

ANTI-DECTIN-2 ANTIBODIES

CROSS-REFERENCE TO PRIOR APPLICATIONS

[0001] This application claims benefit to U.S. Provisional Patent Application No. 63/018,952, filed May 1, 2020, which is hereby incorporated by reference in its entirety.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED
ELECTRONICALLY

[0002] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 222,025 Byte ASCII (Text) file named "753797_ST25.txt," created on April 30, 2021.

BACKGROUND OF THE INVENTION

[0003] Dectin-2 (dendritic cell-associated C-type lectin 2, CLEC6A, CLEC4N, CLECSF10) belongs to the family of C-type lectin receptors. Dectin-2 is thought to primarily play a role in antifungal immunity, by binding to carbohydrate ligands such as mannans, which are typically found on fungal cell surfaces. Dectin-2 is expressed mainly by cells of myeloid lineage, including monocytes, macrophages and dendritic cells. Activation of the Dectin-2 pathway can elicit a pro-inflammatory immune response in these cells, including activation of the NF- κ B pathway and subsequent production of pro-inflammatory cytokines, as well as increased phagocytic activity. A pro-inflammatory immune response driven by Dectin-2 activation on Dectin-2 expressing myeloid cells in the tumor microenvironment can ultimately lead to an anti-tumor immune response. Accordingly, agents that bind to Dectin-2, including those that act as Dectin-2 agonists, can be useful in the treatment of cancer.

[0004] There is still a need for additional methods of preventing and treating cancer given that most cancer patients ultimately fail standard of care therapies. Dectin-2 binding agents, including those that act to agonize the Dectin-2 signaling pathway, can be used to address this need.

BRIEF SUMMARY OF THE INVENTION

[0005] Provided herein are Dectin-2 binding agents comprising an immunoglobulin heavy chain variable region polypeptide and an immunoglobulin light chain variable region

polypeptide. In some embodiments, the Dectin-2 binding agents comprise an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 243-282 or 324, or at least the CDRs thereof; and an immunoglobulin light chain variable region of any one of SEQ ID NOs: 283-322 or at least the CDRs thereof. In other embodiments, the Dectin-2 binding agents comprise an immunoglobulin heavy chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 243-282 or 324, and an immunoglobulin light chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 283-322. In yet other embodiments of the Dectin-2 binding agent, the immunoglobulin heavy chain variable region polypeptide comprises a complementarity determining region 1 (HCDR1) comprising any one of SEQ ID NOs: 1-30, a complementarity determining region 2 (HCDR2) comprising any one of SEQ ID NOs: 31-64, and a complementarity determining region 3 (HCDR3) comprising any one of SEQ ID NOs: 65-103 or 323; and/or the immunoglobulin light chain variable region polypeptide comprises a complementarity determining region 1 (LCDR1) comprising any one of SEQ ID NOs: 104-125, a complementarity determining region 2 (LCDR2) comprising any one of SEQ ID NOs: 126-148, and a complementarity determining region 3 (LCDR3) comprising any one of SEQ ID NOs: 149-181. In further embodiments, the Dectin-2 binding agents comprise an immunoglobulin heavy chain polypeptide of any one of SEQ ID NOs: 328-345, and an immunoglobulin light chain polypeptide of any one of SEQ ID NOs: 325-327. In still further embodiments, the Dectin-2 binding agents comprise an immunoglobulin heavy chain polypeptide that is at least 90% identical to any one of SEQ ID NOs: 328-345, and an immunoglobulin light chain polypeptide that is at least 90% identical to any one of SEQ ID NOs: 325-327. Also provided are nucleic acids encoding the Dectin-2 binding agents, or the individual heavy and light chains thereof; vectors and cells comprising the nucleic acids; and compositions comprising the binding agents or nucleic acids.

[0006] Also provided is a method of preparing a binding agent as described herein, which method comprises expressing in a cell one or more nucleic acids encoding the heavy and light chain variable region polypeptides of the binding agent.

[0007] Also provided is a method for treating a disease, disorder, or condition in a mammal that is responsive to Dectin-2 activation or inhibition, which method comprises administering a binding agent as described herein, or conjugate thereof, to the mammal.

[0008] Also provided is a method of stimulating an antigen presenting cell (APC), which method comprises contacting an APC with a Dectin-2 binding agent at a dose and for a

period of time sufficient to enhance Dectin-2 signaling in the APC, thereby generating a stimulated APC.

[0009] Additional aspects and embodiments of the invention are as provided in the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure 1 is a bar graph of Tumor Necrosis Factor alpha (TNF α (pg/mL)) secreted by GM-CSF-treated human monocytes which have been exposed to certain soluble anti-Dectin-2 antibodies at a concentration of 100 μ g/mL.

[0011] Figure 2 is a bar graph of TNF α (pg/mL) secreted by GM-CSF-treated human monocytes which have been exposed to certain plate-adsorbed anti-Dectin-2 antibodies at a concentration of 25 μ g/mL.

[0012] Figure 3 is a graph of TNF α (pg/mL) secreted by GM-CSF-treated human monocytes stimulated with different concentrations (nM) of each of the indicated antibodies.

[0013] Figure 4 is a graph of TNF α (pg/mL) secreted by GM-CSF-treated human monocytes stimulated with different concentrations (nM) of each of the indicated antibodies.

[0014] Figures 5A and 5B are graphs of TNF α (pg/mL) secreted by M-CSF-treated human monocytes stimulated with different concentrations (nM) of each of the indicated antibodies.

[0015] Figure 6 is a graph of TNF α (pg/mL) secreted by M-CSF-treated human monocytes stimulated with different concentrations (nM) of each of the indicated antibodies.

[0016] Figure 7 is a graph of TNF α (pg/mL) secreted by GM-CSF-treated human monocytes stimulated with different concentrations (nM) of each of the indicated antibodies.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The invention provides a Dectin-2 binding agent comprising an immunoglobulin heavy chain variable region polypeptide and an immunoglobulin light chain variable region polypeptide. The Dectin-2 binding agent specifically binds Dectin-2, and allows for targeting Dectin-2 expressing cells, for instance, to activate (induce) one or more Dectin-2-associated pathways in the Dectin-2 expressing cells.

[0018] In some embodiments, the Dectin-2 binding agent binds Dectin-2, which is a receptor, without substantially inhibiting or preventing binding of one or more of its natural ligands to Dectin-2. In some embodiments, the Dectin-2 binding agent agonistically binds

Dectin-2, thereby completely or partially activating Dectin-2 signaling in Dectin-2 expressing cells (e.g., for therapeutic purposes). In some embodiments, the Dectin-2 binding agent binds Dectin-2 as a monomer. In some embodiments, the Dectin-2 binding agent binds Dectin-2 as a homodimer or a heterodimer with another protein, such as Dectin-3. When the Dectin-2 binding agent binds to Dectin-2 as a homodimer or heterodimer (e.g., Dectin-2/Dectin-3 heterodimer), the binding agent can bind to the Dectin-2 prior to formation of the homodimer or heterodimer or, in other embodiments, the Dectin-2 binding agent binds Dectin-2 after it has formed a homodimer or heterodimer.

[0019] In some embodiments, the Dectin-2 binding agent binds to human Dectin-2, for example, a protein comprising SEQ ID NO: 346

(MMQEQQPQSTKRGWLSLRLWSVAGISIALLSACFIVSCVVTYHFTYGETGKRLSEL
HSYHSSLTCFSEGTKVPAWGCCPASWKSFGSSCYFISSEKVVWSKSEQNCVEMGAHL
VVFNTEAEQNFIVQQLNESFSYFLGLSDPQGNNNWQWIDKTPYEKNVRFWHLGEPN
HSAEQCASIVFWKPTGWGWNDVICETRRNSICEMNKIYL). However, binding agents that bind to any Dectin-2 homolog or paralog also are encompassed. In some embodiments, the Dectin-2 protein comprises at least about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more sequence identity to SEQ ID NO: 346. In some embodiments, the binding agent binds human and/or mouse Dectin-2.

[0020] Nucleic acid or amino acid sequence “identity,” as referenced herein, can be determined by comparing a nucleic acid or amino acid sequence of interest to a reference nucleic acid or amino acid sequence. The percent identity is the number of nucleotides or amino acid residues that are the same (i.e., that are identical) as between the optimally aligned sequence of interest and the reference sequence divided by the length of the longest sequence (i.e., the length of either the sequence of interest or the reference sequence, whichever is longer). Alignment of sequences and calculation of percent identity can be performed using available software programs. Examples of such programs include CLUSTAL-W, T-Coffee, and ALIGN (for alignment of nucleic acid and amino acid sequences), BLAST programs (e.g., BLAST 2.1, BL2SEQ, BLASTp, BLASTn, and the like) and FASTA programs (e.g., FASTA3x, FASTM, and SSEARCH) (for sequence alignment and sequence similarity searches). Sequence alignment algorithms also are disclosed in, for example, Altschul et al., *J. Molecular Biol.*, 215(3): 403-410 (1990), Beigert et al., *Proc. Natl. Acad. Sci. USA*, 106(10): 3770-3775 (2009), Durbin et al., eds., *Biological Sequence*

Analysis: Probabilistic Models of Proteins and Nucleic Acids, Cambridge University Press, Cambridge, UK (2009), Soding, *Bioinformatics*, 21(7): 951-960 (2005), Altschul et al., *Nucleic Acids Res.*, 25(17): 3389-3402 (1997), and Gusfield, *Algorithms on Strings, Trees and Sequences*, Cambridge University Press, Cambridge UK (1997)). Percent (%) identity of sequences can be also calculated, for example, as $100 \times [(\text{identical positions}) / \min(\text{TG}_A, \text{TG}_B)]$, where TG_A and TG_B are the sum of the number of residues and internal gap positions in peptide sequences A and B in the alignment that minimizes TG_A and TG_B . See, e.g., Russell et al., *J. Mol Biol.*, 244: 332-350 (1994).

[0021] The binding agent comprises Ig heavy and light chain variable region polypeptides that together form the antigen binding site. Each of the heavy and light chain variable regions are polypeptides comprising three complementarity determining regions (CDR1, CDR2, and CDR3) connected by framework regions. The binding agent can be any of a variety of types of binding agents known in the art that comprise Ig heavy and light chains. For instance, the binding agent can be an antibody, an antigen-binding antibody “fragment,” or a T-cell receptor.

