR FDIKHY (SEQ ID NO:301)
ABhit_0246 (SEQ ID NO:219)	EVQLVESGGGLVQPG GSLRLSCAASGSIKSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCIGAIKYGSGRFDIK VYSGQGTQVTVSS	GSIKSIMA (SEQ ID NO:261)	IDTGGGT (SEQ ID NO:2)	IGAIKYGSGR FDIKVY (SEQ ID NO:302)
ABhit_0247 (SEQ ID NO:220)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSFAIKYGSGRFDIK NYSGQGTQVTVSS	GSIFSIMA (SEQ ID NO:262)	IDTGGGT (SEQ ID NO:2)	SFAIKYGSGR FDIKNY (SEQ ID NO:303)
ABhit_0248 (SEQ ID NO:221)	EVQLVESGGGLVQPG GSLRLSCAASGSIGSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD	GSIGSIMA (SEQ ID NO:263)	IDTGGGT (SEQ ID NO:2)	LGAIKYGSG RFDIKLY (SEQ ID NO:304)

	SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCLGAIKYGSGRFDI KLYSGQGTQVTVSS			
ABhit_0249 (SEQ ID NO:222)	EVQLVESGGGLVQPG GSLRLSCAASGSIGSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCIGAIKYGSGRFDIK VYSGQGTQVTVSS	GSIGSIMA (SEQ ID NO:264)	IDTGGGT (SEQ ID NO:2)	IGAIKYGSGR FDIKVY (SEQ ID NO:305)
ABhit_0250 (SEQ ID NO:223)	EVQLVESGGGLVQPG GSLRLSCAASGSIRSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCIGAIKYGRGRFDI KNYSGQGTQVTVSS	GSIRSIMA (SEQ ID NO:265)	IDTGGGT (SEQ ID NO:2)	IGAIKYGRG RFDIKNY (SEQ ID NO:306)
ABhit_0251 (SEQ ID NO:224)	EVQLVESGGGLVQPG GSLRLSCAASGDIFSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCLFAIKYGSGRFDI KNYSGQGTQVTVSS	GDIFSIMA (SEQ ID NO:266)	IDTGGGT (SEQ ID NO:2)	LFAIKYGS RFDIKNY (SEQ ID NO:307)
ABhit_0252 (SEQ ID NO:225)	EVQLVESGGGLVQPG GSLRLSCAASGSIYSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAES VKGRFTISNDNSKNTL YLQMNSLKPEDTAVY YCYGAIKYGSGAFDIK VYSGQGTQVTVSS	GSIYSIMA (SEQ ID NO:267)	IDTGGGT (SEQ ID NO:2)	YGAIKYGS AFDIKVY (SEQ ID NO:308)
ABhit_0253 (SEQ ID NO:226)	EVQLVESGGGLVQPG GSLRLSCAASGSISSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCIGAIKYGSGRFDIK AYWGQGTQVTVSS	GSISSIMA (SEQ ID NO:268)	IDTGGGT (SEQ ID NO:2)	IGAIKYGSGR FDIKAY (SEQ ID NO:309)

ABhit_0254 (SEQ ID NO:227)	EVQLVESGGGLVQPG GSLRLSCAASGSIWSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCLGAIKYGSGRFDI KAYWGQGTQVTVSS	GSIWSIMA (SEQ ID NO:269)	IDTGGGT (SEQ ID NO:2)	LGAIKYGSG RFDIKAY (SEQ ID NO:310)
ABhit_0255 (SEQ ID NO:228)	EVQLVESGGGLVQPG GSLRLSCAASGSIGSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCLGVIKYGSGSFDI KNYSQGQTQVTVSS	GSIGSIMA (SEQ ID NO:270)	IDTGGGT (SEQ ID NO:2)	LGVIKYGSG SFDIKNY (SEQ ID NO:311)
ABhit_0256 (SEQ ID NO:229)	EVQLVESGGGLVQPG GSLRLSCAASGSITSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSGLIKYGSGRFDI KVYSGQGTQVTVSS	GSITSIMA (SEQ ID NO:271)	IDTGGGT (SEQ ID NO:2)	SGLIKYGSG RFDIKVY (SEQ ID NO:312)
ABhit_0258 (SEQ ID NO:231)	EVQLVESGGGLVQPG GSLRLSCAASGSIRSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTPVY YCIGAIAKTGSGRFDIKN GSGQGTQVTVSS	GSIRSIMA (SEQ ID NO:272)	IDTGGGT (SEQ ID NO:2)	IGAIAKTGSGR FDIKNG (SEQ ID NO:313)
ABhit_0259 (SEQ ID NO:232)	EVQLVESGGGLVQPG GSLRLSCAASGSHFSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCFLAIKYGSKIFDIK NYSQGQTQVTVSS	GSHFSIMA (SEQ ID NO:273)	IDTGGGT (SEQ ID NO:2)	FLAIKYGSKI FDIKNY (SEQ ID NO:314)
ABhit_0260 (SEQ ID NO:233)	EVQLVESGGGLVQPG GSLRLSCAASGSIKSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV	GSIKSIMA (SEQ ID NO:274)	IDTGGGT (SEQ ID NO:2)	SGLIKYGSG RLDIKNY (SEQ ID NO:315)

	YYCSGLIKYGSGRLDI KNYWGGGTQVTVSS			
ABhit_0261 (SEQ ID NO:234)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIG AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSVIIKYGSGDFDIK AYSGQGTQVTVSS	GSIFSIGA (SEQ ID NO:275)	IDTGGGT (SEQ ID NO:2)	SVIIKYGSGD FDIKAY (SEQ ID NO:316)
ABhit_0262 (SEQ ID NO:235)	EVQLVESGGGLVQPG GSLRLSCAASGSIRSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCIAAIKYGSGRFDIK GYSQGTQVTVSS	GSIRSIMA (SEQ ID NO:276)	IDTGGGT (SEQ ID NO:2)	IAAIKYGSGR FDIKGY (SEQ ID NO:317)
ABhit_0263 (SEQ ID NO:236)	EVQLVESGGGLVQPG GSLRLSCAASGSIHSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCIGAIKYGSGLFDIK NYSQGTQVTVSS	GSIHSIMA (SEQ ID NO:277)	IDTGGGT (SEQ ID NO:2)	IGAIKYGSGL FDIKNY (SEQ ID NO:318)
ABhit_0264 (SEQ ID NO:237)	EVQLVESGGGLVQPG GSLRLSCAASGSIESIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCLGAIKYGSGIFDIK NASQGTQVTVSS	GSIESIMA (SEQ ID NO:278)	IDTGGGT (SEQ ID NO:2)	LGAIKYGSGI FDIKNA (SEQ ID NO:319)
ABhit_0266 (SEQ ID NO:238)	EVQLVESGGGLVQPG GSLRLSCAASGSIRSIM AMGWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCSVIIKYGSGDFDIK AYSGQGTQVTVSS	GSIRSIMA (SEQ ID NO:279)	IDTGGGT (SEQ ID NO:2)	SVIIKYGSGD FDIKAY (SEQ ID NO:320)
ABhit_0267 (SEQ ID NO:239)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIM GMACYRQAPGKEREW VSGIDTGGGTYYADSV	GSIFSIMG (SEQ ID NO:280)	IDTGGGT (SEQ ID NO:2)	SGIIKYGSGR FDIKTY (SEQ ID NO:321)

	KGRFTISRDN SKNTLY LQMNSLKPEDTPVYYC SGIIKYGSGRFDIKTYS GQGTQVTVSS			
ABhit_0268 (SEQ ID NO:240)	EVQLVESGGGLVQPG GSLRLSCAASGSIK SIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCSVIIKYGSGDFDIK AYSGQGTQVTVSS	GSIKSIMA (SEQ ID NO:281)	IDTGGGT (SEQ ID NO:2)	SVIIKYGSGD FDIKAY (SEQ ID NO:322)
ABhit_0269 (SEQ ID NO:241)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIM GMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCSGKIKYSGRFDI KTYSGQGTQVTVSS	GSIFSIMG (SEQ ID NO:282)	IDTGGGT (SEQ ID NO:2)	SGKIKYSGS RFDIKTY (SEQ ID NO:323)
ABhit_0270 (SEQ ID NO:242)	EVQLVESGGGLVQPG GSLRLSCAASGSIFS I AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCHGLIKYSGRFDI KVYSGQGTQVTVSS	GSIFS IKA (SEQ ID NO:283)	IDTGGGT (SEQ ID NO:2)	HGLIKYSGS RFDIKVY (SEQ ID NO:324)
ABhit_0271 (SEQ ID NO:243)	EVQLVESGGGLVQPG GSLRLSCAASGSIQSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCLGVIKYSGRFDI KTYSGQGTQVTVSS	GSIQSIMA (SEQ ID NO:284)	IDTGGGT (SEQ ID NO:2)	LGVIKYSGS RFDIKTY (SEQ ID NO:325)
ABhit_0272 (SEQ ID NO:244)	EVQLVESGGGLVQPG GSLRLSCAASGSIFSIM GMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDN SKNT LYLQMNSLKPEDTAV YYCVVAIKYSGRFDI KNTSGQGTQVTVSS	GSIFSIMG (SEQ ID NO:285)	IDTGGGT (SEQ ID NO:2)	VVAIKYSGS RFDIKNT (SEQ ID NO:326)

ABhit_0320 (SEQ ID NO:245)	EVQLVESGGGLVQPG GSLRLSCAASGSIRSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRKNTLYL QMNSLKPEDTAVYYCI VAIKYGSGRFDIKNGS GQGTQVTVSSYP	GSIRSIMA (SEQ ID NO:286)	IDTGGGT (SEQ ID NO:2)	IVAIKYGSGR FDIKNG (SEQ ID NO:327)
ABhit_0321 (SEQ ID NO:246)	EVQLVESGGGLVQPG GSLRLSCAASGSIYSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCYGAIKYGSGRFDI KVYSGQGTQVTVSS	GSIYSIMA (SEQ ID NO:287)	IDTGGGT (SEQ ID NO:2)	YGAIKYGSG RFDIKVY (SEQ ID NO:328)
ABhit_0322 (SEQ ID NO:247)	EVQLVESGGGLVQPG GSLRLSCAASGSIQSIM AMAWYRQAPGKERE WVSGIDTGGGTYYAD SVKGRFTISRDNKNT LYLQMNSLKPEDTAV YYCLGAIKYGSGRFDI KSYWGQGTQVTVSS	GSIQSIMA (SEQ ID NO:288)	IDTGGGT (SEQ ID NO:2)	LGAIKYGSG RFDIKSY (SEQ ID NO:329)

[0254] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:205, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:205.

[0255] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:206, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:206.

[0256] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:207, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:207.

[0257] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:208, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:208.

[0258] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:209, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:209.

[0259] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:210, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:210.

[0260] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:211, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:211.

[0261] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:212, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:212.

[0262] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:214, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:214.

[0263] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:215, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:215.

[0264] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:216, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:216.

[0265] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:217, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:217.

[0266] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:218, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:218.

[0267] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:219, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:219.

[0268] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:220, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:220.

[0269] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:221, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:221.

[0270] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:222, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:222.

[0271] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:223, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:223.

[0272] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:224, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:224.

[0273] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:225, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:225.

[0274] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:226, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:226.

[0275] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:227, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:227.

[0276] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:228, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:228.

[0277] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:229, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:229.

[0278] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:231, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:231.

[0279] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:232, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:232.

[0280] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:233, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:233.

[0281] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:234, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:234.

[0282] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:235, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:235.

[0283] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:236, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:236.

[0284] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:237, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:237.

[0285] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:238, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:238.

[0286] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:239, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:239.

[0287] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:240, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:240.

[0288] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:241, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:241.

[0289] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:242, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:242.

[0290] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:243, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:243.

[0291] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:244, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:244.

[0292] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:245, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:245.

[0293] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:246, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:246.

[0294] In some embodiments, the CB2 antibody comprises the amino acid sequence of SEQ ID NO:247, or a variant thereof having at least 85%, such as at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, sequence identity to the amino acid sequence of SEQ ID NO:247.

CB2

[0295] The cannabinoid receptor type 2 (CB2) is a G protein-coupled receptor from the cannabinoid receptor family. In humans, it is encoded by the *CNR2* gene. It is closely related to the cannabinoid receptor type 1 (CB1). CB1 agonism is primarily responsible for the psychotropic effects of cannabis, particularly tetrahydrocannabinol (THC). Due to the psychoactive effect of CB1 agonism, antibodies which specifically bind CB2 but which do not exhibit specific binding to CB1 are desirable. Thus, in one aspect, the CB2 antibodies provided herein are specific for CB2 and do not exhibit significant affinity and do not specifically bind CB1. The CB2 receptor comprises seven transmembrane-spanning domains, contains a glycosylated N-terminus, and an intracellular C-terminus.

[0296] The terms “cannabinoid receptor type 2”, “CB2”, “CB2 antigen”, and “CB2 epitope” are used interchangeably, and include variants, isoforms, species homologs of human CB2, and analogs having at least one common epitope with CB2. In some embodiments, the CB2 is human CB2, and the CB2 antibody specifically binds human CB2. CB2 gene and polypeptide sequences (*e.g.*, human *CNR2* gene and polypeptide sequences) are known in the art. An exemplary human CB2 sequence is provided at GenBank Accession Number P34972. In some embodiments, a human CB2 may be at least about 90%, 95%, 96%, 97%, 98%, or 99% identical in amino acid sequence to the human CB2 of Genbank Accession Number P34972. In some embodiments, a

human CB2 sequence has no more than about 10 amino acid differences from the human CB2 of Genbank Accession Number P34972. In some embodiments, the human CB2 may display no more than 5, 4, 3, 2, or 1 amino acid difference from the human CB2 of Genbank Accession Number P34972. In some embodiments, a human CB2 sequence may differ from the human CB2 of Genbank Accession Number P34972 by having, for example, conserved mutations or mutations in non-conserved regions and the CB2 has substantially the same biological function as the human CB2 of Genbank Accession Number P34972.

[0297] In some embodiments, the CB2 antibodies described herein specifically recognize a CB2 polypeptide having at least about 90% amino acid sequence identity to the human CB2 of Genbank Accession Number P34972. In some embodiments, the CB2 antibody may cross-react with CB2 from species other than human (such as rat, murine, and/or cynomolgus CB2), or other proteins which are structurally related to human CB2 (*e.g.*, human CB2 homologs). In some embodiments, the CB2 antibody does not specifically bind CB1.