[0022] In some embodiments, the binding agent is a whole (or complete) antibody, which comprises an antigen binding domain comprising the Ig heavy and light variable domains as well as a fragment crystallizable (Fc) domain. An exemplary antibody structure is a tetramer composed of two pairs of polypeptide chains, each pair having one “light” (a smaller chain, such as about 25 kDa) and one “heavy” chain (a larger chain, such as about 50-70 kDa), typically connected by disulfide bonds. Each chain is composed of structural domains, which are referred to as immunoglobulin domains. These domains are classified into different categories by size and function, e.g., variable domains or regions on the light and heavy chains (V_L and V_H , respectively) and constant domains or regions on the light and heavy chains (C_L and C_H , respectively). The N-terminus of each chain defines a variable region, typically about 100 to 110 or more amino acids (but not limited thereto), referred to as the paratope, primarily responsible for antigen recognition, i.e., the antigen binding domain. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively. The classes can be further divided into subclasses. For instance, there are four IgG subclasses (IgG1, IgG2, IgG3, and IgG4) in humans, named in order of their abundance in serum (i.e., IgG1 is the most abundant).

[0023] In some embodiments, the binding agent is an antigen-binding antibody “fragment,” which is a construct that comprises at least an antigen-binding region of an antibody, alone or with other components that together constitute the antigen-binding construct. Many different types of antibody “fragments” are known in the art, including, for instance, (i) a Fab fragment, which is a monovalent fragment consisting of the V_L , V_H , C_L , and CH_1 domains, (ii) a $F(ab')_2$ fragment, which is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region, (iii) a F_v fragment consisting of the V_L and V_H domains of a single arm of an antibody, (iv) a Fab’ fragment, which results from breaking the disulfide bridge of an $F(ab')_2$ fragment using mild reducing conditions, (v) a disulfide-stabilized F_v fragment (dsF_v), and (vi) a single chain F_v (scF_v), which is a monovalent molecule consisting of the two domains of the F_v fragment (i.e., V_L and V_H) joined by a synthetic linker which enables the two domains to be synthesized as a single polypeptide chain.

[0024] The antibody or antibody fragments can be part of a larger construct, for example, a conjugate or fusion construct of the antibody fragment to additional regions. For instance, in some embodiments, the antibody fragment can be fused to an Fc region as described herein. In other embodiments, the antibody fragment (e.g., a Fab or scF_v) can be part of a chimeric antigen receptor or chimeric T-cell receptor, for instance, by fusing to a transmembrane domain (optionally with an intervening linker or “stalk” (e.g., hinge region)) and optional intercellular signaling domain. For instance, the antibody fragment can be fused to the gamma and/or delta chains of a t-cell receptor, so as to provide a T-cell receptor like construct that binds Dectin-2. In yet another embodiment, the antibody fragment is part of a bispecific T-cell engager (BiTEs) comprising a CD1 or CD3 binding domain and linker.

[0025] The antibody or antigen-binding antibody fragment can be monospecific for Dectin-2, or can be bispecific or multi-specific. For instance, in bivalent or multivalent antibodies or antibody fragments, the binding domains can be different, and each binding domain can target different epitopes of the same antigen or target different antigens. In certain embodiments, the antibody or antigen binding antibody fragment is bispecific or multi-specific, wherein at least one binding domain specifically binds to Dectin-2, and at least one binding domain specifically binds a tumor targeting protein. Examples of tumor targeting proteins include 5T4, ABL, ABCF1, ACVR1, ACVR1B, ACVR2, ACVR2B, ACVRL1, ADORA2A, AggreCAN, AGR2, AICDA, AIF1, AIGI, AKAP1, AKAP2, AMH, AMHR2, ANGPT1, ANGPT2, ANGPTL3, ANGPTL4, ANPEP, APC, APOC1, AR,

aromatase, ATX, AX1, AZGP1 (zinc- α -glycoprotein), B7.1, B7.2, B7-H1, BAD, BAFF, BAG1, BAI1, BCR, BCL2, BCL6, BDNF, BLNK, BLR1 (MDR15), BlyS, BMP1, BMP2, BMP3B (GDF10), BMP4, BMP6, BMP8, BMPR1A, BMPR1B, BMPR2, BPAG1 (plectin), BRCA1, C19orf10 (IL27w), C3, C4A, C5, C5R1, CANT1, CAPRIN-1, CASP1, CASP4, CAV1, CCBP2 (D6/JAB61), CCL1 (1-309), CCL11 (eotaxin), CCL13 (MCP-4), CCL15 (MIP-Id), CCL16 (HCC-4), CCL17 (TARC), CCL18 (PARC), CCL19 (MIP-3b), CCL2 (MCP-1), MCAF, CCL20 (MIP-3a), CCL21 (MEP-2), SLC, exodus-2, CCL22(MDC/STC-I), CCL23 (MPIF-I), CCL24 (MPIF-2/eotaxin-2), CCL25 (TECK), CCL26(eotaxin-3), CCL27 (CTACK/ILC), CCL28, CCL3 (MIP-1a), CCL4 (MIP1b), CCL5(RANTES), CCL7 (MCP-3), CCL8 (mcp-2), CCNA1, CCNA2, CCND1, CCNE1, CCNE2, CCR1 (CKR1/HM145), CCR2 (mcp-IRB/RA), CCR3 (CKR3/CMKBR3), CCR4, CCR5(CMKBR5/ChemR13), CCR6 (CMKBR6/CKR-L3/STRL22/DRY6), CCR7 (CKR7/EBI1), CCR8 (CMKBR8/TER1/CKR-L1), CCR9 (GPR-9-6), CCRL1 (VSHK1), CCRL2 (L-CCR), CD164, CD19, CDIC, CD2, CD20, CD21, CD200, CD-22, CD24, CD27, CD28, CD3, CD33, CD35, CD37, CD38, CD3E, CD3G, CD3Z, CD4, CD38, CD40, CD40L, CD44, CD45RB, CD47, CD52, CD69, CD72, CD74, CD79A, CD79B, CD8, CD80, CD81, CD83, CD86, CD137, CD152, CD274, CDH1 (Ecadherin), CDH10, CDH12, CDH13, CDH18, CDH19, CDH20, CDH5, CDH7, CDH8, CDH9, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK9, CDKN1A (p21Wap1/Cip1), CDKN1B (p27Kip1), CDKN1C, CDKN2A (p16INK4a), CDKN2B, CDKN2C, CDKN3, CEBPB, CER1, CHGA, CHGB, Chitinase, CHST10, CKLFSF2, CKLFSF3, CKLFSF4, CKLFSF5, CKLFSF6, CKLFSF7, CKLFSF8, CLDN3, CLDN7 (claudin-7), CLN3, CLU (clusterin), CMKLR1, CMKOR1 (RDC1), CNR1, COL18A1, COLIA1, COL4A3, COL6A1, CR2, Cripto, CRP, CSF1 (M-CSF), CSF2 (GM-CSF), CSF3 (G-CSF), CTL8, CTNNB1 (b-catenin), CTSB (cathepsin B), CX3CL1 (SCYD1), CX3CR1 (V28), CXCL1 (GRO1), CXCL10 (IP-10), CXCL11 (1-TAC/IP-9), CXCL12 (SDF1), CXCL13, CXCL14, CXCL16, CXCL2 (GRO2), CXCL3 (GRO3), CXCL5 (ENA-78/LIX), CXCL6 (GCP-2), CXCL9 (MIG), CXCR3 (GPR9/CKR-L2), CXCR4, CXCR6 (TYMSTR/STRL33/Bonzo), CYB5, CYC1, CYSLTR1, DAB2IP, DES, DKFZp451J0118, DNCL1, DPP4, E2F1, Engel, Edge, Fennel, EFNA3, EFNB2, EGF, EGFR, ELAC2, ENG, Enola, ENO2, ENO3, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA9, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, EPHB6, EPHRIN-A1, EPHRIN-A2, EPHRINA3, EPHRIN-A4, EPHRIN-A5, EPHRIN-A6, EPHRIN-B1, EPHRIN-B2, EPHRIN-B3, EPHB4, EPG, ERBB2 (Her-2), EREG, ERK8, Estrogen receptor, Ear1,

ESR2, F3 (TF), FADD, farnesyltransferase, FasL, FASNf, FCER1A, FCER2, FCGR3A, FGF, FGF1 (aFGF), FGF10, FGF11, FGF12, FGF12B, FGF13, FGF14, FGF16, FGF17, FGF18, FGF19, FGF2 (bFGF), FGF20, FGF21, FGF22, FGF23, FGF3 (int-2), FGF4 (HST), FGF5, FGF6 (HST-2), FGF7 (KGF), FGF8, FGF9, FGFR3, FIGF (VEGFD), FIL1(EPSILON), FBL1 (ZETA), FLJ12584, FLJ25530, FLRT1 (fibronectin), FLT1, FLT-3, FOS, FOSL1(FRA-1), FY (DARC), GABRP (GABAa), GAGEB1, GAGEC1, GALNAC4S-6ST, GATA3, GD2, GDF5, GFI1, GGT1, GM-CSF, GNAS1, GNRH1, GPR2 (CCR10), GPR31, GPR44, GPR81 (FKSG80), GRCC10 (C10), GRP, GSN (Gelsolin), GSTP1, HAVCR2, HDAC, HDAC4, HDAC5, HDAC7A, HDAC9, Hedgehog, HGF, HIF1A, HIP1, histamine and histamine receptors, HLA-A, HLA-DRA, HLA-E, HM74, HMOXI, HSP90, HUMCYT2A, ICEBERG, ICOSL, ID2, IFN- α , IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNB1, IFN γ , IFNW1, IGBP1, IGF1, IGFIR, IGF2, IGFBP2, IGFBP3, IGFBP6, DL-1, IL10, IL10RA, IL10RB, IL-1, IL1R1 (CD121a), IL1R2(CD121b), IL-IRA, IL-2, IL2RA (CD25), IL2RB(CD122), IL2RG(CD132), IL-4, IL-4R(CD123), IL-5, IL5RA(CD125), IL3RB(CD131), IL-6, IL6RA, (CD126), IL6RB(CD130), IL-7, IL7RA(CD127), IL-8, CXCR1 (IL8RA), CXCR2, (IL8RB/CD128), IL-9, IL9R(CD129), IL-10, IL10RA(CD210), IL10RB(CDW210B), IL-11, IL11RA, IL-12, IL-12A, IL-12B, IL-12RB1, IL-12RB2, IL-13, IL13RA1, IL13RA2, IL14, IL15, IL15RA, IL16, IL17, IL17A, IL17B, IL17C, IL17R, IL18, IL18BP, IL18R1, IL18RAP, IL19, IL1A, IL1B, IL1F10, IL1F5, IL1F6, IL1F7, IL1F8, IL1F9, IL1HY1, IL1R1, IL1R2, IL1RAP, IL1RAPL1, IL1RAPL2, IL1RL1, IL1RL2, IL1RN, IL2, IL20, IL20RA, IL21R, IL22, IL22R, IL22RA2, IL23, IL24, IL25, IL26, IL27, IL28A, IL28B, IL29, IL2RA, IL2RB, IL2RG, IL3, IL30, IL3RA, IL4, IL4, IL6ST (glycoprotein 130), ILK, INHA, INHBA, INSL3, INSL4, IRAK1, IRAK2, ITGA1, ITGA2, ITGA3, ITGA6 (α 6 integrin), ITGAV, ITGB3, ITGB4 (β 4 integrin), JAG1, JAK1, JAK3, JTB, JUN, K6HF, KAI1, KDR, KITLG, KLF5 (GC Box BP), KLF6, KLK10, KLK12, KLK13, KLK14, KLK15, KLK3, KLK4, KLK5, KLK6, KLK9, KRT1, KRT19 (Keratin 19), KRT2A, KRTHB6(hair-specific type II keratin), LAMA5, LEP (leptin), Lingo-p75, Lingo-Troy, LPS, LTA (TNF-b), LTB, LTB4R (GPR16), LTB4R2, LTBR, MACMARCKS, MAG or OMgp, MAP2K7 (c-Jun), MCP-1, MDK, MIB1, midkine, MIF, MISRII, MJP-2, MK, MKI67 (Ki-67), MMP2, MMP9, MS4A1, MSMB, MT3 (metallothionein-UI), mTOR, MTSS1, MUC1 (mucin), MYC, MYD88, NCK2, neurocan, NFKBI, NFKB2, NGFB (NGF), NGFR, NgR-Lingo, NgRNogo66, (Nogo), NgR-p75, NgR-Troy, NMEI (NM23A), NOTCH, NOTCH1, NOX5, NPPB, NROB1, NROB2, NR1D1, NR1D2, NR1H2, NR1H3, NR1H4,

NR112, NR113, NR2C1, NR2C2, NR2E1, NR2E3, NR2F1, NR2F2, NR2F6, NR3C1, NR3C2, NR4A1, NR4A2, NR4A3, NR5A1, NR5A2, NR6A1, NRP1, NRP2, NT5E, NTN4, ODZ1, OPRDI, P2RX7, PAP, PART1, PATE, PAWR, PCA3, PCDGF, PCNA, PDGFA, PDGFB, PDGFRA, PDGFRB, PECAMI, peg-asparaginase, PF4 (CXCL4), PGF, PGR, phosphacan, PIAS2, PI3 Kinase, PIK3CG, PLAU (uPA), PLG, PLXDCI, PKC, PKC-beta, PPBP (CXCL7), PPID, PR1, PRKCQ, PRKD1, PRL, PROC, PROK2, PSAP, PSCA, PTAFR, PTEN, PTGS2 (COX-2), PTN, RAC2 (P21Rac2), RANK, RANK ligand, RARB, RGS1, RGS13, RGS3, RNFI1O (ZNF144), Ron, ROBO2, RXR, S100A2, SCGB 1D2 (lipophilin B), SCGB2A1 (mammaglobin 2), SCGB2A2 (mammaglobin 1), SCYE1 (endothelial Monocyte-activating cytokine), SDF2, SERPENA1, SERPINA3, SERPINB5 (maspin), SERPINE1 (PAI-I), SERPINF1, SHIP-1, SHIP-2, SHB1, SHB2, SHBG, SIRP α (SHPS1), SfcAZ, SLC2A2, SLC33A1, SLC43A1, SLIT2, SPP1, SPRR1B (Spr1), ST6GAL1, STAB1, STATE, STEAP, STEAP2, TB4R2, TBX21, TCP1O, TDGF1, TEK, TGFA, TGFB1, TGFB1I1, TGFB2, TGFB3, TGFBI, TGFB1R1, TGFB1R2, TGFB1R3, THIL, THBS1 (thrombospondin-1), THBS2, THBS4, THPO, TIE (Tie-1), TIMP3, tissue factor, TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, TNF, TNF-a, TNFAIP2 (B94), TNFAIP3, TNFRSF11A, TNFRSF1A, TNFRSF1B, TNFRSF21, TNFRSF5, TNFRSF6 (Fas), TNFRSF7, TNFRSF8, TNFRSF9, TNFSF10 (TRAIL), TNFSF11 (TRANCE), TNFSF12 (APO3L), TNFSF13 (April), TNFSF13B, TNFSF14 (HVEM-L), TNFRSF14 (HVEM), TNFSF15 (VEGI), TNFSF18, TNFSF4 (OX40 ligand), TNFSF5 (CD40 ligand), TNFSF6 (FasL), TNFSF7 (CD27 ligand), TNFSF8 (CD30 ligand), TNFSF9 (4-1BB ligand), TOLLIP, Toll-like receptors, TOP2A (topoisomerase Iia), TP53, TPM1, TPM2, TRADD, TRAF1, TRAF2, TRAF3, TRAF4, TRAF5, TRAF6, TRKA, TREM1, TREM2, TRPC6, TSLP, TWEAK, Tyrosinase, uPAR, VEGF, VEGFB, VEGFC, versican, VHL C5, VLA-4, VTCN1 (B7-H4), Wnt-1, XCL1 (lymphotactin), XCL2 (SCM-Ib), XCRI (GPR5/CCXCR1), YY1, ZFPM2, CLEC4C (BDCA-2, DLEC, CD303, CLECSF7), CLEC4D (MCL, CLECSF8), CLEC4E (Mincle), CLEC5A (MDL-1, CLECSF5), CLEC1B (CLEC-2), CLEC9A (DNGR-1), CLEC7A (Dectin-1), PDGFRa, SLAMF7, GP6 (GPVI), LILRA1 (CD85I), LILRA2 (CD85H, ILT1), LILRA4 (CD85G, ILT7), LILRA5 (CD85F, ILT11), LILRA6 (CD85b, ILT8), NCR1 (CD335, LY94, NKp46), NCR3 (CD335, LY94, NKp46), NCR3 (CD337, NKp30), OSCAR, TARM1, CD300C, CD300E, CD300LB (CD300B), CD300LD (CD300D), KIR2DL4 (CD158D), KIR2DS, KLRC2 (CD159C, NKG2C), KLRK1 (CD314, NKG2D), NCR2 (CD336, NKp44), PILRB, SIGLEC1 (CD169,

SN), SIGLEC14, SIGLEC15 (CD33L3), SIGLEC16, SIRPB1 (CD172B), TREM1 (CD354), TREM2, TROP2 (tumor-associated calcium signal transducer 2), and KLRF1 (Nkp80).

[0026] Methods of constructing multivalent binding constructs are known in the art. Bispecific and multispecific antibodies are known in the art. Furthermore, a diabody, triabody, tetrabody, or hexabody can be provided, which is a dimer, trimer, tetramer, or hexamer of polypeptide chains each comprising a V_H connected to a V_L by a peptide linker that is too short to allow pairing between the V_H and V_L on the same polypeptide chain, thereby driving the pairing between the complementary domains on different V_H - V_L polypeptide chains to generate a multimeric molecule having two, three, four, or six functional antigen binding sites. Also, bis-scFv fragments, which are small scFv fragments with two different variable domains can be generated to produce bispecific bis-scFv fragments capable of binding two different epitopes. Fab dimers (Fab2) and Fab trimers (Fab3) can be produced using genetic engineering methods to create multispecific constructs based on Fab fragments.

[0027] The Dectin-2 binding agent also can be an antibody conjugate. In this respect, the Dectin-2 binding agent can be a conjugate of (1) an antibody, an alternative scaffold, or fragments thereof, and (2) a protein or non-protein moiety. For example, the Dectin-2 binding agent can be conjugated to a peptide, a fluorescent molecule, chemotherapeutic or other cytotoxic payload, immune-activating or immune-suppressive agent.

[0028] The Dectin-2 binding agent can be, or can be obtained from, a human antibody, a non-human antibody, a humanized antibody, or a chimeric antibody, or corresponding antibody fragments. A “chimeric” antibody is an antibody or fragment thereof typically comprising human constant regions and non-human variable regions. A “humanized” antibody is a monoclonal antibody typically comprising a human antibody scaffold but with non-human origin amino acids or sequences in at least one CDR (e.g., 1, 2, 3, 4, 5, or all six CDRs).

[0029] Methods for generating such antibodies are known in the art and are described in, for example, Köhler and Milstein, *Eur. J. Immunol.*, 5: 511-519 (1976); Harlow and Lane (eds.), *Antibodies: A Laboratory Manual*, CSH Press (1988); and Janeway et al. (eds.), *Immunobiology, 9th Ed.*, Garland Publishing, New York, NY (2017). In certain embodiments, a human or chimeric antibody or antibody fragment can be generated using a transgenic animal (e.g., a mouse) wherein one or more endogenous immunoglobulin genes are replaced with one or more human immunoglobulin genes. Examples of transgenic mice

wherein endogenous antibody genes are effectively replaced with human antibody genes include, but are not limited to, the Medarex HUMAB-MOUSE™, the Kirin TC MOUSE™, and the Kyowa Kirin KM-MOUSE™ (see, e.g., Lonberg, *Nat. Biotechnol.*, 23(9): 1117-25 (2005), and Lonberg, *Handb. Exp. Pharmacol.*, 181: 69-97 (2008)). A humanized antibody can be generated using any suitable method known in the art (see, e.g., An, Z. (ed.), *Therapeutic Monoclonal Antibodies: From Bench to Clinic*, John Wiley & Sons, Inc., Hoboken, New Jersey (2009)), including, e.g., grafting of non-human CDRs onto a human antibody scaffold (see, e.g., Kashmiri et al., *Methods*, 36(1): 25-34 (2005); and Hou et al., *J. Biochem.*, 144(1): 115-120 (2008) and use of phage display (see, e.g., Fellouse, et al., *Journal of Molecular Biology*, 373(4): 924-940 (2007) and Glanville, et al., *PNAS*, 106(48): 20216-20221 (2009)).