Biological activities

[0298] The CB2 antibodies described herein comprise an ISVD (*e.g.*, a VHH or a camelid), and has one or more of the following characteristics: (a) the ISVD is an agonist of a CB2; (b) the ISVD does not agonize a CB1; (c) the ISVD reduces forskolin-induced cyclic adenosine monophosphate (cAMP) level in HEK293 cells overexpressing human CB2 with a half maximal effective concentration (EC_{50}) that is less than 55 nM; (d) the ISVD reduces forskolin-induced cyclic adenosine monophosphate (cAMP) level in HEK293 cells overexpressing mouse CB2 with an EC_{50} that is less than 30 nM; (e) the ISVD does not specifically bind a CB1; and (f) the CB2 antibody binds HEK293 cells overexpressing human CB2 with an EC_{50} that is less than 850 nM.

[0299] The CB2 antibody described herein binds CB2 with high affinity and specificity. In some embodiments, the CB2 antibody binds human CB2 with a K_D of about 0.001 nM to about 10 nM (*e.g.*, 10nM or less, 1nM or less, 0.1nM or less, 0.01 nM or less, or 0.001 nM or less), including any value or range in between these values. In some embodiments, the CB2 antibody binds cynomolgus CB2 with a K_D of about 0.001 nM to about 10 nM (*e.g.*, 10nM or less, 1nM or less, 0.1nM or less, 0.01 nM or less), or 0.001 nM or less, including any value or range in between these values. In some embodiments, the CB2 antibody binds rat CB2 with a K_D of about 0.001

nM to about 10 nM (*e.g.*, 10nM or less, 1nM or less, 0.1nM or less, 0.01 nM or less, or 0.001 nM or less), including any value or range in between these values. In some embodiments, the CB2 antibody binds murine CB2 with a K_D of about 0.001 nM to about 10 nM (*e.g.*, 10nM or less, 1nM or less, 0.1nM or less, 0.01 nM or less, or 0.001 nM or less), including any value or range in between these values.

[0300] In some embodiments, the CB2 antibody is a selective CB2 agonist. In some embodiments, a CB2 antibody is a selective CB2 agonist if it exhibits detectable CB2 agonist activity and does not exhibit detectable CB1 agonist activity. In some embodiments, a CB2 antibody is a selective CB2 agonist if it exhibits detectable CB2 agonist activity and does not exhibit detectable CB1 agonist activity as assessed by reduction of forskolin-induced cyclic adenosine monophosphate (cAMP) production in HEK293 cells overexpressing CB2 (for CB2 agonism assessment) or overexpressing CB1 (for CB1 agonism assessment). In some embodiments, agonist activity is not detectable if the reduction in cAMP as compared to a control is not statistically significant (such as when p is not < 0.05). In some embodiments, CB1 agonist activity is not detectable if the degree of measured activity is an order of magnitude different between CB2 agonism and CB1 agonism. In some embodiments, the CB2 antibody agonism activity (such as for CB1 or CB2) is assessed at a concentration of about 1 μ M.

[0301] In some embodiments, the CB2 antibody selectively binds CB2 and does not selectively bind CB1. In some embodiments, the CB2 antibody does not selectively bind CB1 if the CB2 antibody binds a CB1 with a K_D of greater than about 1,000 nM, such as greater than about 1,000 nM, 2,000 nM, 3,000 nM, 4,000 nM, 5,000 nM, or more, including values and ranges therebetween. In some embodiments, the CB1 is a human, rat, murine, or cynomolgus CB1.

[0302] The K_D and k_{off} of the CB2 antibodies provided herein for human CB2, rat CB2, murine CB2, and/or cynomolgus CB2 can be determined by any method known in the art, including, but not limited to, *e.g.*, ELISA, fluorescence activated cell sorting (FACS) analysis, radioimmunoprecipitation (RIA), and surface plasmon resonance (SPR). In some embodiments, the K_D and/or k_{off} of a CB2 antibody provided herein for human CB2, murine CB2, rat CB2, and/or cynomolgus CB2 is determined via SPR. In some embodiments, the K_D and/or k_{off} of a CB2 antibody provided herein is determined by surface plasmon resonance (SPR).

[0303] The characteristics of the CB2 antibodies described herein can be assessed using well known methods, *e.g.*, methods used in the Examples below. In some embodiments, the CB2 antibody does not bind (*e.g.*, specifically bind) to a CB1, such as a human CB1.

[0304] The biological activity of the CB2 antibodies described herein can be determined by measuring its half maximal effective concentration (EC_{50}), which is a measure of the effectiveness of an antibody in binding to its target. For example, the EC_{50} can be used to indicate the effective concentration of a CB2 antibody needed to bind 50% CB2 on a cell surface. EC_{50} also represents the plasma concentration required for obtaining 50% of a maximum effect *in vivo*. EC_{50} can be measured by assays known in the art, for example, bioassays such as FACS binding analysis, inhibition of ligand binding by FACS analysis (competition binding assay), cell-based cytokine release assay, or amplified luminescent proximity homogeneous assay (AlphaLISA).

[0305] For example, agonist activity of CB2 antibodies can be studied by measuring reduction in forskolin-induced cAMP levels in HEK293 cells over-expressing human CB2 (but not CB1, if assessing CB2 agonism) or human CB1 (but not CB2, if assessing CB1 agonism), as described in Example 2, below. The results of the study can demonstrate the ability of the CB2 antibody to agonize CB2, to not agonize CB1, and to compare the CB2 antibody to other CB1 or CB2 agonists.

[0306] The agonist EC_{50} of binding to CB2 by the CB2 antibodies can be studied by evaluating binding of the CB2 antibody to CB2-expressing HEK293 stable cells. Similarly, agonist EC_{50} of binding to CB1 by the CB2 antibodies can be studied by evaluating binding of the CB2 antibody to CB1-expressing HEK293 stable cells. As discussed in Example 2, below, after incubating the CB2 antibodies with the CB1-expressing or CB2-expressing HEK293 stable cells in the presence of forskolin, cells may be lysed by addition of tracer and detection reagents. After incubating, FRET allows quantification of cAMP levels and calculation of EC_{50} . In some embodiments, there is not detectable agonist activity of CB1 (such as a human, mouse, cynomolgus, and/or rat CB1) by the CB2 antibodies described herein.

(II) Fusion constructs

[0307] The present application further provides anti-CB2 fusion constructs comprising any one of the CB2 antibodies or antigen-binding fragments (*e.g.*, ISVD or VHH) described herein and a second polypeptide, such as a second antibody or antigen binding fragment thereof, or an Fc

fragment of an immunoglobulin. In some embodiments, the anti-CB2 construct comprises two or more polypeptides other than the CB2 antibody. The additional polypeptide(s) may or may not change or otherwise influence the biological properties of the CB2 antibody, and may or may not add further functionality to the CB2 antibody. In some embodiments, the second polypeptide confers one or more desired properties or functionalities to the CB2 antibody.

[0308] In some embodiments, the anti-CB2 construct comprises a second antibody or antigen binding fragment thereof (such as ISVD, scFv, Fab, full-length antibody, etc.) that specifically recognizes a second epitope. In some embodiments, the second epitope is from a CB2. In some embodiments, the second epitope is not from a CB2. In some embodiments, the second antibody specifically recognizes the same epitope on a CB2 as the CB2 antibody described herein. In some embodiments, the second antibody specifically recognizes a different epitope on CB2 as the CB2 antibody described herein.

[0309] In some embodiments, there is provided an anti-CB2 construct comprising a plurality (such as 2, 3, 4, or more) of CB2 antibodies described herein. In some embodiments, the plurality of the CB2 antibodies are fused to each other via a linker (such as a peptide linker). The plurality of the CB2 antibodies can be the same or different.

[0310] In some embodiments, the CB2 antibody comprises a second polypeptide that enhances the half-life, solubility, and/or absorption, reduces immunogenicity or toxicity, eliminates or attenuates undesirable side effects, confers other advantageous properties to and/or reduces other undesired properties of the CB2 antibody, compared to the CB2 antibody alone. Some non-limiting examples of such polypeptides include serum proteins, such as human serum albumin (HSA; *see, e.g.* WO 2000/027435) or haptenic molecules (*e.g.* haptens that are recognized by circulating antibodies, *see, e.g.* WO 98/22141). It was shown that linking fragments of immunoglobulins (such as V_H domains) to serum albumin or fragments thereof may increase antibody half-life (*see, e.g.* WO 00/27435 and WO 01/077137). Thus, in some embodiments, the CB2 antibody comprises a CB2 antibody fused to serum albumin or a fragment thereof, optionally via a suitable linker (such as peptide linker). In some embodiments, the serum albumin comprises at least domain III (*see* PCT/EP2007/002817).

CB2 heavy chain-only antibody (HCAb)

[0311] In some embodiments, the CB2 antibody is a heavy chain-only antibody (HCAb) comprising a CB2 ISVD described herein. In some embodiments, the CB2 ISVD is fused to one

or more C_{H2} and/or C_{H3} domains, *e.g.*, an Fc fragment. In some embodiments, C_{H2} and/or C_{H3} domains are derived from human immunoglobulins. In some embodiments, the CB2 antibody is fused to the C_{H2} and/or C_{H3} domains via a peptide linker. The C_{H2} and/or C_{H3} domains may increase the half-life of the CB2 antibody *in vivo*.

[0312] Thus, in some embodiments, there is provided an isolated CB2 HCAb comprising a CB2 ISVD (meaning an ISVD which specifically binds a CB2) described herein fused to an Fc fragment of an immunoglobulin, such as IgA, IgD, IgE, IgG, or IgM. In some embodiments, the CB2 HCAb comprises an Fc fragment of IgG, such as IgG1, IgG2, IgG3, or IgG4. In some embodiments, the Fc fragment is a human Fc, such as human IgG1 (hIgG1) Fc, hIgG2 Fc, or hIgG4 Fc. In some embodiments, the Fc fragment is effectorless, with reduced, minimized, or eliminated antibody effector functions such as ADCC, CDC, and/or ADCP (antibody-dependent cellular phagocytosis). In some embodiments, the effectorless Fc comprises an N297A or DANA mutation (D265A+N297A) in the C_{H2} region. In some embodiments, the effectorless Fc comprises K322A and L234A/L235A (LALA) mutations. In some embodiments, the effectorless Fc comprises F234A and L235A (FALA) mutations. In some embodiments, the Fc fragment is an effectorless IgG1 Fc, such as effectorless hIgG1 Fc. In some embodiments, the Fc fragment is a human IgG4 Fc (S228P). In some embodiments, the Fc fragment is an IgG4 Fc (FALA). In some embodiments, the CB2 HCAb is monomeric. In some embodiments, the CB2 HCAb is dimeric. In some embodiments, the CB2 HCAb is multispecific and multivalent (such as bispecific and bivalent), *e.g.*, comprising two or more different CB2 antibodies described herein. In some embodiments, the CB2 HCAb is monospecific and multivalent (*e.g.*, bivalent), *e.g.*, comprising two or more copies of the same CB2 ISVD. An exemplary IgG4 Fc is provided:

APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK
AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLG
(SEQ ID NO:130)

[0313] Exemplary IgG1 Fc sequences are also provided:

EPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV

EWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK (SEQ ID NO:363)

EPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK (SEQ ID NO:364)

EPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK (SEQ ID NO:365)

[0314] In some embodiments, the CB2 antibody and the Fc fragment are fused to each other via a peptide linker. In some embodiments, the peptide linker is a (G4S)₃ (SEQ ID NO:132).

[0315] Thus, in some embodiments, there is provided an isolated CB2 HCAb comprising an ISVD specifically recognizing CB2, wherein the CB2 antibody comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:1, or a variant thereof comprising up to 3 (such as any of 1, 2, or 3) amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO:2, or a variant thereof comprising up to 3 (such as any of 1, 2, or 3) amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NOs:3, or a variant thereof comprising up to 3 (such as any of 1, 2, or 3) amino acid substitutions, and wherein the CB2 ISVD is fused to an Fc fragment of an immunoglobulin. In some embodiments, the ISVD comprises: (1) a FR1 of any one of SEQ ID NOs:4-15; (2) a FR2 of any one of SEQ ID NOs:16-30; (3) a FR3 of any one of SEQ ID NOs:31-48; and (4) a FR4 of any one of SEQ ID NOs:49-54. In some embodiments, there is provided an isolated CB2 HCAb comprising an ISVD specifically recognizing CB2, wherein the ISVD comprises the amino acid sequence of any one of SEQ ID NOs:55-77 or a variant thereof having at least about 80% (such as at least about any of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity to any one of SEQ ID NOs: 55-77, and wherein the CB2 antibody is fused to an Fc fragment of an

immunoglobulin. In some embodiments, there is provided an isolated CB2 HCAb comprising an ISVD specifically recognizing CB2, wherein the ISVD comprises the amino acid sequence of any one of SEQ ID NOs:55-77, and wherein the CB2 antibody is fused to an Fc fragment of an immunoglobulin. In some embodiments, the CB2 antibody is fused to the Fc fragment via a peptide linker. In some embodiments, the CB2 HCAb is monomeric. In some embodiments, the Fc fragment is a human IgG1 Fc, effectorless human IgG1 Fc, hIgG2 Fc, human IgG4 Fc, IgG4 Fc (F234A/L235A), or IgG1 (L234A/L235A, with numbering according to the EU index of Kabat).

[0316] In some embodiments, there is provided an isolated CB2 HCAb comprising the amino acid sequence of any one of SEQ ID NOs:78-95, or a variant thereof having at least about 80% (such as at least about any of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity to any one of SEQ ID NOs:78-95. In some embodiments, there is provided a polypeptide comprising the amino acid sequence of any one of SEQ ID NOs:78-95.

[0317] Also provided are isolated CB2 HCAs that specifically binds to CB2 competitively with any one of the isolated CB2 HCAs or CB2 antibodies described herein.

Peptide linkers

[0318] The various domains and components, such as CB2 ISVDs (meaning ISVDs which specifically bind a CB2), Fc fragment, the first antigen binding portion, and the second antigen binding portion in the CB2 antibody construct may be fused to each other via a suitable linker, such as a peptide linker. The length, the degree of flexibility and/or other properties of the peptide linker(s) used in the CB2 antibody may have some influence on properties, including but not limited to the affinity, specificity or avidity for one or more particular antigens or epitopes. For example, longer peptide linkers may be selected to ensure that two adjacent domains do not sterically interfere with one another. In some embodiment, a peptide linker comprises flexible residues (such as glycine and serine) so that the adjacent domains are free to move relative to each other. For example, a glycine-serine doublet can be a suitable peptide linker.