[0030] In an embodiment, the Dectin-2 binding agent comprises an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 243-282 or 324, a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NOs: 243-282 or 324, or at least the CDRs thereof; and/or an immunoglobulin light chain variable region of any one of SEQ ID NOs: 283-322, a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NOs: 283-322, or at least the CDRs thereof.

[0031] By way of further illustration, the Dectin-2 binding agent can comprise:

[0032] (1) an immunoglobulin heavy chain variable region of SEQ ID NO: 243, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 283, or at least the CDRs thereof;

[0033] (2) an immunoglobulin heavy chain variable region of SEQ ID NO: 244, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 284, or at least the CDRs thereof;

[0034] (3) an immunoglobulin heavy chain variable region of SEQ ID NO: 245, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 285, or at least the CDRs thereof;

[0035] (4) an immunoglobulin heavy chain variable region of SEQ ID NO: 246, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 286, or at least the CDRs thereof;

[0036] (5) an immunoglobulin heavy chain variable region of SEQ ID NO: 247, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 287, or at least the CDRs thereof;

[0037] (6) an immunoglobulin heavy chain variable region of SEQ ID NO: 248, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 288, or at least the CDRs thereof;

[0038] (7) an immunoglobulin heavy chain variable region of SEQ ID NO: 249, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 289, or at least the CDRs thereof;

[0039] (8) an immunoglobulin heavy chain variable region of SEQ ID NO: 250, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 290, or at least the CDRs thereof;

[0040] (9) an immunoglobulin heavy chain variable region of SEQ ID NO: 251, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 291, or at least the CDRs thereof;

[0041] (10) an immunoglobulin heavy chain variable region of SEQ ID NO: 252, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 292, or at least the CDRs thereof;

[0042] (11) an immunoglobulin heavy chain variable region of SEQ ID NO: 253, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 293, or at least the CDRs thereof;

[0043] (12) an immunoglobulin heavy chain variable region of SEQ ID NO: 254, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 294, or at least the CDRs thereof;

[0044] (13) an immunoglobulin heavy chain variable region of SEQ ID NO: 255, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 295, or at least the CDRs thereof;

[0045] (14) an immunoglobulin heavy chain variable region of SEQ ID NO: 256, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 296, or at least the CDRs thereof;

[0046] (15) an immunoglobulin heavy chain variable region of SEQ ID NO: 257, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 297, or at least the CDRs thereof;

[0047] (16) an immunoglobulin heavy chain variable region of SEQ ID NO: 258, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 298, or at least the CDRs thereof;

[0048] (17) an immunoglobulin heavy chain variable region of SEQ ID NO: 259, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 299, or at least the CDRs thereof;

[0049] (18) an immunoglobulin heavy chain variable region of SEQ ID NO: 256, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 300, or at least the CDRs thereof;

[0050] (19) an immunoglobulin heavy chain variable region of SEQ ID NO: 260, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 301, or at least the CDRs thereof;

[0051] (20) an immunoglobulin heavy chain variable region of SEQ ID NO: 261, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 302, or at least the CDRs thereof;

[0052] (21) an immunoglobulin heavy chain variable region of SEQ ID NO: 262, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 303, or at least the CDRs thereof;

[0053] (22) an immunoglobulin heavy chain variable region of SEQ ID NO: 263, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 304, or at least the CDRs thereof;

[0054] (23) an immunoglobulin heavy chain variable region of SEQ ID NO: 264, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 305, or at least the CDRs thereof;

[0055] (23a) an immunoglobulin heavy chain variable region of SEQ ID NO: 265, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 305, or at least the CDRs thereof;

[0056] (23b) an immunoglobulin heavy chain variable region of SEQ ID NO: 324, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 305, or at least the CDRs thereof;

[0057] (24) an immunoglobulin heavy chain variable region of SEQ ID NO: 266, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 306, or at least the CDRs thereof;

[0058] (25) an immunoglobulin heavy chain variable region of SEQ ID NO: 267, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 307, or at least the CDRs thereof;

[0059] (26) an immunoglobulin heavy chain variable region of SEQ ID NO: 268, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 308, or at least the CDRs thereof;

[0060] (27) an immunoglobulin heavy chain variable region of SEQ ID NO: 269, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 309, or at least the CDRs thereof;

[0061] (28) an immunoglobulin heavy chain variable region of SEQ ID NO: 270, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 310, or at least the CDRs thereof;

[0062] (29) an immunoglobulin heavy chain variable region of SEQ ID NO: 271, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 311, or at least the CDRs thereof;

[0063] (30) an immunoglobulin heavy chain variable region of SEQ ID NO: 272, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 312, or at least the CDRs thereof;

[0064] (31) an immunoglobulin heavy chain variable region of SEQ ID NO: 273, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 313, or at least the CDRs thereof;

[0065] (32) an immunoglobulin heavy chain variable region of SEQ ID NO: 274, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 314, or at least the CDRs thereof;

[0066] (33) an immunoglobulin heavy chain variable region of SEQ ID NO: 275, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 315, or at least the CDRs thereof;

[0067] (34) an immunoglobulin heavy chain variable region of SEQ ID NO: 276, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 316, or at least the CDRs thereof;

[0068] (35) an immunoglobulin heavy chain variable region of SEQ ID NO: 277, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 317, or at least the CDRs thereof;

[0069] (36) an immunoglobulin heavy chain variable region of SEQ ID NO: 278, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 318, or at least the CDRs thereof;

[0070] (37) an immunoglobulin heavy chain variable region of SEQ ID NO: 279, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 319, or at least the CDRs thereof;

[0071] (38) an immunoglobulin heavy chain variable region of SEQ ID NO: 280, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 320, or at least the CDRs thereof;

[0072] (39) an immunoglobulin heavy chain variable region of SEQ ID NO: 281, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 321, or at least the CDRs thereof;

[0073] (40) an immunoglobulin heavy chain variable region of SEQ ID NO: 282, or at least the CDRs thereof, and/or an immunoglobulin light chain variable region of SEQ ID NO: 322, or at least the CDRs thereof; and/or

[0074] (41) an immunoglobulin heavy chain variable region of Table 4 and/or an immunoglobulin light chain variable region of Table 5, or at least the CDRs thereof.

[0075] The CDRs of a given heavy or light chain Ig sequence can be determined in accordance with any of the various known Ig numbering schemes, such as Kabat, Chothia, Martin (Enhanced Chothia), IGMT, AbM or AHo (see, e.g., Kabat, et al., *Sequences of Proteins of Immunological Interest*, U.S. Department of Health and Human Services, NIH (1991); Chothia, et al., *Canonical Structures for the Hypervariable Regions of Immunoglobulins*, J. Mol. Biol., 196:901-917 (1987); Al-Lazikani et al., *Standard Conformations for the Canonical Structures of Immunoglobulins*, J. Mol. Biol., 273:927 – 948 (1997); Abhinandan et al., *Analysis and Improvements to Kabat and Structurally Correct Numbering of Antibody Variable Domains*, Mol. Immunol., 45: 3832 – 3839 (2008); Lefranc et al., *The IMGT unique numbering for immunoglobulins, T cell Receptors and Ig-like domains*, The Immunologist, 7: 132-136 (1999); Lefranc et al., *IMGT unique numbering for immunoglobulin and T cell receptor variable domains and I superfamily V-like domains*, Dev. Comp. Immunol., 27: 55 – 77 (2003); and Honegger et al., *Yet another numbering*

scheme for immunoglobulin variable domains: an automatic modeling and analysis tool, J. Mol. Biol. 309: 657 – 670 (2001).). In particular embodiments, Kabat is used to determine the CDRs of a given heavy or light chain Ig sequence. In certain embodiments, the Dectin-2 binding agent comprises one or more of the following CDRs:

[0076] a HCDR1 comprising or consisting of any one of SEQ ID NOs: 1-30 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 1-30;

[0077] a HCDR2 comprising or consisting of any one of SEQ ID NOs: 31-64 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 31-64; and

[0078] a HCDR3 comprising or consisting of any one of SEQ ID NOs: 65-103 or 323 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 65-103 or 323; and/or the immunoglobulin light chain polypeptide comprises

[0079] a LCDR1 comprising or consisting of any one of SEQ ID NOs: 104-125 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 104-125;

[0080] a LCDR2 comprising or consisting of any one of SEQ ID NOs: 126-148 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 126-148; and

[0081] a LCDR3 comprising or consisting of any one of SEQ ID NOs: 149-181 or a sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NOs: 149-181.

[0082] In particular embodiments, the binding agent comprises an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide, wherein:

[0083] (1) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 1, a HCDR2 comprising or consisting of SEQ ID NO: 31, and a

HCDR3 comprising or consisting of SEQ ID NO: 65; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 104, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 149;

[0084] (2) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 2, a HCDR2 comprising or consisting of SEQ ID NO: 32, and a HCDR3 comprising or consisting of SEQ ID NO: 66; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 105, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 150;

[0085] (3) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 3, a HCDR2 comprising or consisting of SEQ ID NO: 33, and a HCDR3 comprising or consisting of SEQ ID NO: 67; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 106, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 151;

[0086] (4) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 4, a HCDR2 comprising or consisting of SEQ ID NO: 34, and a HCDR3 comprising or consisting of SEQ ID NO: 68; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 107, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 150;

[0087] (5) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 5, a HCDR2 comprising or consisting of SEQ ID NO: 35, and a HCDR3 comprising or consisting of SEQ ID NO: 69; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 108, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 152;

[0088] (6) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 6, a HCDR2 comprising or consisting of SEQ ID NO: 36, and a HCDR3 comprising or consisting of SEQ ID NO: 70; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 104, a LCDR2

comprising or consisting of SEQ ID NO: 128, and a LCDR3 comprising or consisting of SEQ ID NO: 153;

[0089] (7) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 6, a HCDR2 comprising or consisting of SEQ ID NO: 37, and a HCDR3 comprising or consisting of SEQ ID NO: 71; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 104, a LCDR2 comprising or consisting of SEQ ID NO: 129, and a LCDR3 comprising or consisting of SEQ ID NO: 154;

[0090] (8) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 7, a HCDR2 comprising or consisting of SEQ ID NO: 38, and a HCDR3 comprising or consisting of SEQ ID NO: 72; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 109, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 155;