[0319] The peptide linker can be of any suitable length. In some embodiments, the peptide linker is at least about any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 50, 75, 100 or more amino acids long. In some embodiments, the peptide linker is no more than about any of 100, 75, 50, 40, 35, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5 or fewer amino acids long. In some embodiments, the length of the peptide linker is any of

about 1 amino acid to about 10 amino acids, about 1 amino acid to about 20 amino acids, about 1 amino acid to about 30 amino acids, about 5 amino acids to about 15 amino acids, about 10 amino acids to about 25 amino acids, about 5 amino acids to about 30 amino acids, about 10 amino acids to about 30 amino acids long, about 30 amino acids to about 50 amino acids, about 50 amino acids to about 100 amino acids, or about 1 amino acid to about 100 amino acids.

[0320] The peptide linker may have a naturally occurring sequence, or a non-naturally occurring sequence. For example, a sequence derived from the hinge region of heavy chain only antibodies may be used as the linker. *See*, for example, WO1996/34103. In some embodiments, the linker is a (G4S)₃ linker (SEQ ID NO:132).

(III) Antibody variants

[0321] In some embodiments, amino acid sequence variants of the CB2 antibody provided herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleic acid sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, *e.g.*, antigen-binding.

a) Substitution, insertion, deletion and variants

[0322] In some embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the CDRs and FRs.

Conservative substitutions are shown in **Table 5** under the heading of “Preferred substitutions.”

More substantial changes are provided in **Table 5** under the heading of “exemplary substitutions,” and as further described below in reference to amino acid side chain classes.

Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, *e.g.*, retained/improved antigen binding, decreased immunogenicity, or modified ADCC or CDC.

Table 5. Amino acid substitutions.		
Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

[0323] Amino acids may be grouped according to common side-chain properties: (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

[0324] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[0325] In some embodiments, the CB2 antibody provided herein comprises a ISVD comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs:55-77. In some embodiments, an ISVD sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence, but the CB2 antibody comprising that sequence retains the ability to bind CB2 (*e.g.*, a human CB2, a murine CB2, a rat CB2, and/or a

cynomolgus CB2). In some embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any of SEQ ID NOs:55-77. In some embodiments, substitutions, insertions, or deletions occur in regions outside the CDRs (*i.e.*, in the FRs). In some embodiments, the CB2 antibody comprises the ISVD set for in any one of SEQ ID NOs:55-77, including post-translational modifications of that sequence.

[0326] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (*e.g.*, a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (*e.g.*, improvements) in certain biological properties (*e.g.*, increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated.

[0327] A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called “alanine scanning mutagenesis” as described by Cunningham and Wells (1989) *Science*, 244:1081-1085. In this method, a residue or group of target residues (*e.g.*, charged residues such as Arg, Asp, His, Lys, and Glu) are identified and replaced by a neutral or negatively charged amino acid (*e.g.*, alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[0328] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (*e.g.*, for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

b) Glycosylation variants

[0329] In some embodiments, an isolated CB2 antibody provided herein is altered to increase or decrease the extent to which the construct is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0330] Where the CB2 antibody comprises an Fc region (*e.g.*, CB2 antibody-Fc fusion protein (*e.g.*, HCAb), the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the C_H2 domain of the Fc region. *See, e.g.*, Wright *et al.* *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, *e.g.*, mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the “stem” of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in a CB2 antibody of the present application may be made in order to create antibody variants with certain improved properties.

[0331] In some embodiments, CB2 antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (*e.g.*, complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (EU numbering of Fc region residues); however, Asn297 may also be located about ± 3 amino acids upstream or downstream of position 297, *i.e.*, between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. *See, e.g.*, US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to “defucosylated” or “fucose-deficient” antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki *et al.* *J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki *et al.*

Biotech. Bioeng. 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka *et al. Arch. Biochem. Biophys.* 249:533-545 (1986); US Patent Application No. US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams *et al.*, especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, *FUT8*, knockout CHO cells (*see, e.g., Yamane-Ohnuki et al. Biotech. Bioeng.* 87: 614 (2004); Kanda, Y. *et al., Biotechnol. Bioeng.*, 94(4):680-688 (2006); and WO2003/085107).

[0332] CB2 antibody variants are further provided with bisected oligosaccharides, *e.g.*, in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, *e.g.*, in WO 2003/011878 (Jean-Mairet *et al.*); US Patent No. 6,602,684 (Umana *et al.*); and US 2005/0123546 (Umana *et al.*). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, *e.g.*, in WO 1997/30087 (Patel *et al.*); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

c) Fc region variants

[0333] In some embodiments, one or more amino acid modifications may be introduced into the Fc region of the CB2 antibodies provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (*e.g.*, a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (*e.g.* a substitution) at one or more amino acid positions.

[0334] In some embodiments, the present application contemplates a CB2 antibody comprising an Fc region variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half-life of the CB2 antibody *in vivo* is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only,

whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 2 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is described in U.S. Patent No. 5,500,362 (*see, e.g.* Hellstrom, I. *et al. Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I *et al., Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985); 5,821,337 (*see* Bruggemann, M. *et al., J. Exp. Med.* 166:1351-1361 (1987)).

Alternatively, non-radioactive assays methods may be employed (*see, for example*, ACTITM non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo, e.g.*, in an animal model such as that disclosed in Clynes *et al. Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. *See, e.g.*, C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (*see, for example*, Gazzano-Santoro *et al., J. Immunol. Methods* 202:163 (1996); Cragg, M.S. *et al., Blood* 101:1045-1052 (2003); and Cragg, M.S. and M.J. Glennie, *Blood* 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half-life determinations can also be performed using methods known in the art (*see, e.g.*, Petkova, S.B. *et al., Int'l. Immunol.* 18(12):1759-1769 (2006)).

[0335] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581). Fc mutants are described in Schlothauer *et al. Protein Eng Des Sel.* 2016 Oct;29(10):457-466; Pejchal *et al. Antibodies.* 2023; 12(3):54; Dall'Acqua *et al. J Biol Chem.* 2006 Aug 18;281(33):23514-24. Ramdani *et al. International Journal of Molecular Sciences.* 2022; 23(17):9604, which are hereby incorporated by reference.

[0336] Certain antibody variants with improved or diminished binding to FcRs are described. (*See, e.g.*, U.S. Patent No. 6,737,056; WO 2004/056312, and Shields *et al., J. Biol. Chem.* 9(2): 6591-6604 (2001).)

[0337] In some embodiments, a CB2 antibody variant comprises an Fc region with one or more amino acid substitutions which decreases ADCC activity, *e.g.*, substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

[0338] In some embodiments, alterations are made in the Fc region that result in altered (*i.e.*, either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), *e.g.*, as described in US Patent No. 6,194,551, WO 99/51642, and Idusogie *et al.* *J. Immunol.* 164: 4178-4184 (2000).

[0339] In some embodiments, there is provided a CB2 antibody comprising a variant Fc region comprising one or more amino acid substitutions which increase half-life and/or improve binding to the neonatal Fc receptor (FcRn). Antibodies with increased half-lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer *et al.*, *J. Immunol.* 117:587 (1976) and Kim *et al.*, *J. Immunol.* 24:249 (1994)), are described in US2005/0014934A1 (Hinton *et al.*). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues, *e.g.*, substitution of Fc region residue 434 (US Patent No. 7,371,826).

[0340] See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

[0341] CB2 antibodies comprising any of the Fc variants described herein, or combinations thereof, are contemplated.

d) Antibody derivatives

[0342] In some embodiments, a CB2 antibody provided herein may be further modified to comprise additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, propylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (*e.g.*, glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene

glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, *etc.*

[0343] In some embodiments, conjugates of a CB2 antibody and nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In some embodiments, the nonproteinaceous moiety is a carbon nanotube (Kam *et al.*, *Proc. Natl. Acad. Sci. USA* 102: 11600-11605 (2005)). The radiation may be of any wavelength, and includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody-nonproteinaceous moiety are killed.

[0344] In some embodiments, a CB2 antibody provided herein may be further modified to comprise one or more biologically active protein, polypeptides or fragments thereof. “Bioactive” or “biologically active”, as used herein interchangeably, means showing biological activity in the body to carry out a specific function. For example, it may mean the combination with a particular biomolecule such as protein, DNA, *etc.*, and then promotion or inhibition of the activity of such biomolecule. In some embodiments, the bioactive protein or fragments thereof include proteins and polypeptides that are administered to patients as the active drug substance for prevention of or treatment of a disease or condition, as well as proteins and polypeptides that are used for diagnostic purposes, such as enzymes used in diagnostic tests or *in vitro* assays, as well as proteins and polypeptides that are administered to a patient to prevent a disease such as a vaccine. In some embodiments, the bioactive protein or fragments thereof have immune-stimulatory/immune-regulatory, membrane transport, or enzymatic activities. In some embodiments, the biologically active protein, polypeptides or fragments thereof is an enzyme, a hormone, a growth factor, a cytokine, or a mixture thereof. In some embodiments, the biologically active protein, polypeptides or fragments can specifically recognize a target peptide (such as antigen, or other proteins).

[0345] In some embodiments, the bioactive protein or fragments thereof that can be comprised within the CB2 antibody described herein is a protein-binding protein. In some embodiments, the

bioactive protein or fragments thereof that can be comprised within the CB2 antibody described herein is an antibody mimetics, which are small engineered proteins comprising antigen-binding domains reminiscent of antibodies (Geering and Fussenegger, Trends Biotechnol., 33(2):65-79, 2015). These molecules are derived from existing human scaffold proteins and comprise a single polypeptide. Exemplary antibody mimetics that can be comprised within the CB2 antibody described herein can be, but are not limited to, a Designed ankyrin repeat protein (DARPin; comprising 3-5 fully synthetic ankyrin repeats flanked by N- and C-terminal Cap domains), an avidity multimer (avimer; a high-affinity protein comprising multiple A domains, each domain with low affinity for a target), or an Anticalin (based on the scaffold of lipocalins, with four accessible loops, the sequence of each can be randomized). In some embodiments, the bioactive protein or fragments thereof that can be comprised within the CB2 antibody described herein is an Armadillo repeat protein (*e.g.*, β -catenin, α -importin, plakoglobin, adenomatous polyposis coli (APC)), which comprises armadillo repeat units (characteristic, repetitive amino acid sequence of about 40 residues in length). Each Armadillo repeat is composed of a pair of alpha helices that form a hairpin structure. Multiple copies of the repeat form what is known as an alpha solenoid structure. Armadillo repeat proteins are able to bind different types of peptides, relying on a constant way of binding of the peptide backbone without requiring specific conserved side chains or interactions with free N- or C-termini of a peptide. The possibility of recognizing a peptide residue by residue, combined with the intrinsic modularity of a repeat protein, makes the armadillo repeat proteins promising candidates for the design of a generic scaffold for peptide binding.

[0346] In some embodiments, the biologically active protein or fragments thereof that can be comprised within the CB2 antibody described herein is a ligand, such as lymphokines and cellular factors which interact with specific cellular receptor. Lymphokines are low molecular weight proteins which are secreted by T cells when antigens or lectins stimulate T cell growth.

III. Pharmaceutical compositions

[0347] Further provided by the present application are pharmaceutical compositions comprising any one of the CB2 antibodies described herein, and optionally a pharmaceutically acceptable carrier. Pharmaceutical compositions can be prepared by mixing a CB2 antibody described herein having the desired degree of purity with optional pharmaceutically acceptable carriers,

excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions.

[0348] The pharmaceutical composition is preferably to be stable, in which the CB2 antibody described herein essentially retains its physical and chemical stability and integrity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in *Peptide and Protein Drug Delivery*, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones, A. *Adv. Drug Delivery Rev.* 10: 29-90 (1993). Stability can be measured at a selected temperature for a selected time period. For rapid screening, the formulation may be kept at 40°C for 2 weeks to 1 month, at which time stability is measured. Where the formulation is to be stored at 2-8°C, generally the formulation should be stable at 30°C or 40°C for at least 1 month, and/or stable at 2-8°C for at least 2 years. Where the formulation is to be stored at 30°C, generally the formulation should be stable for at least 2 years at 30°C, and/or stable at 40°C for at least 6 months. For example, the extent of aggregation during storage can be used as an indicator of protein stability. In some embodiments, the stable formulation of CB2 antibody described herein may comprise less than about 10% (preferably less than about 5%) of the CB2 antibody present as an aggregate in the formulation.

[0349] Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers, antioxidants including ascorbic acid, methionine, Vitamin E, sodium metabisulfite; preservatives, isotonicifiers (*e.g.* sodium chloride), stabilizers, metal complexes (*e.g.* Zn-protein complexes); chelating agents such as EDTA and/or non-ionic surfactants.

[0350] Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counterions such as sodium;

metal complexes (*e.g.* Zn-protein complexes); and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONIC™ or polyethylene glycol (PEG).

[0351] Buffers are used to control the pH in a range which optimizes the therapeutic effectiveness, especially if stability is pH dependent. Buffers are preferably present at concentrations ranging from about 50 mM to about 250 mM. Suitable buffering agents for use in the present application include both organic and inorganic acids and salts thereof. For example, citrate, phosphate, succinate, tartrate, fumarate, gluconate, oxalate, lactate, acetate. Additionally, buffers may comprise histidine and trimethylamine salts such as Tris.

[0352] Preservatives are added to retard microbial growth, and are typically present in a range from 0.2%-1.0% (w/v). The addition of a preservative may, for example, facilitate the production of a multi-use (multiple-dose) formulation. Suitable preservatives for use in the present application include octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium halides (*e.g.*, chloride, bromide, iodide), benzethonium chloride; thimerosal, phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol, 3-pentanol, and m-cresol.

[0353] Tonicity agents, sometimes known as “stabilizers” are present to adjust or maintain the tonicity of liquid in a composition. When used with large, charged biomolecules such as proteins and antibodies, they are often termed “stabilizers” because they can interact with the charged groups of the amino acid side chains, thereby lessening the potential for inter and intra-molecular interactions. Tonicity agents can be present in any amount between 0.1% to 25% by weight, preferably 1% to 5%, taking into account the relative amounts of the other ingredients. Preferred tonicity agents include polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol.

[0354] Additional excipients include agents which can serve as one or more of the following: (1) bulking agents, (2) solubility enhancers, (3) stabilizers and (4) agents preventing denaturation or adherence to the container wall. Such excipients include: polyhydric sugar alcohols (enumerated above); amino acids such as alanine, glycine, glutamine, asparagine, histidine, arginine, lysine, ornithine, leucine, 2-phenylalanine, glutamic acid, threonine, etc.; organic sugars or sugar alcohols such as sucrose, lactose, lactitol, trehalose, stachyose, mannose, sorbose, xylose, ribose, ribitol, myoinisitol, myoinisitol, galactose, galactitol, glycerol, cyclitols (*e.g.*, inositol), polyethylene glycol; sulfur containing reducing agents, such as urea, glutathione,

thioctic acid, sodium thioglycolate, thioglycerol, α -monothioglycerol and sodium thio sulfate; low molecular weight proteins such as human serum albumin, bovine serum albumin, gelatin or other immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; monosaccharides (*e.g.*, xylose, mannose, fructose, glucose; disaccharides (*e.g.*, lactose, maltose, sucrose); trisaccharides such as raffinose; and polysaccharides such as dextrin or dextran.

[0355] Non-ionic surfactants or detergents (also known as “wetting agents”) are present to help solubilize the therapeutic agent as well as to protect the therapeutic protein against agitation-induced aggregation, which also permits the formulation to be exposed to shear surface stress without causing denaturation of the active therapeutic protein or antibody. Non-ionic surfactants are present in a range of about 0.05 mg/ml to about 1.0 mg/ml, preferably about 0.07 mg/ml to about 0.2 mg/ml.

[0356] Suitable non-ionic surfactants include polysorbates (20, 40, 60, 65, 80, etc.), polyoxamers (184, 188, etc.), PLURONIC[®] polyols, TRITON[®], polyoxyethylene sorbitan monoethers (TWEEN[®]-20, TWEEN[®]-80, etc.), laurmacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. Anionic detergents that can be used include sodium lauryl sulfate, dioctyle sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents include benzalkonium chloride or benzethonium chloride.

[0357] In order for the pharmaceutical compositions to be used for *in vivo* administration, they must be sterile. The pharmaceutical composition may be rendered sterile by filtration through sterile filtration membranes. The pharmaceutical compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0358] The route of administration is in accordance with known and accepted methods, such as by single or multiple bolus or infusion over a long period of time in a suitable manner, *e.g.*, injection or infusion by subcutaneous, intravenous, intraperitoneal, intramuscular, intra-arterial, intralesional or intraarticular routes, topical administration, inhalation or by sustained release or extended-release means.

[0359] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the antagonist, 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 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.

[0360] The pharmaceutical compositions herein may 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 may comprise a cytotoxic agent, chemotherapeutic agent, cytokine, immunosuppressive agent, or growth inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0361] The active ingredients may 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, nanoparticles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 18th edition.

[0362] In some embodiments, the pharmaceutical composition is contained in a single-use vial, such as a single-use sealed vial. In some embodiments, the pharmaceutical composition is contained in a multi-use vial. In some embodiments, the pharmaceutical composition is contained in bulk in a container. In some embodiments, the pharmaceutical composition is cryopreserved.

IV. Methods of treating

[0363] The CB2 antibodies and compositions (such as pharmaceutical compositions) thereof described herein are useful for a variety of applications, such as in diagnosis, molecular assays, and therapy.

[0364] In some embodiments, provided is a method of agonizing CB2 on a cell, comprising contacting the cell with an amount of any one of the CB2 antibodies described herein that is sufficient for activating CB2 on the cell. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2

comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the method is *in vitro*. In some embodiments, the method is *in vivo*. In some embodiments, agonizing CB2 on a cell treats or ameliorates a disease or condition. Agonism of a CB2 in a subject can trigger acute and prolong antinociceptive effects.

[0365] In some embodiments, there is provided a method of treating a disease or condition in a subject, wherein agonizing CB2 ameliorates the disease or condition, comprising administering to the subject an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the disease or condition is chemotherapy induced peripheral neuropathy (CIPN). In some embodiments, the disease or condition is a respiratory infection. In some embodiments, the disease or condition is liver fibrosis. In some embodiments, the disease or condition is cold sensitivity. In some embodiments, the disease or condition is inflammatory bowel disease. In some embodiments, the disease or condition is endometriosis.

[0366] Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of chemotherapy for the treatment of cancer. CIPN is usually associated with neurotoxic chemotherapeutic agents. CIPN is a painful, dose-limiting side effect that can limit treatment tolerance, reduce patient outcomes, reduce treatment compliance, and reduce patient quality of life. Taxol drugs, such as paclitaxel, are commonly associated with CIPN. The CB2 antibodies described herein are useful for treating or ameliorating CIPN, including CIPN induced by taxol drugs.

[0367] In some embodiments, there is provided a method of treating a chemotherapy induced peripheral neuropathy (CIPN) in a subject receiving a chemotherapeutic agent, comprising administering to the subject an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the

chemotherapeutic agent is a taxol drug. In some embodiments, the taxol drug is paclitaxel. In some embodiments, the chemotherapeutic is vincristine. In some embodiments, the chemotherapeutic is cisplatin.

[0368] In some embodiments, provided is a method of treating cancer in a subject in need thereof, the method comprising administering an effective amount of a chemotherapeutic to the subject and an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the chemotherapeutic is a taxol drug. In some embodiments, the taxol drug is paclitaxel. In some embodiments, the chemotherapeutic is vincristine. In some embodiments, the chemotherapeutic is cisplatin. In some embodiments, the chemotherapeutic causes chemotherapy induced peripheral neuropathy (CIPN).

[0369] A large plurality of subjects having cancer treated with neurotoxic chemotherapies experience chemotherapy-induced peripheral neuropathy. CIPN can impact subject health-related quality of life, treatment adherence, appetite, and can exacerbate preexisting pain, among other negative effects. Together, these effects can limit the dose of a neurotoxic chemotherapy which can be tolerated by the subject, where a higher dose may otherwise be more effect in treating the indicated cancer. CIPN may be measured by any suitable means known in the art, including by administration of a questionnaire or application of a diagnostic protocol. Exemplary questionnaires and protocols for CIPN include the Functional Assessment of Cancer Therapy / Gynecologic Oncology Group Neurotoxicity questionnaire (FACT/GOG-Ntx), Chemotherapy-induced Peripheral Neuropathy Assessment Tool (CIPNAT), European Organization for Research & Treatment in Cancer Quality of Life Quest-CIPN 20 (EORTC QLQ-CIPN 20), Modified Total Neuropathy Score (mTNS), Total Neuropathy Score, clinical version (TNSc), 5-item reduced Total Neuropathy Score (TNSr 5-item). Other measures may be used to assess the symptoms of CIPN, including the Fullerton Advanced Balance Scale (FABS), Timed Up and Go (TUG), Activities Specific Balance Confidence Scale (ABC), Balance Evaluation Systems Test (BESTest), Berg Balance Scale (BBS), Repeated Sit to Stand test, Functional Reach test, Short Physical Performance Battery (SPPB), and a grooved peg board test. Any suitable means of assessing CIPN are contemplated by the methods described herein.

[0370] In some embodiments, provided is a method of ameliorating chemotherapy induced peripheral neuropathy (CIPN), the method comprising administering an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the CIPN is caused by a taxol drug. In some embodiments, the taxol drug is paclitaxel. In some embodiments, the chemotherapeutic is vincristine. In some embodiments, the chemotherapeutic is cisplatin.

[0371] In some embodiments, provided is a method of treating a side effect associated with a chemotherapy in a cancer patient, the method comprising administering to the patient an effective amount of any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the side effect is CIPN or a side effect associated with CIPN. In some embodiments, the method further comprises administering the chemotherapeutic. In some embodiments, the chemotherapeutic is a taxol drug. In some embodiments, the taxol drug is paclitaxel. In some embodiments, the chemotherapeutic is vincristine. In some embodiments, the chemotherapeutic is cisplatin.

[0372] In some embodiments, provided is a method of improving the quality of a life of a subject receiving a chemotherapy, the method comprising administering to the patient an effective amount of any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. Quality of life may be assessed by any suitable means known in the art, including a quality of life questionnaire (QoLQ). The QoLQ may be self-reported and/or proxy reported. Any suitable QoLQ is contemplated by the methods described herein. In some embodiments, the method further comprises administering the chemotherapeutic. In some embodiments, the chemotherapeutic is a

taxol drug. In some embodiments, the taxol drug is paclitaxel. In some embodiments, the chemotherapeutic is vincristine. In some embodiments, the chemotherapeutic is cisplatin.

[0373] In some embodiments, provided is a method of improving the compliance of a subject receiving a chemotherapy, the method comprising administering to the patient an effective amount of any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the method further comprises administering the chemotherapeutic. In some embodiments, the chemotherapeutic is a taxol drug. In some embodiments, the taxol drug is paclitaxel. In some embodiments, the chemotherapeutic is vincristine. In some embodiments, the chemotherapeutic is cisplatin.

[0374] In some embodiments, provided is a method of increasing the dose of a chemotherapy regimen being administered to a subject, the method comprising administering to the subject an effective amount of any one of the CB2 antibodies described herein, wherein the dose of the chemotherapy regimen is increased after administration of the CB2 antibody. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the method further comprises administering the chemotherapeutic. In some embodiments, the chemotherapeutic is a taxol drug. In some embodiments, the taxol drug is paclitaxel. In some embodiments, the chemotherapeutic is vincristine. In some embodiments, the chemotherapeutic is cisplatin.

[0375] In some embodiments, provided is a method of treating an individual having a respiratory infection, the method comprising administering to the individual an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the respiratory infection is an influenza infection, such as an influenza infection caused by an influenza A virus or an influenza B virus. In some embodiments, the

influenza infection is caused by an influenza A virus subtype H1N1. In some embodiments, the respiratory infection is caused by a coronavirus, such as SARS-CoV-2 (wherein the respiratory infection is COVID-19).

[0376] In some embodiments, provided is a method of reducing a cytokine release syndrome in an individual in need thereof, comprising administering to the individual an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. In some embodiments, the method decreases IL-16 and/or IL-8 level secreted by airway cells in the individual. In some embodiments, the method decreases IL-16 secretion by airway cells by about 20% or more, such as about 20% or more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, and 90% or more, and values and ranges therebetween. In some embodiments, the method decreases IL-8 secretion by airway cells by about 20% or more, such as about 20% or more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, and 90% or more, and values and ranges therebetween. In some embodiments, the method decreases IL-8 and IL-16 secretion by airway cells by about 20% or more, such as about 20% or more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, and 90% or more, and values and ranges therebetween.

[0377] In some embodiments, provided is a method of treating liver fibrosis, the method comprising administering to the individual an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. Liver fibrosis may be assessed by any suitable means known in the art, including by liver biopsy or noninvasive means such as elastography and/or serum biochemistry.

[0378] In some embodiments, provided is a method of treating cold sensitivity and/or allodynia, the method comprising administering to an individual in need thereof an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and

comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. Cold sensitivity and/or allodynia may be assessed by any suitable means known in the art, including a questionnaire and/or patient-reported ranking of cold sensitivity or allodynia.

[0379] In some embodiments, provided is a method of treating inflammatory bowel disease, the method comprising administering to an individual in need thereof an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT.

[0380] In some embodiments, provided is a method of treating endometriosis, the method comprising administering to an individual in need thereof an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT.

[0381] In some embodiments, provided is a method of treating diabetic peripheral neuropathy (DPN), the method comprising administering to an individual in need thereof an effective amount of a pharmaceutical composition comprising any one of the CB2 antibodies described herein. In some embodiments, the CB2 antibody comprises an ISVD which specifically binds a CB2 and comprises a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT. Dosages and desired drug concentrations of pharmaceutical compositions of the present application may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary artisan. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The Use of Interspecies Scaling in Toxicokinetics," In *Toxicokinetics and New Drug Development*, Yacobi *et al.*, Eds, Pergamon Press, New York 1989, pp. 42-46.

[0382] When *in vivo* administration of the CB2 antibody described herein (including pharmaceutical compositions comprising a CB2 antibody described herein) are used, normal dosage amounts may vary from about 10 ng/kg up to about 100 mg/kg of mammal body weight depending upon the route of administration. It is within the scope of the present application that different formulations will be effective for different treatments and different disorders, and that administration intended to treat a specific organ or tissue may necessitate delivery in a manner different from that to another organ or tissue. Moreover, dosages may be administered by one or more separate administrations, or by continuous infusion. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

[0383] In some embodiments, the pharmaceutical composition is administered for a single time (*e.g.* bolus injection). In some embodiments, the pharmaceutical composition is administered for multiple times (such as any of 2, 3, 4, 5, 6, or more times). If multiple administrations, they may be performed by the same or different routes and may take place at the same site or at alternative sites. The pharmaceutical composition may be administered daily to once per year. The interval between administrations can be about any one of 24 h to a year. Intervals can also be irregular (*e.g.* following tumor progression). In some embodiments, there is no break in the dosing schedule. The optimal dosage and treatment regime for a particular patient can readily be determined by one skilled in the art of medicine by monitoring the patient for signs of disease and adjusting the treatment accordingly.

[0384] The pharmaceutical compositions of the present application, including but not limited to reconstituted and liquid formulations, are administered to an individual in need of treatment, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intravenous (*i.v.*), intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. A reconstituted formulation can be prepared by dissolving a lyophilized CB2 antibody described herein in a diluent such that the protein is dispersed throughout. Exemplary pharmaceutically acceptable (safe and non-toxic for administration to a human) diluents suitable for use in the present application include, but are not limited to, sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.* phosphate-buffered

saline), sterile saline solution, Ringer's solution or dextrose solution, or aqueous solutions of salts and/or buffers.

[0385] In some embodiments, the pharmaceutical compositions are administered to the individual by subcutaneous (*i.e.* beneath the skin) administration. For such purposes, the pharmaceutical compositions may be injected using a syringe. However, other devices for administration of the pharmaceutical compositions are available such as injection devices; injector pens; auto-injector devices, needleless devices; and subcutaneous patch delivery systems. In some embodiments, the pharmaceutical compositions are administered to the individual intravenously. In some embodiments, the pharmaceutical composition is administered to an individual by infusion, such as intravenous infusion. Infusion techniques for immunotherapy are known in the art (*see, e.g.*, Rosenberg *et al.*, New Eng. J. of Med. 319: 1676 (1988)).

[0386] In some embodiments, the administration to the individual is through an injection. In some embodiments, the pharmaceutical composition is injected multiple times. In some embodiments, the pharmaceutical compositions are reinjected 1, 2, 3, 4, 5, or more times. In some embodiments, the pharmaceutical compositions are reinjected after about 20 days and after about 25 days.

V. Methods of preparation

[0387] The CB2 antibody described herein may be prepared using any methods known in the art or as described herein. In some embodiments, there is provided a method of producing a CB2 antibody, comprising: (a) culturing a host cell comprising an isolated nucleic acid or vector encoding the CB2 antibody described herein under conditions effective to express the encoded CB2 antibody; and (b) obtaining the expressed CB2 antibody from said host cell. In some embodiments, the method of step (a) further comprises producing a host cell comprising the isolated nucleic acid or vector encoding the CB2 antibody described herein.