[0091] (9) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 8, a HCDR2 comprising or consisting of SEQ ID NO: 39, and a HCDR3 comprising or consisting of SEQ ID NO: 73; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 110, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 150;

[0092] (10) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 9, a HCDR2 comprising or consisting of SEQ ID NO: 40, and a HCDR3 comprising or consisting of SEQ ID NO: 74; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 104, a LCDR2 comprising or consisting of SEQ ID NO: 130, and a LCDR3 comprising or consisting of SEQ ID NO: 156;

[0093] (11) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 10, a HCDR2 comprising or consisting of SEQ ID NO: 41, and a HCDR3 comprising or consisting of SEQ ID NO: 75; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 110, a LCDR2 comprising or consisting of SEQ ID NO: 131, and a LCDR3 comprising or consisting of SEQ ID NO: 157;

[0094] (12) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 11, a HCDR2 comprising or consisting of SEQ ID NO: 42, and a HCDR3 comprising or consisting of SEQ ID NO: 76; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 111, a LCDR2 comprising or consisting of SEQ ID NO: 132, and a LCDR3 comprising or consisting of SEQ ID NO: 158;

[0095] (13) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 12, a HCDR2 comprising or consisting of SEQ ID NO: 43, and a HCDR3 comprising or consisting of SEQ ID NO: 77; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 104, a LCDR2 comprising or consisting of SEQ ID NO: 133, and a LCDR3 comprising or consisting of SEQ ID NO: 159;

[0096] (14) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 13, a HCDR2 comprising or consisting of SEQ ID NO: 44, and a HCDR3 comprising or consisting of SEQ ID NO: 78; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 112, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 160;

[0097] (15) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 14, a HCDR2 comprising or consisting of SEQ ID NO: 45, and a HCDR3 comprising or consisting of SEQ ID NO: 79; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 113, a LCDR2 comprising or consisting of SEQ ID NO: 134, and a LCDR3 comprising or consisting of SEQ ID NO: 161;

[0098] (16) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 15, a HCDR2 comprising or consisting of SEQ ID NO: 46, and a HCDR3 comprising or consisting of SEQ ID NO: 80; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 114, a LCDR2 comprising or consisting of SEQ ID NO: 135, and a LCDR3 comprising or consisting of SEQ ID NO: 162;

[0099] (17) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 16, a HCDR2 comprising or consisting of SEQ ID NO: 47, and a HCDR3 comprising or consisting of SEQ ID NO: 81; and/or the

immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 115, a LCDR2 comprising or consisting of SEQ ID NO: 136, and a LCDR3 comprising or consisting of SEQ ID NO: 163;

[0100] (18) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 13, a HCDR2 comprising or consisting of SEQ ID NO: 44, and a HCDR3 comprising or consisting of SEQ ID NO: 78; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 112, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 160;

[0101] (19) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 17, a HCDR2 comprising or consisting of SEQ ID NO: 48, and a HCDR3 comprising or consisting of SEQ ID NO: 82; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 116, a LCDR2 comprising or consisting of SEQ ID NO: 137, and a LCDR3 comprising or consisting of SEQ ID NO: 164;

[0102] (20) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 18, a HCDR2 comprising or consisting of SEQ ID NO: 49, and a HCDR3 comprising or consisting of SEQ ID NO: 83; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 117, a LCDR2 comprising or consisting of SEQ ID NO: 138, and a LCDR3 comprising or consisting of SEQ ID NO: 150;

[0103] (21) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 19, a HCDR2 comprising or consisting of SEQ ID NO: 50, and a HCDR3 comprising or consisting of SEQ ID NO: 84; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 118, a LCDR2 comprising or consisting of SEQ ID NO: 139, and a LCDR3 comprising or consisting of SEQ ID NO: 150;

[0104] (22) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 20, a HCDR2 comprising or consisting of SEQ ID NO: 51, and a HCDR3 comprising or consisting of SEQ ID NO: 85; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 116, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 165;

[0105] (23) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 21, a HCDR2 comprising or consisting of SEQ ID NO: 52, and a HCDR3 comprising or consisting of SEQ ID NO: 86; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 110, a LCDR2 comprising or consisting of SEQ ID NO: 140, and a LCDR3 comprising or consisting of SEQ ID NO: 166;

[0106] (23a) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 21, a HCDR2 comprising or consisting of SEQ ID NO: 52, and a HCDR3 comprising or consisting of SEQ ID NO: 86; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 110, a LCDR2 comprising or consisting of SEQ ID NO: 140, and a LCDR3 comprising or consisting of SEQ ID NO: 166;

[0107] (23b) immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 21, a HCDR2 comprising or consisting of SEQ ID NO: 52, and a HCDR3 comprising or consisting of SEQ ID NO: 323; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 110, a LCDR2 comprising or consisting of SEQ ID NO: 140, and a LCDR3 comprising or consisting of SEQ ID NO: 166;

[0108] (24) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 6, a HCDR2 comprising or consisting of SEQ ID NO: 53, and a HCDR3 comprising or consisting of SEQ ID NO: 87; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 104, a LCDR2 comprising or consisting of SEQ ID NO: 141, and a LCDR3 comprising or consisting of SEQ ID NO: 167;

[0109] (25) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 22, a HCDR2 comprising or consisting of SEQ ID NO: 38, and a HCDR3 comprising or consisting of SEQ ID NO: 88; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 119, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 168;

[0110] (26) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 6, a HCDR2 comprising or consisting of SEQ ID NO: 37, and a HCDR3 comprising or consisting of SEQ ID NO: 89; and/or the

immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 120, a LCDR2 comprising or consisting of SEQ ID NO: 142, and a LCDR3 comprising or consisting of SEQ ID NO: 169;

[0111] (27) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 23, a HCDR2 comprising or consisting of SEQ ID NO: 54, and a HCDR3 comprising or consisting of SEQ ID NO: 90; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 121, a LCDR2 comprising or consisting of SEQ ID NO: 143, and a LCDR3 comprising or consisting of SEQ ID NO: 170;

[0112] (28) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 6, a HCDR2 comprising or consisting of SEQ ID NO: 55, and a HCDR3 comprising or consisting of SEQ ID NO: 91; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 122, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 171;

[0113] (29) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 19, a HCDR2 comprising or consisting of SEQ ID NO: 56, and a HCDR3 comprising or consisting of SEQ ID NO: 92; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 123, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 172;

[0114] (30) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 11, a HCDR2 comprising or consisting of SEQ ID NO: 57, and a HCDR3 comprising or consisting of SEQ ID NO: 93; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 109, a LCDR2 comprising or consisting of SEQ ID NO: 144, and a LCDR3 comprising or consisting of SEQ ID NO: 173;

[0115] (31) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 4, a HCDR2 comprising or consisting of SEQ ID NO: 58, and a HCDR3 comprising or consisting of SEQ ID NO: 94; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 104, a LCDR2 comprising or consisting of SEQ ID NO: 136, and a LCDR3 comprising or consisting of SEQ ID NO: 174;

[0116] (32) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 24, a HCDR2 comprising or consisting of SEQ ID NO: 59, and a HCDR3 comprising or consisting of SEQ ID NO: 95; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 110, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 153;

[0117] (33) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 11, a HCDR2 comprising or consisting of SEQ ID NO: 60, and a HCDR3 comprising or consisting of SEQ ID NO: 96; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 111, a LCDR2 comprising or consisting of SEQ ID NO: 145, and a LCDR3 comprising or consisting of SEQ ID NO: 175;

[0118] (34) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 25, a HCDR2 comprising or consisting of SEQ ID NO: 61, and a HCDR3 comprising or consisting of SEQ ID NO: 97; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 111, a LCDR2 comprising or consisting of SEQ ID NO: 146, and a LCDR3 comprising or consisting of SEQ ID NO: 176;

[0119] (35) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 26, a HCDR2 comprising or consisting of SEQ ID NO: 59, and a HCDR3 comprising or consisting of SEQ ID NO: 98; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 110, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 177;

[0120] (36) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 25, a HCDR2 comprising or consisting of SEQ ID NO: 38, and a HCDR3 comprising or consisting of SEQ ID NO: 99; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 124, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 178;

[0121] (37) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 27, a HCDR2 comprising or consisting of SEQ ID NO: 62, and a HCDR3 comprising or consisting of SEQ ID NO: 100; and/or the

immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 111, a LCDR2 comprising or consisting of SEQ ID NO: 147, and a LCDR3 comprising or consisting of SEQ ID NO: 179;

[0122] (38) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 28, a HCDR2 comprising or consisting of SEQ ID NO: 63, and a HCDR3 comprising or consisting of SEQ ID NO: 101; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 116, a LCDR2 comprising or consisting of SEQ ID NO: 148, and a LCDR3 comprising or consisting of SEQ ID NO: 180;

[0123] (39) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 29, a HCDR2 comprising or consisting of SEQ ID NO: 64, and a HCDR3 comprising or consisting of SEQ ID NO: 102; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 121, a LCDR2 comprising or consisting of SEQ ID NO: 126, and a LCDR3 comprising or consisting of SEQ ID NO: 177;

[0124] (40) the immunoglobulin heavy chain polypeptide comprises a HCDR1 comprising or consisting of SEQ ID NO: 30, a HCDR2 comprising or consisting of SEQ ID NO: 38, and a HCDR3 comprising or consisting of SEQ ID NO: 103; and/or the immunoglobulin light chain polypeptide comprises a LCDR1 comprising or consisting of SEQ ID NO: 125, a LCDR2 comprising or consisting of SEQ ID NO: 127, and a LCDR3 comprising or consisting of SEQ ID NO: 181;

[0125] (41) the immunoglobulin heavy chain polypeptide and immunoglobulin light chain polypeptide comprises any combination of the CDRs listed in Table 1;

[0126] (42) the immunoglobulin heavy chain polypeptide comprising or consisting of any one of SEQ ID NOs: 328-345 and immunoglobulin light chain polypeptide comprising or consisting of any one of SEQ ID NOs: 325-327;

[0127] (43) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 328 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 325;

[0128] (44) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 329 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 325;

- [0129] (45) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 330 and light chain polypeptide comprising or consisting of SEQ ID NO: 325;
- [0130] (46) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 331 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 325;
- [0131] (47) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 332 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 325;
- [0132] (48) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 333 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 325;
- [0133] (49) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 334 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 326;
- [0134] (50) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 335 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 326;
- [0135] (51) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 336 and light chain polypeptide comprising or consisting of SEQ ID NO: 326;
- [0136] (52) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 337 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 326;
- [0137] (53) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 338 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 326;
- [0138] (54) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 339 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 326;
- [0139] (55) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 340 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 327;

[0140] (56) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 341 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 327;

[0141] (57) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 342 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 327;

[0142] (58) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 343 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 327;

[0143] (59) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 344 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 327; and/or

[0144] (55) the immunoglobulin heavy chain polypeptide comprising or consisting of SEQ ID NO: 345 and immunoglobulin light chain polypeptide comprising or consisting of SEQ ID NO: 327.