[0388] Methods of preparing antibodies comprising ISVDs are known in the art. *See*, for example, Els Pardon *et al.*, *Nature Protocol*, 2014; 9(3): 674. sdAbs (such as V_HHs) may be obtained using methods known in the art such as by immunizing a *Camelid* species (such as camel or llama) and obtaining hybridomas therefrom, or by cloning a library of single-domain antibodies using molecular biology techniques known in the art and subsequent selection by ELISA with individual clones of unselected libraries or by using phage display.

[0389] For recombinant production of the ISVD, the nucleic acids encoding the antibodies are isolated and inserted into a replicable vector for further cloning (amplification of the DNA) or for expression. DNA encoding the single-domain antibody is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). Many vectors are available. The choice of vector depends in part on the host cell to be used. Generally, preferred host cells are of either prokaryotic or eukaryotic (generally mammalian) origin.

[0390] In some embodiments, a vector (*e.g.*, expression vector) comprising a nucleic acid described herein are provided. In some embodiments, a host cell comprising such nucleic acid or vector is provided. In some embodiments, the host cell is eukaryotic, *e.g.* a Chinese Hamster Ovary (CHO) cell, Expi293 cell, or lymphoid cell (*e.g.*, Y0, NS0, Sp20 cell). In some embodiments, the host cell is prokaryotic, *e.g.* an *E. coli* cell. In some embodiments, a method of making a CB2 antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[0391] For recombinant production of a CB2 antibody, a nucleic acid encoding an antibody, *e.g.*, as described above, is isolated and inserted into a vector for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0392] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, *see, e.g.*, U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523. (*See also* Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*). After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0393] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast

strains whose glycosylation pathways have been “humanized,” resulting in the production of an antibody with a partially or fully human glycosylation pattern. *See* Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li *et al.*, *Nat. Biotech.* 24:210-215 (2006).

[0394] Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[0395] Plant cell cultures can also be utilized as hosts. *See, e.g.*, US Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0396] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, *e.g.*, in Graham *et al.*, *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, *e.g.*, in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, *e.g.*, in Mather *et al.*, *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR⁻ CHO cells (Urlaub *et al.*, *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, *see, e.g.*, Yazaki and Wu, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

[0397] In some embodiments, the CB2 antibodies described herein may undergo functional maturation or be the result thereof. As described herein, functional maturation comprises using variable regions from a library to introduce variability into an antibody backbone. In some embodiments, the antibody backbone is ABt285. In some embodiments, the library comprises sequences of ABt251 with one or more of the following modifications: one of two amino acids at each of six toggle positions, randomization of one of six CDR1 (SEQ ID NO:1) positions, or

randomization of two of sixteen CDR3 (SEQ ID NO:3) positions. In some embodiment, the six toggle positions are IMGT position 15 (A or P), position 52 (F or W), position 54 (A or S), position 55 (A or G), position 103 (S or W), and position 118 (S or W). In some embodiments, the mutated positions within CDR1 (SEQ ID NO:1) are IMGT positions 27, 28, 29, 31, 32, or 33 (*i.e.*, positions 2-4 and 6-7 of SEQ ID NO:1). In some embodiments, the randomized positions within CDR1 and CDR3 can be any amino acid except C and M.

[0398] The human CB2 receptor was expressed in the yeast cell membrane and coupled to a yeast growth pathway. The CB2 receptor-expressing yeast were transformed with the VHH library of ABt285 variants. Stronger (more potent and/or efficacious) variants induced growth under different conditions than ABt285. Agonist antibody clones were identified by DNA sequencing of the antibody-encoding nucleic acid in the transformed yeast.

VI. Articles of manufacture and kits

[0399] Further provided are kits and articles of manufacture comprising any of the isolated CB2 antibodies described herein, pharmaceutical compositions comprising any of the CB2 antibodies describes herein, isolated nucleic acids or vectors encoding thereof, or isolated host cells comprising the isolated nucleic acids or vectors encoding the CB2 antibodies described herein. In some embodiments, a kit is provided which comprises any one of the pharmaceutical compositions described herein and preferably provides instructions for its use.

[0400] The kits of the present application are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (*e.g.*, sealed Mylar or plastic bags), and the like. Kits may optionally provide additional components such as buffers and interpretative information. The present application thus also provides articles of manufacture, which include vials (such as sealed vials), bottles, jars, flexible packaging, and the like.

[0401] The article of manufacture can comprise a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, *etc.* The containers may be formed from a variety of materials such as glass or plastic. Generally, the container holds a composition which is effective for treating a disease or disorder (such as cancer) described herein, and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The label or package insert indicates that the composition is used for treating the particular condition in an individual. The label or package insert will further comprise

instructions for administering the composition to the individual. The label may indicate directions for reconstitution and/or use. The container holding the pharmaceutical composition may be a multi-use vial, which allows for repeat administrations (*e.g.* from 2-6 administrations) of the reconstituted formulation. Package insert refers to instructions customarily included in commercial packages of therapeutic products that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0402] The kits or article of manufacture may include multiple unit doses of the pharmaceutical composition and instructions for use, packaged in quantities sufficient for storage and use in pharmacies, for example, hospital pharmacies and compounding pharmacies.

EXAMPLES

[0403] The examples below are intended to be purely exemplary of the invention and should therefore not be considered to limit the invention in any way. The following examples and detailed description are offered by way of illustration and not by way of limitation.

Example 1: Generation of CB2 antibodies.

[0404] Antibodies that functionally activate CB2 were selected using Abalone Bio's proprietary Functional Antibody Screening Technology (FAST) system, which is described in more detail in US 2021/0198806 A1, the contents of which are hereby incorporated by reference for all purposes. Briefly, the human CB2 receptor was expressed in the yeast cell membrane and coupled to the pheromone response pathway, which, upon agonist engagement, drives the expression of HIS3 and leads to growth of *his3⁻* yeast cells in media lacking histidine (H- media). These CB2 receptor-expressing yeast were transformed with a VHH library encoded in a plasmid that leads to periplasmic expression of each VHH that is linked to the cell membrane via a YPS1 glycosylphosphatidylinositol anchoring domain (as further described in US 2021/0198806 A1). Agonist antibodies were identified by selecting yeast clones that grow in the H- media, followed

by DNA sequencing of the antibody-encoding plasmid in each of these clones to identify unique agonist clones that were subjected to further testing as shown in subsequent examples. One of the identified VHHs was designated AB101 (VHH according to SEQ ID NO:55; see **Table 3** above).

Example 2. Quantification of cAMP levels for measurement of agonist activity at CB1 and CB2 receptors.

[0405] Agonist antibody activity for the CB2 receptor (*e.g.*, human CB2 receptor) and CB1 receptor (*e.g.*, human CB1 receptor) were measured using the PerkinElmer's LANCE ultra-cAMP kit (cat. no. TRF0262; PerkinElmer, Boston, MA) per the manufacturer's instructions. All assays were performed at room temperature using 384-optiplates (cat. no. 6007299; PerkinElmer). Briefly, HEK cells stably transfected with the CB2 or CB1 receptors (HEK CB2 and HEK CB1) were harvested, pelleted, and resuspended in 1X stimulation buffer (1X Hanks' balanced salt solution, 5 mM HEPES, 0.5 mM IBMX, 0.1% bovine serum albumin (BSA), pH 7.4, made fresh on the day of experiment). The cells were incubated in 1X stimulation buffer for 1 hour at 37° C, 5% CO₂, and humidified air and then transferred to a 384-optiplate (500 cells/well), followed by stimulation with drugs/compounds and forskolin (2 μ M final concentration) made in 1X stimulation buffer, as appropriate, for 5 minutes. Cells were then lysed by addition of Eu-cAMP tracer and Ulight anti-cAMP detection reagents (both 4X solutions, made fresh in lysis buffer supplied with the kit, under subdued light conditions). Reactions were incubated for 1 hour at room temperature under subdued light. Plates were then read in TR FRET mode (340nm excitation, 665nm/615nm emission) on an Enspire plate reader (PerkinElmer). These measurements were used to determine the EC₅₀ values for CB2 receptor agonism. EC₅₀ values for AB101 were found to be 56 nM for human CB2, 30 nM for mouse CB2, and no activity was observed against human CB1 (**FIG. 1**).

[0406] As shown in **FIG. 1A**, 1 μ M AB101 reduced forskolin-induced cAMP levels in HEK293 cells over-expressing human CB2 but not CB1, while 1 μ M of the small molecule agonist CP55940, which potently activates CB1 and CB2, reduced cAMP in both. Data normalized to forskolin stimulated and unstimulated responses. Co-treatment with the CB2-specific inverse agonist SR144528 eliminates the effect of CP55940 and AB101. 1 μ M control anti-GFP Ab had no effect on cAMP. ****: $P < 0.0001$ vs. no treatment; ** $P = 0.002$ vs. no treatment; (all comparisons: one-way ANOVA). As shown in **FIG. 1B**, AB101 is a potent agonist of human and mouse CB2. Normalized cAMP levels after AB101 treatment of cells over-expressing

human (grey squared) or mouse (black circles) CB2 (n=3). EC50: hsCB2: 56 nM; mmCB2: 30 nM. All values shown are mean $\pm$ SEM, n=3-4.

Example 3A. Paclitaxel model of chemotherapy-induced peripheral neuropathy (CIPN).

[0407] Paclitaxel at 4 mg/kg (“CIPN”) or cremophor vehicle control (“Healthy”) was injected by intraperitoneal injection (i.p.) into C57BL/6 mice on days 1, 3, 5, and 7. When allodynia was established and stable on day 16, Abt140 (25 mg/kg i.p.) or vehicle was injected. Mechanical allodynia was assessed by measuring withdrawal thresholds (g) in duplicate for each paw with an electronic von Frey anesthesiometer. Cold allodynia was assessed by measuring response times (s) spent attending to (*i.e.*, elevating, licking, biting, or shaking) the paw stimulated with acetone, measured in triplicate. Data are shown in **FIGs. 2A** (mechanical) and **2B** (cold). N=6 female mice. Data are mean $\pm$ SEM. BL:pre-paclitaxel baseline. PacBL:post-paclitaxel baseline. *** $P < .001$, CIPN+Ab vs. CIPN+Vehicle (veh), statistics analyzed using one way ANOVA followed by Bonferroni post hoc test.

[0408] Further, as shown in **FIG. 3A**, ABt140 (SEQ ID NO:94) agonizes human CB2. cAMP levels after ABt140 or CP55940 (CB1/CB2 small molecule agonist) treatment of cells overexpressing human CB2. (n=2). EC50: ABt140 (squares) 30nM; CP55940 (circles) 9.5nM.

Example 3B. Paclitaxel model of chemotherapy-induced peripheral neuropathy (CIPN).

[0409] ABt269 is an anti-GFP VHH-Fc antibody used as a control in some of the following experiments, and having the sequence:

QVQLVESGGALVQPGGSLRLSCAASGFPVNRYSMRWYRQAPGKEREWVAGMS
SAGDRSSYEDSVKGRFTISRDDARNTVYLQMNSLKPEDTAVYYCNVNVGFEYW
GQGTQVTVSSGGGGSGGGGSGGGGSEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSVMSVHEALHNHYTQKSLSLSPGK (SEQ ID NO:204)

[0410] Paclitaxel at 4 mg/kg (“CIPN”) or cremophor vehicle control (“Healthy”) was injected by intraperitoneal injection (i.p.) into C57BL/6 mice on days 1, 3, 5, and 7. When allodynia was established and stable on day 16, ABt281 (5 or 25 mg/kg i.p.) antibody control ABt269 (25 mg/kg i.p.), or vehicle (PBS) was injected. Mechanical allodynia was assessed by measuring

withdrawal thresholds (g) in duplicate for each paw with an electronic von Frey anesthesiometer. Cold allodynia was assessed by measuring response times (s) spent attending to (*i.e.*, elevating, licking, biting, or shaking) the paw stimulated with acetone, measured in triplicate. Data are shown in **FIG. 8A** (mechanical) and **FIG. 8B** (cold). N=6 female mice. Data are mean $\pm$ SEM. BL:pre-paclitaxel baseline. PacBL:post-paclitaxel baseline. *** $P<.001$, CIPN+Ab vs. CIPN+Control (ABt269), statistics analyzed using one way ANOVA followed by Bonferroni post hoc test.

[0411] **FIG. 9A** and **FIG. 9B** show the same experiment performed with CB2 knockout mice. There is no difference between CIPN + Ab (ABt281) versus CIPN + Control (ABt269) in the CB2 knockout mice, confirming antibody specificity and the requirement of CB2 receptor for antibody activity.

[0412] In **FIG. 10A** and **FIG. 10B**, the antibody or control was administered daily for five days, and, on each day, the mechanical and cold allodynia was assessed two hours after administration. Superior ABt281 activity was demonstrated with the lower dose of ABt281 (5 mg/kg) compared to the higher dose (25 mg/kg).

[0413] Groups were treated with CB2 specific agonist, AM1710, 24 hours after ABt281 or PBS dosing. For the PBS groups, as expected, CB2 agonist activity with AM1710 resulted in an improvement in efficacy with increased mechanical threshold (**FIG. 11A**) and decreased time of response (**FIG. 11B**). In contrast, treatment with AM1710 did not further improve the response in Abt281-treated mice, indicating that free CB2 receptor is not present for AM1710 activation and increased response to CB2 agonism. The experiment provides further evidence that there is antibody-mediated CB2 depletion upon treatment with ABt281. AM1710 is (3-(1,1-dimethyl-heptyl)-1-hydroxy-9-methoxy-benzo(c) chromen-6-one), a cannabylactone cannabinoid receptor 2 (CB2) agonist (see Khanolkar *et al.*, J. Med. Chem. 2007 Dec 27;50(26):6493-500).

Example 4. Decrease in IL-6 and IL-8 secretion by BEAS2B human airway cells

[0414] BEAS2B human airway epithelial cells (ATCC CRL-9609) were cultured as instructed and treated with 10 micrograms/mL LPS in the presence of either ABt140 or control anti-lysozyme IgG4 (Control Ab) at the concentrations indicated in **FIG. 3B** and **FIG. 3C** for 24 hours. IL-6 and IL-8 concentrations in the supernatant were measured using (Invitrogen ELISA kit, EH2IL6). Abt140 decreased both IL-6 secretion (**FIG. 3B**) and IL-8 (**FIG. 3C**) secretion by

BEAS2B human airway cells. (n=2). Two-way ANOVA: * $p < 0.05$, *** $p = 0.0001$, **** $p < 0.0001$.

Example 5. ABt140 improves clinical scores and reduces mortality in a mouse model of H1N1 (PR8) influenza infection.

[0415] Adult female BALB/c mice were challenged with 38 TCID₅₀ A/PR/8/34 (H1N1) (Charles River) on Day 0, and treated with vehicle (n=3), control Ab IgG4 at 25 mg/kg (n=10), or ABt140 (SEQ ID NO:94) at 25 mg/kg (n=10) on days 3 and 5. Results are shown in **FIGs. 4A-4C**.

[0416] FIG. 4A shows Area under curve (AUC) of clinical score (1-5) of coat condition, posture, breathing, mobility, and eye discharge/ closure over 7 days. **** $p < 0.0001$, ** $p = 0.0018$. ABt140 improved clinical score of mice.

[0417] FIG. 4B shows survival of mice challenged with 38 TCID₅₀ A/PR/8/34 (H1N1) on Day 7. ABt140 increased 7-day survival of mice as compared to vehicle control or antibody control.

[0418] FIG. 4C shows viral load. Adult female BALB/c mice were challenged with 89 TCID₅₀ A/PR/8/34 (H1N1) on Day 0, and treated with vehicle (n=3), control Ab IgG4 at 25 mg/kg (n=10), or ABt140 at 25 mg/kg (n=10) at 2 hours and day 2. Viral load was determined from lung homogenates. Data are shown as 50% tissue culture infective dose (TCID₅₀) per group (n = 10). Data analyzed by Log-rank (Mantel-Cox) test, comparing against control Ab. ABt140 treatment did not reduce viral titer.

Example 6. Stability mutation and testing.

[0419] Several mutations were tested for improved manufacturability, decreased immunogenicity and improved stability. The M5V mutation is thought to be beneficial as it removes a methionine, which is a potential side chain prone to oxidation. The R39Q mutation was chosen because Q is conserved at this position in humans, and the original R is not found in a majority VHH sequences. I58Y was chosen because Y is more conserved at this position, and it was found in the original AB101 parental clone during screening. Finally D65G was chosen due to its greater conservation in known VHH sequences. A combination of these four mutations were tested to evaluate manufacturability and VHH activity

[0420] The VHH clones were expressed in the periplasm of *E. coli* using a pET-28b expression vector (Sigma-Aldrich 69865) modified to include a pelB secretion signal. Vectors were

transformed into BL21(DE3) cells (Sigma-Aldrich 70235) according to the manufacturer's instructions. A single colony from the transformation was grown in LB+kanamycin to an OD₆₀₀ between 0.4 and 0.6 and induced with IPTG to 1 mM and grown overnight at 18°C. After 16 hours of induction, the cultures are spun at 4750 rpm for 20 min at 4°C and the supernatant is discarded. Pellets are washed with 200mM Tris-HCl and centrifuged at 4750 rpm. The supernatant is discarded and pellets are resuspended in 200mM Tris-HCl with 20% sucrose, 500 ug/mL lysozyme, 1mM PMSF, pH 7.4 for 15 min at 25°C. Three volumes of water are added and the solution is rocked for 15 min at 4°C. The solution is centrifuged at 4750 rpm for 20 min and the supernatant is transferred to a small flask for antibody purification. The resulting VHH antibody is purified using HisPur Cobalt Resin (ThermoFisher 89964) following the manufacturer's recommendation for purification of his-tagged proteins using a gravity flow column. Resulting antibodies are tested for thermal stability using the UNCLE system (Unchained Labs). Nine uL of each antibody was loaded in triplicate into Uni cuvettes. A temperature scan was performed from 25 to 95°C at a 0.3 °C per minute scan rate. T_m values were calculated by Barycentric Mean Method of analysis.

Table 6. Melting temperatures of VHH antibodies		
Sample	T_m1 (°C)	%CV T_m1
AB101 (SEQ ID NO:55)	< 50	---
ABt247 (SEQ ID NO:72)	62.2	0.31
ABt250 (SEQ ID NO:73)	66.9	0.21
ABt251 (SEQ ID NO:74)	68.5	0.06
ABt252 (SEQ ID NO:75)	67.1	0.21
ABt253 (SEQ ID NO:76)	63.4	0.02
ABt254 (SEQ ID NO:77)	65.2	0.15

Example 7. CB2 Activation Reduces LPS or IL-4 Induced Inflammatory Response on Macrophages.

[0421] Serum-starved RAW264.7 mouse macrophage cells (ATCC TIB-71) were cultured and exposed to HU-308 (onternabez), ABt281, ABt285, or ABt269 (1uM and 100nM) for 6 hours and followed by either LPS (100ng/ml; **FIG. 5A**) or IL-4 (10ng/ml; **FIG. 5B**) for 12 hours. M1

and M2 macrophage gene expressions were measured by using RTPCR. CB2 specific agonist (HU-308) and CB2-specific agonistic antibodies (ABt281 and ABt285) significantly reduced LPS or IL-4 induced inflammatory response compared to buffer control, LPS alone, or IL-4 alone.

Example 8. CB2 activation decreases IL-6 secretion by RAW264.7 mouse macrophage cells.

[0422] RAW264.7 cells were serum starved for 4 hours exposed to LPS at 1 ug/ml in the presence of CB2 agonist (CP55,940), CB2-specific agonistic antibodies (ABt281 or ABt285), or isotype control ABt269 for 12 hours. IL-6 concentrations in the supernatant were measured using (Perkin Elmer IL-6 LANCE Ultra TR- FRET kit, TRF1223C). CP-55,940, ABt281 and ABt269 decreased IL-6 secretion in a dose dependent manner by RAW264.7 mouse macrophage cells (FIG. 6).

Example 9. *In vitro* activation of CB2 receptor inhibits cAMP signaling in RAW264.7 mouse macrophage cells.

[0423] RAW264.7 cells were cultured and treated with cAMP activator NKH477 to stimulate cAMP production. The cells were then treated with CB2 agonist HU308 or CB2 specific agonist antibodies (ABt281, ABt285) or isotype control (ABt269) (FIG. 7) and CB2 mediated Gi-cAMP signaling efficacy was measured using the cAMP-Glo assay (Promega), whereby luminescence is inversely proportional to cAMP concentration. Application of HU308, ABt281 and ABt285 decreased NKH477 stimulated cAMP production. EC50 values for HU308, ABt281 and ABt285 were 32nM, 4.5nM, and 1.5nM, respectively.

Example 10. CB2 Agonist antibody reduces fibrotic and inflammatory response in a precision cut human liver slice model.

[0424] The precision cut human liver slice model (hPCLS) preserves all cell types within their native architecture to uniquely capture endogenous cell-cell interactions. PCLS from de-identified resection samples of two injured, human male livers were used to test the activity of ABt281 and ABt285 (100nM and 1μM), ABt269 isotype control (1μM), Alk5i (positive control), or PBS (vehicle) following 24-hour and 48-hour incubation. Alk5i is a TGF-beta type I receptor kinase (ALK5) inhibitor (CAS 446859-33-2).

[0425] Human precision-cut liver slices (hPCLS) were generated from discarded remnants of surgically resected human livers. Normal-appearing resection margins surrounding HCC were selected for hPCLS generation. The ischemic time between post-hepatectomy and generated PCLS was 3-4 hours. Cores of 8 mm diameter were generated from which intact liver slices (200 μ m thickness) and collected from the buffer tray using a soft bristle brush and transferred to six well tissue culture plate (3 slices/well) filled with 37 °C warm William's E GlutaMAX media supplemented with 25 mM glucose and 50 μ g/ml gentamycin. The slices were pre-incubated for 24 hours to equilibrate the tissues. After pre-incubation, fresh medium was added containing either ABt281 (100 nM, 1 μ M), ABt285 (100 nM, 1 μ M), ABt269 isotype control (1 μ M), Alk5i (10 μ M), or PBS for an additional 24 and 48 hours.

[0426] For efficacy assessment, at the end of drug treatment from each condition, secretion of collagen1a1 (Col1a1) into the media was assessed by ELISA (**FIG. 12A**). At 48-hours the CB2, the agonist antibodies and Alk5i all significantly reduced Col1a1 compared to the PBS control. The ABt269 isotype control was not significantly different from the PBS control.

[0427] Also, at the end of drug treatment from each condition, slices were used for total mRNA extraction. Collagen1a1 (COL1A1, **FIG. 12B**), alpha smooth muscle actin (ACTA2, **FIG. 12C**), interleukin 6 (IL6, **FIG. 12D**), interleukin 10 (IL10, **FIG. 12E**) and tumor necrosis factor alpha (TNF α , **FIG. 12F**) mRNA levels were quantified using RT-qPCR. For COL1A1, ACTA2, IL6, and IL10, treatment with ABt281, ABt285, or positive control Alk5i resulted in statistically significant reduction of these inflammatory or fibrotic factors, however, no significant change was observed upon treatment with ABt269 (isotype control antibody) or PBS (vehicle, negative control). For TNF α , 1 mm treatment with ABt281 or ABt285 led to a reduction in this highly inflammatory factor, while no significant change was observed in the other groups.

Example 11. *In vitro* activation of CB2 receptor activates pERK1/2 signaling in RAW264.7 mouse macrophage cells.

[0428] RAW264.7 cells were cultured and serum starved for 4 hours and exposed to CB2-specific agonist HU-308, CB2-specific agonist antibodies (ABt281 or ABt285), or isotype control (ABt269), and pERK activator (PMA) overnight. CB2-mediated pERK1/2 signaling efficacy was measured by using TR-FRET pERK1/2 kit (LANCE Ultra pERK1/2 kit, Perkin Elmer, TRF4000). Application of PMA, HU308, ABt 281, and ABt285 increased TR-FRET signal in a dose dependent manner, while no ERK phosphorylation was observed with the

isotype control ABt269. EC₅₀ values for HU-308, ABt281, ABt285 and PMA were 53 nM, 98 nM, 159 nM, and 25 nM, respectively (**FIG. 13A**). The experiment was repeated, obtaining EC₅₀ values for HU-308, ABt281, ABt285 and PMA were 120nM, 95 nM, 99nM, and 109nM, respectively (**FIG. 13B**), demonstrating consistent CB2 receptor-mediated activation of pERK1/2 signaling in RAW264.7 mouse macrophage cells.

Example 12. Paclitaxel model of chemotherapy-induced peripheral neuropathy (CIPN).

[0429] Paclitaxel at 4 mg/kg (to induce “CIPN”) or cremophor vehicle control was injected by intraperitoneal injection (i.p.) into C57BL/6 mice on days 0, 2, 4, and 6. When allodynia was established and stable on day 15, ABt281 (5 mg/kg i.p.), ABt285 (5 or 25 mg/kg i.p.), ABt140 (5 or 25 mg/kg i.p.), or vehicle (PBS) was injected. The same antibody dosed were reinjected on days 20 and 25. Mechanical allodynia was assessed by measuring withdrawal thresholds (g) in duplicate for each paw with an electronic von Frey anesthesiometer. Cold allodynia was assessed by measuring response times (s) spent attending to (*i.e.*, elevating, licking, biting, or shaking) the paw stimulated with acetone, measured in triplicate. Data are shown in **FIGs. 15A** (mechanical) and **15B** (cold), with N=6 mice, and data +/- SEM (B: pre-paclitaxel baseline; PAC: post-paclitaxel baseline; mechanical and cold stimulation were evaluated on days 0, 4, 7, 11, and 15 plus the times indicated in **FIGs. 15A-B** after antibody treatment).

Example 13. CB2 agonist antibodies recruit B-Arrestin 2 in RAW264.7 mouse macrophage cells.

[0430] RAW264.7 cells were cultured and transfected with B-Arr2 plasmid (20ng, Revvity, PWTBARR2) and pcDNA3 plasmid (130ng) via lipofectamine 2000. Transfected cells were treated with CB2 specific agonist HU308, CB2 agonist antibodies (ABt0281, ABt0285) or isotype control (ABt269). CB2 mediated B-Arr2 recruitment was measured using TR-FRET B-Arr2 recruitment kit (HTRF B-Arr2 recruitment kit, Revvity, 62BDBARR2PEB). Application of HU308 or CB2 agonist antibodies increases TR-FRET signal.

Example 14. Functional maturation of CB2 antibodies.

[0431] Antibodies that functionally activate CB2 more strongly than ABt285 were selected using Abalone Bio’s proprietary Functional Antibody Screening Technology (FAST) system, which is

described in more detail in US 2021/0198806 A1, the contents of which are hereby incorporated by reference for all purposes.

[0432] To further improve the stability of the antibodies, a library was designed based on the ABt251 sequence (SEQ ID NO:74). Each library member of this experiment has the sequence of ABt251 except for the following modifications: one of two amino acids are used at each of six toggle positions, one of six CDR1 (SEQ ID NO:1) positions is randomized, and two of sixteen CDR3 (SEQ ID NO:3) positions are randomized. The six toggle positions are IMGT position 15 (A or P), position 52 (F or W), position 54 (A or S), position 55 (A or G), position 103 (S or W), and position 118 (S or W). The mutated positions within CDR1 (SEQ ID NO:1) are IMGT positions 27, 28, 29, 31, 32, or 33 (*i.e.*, positions 2-4 and 6-7 of SEQ ID NO:1). All CDR3 (SEQ ID NO:3) positions are included in the randomization strategy as described above. All amino acids are allowed in the randomized positions within CDR1 and CDR3, except C and M. The exception is IMGT position 31, for which the parental Abt251 sequence (SEQ ID NO:74) is M. Therefore, M is allowed and only C is excluded in the randomization for IMGT position 31.

[0433] Briefly, the variable regions of the library described above were ported to the ABt285 backbone. The human CB2 receptor was expressed in the yeast cell membrane and coupled to a yeast growth pathway. The CB2 receptor-expressing yeast were transformed with the VHH library of ABt285 variants. Stronger (more potent and/or efficacious) variants induced growth under different conditions than ABt285. Agonist antibody clones were identified by DNA sequencing of the antibody-encoding plasmid in the selected clones. These clones were validated and scored based on their growth properties in yeast and were subjected to further testing as shown in subsequent examples. **Table 7** shows how ABt285 variants identified from FAST functional maturation were scored based on growth properties (*e.g.*, size and/or number of colonies). Parent (ABt285) growth score was defined as 1, and negative control growth score as 0.

Table 7. Growth scores of functionally matured antibodies	
Sample	Growth score
ABhit_0231	5
ABhit_0232	3
ABhit_0233	4
ABhit_0234	4
ABhit_0235	4

ABhit_0236	0
ABhit_0238	3
ABhit_0239	5
ABhit_0240	1
ABhit_0241	3
ABhit_0242	3
ABhit_0243	2
ABhit_0244	5
ABhit_0245	5
ABhit_0246	4
ABhit_0247	2
ABhit_0248	3
ABhit_0249	4
ABhit_0250	3
ABhit_0251	4
ABhit_0252	4
ABhit_0253	4
ABhit_0254	5
ABhit_0255	4
ABhit_0256	4
ABhit_0257	5
ABhit_0258	0
ABhit_0259	4
ABhit_0260	4
ABhit_0261	1
ABhit_0262	5
ABhit_0263	3
ABhit_0264	3
ABhit_0266	1
ABhit_0267	0
ABhit_0268	3
ABhit_0269	0
ABhit_0270	4
ABhit_0271	4
ABhit_0272	4
ABhit_0320	4
ABhit_0321	3
ABhit_0322	4
Parent (ABt285)	1

Negative control	0
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Example 15. Functional maturation of CB2 antibodies have increased efficacy and potency.