[0145] In particular embodiments, the binding agent comprises an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide, wherein the immunoglobulin heavy chain polypeptide comprises a first framework region, a second framework region, a third framework region, and/or a fourth framework region; and/or the immunoglobulin light chain polypeptide comprises a first framework region, a second framework region, a third framework region, and/or a fourth framework region; and/or the immunoglobulin heavy chain polypeptide and light chain polypeptide comprises any combination of the framework regions listed in Tables 2 and 3.

Table 1

Binding Agent	SEQ ID	HCDR1	SEQ ID	HCDR2	SEQ ID	HCDR3	SEQ ID	LCDR1	SEQ ID	LCDR2	SEQ ID	LCDR3
1	1	SYVMQ	31	WINPKSGGTN YAQKFG	65	GYLRTGSSLS GYYYGMDV	104	QASQDISNYLN	126	AASSLQS	149	QQTDSIPIT
2	2	TYVMH	32	IINPSGGSTSY AQKFG	66	SHYGDLNGGFD L	105	RASQYISSYLA	127	AASTLQS	150	QQSYSTPLT
3	3	NFGIN	33	WINPNSGGAN YAQKFG	67	GVVAARYYYM DV	106	RASQINIGSYLN	126	AASSLQS	151	QQTNSFPIT
4	4	SYDIN	34	WINPNSGATN SAQKFG	68	AGYSSSWDGY YYYGMDV	107	RASQSISSHLN	127	AASTLQS	150	QQSYSTPLT
5	5	GYVVH	35	IHPNNGGSTSY AQKFG	69	DQAGTGGHGM DV	108	RASQSISSHLN	127	AASTLQS	152	EQNYRLPIT
6	6	SYWMS	36	DISGSRSTYY ADSVKG	70	GRYLEWVLSSE DYFYGMDV	104	QASQDISNYLN	128	AASSLHP	153	QQSDSFPLT
7	6	SYWMS	37	AISGSGGSTY YADSVKG	71	GRYSRSWERW YFDL	104	QASQDISNYLN	129	AASNLES	154	QQTNSFPIT
8	7	SQVMH	38	WMNPNSGNT GYAQKFG	72	GOYDSSGGYYF DY	109	QASQDIRNYLN	127	AASTLQS	155	QQSYSFPLT
9	8	TYVMN	39	ILSPSGGSTSY APKFG	73	ATYYDFWGSGL DY	110	RASQSISSYLN	126	AASSLQS	150	QQSYSTPLT
10	9	SYFMH	40	WMNPNSGNT GYAQKFG	74	QAGYSSGWDY	104	QASQDISNYLN	130	AAFNLQG	156	QQAHSFPLT
11	10	TWYMQ	41	WISPYTGNIT APNVQG	75	AVYDILTGAYY FDY	110	RASQSISSYLN	131	GASTLES	157	QQSYSTPIT
12	11	SYAIS	42	WISTYNGNTN YAQKFG	76	GRLPYYYYGM DV	111	KSSQSVLYSSN NKNYLA	132	WASTRES	158	QQYYSTPLT
13	12	RYYLH	43	RIPILGANYA QKFG	77	MATVTKHTYW YFDL	104	QASQDISNYLN	133	ATSTLQS	159	QQANSLPYS
14	13	GQWVH	44	LISYDGGSTY YADSVKG	78	AGRSTSRYYY YMDV	112	RASENIGNWLA	127	AASTLQS	160	QQGYSTPYT
15	14	PNYIQ	45	IINPSGRSTSY AQKFG	79	SSSGYTTDAFDI	113	RASQSVSSNLA	134	GASTRAT	161	QQYGTSPFT
16	15	ASYIH	46	GIPIFGSPNYA QKFG	80	EYQLMNVGMD V	114	RASQGISNNLN	135	AASILQS	162	QQSYTTTLT

Binding Agent	SEQ ID	HCDR1	SEQ ID	HCDR2	SEQ ID	HCDR3	SEQ ID	LCDR1	SEQ ID	LCDR2	SEQ ID	LCDR3
17	16	DSHLH	47	VYAGGSRY ADSVKG	81	GKQRADAFDI	115	RASQISKFLN	136	SASNLOS	163	QQANSFPPLT
18	13	GQWVH	44	LISYDGGSTY YADSVKG	78	AGRSTRYYYY YMDV	112	RASENIGNWLA	127	AASTLOS	160	QQGYSTPYT
19	17	SYWMH	48	TISGSGAGTW YADSVKG	82	DVDPQRQSYH GVDV	116	RSSQSLHNSG YNYLD	137	LGSNRAS	164	MQGAHWPYT
20	18	NYWIQ	49	WINPNSGGTR YARNFQG	83	GRYYGSGSQY HAFDI	117	RASQISGYLN	138	AASRLQS	150	QQSYSTPLT
21	19	NYVMH	50	WLNPNSTNY AQKFQ	84	GRYDSSGYFY DY	118	QASQIEIGNYLN	139	GASSLOS	150	QQSYSTPLT
22	20	GYDMQ	51	IINPSGAGTNY AQKFQ	85	TVTTPYQYGY MDV	116	RSSQSLHNSG YNYLD	126	AASSLOS	165	MQALQTPPLT
23	21	SYSMN	52	VISYDGRKID YADSVKG	86	VRGFSWFDP	110	RASQISSYLN	140	LASSLOS	166	QQSYGIPLT
23a	21	SYSMN	52	VISYDGRKID YADSVKG	86	VRGFSWFDP	110	RASQISSYLN	140	LASSLOS	166	QQSYGIPLT
23b	21	SYSMN	52	VISYDGRKID YADSVKG	323	VRGFSWFEP	110	RASQISSYLN	140	LASSLOS	166	QQSYGIPLT
24	6	SYWMS	53	GISWNGGKTH YADSVKG	87	GGGYFDY	104	QASQDISNYLN	141	KASSLES	167	QQANTFPLT
25	22	GYIYH	38	WMNPNSGNT GYAQKFQ	88	GRYGSSGWSPG YYYYYMDV	119	QASQDITNFLN	126	AASSLOS	168	QQTYSEFPLT
26	6	SYWMS	37	AISGSGGSTY YADSVKG	89	ARDSGSPKDFD Y	120	RASQISSTFLN	142	AASSLQT	169	QQSYSTPP
27	23	SYAMH	54	GTSLDGNKNY YADSVKG	90	GTMARGS	121	QASQDISKYLN	143	AASNLOK	170	QQANSFPRT
28	6	SYWMS	55	TISGSGGTYY ADSVKG	91	ATDYPGMDV	122	QASQDIGNYLN	126	AASSLOS	171	LQHNSFPPT
29	19	NYVMH	56	WINPHSGGTN YAKFQ	92	GRMHYDSSVH YYYYYMDV	123	RASQDIRNYLA	127	AASTLOS	172	LQAISFPPT
30	11	SYAIS	57	LIDPSGTYY AQKFQ	93	VSIVGATPDYY YGMV	109	QASQDIRNYLN	144	DTSNLET	173	QQAYSLPWT
31	4	SYDIN	58	RINPNSGGTNF AQKFQ	94	VIRGGKFDP	104	QASQDISNYLN	136	SASNLOS	174	QQSYTTPYT

Binding Agent	SEQ ID	HCDR1	SEQ ID	HCDR2	SEQ ID	HCDR3	SEQ ID	LCDR1	SEQ ID	LCDR2	SEQ ID	LCDR3
32	24	NYGIT	59	WMNPNSANT GYAQKFQG	95	GLYAAAGDQY YYGMDV	110	RASQSISSYLN	127	AASTLQS	153	QQSDSFPLT
33	11	SYAIS	60	VINPSGGGTT YAKKFQG	96	GAAFDY	111	KSSQSVLYSSN NKNYLA	145	WASFRES	175	QQYYTTPLT
34	25	GYMH	61	WINPDSGDTN FAQKFQG	97	EYGDYGYYY GMDV	111	KSSQSVLYSSN NKNYLA	146	WASARES	176	QQYKSAPYT
35	26	NYITH	59	WMNPNSANT GYAQKFQG	98	GIYYDSSGGS YYYGMDV	110	RASQSISSYLN	126	AASSLQS	177	QQSNSFPLT
36	25	GYMH	38	WMNPNSGNT GYAQKFQG	99	ELSSWYSYGM DV	124	RASQSISSYLN	126	AASSLQS	178	QQSYQTPLT
37	27	DYGMV	62	YISSGSTIYY ADSVKG	100	VSGGSWYDRL	111	KSSQSVLYSSN NKNYLA	147	WASIRES	179	QQYYSSPFT
38	28	SYGIN	63	RUIFGAANY AQKFQG	101	TYFDWFFFDY	116	RSSQSLHSNG YNYLD	148	DASNLHA	180	MQALQAPVT
39	29	SYGIS	64	WINPNSGNT YAKKFQG	102	GRYSGHFGVYY YGMDV	121	QASQDISKYN	126	AASSLQS	177	QQSNSFPLT
40	30	SYMH	38	WMNPNSGNT GYAQKFQG	103	EPYGDYGFY	125	RASQTVRSYLN	127	AASTLQS	181	QQTYRTPLT

Table 2

Binding Agent	SEQ ID	HFW1	SEQ ID	HFW2	SEQ ID	HFW3	SEQ ID	HFW4
1	182	QVQLVQSGAEVKKPGASVK VCKASGYTFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	216	WGQGTTLVT VSS
2	183	QVQLVQSGAEVKKPGASVK VCKASGYTFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	217	WGRGTLVT VSS
3	184	QVQLVQSGAEVKKPGASVK VCKASGGTLN	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	218	WGKGTTLVT VSS
4	182	QVQLVQSGAEVKKPGASVK VCKASGYTFT	202	WVRQAPGQG LEWLG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	216	WGQGTTLVT VSS
5	182	QVQLVQSGAEVKKPGASVK VCKASGYTFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	219	WGQGTMTVT VSS
6	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	203	WVRQAPGKG LEWVS	209	RFTISRDNKNTLYLQMNSLR AEDTAVYYCAR	216	WGQGTTLVT VSS
7	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	203	WVRQAPGKG LEWVS	209	RFTISRDNKNTLYLQMNSLR AEDTAVYYCAR	217	WGRGTLVT VSS
8	182	QVQLVQSGAEVKKPGASVK VCKASGYTFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	220	WGQGTTLVT VSS
9	182	QVQLVQSGAEVKKPGASVK VCKASGYTFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	220	WGQGTTLVT VSS
10	182	QVQLVQSGAEVKKPGASVK VCKASGYTFT	201	WVRQAPGQG LEWMG	210	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCTR	220	WGQGTTLVT VSS
11	186	QVQLVQSGAEVKKPGASVK VCKASGYTLT	201	WVRQAPGQG LEWMG	210	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCTR	220	WGQGTTLVT VSS

Binding Agent	SEQ ID	FW1	SEQ ID	FW2	SEQ ID	FW3	SEQ ID	FW4
12	187	QVQLVQSGAEVKKPGASVK VCKASGGTFS	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	216	WGQGTIVT VSS
13	188	QVQLVQSGVWRWRLGPPVK VCKASGDTFS	201	WVRQAPGQG LEWMG	211	RVTITADESTSTAYMELSSLR EDTAVYYCAR	217	WGRGTLVT VSS
14	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	204	WVRQAPGKG LEWVA	209	RFTISRDNKNTLYLQMNSLR AEDTAVYYCAR	218	WGKGTIVT VSS
15	183	QVQLVQSGAEVKKPGASVK VCKASGYIFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	216	WGQGTIVT VSS
16	189	QVQLVQSGAEVKKPGSSVK VCKASGYIFT	201	WVRQAPGQG LEWMG	211	RVTITADESTSTAYMELSSLR EDTAVYYCAR	216	WGQGTIVT VSS
17	190	EVQLLESGGGLVQPGGSLRL SCAASGFIFS	205	WVRQAPGKG LEWLS	209	RFTISRDNKNTLYLQMNSLR AEDTAVYYCAR	220	WGQGTIVT VSS
18	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	204	WVRQAPGKG LEWVA	209	RFTISRDNKNTLYLQMNSLR AEDTAVYYCAR	218	WGKGTIVT VSS
19	191	EVQLLESGGGLVKPGGSLRL SCAASGFTFS	203	WVRQAPGKG LEWVS	212	RFTISRDDSKNTLYLQMNSLK TEDTAVYYCAR	216	WGQGTIVT VSS
20	183	QVQLVQSGAEVKKPGASVK VCKASGYIFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	219	WGQGTIVT VSS
21	192	QVQLVQSGAEVKKPGASVK VCKASEYIFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	220	WGQGTIVT VSS
22	193	QVQLVQSGAEVKKPGSSVK VCKASGDTFT	201	WVRQAPGQG LEWMG	213	RVTITADESTSTAYMELSSLR EDTAVYYCAR	216	WGQGTIVT VSS
23	194	EVQLLESGGGLVQPGGSLRL SCAASGTFPS	204	WVRQAPGKG LEWVA	209	RFTISRDNKNTLYLQMNSLR AEDTAVYYCAR	220	WGQGTIVT VSS
23a	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	204	WVRQAPGKG LEWVA	209	RFTISRDNKNTLYLQMNSLR AEDTAVYYCAR	220	WGQGTIVT VSS

Binding Agent	SEQ ID	FW1	SEQ ID	FW2	SEQ ID	FW3	SEQ ID	FW4
23b	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	204	WVRQAPGKG LEWVA	209	RFTISRDN SKNTLYLQMNSLR AEDTAVYYCAR	220	WGQGTLLVT VSS
24	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	203	WVRQAPGKG LEWVS	209	RFTISRDN SKNTLYLQMNSLR AEDTAVYYCAR	220	WGQGTLLVT VSS
25	195	QVQLVQSGAEVKKPGASVK VSCASGYST	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SED TAVYYCAR	218	WGKGTTVT VSS
26	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	203	WVRQAPGKG LEWVS	209	RFTISRDN SKNTLYLQMNSLR AEDTAVYYCAR	220	WGQGTLLVT VSS
27	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	204	WVRQAPGKG LEWVA	209	RFTISRDN SKNTLYLQMNSLR AEDTAVYYCAR	220	WGQGTLLVT VSS
28	185	EVQLLESGGGLVQPGGSLRL SCAASGFTFS	203	WVRQAPGKG LEWVS	214	RFTISRDN SKNTLYLQNEQPGA EDTAVYYCAR	216	WGQGTLLVT VSS
29	186	QVQLVQSGAEVKKPGASVK VSCASGYTLT	201	WVRQAPGQG LEWMG	210	RVTMTTRDTSTSTVYMELSSLR SED TAVYYCTR	220	WGQGTLLVT VSS
30	196	QVQLVQSGAEVKKPGASVK VSCASGGTGS	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SED TAVYYCAR	221	WGKGTLVT VSS
31	182	QVQLVQSGAEVKKPGASVK VSCASGYTFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SED TAVYYCAR	220	WGQGTLLVT VSS
32	189	QVQLVQSGAEVKKPGSSVK VSCASGYTFT	206	WVRQAPGKG LEWMG	211	RVITADESTSTAYMELSSLRS EDTAVYYCAR	220	WGQGTLLVT VSS
33	197	QVQLVQSGAEVKKPGASVK VSCASGDTFS	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SED TAVYYCAR	220	WGQGTLLVT VSS
34	189	QVQLVQSGAEVKKPGSSVK VSCASGYTFT	201	WVRQAPGQG LEWMG	211	RVITADESTSTAYMELSSLRS EDTAVYYCAR	219	WGQGTMTVT VSS
35	182	QVQLVQSGAEVKKPGASVK VSCASGYTFT	201	WVRQAPGQG LEWMG	208	RVTMTTRDTSTSTVYMELSSLR SED TAVYYCAR	216	WGQGTLLVT VSS

Binding Agent	SEQ ID	HFW1	SEQ ID	HFW2	SEQ ID	HFW3	SEQ ID	HFW4
36	182	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	201	WVRQAPGQG LEWVG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	216	WGQGTIVT VSS
37	198	EVQLLESGGGLVKPGGSLRL SCAASGFTLS	203	WVRQAPGKG LEWVS	212	RFTISRDDSKNTLYLQMNSLK TEDTAVYYCAR	222	LGPGNPVTV SS
38	199	QVQLVQSGAEVKKPGSSVK VSCKASGYTFS	201	WVRQAPGQG LEWVG	215	RVTITADESTSTAYMELSSLRS EDTAVYYCTR	220	WGQGTIVT VSS
39	182	QVQLVQSGAEVKKPGASVK VSCKASGYTFT	201	WVRQAPGQG LEWVG	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	216	WGQGTIVT VSS
40	200	QVQLVQSGAEVKKPGASVK VSCKASGYTFS	207	WVRQAPGQG LEWMA	208	RVTMTTRDTSTSTVYMELSSLR SEDTAVYYCAR	220	WGQGTIVT VSS

Table 3

Binding Agent	SEQ ID	LFW1	SEQ ID	LFW2	SEQ ID	LFW3	SEQ ID	LFW4
1	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	237	FGQGTKVE IK
2	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	238	FGPGTKVD IK
3	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	239	FGGGTKVE IK
4	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	237	FGQGTKVE IK
5	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	240	FGQGTREI K
6	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	239	FGGGTKVE IK
7	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	241	FGQGTKLE IK
8	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	239	FGGGTKVE IK
9	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	239	FGGGTKVE IK
10	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	238	FGPGTKVD IK
11	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTITSSL QPEDFATYYC	241	FGQGTKLE IK

Binding Agent	SEQ ID	LFW1	SEQ ID	LFW2	SEQ ID	LFW3	SEQ ID	LFW4
12	224	DIVMTQSPDSLAVSLGERA TINC	229	WYQQKPGQP PKLLIY	234	GVPDFSGSGGTDFTLTISL QAEDVAVYYC	237	FGQGTKVE IK
13	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGGTDFTLTISL QPEDFATYYC	241	FGQGTKLE IK
14	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGGTDFTLTISL QPEDFATYYC	241	FGQGTKLE IK
15	225	EIVMTQSPATLSVSPGERA TLSC	230	WYQQKPGQ APRLIY	235	GIPARFSGSGGTEFTLTISLQ SEDFAVYYC	240	FGQGRLEI K
16	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGGTDFTLTISL QPEDFATYYC	238	FGPGTKVD IK
17	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGGTDFTLTISL QPEDFATYYC	237	FGQGTKVE IK
18	223	DIQMTQSPSSLSASVGDRV TITC	231	WYHQKPGK APKLLIY	233	SGVPSRFSGSGGTDFTLTISL QPEDFATYYC	241	FGQGTKLE IK
19	226	DIVMTQSPFLPVPVTPGEPAS ISC	232	WYQQKPGQS PQLLIY	236	GVPDFSGSGGTDFTLKISRV EAEDVGVYYC	241	FGQGTKLE IK
20	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGGTDFTLTISL QPEDFATYYC	237	FGQGTKVE IK
21	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGGTDFTLTISL QPEDFATYYC	239	FGGGTKVE IK
22	227	DIVMTQSPSLPVPVTPGEPAS ISC	232	WYQQKPGQS PQLLIY	236	GVPDFSGSGGTDFTLKISRV EAEDVGVYYC	239	FGGGTKVE IK
23	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGGTDFTLTISL QPEDFATYYC	239	FGGGTKVE IK

Binding Agent	SEQ ID	LFW1	SEQ ID	LFW2	SEQ ID	LFW3	SEQ ID	LFW4
23a	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	239	FGGGTKVE IK
23b	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	239	FGGGTKVE IK
24	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	239	FGGGTKVE IK
25	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	238	FGPGTKVD IK
26	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	238	FGPGTKVD IK
27	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	237	FGQGTKVE IK
28	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	239	FGGGTKVE IK
29	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	238	FGPGTKVD IK
30	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	241	FGQGTKLE IK
31	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	241	FGQGTKLE IK
32	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFSGSGTDFLTISL QPEDFATYYC	237	FGQGTKVE IK
33	224	DIVMTQSPDLSLVSLGERA TINC	229	WYQQKPGQP PKLLIY	234	GVPSRFSGSGTDFLTISL QAEDVAVYYC	239	FGGGTKVE IK