[0434] *In vitro* activation by agonist antibodies of CB2 receptor inhibits cAMP signaling in RAW264.7 mouse macrophage cells and THP-1 human monocyte cells differentiated to macrophages. RAW264.7 cells were cultured and treated with CB2 agonist HU308 (onternabez) or CB2 positive control agonist antibody (ABt285, SEQ ID NO:203), isotype control (ABt269, SEQ ID NO:204), or ABhit231-272 (see **Table 7**). THP-1 cells were differentiated to macrophages by treatment with 200nM Phorbol 12-myristate 13-acetate (PMA) prior to CB2 agonist treatment. ABhit231-272 represent the top functionally matured CB2 agonist antibodies (Example 14). For two to three concentrations of antibody, CB2 mediated GI-cAMP signaling efficacy was measured using cAMP-Glo assay (Promega, V1501), whereby luminescence is inversely proportional to cAMP concentration (**FIG. 16**). Application of HU308 or ABt285 increased luminescence signal in a dose dependent manner. Low response was observed with negative control antibody ABt269. Several ABhit antibodies showed dose dependent changes in luminescence consistent with CB2 agonism (**FIG. 17, Tables 8 and 9**).

Table 8	cAMP RAW264.7		B Arrestin RAW264.7	
Name	EC50 (nM)	% eff vs. HU308	EC50 (nM)	% eff vs. HU308
anti-CB2 pos ctrl				
ABt_281	5	79%	443	75%
ABt_285	10.9	112%	130	45%
ABhit_0231	4.4	123%	81	41%
ABhit_0239	6.6	116%	188	54%
ABhit_0242	6.2	145%	86	34%
ABhit_0244	1.4	104%	174	59%
ABhit_0245	7.4	71%	86	59%
ABhit_0249	5.9	92%	144	71%
ABhit_0252	2.9	120%	208	57%
ABhit_0253	10.5	102%	168	67%
ABhit_0254	3.5	149%	232	53%
ABhit_0256	10.5	87%	110	69%

ABhit_0268	6.1	144%	168	41%
ABhit_0269	6.6	139%	243	45%

Table 9	cAMP THP-1		B Arrestin THP-1	
Name	EC50 (nM)	% eff vs. HU308	EC50 (nM)	% eff vs. HU308
ABt_285	8.1	85%	112	59%
ABhit_0231	13.7	95%	74	48%
ABhit_0244	7.5	82%	65	48%

Example 16. CB2 agonist antibodies having undergone functional maturation recruit B-Arrestin 2 in RAW264.7 mouse macrophage cells.

[0435] RAW264.7 and THP-1 cells were cultured and transfected with B-Arr2 plasmid (20ng, Revvity, PWTBARR2) and pcDNA3 plasmid (130ng) via lipofectamine 2000. THP-1 cells were differentiated to macrophages by treatment with 200nM Phorbol 12-myristate 13-acetate (PMA) prior to CB2 agonist treatment. Transfected cells were treated with CB2 specific agonist HU308, CB2 agonist antibody (ABt0285) or isotype control (ABt269). CB2 mediated B-Arr2 recruitment was measured using TR-FRET B-Arr2 recruitment kit (HTRF B-Arr2 recruitment kit, Revvity, 62BDBARR2PEB). Application of HU308 or CB2 agonist antibodies increased TR-FRET signal in a dose dependent manner (**FIG. 17, Tables 8 and 9**).

Example 17. Analysis of allowed mutations in ABt285 CDR1 and CDR3.

[0436] The sequences of antibodies that were enriched over the rounds of functional maturation were analyzed and the frequencies of amino acid usage at each position were calculated. To quantify how close to fixation a given site is, we calculated Shannon's entropy $H = -\sum(p_i \cdot \log_2(p_i))$. The cutoff of 0.2 for fixed amino acids was determined based the sequencing noise identified in the fixed library positions (CDR1, positions 1 and 5) and small variation in the selection process. Four positions are fixed: CDR1-position 6: S, CDR3-position 4: I, CDR3-position 5: K, CDR3-position 13: I. Five positions have entropy above the cutoff, and can tolerate 2 or 3 amino acids with one dominating: CDR1-position 2: S/Q, CDR3-position 7: G/A, CDR3-position 9: G/K, CDR3-position 11: F/L, CDR3-position 14: K/N. The results of this analysis are provided in **Tables 10 and 11**.

Table 10. Amino acid frequency at each CDR1 position.	Position 1	Position 2	Position 3	Position 4	Position 5	Position 6	Position 7	Position 8
A	0.002046	0.000256	0.001535	0.001535	0	0.000256	0.001023	0.761637
C	0.000256	0.000256	0	0.000256	0.002813	0	0	0.000512
D	0	0.006394	0.00179	0.011765	0	0.000256	0.000256	0.001023
E	0	0.001535	0.000767	0.051662	0	0.001023	0.004348	0.000512
F	0	0.000767	0.001279	0.518926	0	0.000256	0.001535	0.002302
G	0.995141	0.001023	0.009719	0.011509	0.000256	0	0.180051	0.223018
H	0	0.002046	0.044501	0.055243	0	0	0.002302	0.000512
I	0	0.001023	0.897442	0.005627	0.000256	0.990793	0.003325	0.000256
K	0	0.000512	0.028133	0.086701	0	0.000256	0.024041	0.000256
L	0	0.000512	0.001023	0.003836	0	0.000512	0.004348	0.001023
M	0	0	0.000767	0	0	0.001279	0.721995	0
N	0	0.001279	0.002813	0.006905	0	0.00179	0.002558	0
P	0	0.001535	0.000767	0.000512	0	0	0.003581	0.001279
Q	0	0.01509	0.002558	0.033504	0	0	0.00179	0.001023
R	0.002302	0.004604	0.002046	0.115857	0.00179	0	0.014322	0.001279
S	0	0.958312	0.001279	0.014322	0.991304	0	0.000512	0.002302
T	0	0.003325	0.000767	0.007417	0.003581	0.000767	0.001279	0.000512
V	0.000256	0	0.001279	0.051407	0	0.002302	0.002302	0.000767
W	0	0.000767	0.000256	0.011765	0	0.000512	0.002813	0.000512
Y	0	0.000767	0.001279	0.011253	0	0	0.027621	0.001279
Entropy	<i>0.05</i>	<i>0.38</i>	<i>0.74</i>	<i>2.58</i>	<i>0.09</i>	<i>0.10</i>	<i>1.42</i>	<i>0.93</i>

Table 11. Amino acid frequency at each CDR3 position.

	Position 1	Position 2	Position 3	Position 4	Position 5	Position 6	Position 7	Position 8
A	0.001279	0.037596	0.581074	0.000512	0.000767	0.000767	0.019437	0.000256
C	0.002558	0.001535	0	0	0	0.000512	0.00179	0.002813
D	0.002302	0.00179	0.000256	0.000256	0.000256	0.009207	0.000767	0.000767
E	0	0.005627	0.004348	0.000256	0.000256	0.001023	0.000767	0
F	0.037852	0.025831	0.009974	0.002046	0.000256	0.007417	0.000256	0
G	0.002046	0.619949	0.006905	0.000767	0.000256	0.000512	0.963171	0.000512
H	0.068286	0.002302	0.001279	0.000512	0	0.001023	0.000256	0
I	0.202558	0.011253	0.257801	0.98133	0.000256	0.001279	0.000256	0.004092
K	0.011253	0.000512	0.048082	0.000512	0.985678	0.001279	0.000256	0.002046
L	0.17954	0.040409	0.056777	0.000256	0	0.000256	0	0
M	0.004604	0.000256	0.000512	0.00665	0.002302	0	0	0
N	0.004604	0.001279	0.005882	0.002046	0.006394	0.01202	0.000512	0.001535
P	0	0.002302	0.003836	0	0.000256	0.000256	0	0.000767
Q	0.001535	0.021739	0.001279	0.000256	0.000256	0.000512	0	0

R	0.007417	0.007673	0.000256	0.000256	0.000512	0.001279	0.006905	0.007673
S	0.440153	0.002302	0.003581	0.002558	0.000256	0.001023	0.003325	0.962404
T	0.008951	0.000256	0.000512	0.000512	0.000767	0.032481	0	0.003325
V	0.018159	0.212276	0.017647	0.001023	0.001023	0.002046	0.00179	0.003581
W	0.000256	0.001279	0	0	0.000256	0.004604	0.000512	0.008696
Y	0.00665	0.003836	0	0.000256	0.000256	0.922506	0	0.001535
Entropy	2.38	1.85	1.80	0.19	0.15	0.61	0.31	0.35

Table 11 (cont.).

	Position 9	Position 10	Position 11	Position 12	Position 13	Position 14	Position 15	Position 16
A	0.004092	0.001279	0.001023	0.003581	0	0.000256	0.164194	0.015601
C	0	0	0.001535	0	0	0	0.000256	0.000767
D	0.00844	0.177749	0	0.93734	0	0.000256	0.001023	0.01023
E	0.000767	0.004348	0.000256	0.022506	0.000256	0.000256	0.001535	0.000512
F	0.000767	0.000767	0.940409	0.000512	0.001535	0	0.005115	0.004859
G	0.948082	0.002046	0.002046	0.000256	0.000256	0.000256	0.03734	0.073657
H	0.003581	0.001023	0.001535	0.007417	0.000256	0.000767	0.024041	0.004859
I	0.000256	0.042711	0.000767	0.000256	0.982864	0	0.027621	0.000767
K	0.023274	0.000256	0.000256	0.002302	0.000256	0.974425	0.004604	0.003325
L	0	0.020205	0.037852	0	0.00179	0	0.081841	0.001023
M	0.000256	0.001023	0	0	0.00179	0.00179	0.000256	0
N	0.000512	0.000512	0.000767	0.001023	0.00179	0.018159	0.32046	0.004348
P	0	0.000512	0	0.001023	0	0	0.009463	0.000767
Q	0.000256	0.00665	0.000256	0.018926	0.000256	0.000512	0.001535	0.000512
R	0.007161	0.702813	0.001023	0.000256	0.000256	0.002046	0.004604	0.001023
S	0.000256	0.012532	0.000767	0.000767	0.007417	0	0.035038	0.000767
T	0.000512	0.01867	0.007673	0	0.000256	0.000256	0.135294	0.007673
V	0.001535	0.002558	0.003069	0.002046	0.000256	0.001023	0.131969	0.001535
W	0	0.003325	0.000512	0	0.000256	0	0.011765	0.000256
Y	0.000256	0.001023	0.000256	0.00179	0.000512	0	0.002046	0.867519
Entropy	0.43	1.51	0.45	0.50	0.17	0.22	2.96	0.89

Example 18. Creation of CB2 antibodies with increased functional activity.

[0437] Historically, the discovery and design of antibodies relied on laborious biopanning techniques, serendipitous screening libraries, or complex rational engineering approaches. When effective, these methods often proved time-consuming, expensive, and limited in scope, and sometimes they failed to find any hits for difficult targets. The recent emergence of protein language models (PLMs)—models based on large language models (LLMs) originally developed for natural language—has ushered in a paradigm shift, revolutionizing the way we explore, manipulate, and generate antibody sequences. PLMs, trained on vast datasets of antibody sequences and associated properties such as binding, stability, and immunogenicity, now offer

the tantalizing prospect of accelerating antibody discovery and design with unprecedented speed, precision, and creativity.

[0438] PLMs have not been previously applied to the problem of generating antibodies that go beyond specifically binding a target to also modulating the target's signaling activity for a therapeutic effect, *i.e.*, "functional antibodies". PLMs are primarily trained either to predict the next amino acids (AAs) given a sequence of AAs or to fill-in a set of AA's masked in a larger sequence. By training on a large corpora of observed sequences, PLM's can learn sequence to structure relationships. Given functional information about sequences, PLM's pre-trained using the language modeling task on large corpora of sequences can be finetuned to classify sequences into likely active or inactive. The key roadblock for PLMs in the discovery and ultimately design of functional antibodies is the lack of large-scale, high-quality functional dataset.

[0439] Abalone Bio's Functional Antibody Selection Technology (FAST) platform is capable of generating large-scale, high-quality functional datasets of antibody sequence-function relationships against targets such as GPCRs. The data generated from an agonist antibody selection campaign against the receptor CB2 were combined. A pre-trained antibody PLM was fine-tuned to be a binary classifier of antibody functionality with our ten-fold cross-validation subsets of the data. The trained models were used to score test set sequences the models had not been presented. This ensemble of ten models was used to score novel sequences that were generated by modifying a seed sequence, the highest scoring sequence in the training set. The novel sequences were generated by identifying high entropy sites and amino acids from the FAST selection, *i.e.* those sites that showed variation from the starting sequence post-selection. Given the identified sites and residues, all possible variants of the seed sequence were scored by the ensemble of models. All sequences with an average log-odds ratio (logit) greater than 2.5 were clustered based on their sequence identity into 256 clusters using the k-means algorithm. To ensure sequence diversity, the top-4 sequences from each cluster were chosen as the candidate sequences to validate experimentally. As the volume of sequences with more edits is greater than those for fewer, sequences with less than six edits were largely absent from the candidate set; thus, we sample an additional set of sequences from this edit distance radius. The complete candidate set of novel sequences along with negative controls (low logit scores) was synthesized and evaluated with the FAST platform. A number of sequences amongst the candidate set were identified that demonstrate agonist activity in a CB2 FAST yeast strain –

demonstrating a greater hit rate (3.5%) than the functional maturation (0.18%) variants (**FIG. 19**). In addition, the candidate set included antibody sequences that showed greater activity than the seed sequence (**FIG. 20**).

Example 19. GenAI-created CB2 agonist antibodies induce growth in yeast expressing human CB2.

[0440] Antibodies that functionally activate CB2 were selected using Abalone Bio’s proprietary Functional Antibody Screening Technology (FAST) system, which is described in more detail in US 2021/0198806 A1, the contents of which are hereby incorporated by reference for all purposes. Briefly, sequences created by genAI were selected, the coding regions synthesized and cloned into the same backbone as ABhit_0231. The human CB2 receptor was expressed in the yeast cell membrane and coupled to a yeast growth pathway. The CB2 receptor-expressing yeast were transformed with the genAI VHH library. VHHs with agonist activity were selected for under different conditions. Agonists induced growth under selective conditions. Stronger (more potent and/or efficacious) agonists induced growth under different conditions than ABhit_0231. Agonist antibody clones were identified by DNA sequencing of the antibody-encoding plasmid in the selected clones. These clones were validated based on their growth properties in yeast. **Table 12** shows how genAI variants identified from FAST were scored based on growth properties (*e.g.*, size and/or number of colonies). Seed (ABhit_0231) growth score was defined as 5 in Example 14, ABt285 growth score was defined as 1, and negative control growth score as 0.

Table 12	
VHH	score
ABhit_0428	7
ABhit_0429	7
ABhit_0430	7
ABhit_0431	7
ABhit_0432	6
ABhit_0433	7
ABhit_0434	7
ABhit_0436	7

ABhit_0438	6
ABhit_0439	6
ABhit_0440	6
Seed (ABhit_0231)	5
ABt_0285	1
Negative Control	0

CLAIMS

What is claimed is:

1. A cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises a complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO:1, a CDR2 comprising the amino acid sequence of SEQ ID NO:2, and a CDR3 comprising the amino acid sequence of SEQ ID NO:3, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT.
2. A CB2 antibody comprising an ISVD that specifically binds to a CB2, wherein the ISVD comprises a CDR1, a CDR2, and a CDR3 of an ISVD comprising the amino acid sequence of SEQ ID NO:201.
3. The CB2 antibody of claim 1 or 2, wherein the ISVD comprises one or more amino acid residues selected from the group consisting of V5, Q39, Y58, G65, R71, A74, and L78 in one or more framework regions (FRs), wherein the amino acid numbering is according to Kabat.
4. The CB2 antibody of claim 3, wherein the ISVD comprises amino acid residues V5, Q39, Y58 and G65 in one or more FRs.
5. The CB2 antibody of any one of claims 1-4, wherein the ISVD comprises:
 - an FR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:4-15;
 - an FR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-30;
 - an FR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:31-48 and 200; and
 - an FR4 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:49-54.
6. The CB2 antibody of claim 5, wherein the ISVD comprises:
 - (i) an FR1 comprising the amino acid sequence of SEQ ID NO:14, an FR2 comprising the amino acid sequence of SEQ ID NO:29, an FR3 comprising the amino

acid sequence of SEQ ID NO:43, and an FR4 comprising the amino acid sequence of SEQ ID NO:54;

(ii) an FR1 comprising the amino acid sequence of SEQ ID NO:15, an FR2 comprising the amino acid sequence of SEQ ID NO:23, an FR3 comprising the amino acid sequence of SEQ ID NO:45, and an FR4 comprising the amino acid sequence of SEQ ID NO:54; or

(iii) an FR1 comprising the amino acid sequence of SEQ ID NO:4, an FR2 comprising the amino acid sequence of SEQ ID NO:16, an FR3 comprising the amino acid sequence of SEQ ID NO:200, and an FR4 comprising the amino acid sequence of SEQ ID NO:49.

7. The CB2 antibody of any one of claims 1-6, wherein the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:55-77 and 201, or a variant thereof having at least about 85% sequence identity to the amino acid sequence of any one of SEQ ID NOs:55-77 and 201.

8. The CB2 antibody of claim 7, wherein the ISVD comprises the amino acid sequence of SEQ ID NO:201, 70, or 74.

9. The CB2 antibody of any one of claims 1-8, comprising a polypeptide chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:78-95 and 202-203, or a variant thereof having at least about 85% sequence identity to the amino acid sequence of any one of SEQ ID NOs:78-95 and 202-203.

10. The CB2 antibody of claim 9, comprising a polypeptide chain comprising the amino acid sequence of SEQ ID NO:203.

11. A cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises

i) a complementarity determining region (CDR) 1 having the amino acid formula G-X1-X2-X3-S-I-X4-X5, wherein X1 is selected from D, S, or Q; X2 is selected from G, H, I, or K; X3 is selected from D, E, F, G, H, I, K, N, Q, R, S, T, V, W, or Y; X4 is selected from G, K, M, R, or Y; and X5 is selected from A or G; and

ii) a CDR3 having the amino acid formula C1-C2-C3-I-K-C4-C5-C6-C7-C8-C9-C10-I-C11-C12-C13, wherein C1 is selected from F, H, I, K, L, R, S, T, V, or Y; wherein C2 is selected from A, E, F, G, I, L, Q, R, or V; wherein C3 is selected from A, F, G, I, K, L, N, or V; wherein C4 is selected from D, F, N, T, or Y; wherein C5 is selected from A, G, or R; wherein C6 is selected from R, S, or W; wherein C7 is selected from D, G, K, or R; wherein C8 is selected from D, I, L, Q, R, S, or T; wherein C9 is selected from F, L, or T; wherein C10 is selected from any D, E, H, or Q; wherein C11 is selected from K or N; wherein C12 is selected from A, F, G, H, I, K, L, N, P, R, S, V, T, or W; and wherein C13 is selected from A, D, F, G, H, T, or Y.

12. The CB2 antibody of claim 11, wherein CDR2 is SEQ ID NO:2.
13. A cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:248-288, CDR2 comprising an amino acid sequence of SEQ ID NO:2, and a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:289-329, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT.
14. The CB2 antibody of any one of claims 11-13 wherein the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:205-212, 214-229, and 231-247, or a variant thereof having at least about 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs:205-212, 214-229, and 231-247.
15. The CB2 antibody of claim 11, wherein the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NO:205, SEQ ID NO:212, SEQ ID NO:215, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:222, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:229, SEQ ID NO:240, and SEQ ID NO:241, or a variant thereof having at least about 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:205, SEQ ID NO:212, SEQ ID NO:215, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:222, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:229, SEQ ID NO:240, and SEQ ID NO:241.

16. A cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises a CDR3 having the amino acid formula C1-C2-C3-I-K-Y-G-S-G-C4-F-D-I-K-C5-C6, wherein C1 is selected from L, I, V, Y, or F; wherein C2 is selected from F, A, or V; wherein C3 is selected from A, I, or V; wherein C4 is selected from D or L; wherein C5 is selected from G, T, or V; and wherein C6 is selected from Y, A, or F, wherein the CDR3 is defined according to IMGT.
17. The CB2 antibody of claim 16, wherein CDR1 is SEQ ID NO:248 and CDR2 is SEQ ID NO:2, wherein the CDR1 and CDR2 are defined according to IMGT.
18. A cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises a CDR1 comprising an amino acid sequence of SEQ ID NO:248, CDR2 comprising an amino acid sequence of SEQ ID NO:2, and a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:345-359, wherein the CDR1, CDR2 and CDR3 are defined according to IMGT.
19. The CB2 antibody of any one of claims 16-18 wherein the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:330-344, or a variant thereof having at least about 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs:330-344.
20. The CB2 antibody of claim 16, wherein the ISVD comprises an amino acid sequence selected from the group consisting of SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, and SEQ ID NO:344, or a variant thereof having at least about 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, and SEQ ID NO:344.
21. A cannabinoid receptor type 2 (CB2) antibody comprising an immunoglobulin single variable domain (ISVD) that specifically binds a CB2, wherein the ISVD comprises:

- a CDR1 comprising the amino acid sequence of SEQ ID NO:248;
a CDR2 comprising the amino acid sequence of SEQ ID NO:2; and
a CDR3 having the amino acid formula C1-C2-C3-I-K-Y-G-S-G-C4-F-D-I-K-C5-C6,
wherein C1 is selected from L, I, V, Y, or F; wherein C2 is selected from F, A, or V;
wherein C3 is selected from A, I, or V; wherein C4 is selected from D or L; wherein C5
is selected from G, T, or V; and wherein C6 is selected from Y, A, or F,
wherein the CDR1, CDR2, and CDR3 are defined according to IMGT.
22. The CB2 antibody of claim 21, wherein the ISVD comprises:
a CDR1 comprising the amino acid sequence of SEQ ID NO:248;
a CDR2 comprising the amino acid sequence of SEQ ID NO:2; and
a CDR3 comprising the amino acid sequence selected from the group consisting of
SEQ ID NOS:345-359.
23. The CB2 antibody of any one of claims 1-22, wherein the ISVD is a variable domain of
the heavy chain of a heavy chain antibody (VHH).
24. The CB2 antibody of claim 23, wherein the ISVD is camelid.
25. The CB2 antibody of claim 23, wherein the ISVD is chimeric.
26. The CB2 antibody of claim 23, wherein the ISVD is humanized.
27. The CB2 antibody of any one of claims 1-26, wherein the antibody comprises an Fc
region.
28. The CB2 antibody of claim 27, wherein the antibody comprises an Fc region of an IgG1
or IgG4.
29. The CB2 antibody of claim 28, wherein the antibody comprises a variant IgG4 Fc region
exhibiting reduced effector function.
30. The CB2 antibody of claim 29, wherein the Fc region comprises amino acid substitutions
F234A and L235A, with numbering according to the EU index of Kabat.

31. The CB2 antibody of claim 27 or 28, wherein the Fc region comprises the amino acid sequence of SEQ ID NO:130.
32. The CB2 antibody of claim 28, wherein the antibody comprises a variant IgG1 Fc region exhibiting reduced effector function.
33. The CB2 antibody of claim 32, wherein the variant IgG1 Fc region comprises amino acid substitutions L234A, L235A, M252Y, S254T, and T256E, wherein the residues are numbered according to the EU index.
34. The CB2 antibody of claim 33, wherein the variant IgG1 Fc region comprises the amino acid sequence of SEQ ID NO:363.
35. The CB2 antibody of claim 32, wherein the variant IgG1 Fc region comprises amino acid substitutions L234A, L235A, and P329G, wherein the residues are numbered according to the EU index.
36. The CB2 antibody of claim 35, wherein the variant IgG1 Fc region comprises the amino acid sequence of SEQ ID NO:364.
37. The CB2 antibody of claim 32, wherein the variant IgG1 Fc region comprises amino acid substitutions L234A, L235A, M252Y, S254T, T256E, and P329G, wherein the residues are numbered according to the EU index.
38. The CB2 antibody of claim 37, wherein the variant IgG1 Fc region comprises the amino acid sequence of SEQ ID NO:365.
39. The CB2 antibody of any one of claims 27-38, wherein the antibody comprises a hinge region.
40. The CB2 antibody of claim 39, wherein the hinge region comprises the amino acid sequence of SEQ ID NO:131.
41. The CB2 antibody of any one of claims 27-40, wherein the ISVD is fused to the Fc region via a peptide linker.

42. The CB2 antibody of claim 41, wherein the peptide linker comprises the amino acid sequence of SEQ ID NO:132.
43. The CB2 antibody of claim 41 or 42, wherein the antibody comprises a polypeptide chain comprising from the N-terminus to the C-terminus: the ISVD, a peptide linker, a hinge region, and an Fc region.
44. The CB2 antibody of any one of claims 1-43, wherein the CB2 is human, mouse, rat or cynomolgus monkey CB2.
45. The CB2 antibody of claim 44, wherein the CB2 is a human CB2.
46. The CB2 antibody of any one of claims 1-45, wherein the CB2 antibody is a CB2 agonist.
47. The CB2 antibody of claim 46, wherein the CB2 antibody does not agonize CB1.
48. The CB2 antibody of claim 46 or 47, wherein:
- (i) the ISVD reduces forskolin-induced cyclic adenosine monophosphate (cAMP) level in HEK293 cells overexpressing human CB2 with a half maximal effective concentration (EC_{50}) that is less than 55 nM; and/or
 - (ii) the ISVD reduces forskolin-induced cyclic adenosine monophosphate (cAMP) level in HEK293 cells overexpressing mouse CB2 with an EC_{50} that is less than 30 nM.
49. The CB2 antibody of any one of claims 1-48, wherein the ISVD does not specifically bind a cannabinoid receptor type 1 (CB1).
50. The CB2 antibody of any one of claims 1-49, wherein the CB2 antibody binds HEK293 cells overexpressing human CB2 with an EC_{50} that is less than 850 nM.
51. An isolated nucleic acid encoding the CB2 antibody of any one of claims 1-50.
52. An expression vector comprising the nucleic acid of claim 51.
53. A host cell comprising the nucleic acid of claim 51 or the expression vector of claim 52.
54. A method of producing a CB2 antibody, comprising culturing the host cell of claim 53 under conditions where the CB2 antibody is produced.

55. The method of claim 54, further comprising recovering the CB2 antibody produced by the host cell.
56. A pharmaceutical composition comprising the CB2 antibody of any one of claims 1-50 and a pharmaceutically acceptable carrier.
57. A method of agonizing CB2 on a cell, comprising contacting the cell with an amount of the CB2 antibody of any one of claims 1-50 that is sufficient for activating CB2 on the cell.
58. The method of claim 57, wherein the method is *in vitro*.
59. The method of claim 57, wherein the method is *in vivo*.
60. A method of treating an individual in need thereof having a disease or condition, wherein agonizing CB2 ameliorates the disease or condition, comprising administering to the individual an effective amount of the CB2 antibody of any one of claims 1-50.
61. The method of claim 60, wherein the disease or condition is selected from the group consisting of chemotherapy induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy, respiratory infections, liver fibrosis, cold sensitivity, inflammatory bowel disease, and endometriosis.
62. The method of claim 61, wherein the disease or condition is chemotherapy induced peripheral neuropathy (CIPN).
63. The method of claim 62, wherein the CIPN is caused by a taxol drug.
64. The method of claim 63, wherein the taxol drug is paclitaxel.
65. A method of treating a cancer in an individual in need thereof, comprising administering to the individual an effective amount of a chemotherapeutic agent, and an effective amount of the CB2 antibody of any one of claims 1-50.
66. The method of claim 61, wherein the disease or condition is a respiratory infection.
67. The method of claim 66, wherein the respiratory infection is caused by a virus selected from the group consisting of influenza viruses and coronaviruses.

- 68. The method of claim 66, wherein the respiratory infection is caused by SARS-CoV-2.
- 69. The method of claim 66, wherein the respiratory infection is caused by H1N1 influenza.
- 70. A method of reducing a cytokine release syndrome in an individual in need thereof, comprising administering to the individual an effective amount of the CB2 antibody of any one of claims 1-50.
- 71. The method of claim 70, wherein the method decreases IL-16 and/or IL-8 level secreted by airway cells in the individual.
- 72. The method of claim 61, wherein the disease or condition is liver fibrosis.
- 73. The method of claim 61, wherein the disease or condition is diabetic peripheral neuropathy.
- 74. The method of any one of claims 60-73, wherein the individual is a human.
- 75. A kit comprising the CB2 antibody of any one of claims 1-50 or the pharmaceutical composition of claim 49, and instructions for use.