Binding Agent	SEQ ID	LFW1	SEQ ID	LFW2	SEQ ID	LFW3	SEQ ID	LFW4
34	224	DIVMTQSPDSLAVSLGERA TINC	229	WYQQKPGQP PKLLIY	234	GVPDFRFGSGSGTDFLTISL QAEDVAVYYC	237	FGQGTKVE IK
35	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFGSGSGTDFLTISL QPEDFATYYC	238	FGPGTKVD IK
36	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFGSGSGTDFLTISL QPEDFATYYC	239	FGGGTKVE IK
37	224	DIVMTQSPDSLAVSLGERA TINC	229	WYQQKPGQP PKLLIY	234	GVPDFRFGSGSGTDFLTISL QAEDVAVYYC	241	FGQGTKLE IK
38	227	DIVMTQSPSLPVTGPASP ISC	232	WYLOKPGQS PQLLIY	236	GVPDFRFGSGSGTDFLTISR VAEDVGVYYC	240	FGQGTRLEI K
39	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFGSGSGTDFLTISL QPEDFATYYC	242	FGGGTKLE IK
40	223	DIQMTQSPSSLSASVGDRV TITC	228	WYQQKPGK APKLLIY	233	GVPSRFGSGSGTDFLTISL QPEDFATYYC	237	FGQGTKVE IK

Table 4

Binding Agent	SEQ ID	VH
1	243	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMQWVRQAPGQGLEWMGWINPKSGGTNYAQKFQGRVTMTR DTSTSTVYMELSSLRSEDTAVYYCARGTYLRTGSSLGYYYGMDVWGQGTITVTVSS
2	244	QVQLVQSGAEVKKPGASVKVSCKASGYFTTYMHWVRQAPGQGLEWMGIHPNPGGTSY AQKFQGRVTMTRDT STSTVYMELSSLRSEDTAVYYCARSHYGDNLGGFDLWGRGTLVTVSS
3	245	QVQLVQSGAEVKKPGASVKVSCKASGGTLNFGINWVRQAPGQGLEWMGWINPNSSGGANYAQKFQGRVTMTR DTSTSTVYMELSSLRSEDTAVYYCARGVVAARYYYMDVWGKGTITVTVSS
4	246	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQAPGQGLEWLGWLNPNSGATNSAQKFQGRVTMTRD TSTSTVYMELSSLRSEDTAVYYCARAGYSSWDGYYYYGMDVWGQGTITVTVSS
5	247	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYVHWVRQAPGQGLEWMGIHPNPGGTSY AQKFQGRVTMTRD TSTSTVYMELSSLRSEDTAVYYCARDQAGTGGHGMVWGQGTMTVTVSS
6	248	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYWMWVRQAPGKGLEWVSDISGSGRSTYYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARGYLEWVLSSEDIYFGMDVWGQGTITVTVSS
7	249	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYWMWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARGYSRWERWYFDLWGRGTLVTVSS
8	250	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSQYMHWVRQAPGQGLEWMGMNPNNSGNTGYAQKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARGQYDSSGYYFYFDYWGQGTITVTVSS
9	251	QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYMNVVRQAPGQGLEWMGILSPSGGGTSYAPKFQGRVTMTRD TSTSTVYMELSSLRSEDTAVYYCARATYDYDFWSGSLDYWGQGTITVTVSS
10	252	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYFMHWVRQAPGQGLEWMGMNPNNGNTGYAQKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCTRAGYSSGWDYWGQGTITVTVSS
11	253	QVQLVQSGAEVKKPGASVKVSCKASGYTLTTWYMQWVRQAPGQGLEWMGWISPYTGNTIYAPNVQGRVTMTR DTSTSTVYMELSSLRSEDTAVYYCTRAYDILTGAIFYDYWGQGTITVTVSS
12	254	QVQLVQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGWISTYNGNTNYAQKFQGRVTMTRD TSTSTVYMELSSLRSEDTAVYYCARGLPPYYGMDVWGQGTITVTVSS

Binding Agent	SEQ ID	VH
13	255	QVQLVQSGVWRSLGPPVKVSCKASGDTFSRYLHWVRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARMAVTVKHTYWFYDLWGRGTLVTVSS
14	256	EVQLLESGGGLVQPGGSLRLSCAASGFTFSQWVHWVRQAPGKGLEWVALISYDGGSTYYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARAGRSTSRYYYYMDVWGKGTITVTVSS
15	257	QVQLVQSGAEVKKPGASVKVSCKASGYIFTNYYIQWVRQAPGQGLEWMGIHNPGRSTSYAQKFQGRVTMTTRDTS TSTVYMELSSLRSEDTAVYYCARSSSGYTTDAFDIWGQGTITVTVSS
16	258	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTASYIHWVRQAPGQGLEWMGGIPIFGSPNYAQKFQGRVTITADEST STAYMELSSLRSEDTAVYYCAREYQLMNVGMDVWGQGTITVTVSS
17	259	EVQLLESGGGLVQPGGSLRLSCAASGFIFSDSHLHWVRQAPGKGLEWLSVIYAGGSRYYADSVKGRFTISRDN TLYLQMNSLRAEDTAVYYCARGKQRADAFDIWGQGTITVTVSS
18	256	EVQLLESGGGLVQPGGSLRLSCAASGFTFSQWVHWVRQAPGKGLEWVALISYDGGSTYYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARAGRSTSRYYYYMDVWGKGTITVTVSS
19	260	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYWMHWVRQAPGKGLEWVSTISGSGAGTWYADSVKGRFTISRDDS KNTLYLQMNSLKTEDTAVYYCARDVDPSRQSYHGVVDVWGQGTITVTVSS
20	261	QVQLVQSGAEVKKPGASVKVSCKASGYIFTNYYIQWVRQAPGQGLEWMGWINPNPNSGGTRYARNFQGRVTMTTRD TSTSTVYMELSSLRSEDTAVYYCARGRYYYGSGSQYHAFDIWGQGTITVTVSS
21	262	QVQLVQSGAEVKKPGASVKVSCKASEYFTNTNYYMHWVRQAPGQGLEWMGWLNPNSGNTNYAQKFQGRVTMTTR DTSTSTVYMELSSLRSEDTAVYYCARGRYDSSGYYYFDYWGQGTITVTVSS
22	263	QVQLVQSGAEVKKPGSSVKVSCKASGDTFTGYDMQWVRQAPGQGLEWMGIHNPAGTNYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCAGTVPYQYYGMDVWGQGTITVTVSS
23	264	EVQLLESGGGLVQPGGSLRLSCAASFTFSSYSMNWVRQAPGKGLEWVAVISYDGRIKDYADSVKGRFTISRDN NTLYLQMNSLRAEDTAVYYCARVRGFSFDFPWGQGTITVTVSS
23a	265	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVAVISYDGRIKDYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARVRGFSFDFPWGQGTITVTVSS
23b	324	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVAVISYDGRIKDYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARVRGFSFDFPWGQGTITVTVSS
24	266	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMWVRQAPGKGLEWVSGISWNGGKTHYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARGGGYFDYWGQGTITVTVSS

Binding Agent	SEQ ID	VH
25	267	QVQLVQSGAEVKKPGASVKVSCKASGYSTFTGYIHWVRQAPGQGLEWMGMWNPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDNAVYYCARGRYGSSGWSPGYYYMDVWGKGTITVTVSS
26	268	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYWMWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARARDSGSPKDFDYWGQGTITVTVSS
27	269	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMHWVRQAPGKGLEWVAGTSLDGNKNYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARGTMARGSWGQGTITVTVSS
28	270	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYWMWVRQAPGKGLEWVSTISGSGGTYYADSVKGRFTISRDNKNTLYLQNEQPGAEDTAVYYCARATDYPGMDVWGQGTITVTVSS
29	271	QVQLVQSGAEVKKPGASVKVSCKASGYTLTNYMHWVRQAPGQGLEWMGMWNPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDNAVYYCTRGRMHYDSSVHYYYGMDVWGQGTITVTVSS
30	272	QVQLVQSGAEVKKPGASVKVSCKASGGTGSYASISWVRQAPGQGLEWMGLIDPSPGTYYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDNAVYYCARVSVGATPDYYGMDVWGKGTITVTVSS
31	273	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQAPGQGLEWMGRINPNSGGTNFAQKFQGRVTMTRDTSTSTVYMELSSLRSEDNAVYYCARVIRGGKFDPPWGQGTITVTVSS
32	274	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTNYGITWVRQAPGKGLEWMGMWNPNSANTGYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARGLYAAAGDQYYGMDVWGQGTITVTVSS
33	275	QVQLVQSGAEVKKPGASVKVSCKASGDTFSYASISWVRQAPGQGLEWMGVINPNSGGTYYAKKFQGRVTMTRDTSTSTVYMELSSLRSEDNAVYYCARGAAFDYWGQGTITVTVSS
34	276	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTGYIMHWVRQAPGQGLEWMGMWNPDSGDTNFAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCAREYGDYGYYYGMDVWGQGTITVTVSS
35	277	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYIHWVRQAPGQGLEWMGMWNPNSANTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDNAVYYCARGIYYDSSGSSYYGMDVWGQGTITVTVSS
36	278	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYIMHWVRQAPGQGLEWMGMWNPNSGNTGYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDNAVYYCARELSSSWYSYGMVWGQGTITVTVSS
37	279	EVQLLESGGGLVQPGGSLRLSCAASGFTLSDYGMWVRQAPGKGLEWVSYSSSSGSTIYYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARVSGGSWYDRLLGPGNPVTVSS
38	280	QVQLVQSGAEVKKPGSSVKVSCKASGYTFSYGINWVRQAPGQGLEWMGRIPFIIGAANYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCTRITYFDWFFFDYWGQGTITVTVSS

Binding Agent	SEQ ID	VH
39	281	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWINPNNGGTNYAQKFQGRVTMTTRD TSTSTVYMESSLRSEDTAVYYCARGRYSGHFGVYYGMDVWGQGTITVTVSS
40	282	QVQLVQSGAEVKKPGASVKVSCKASGYTFSSYYMHWVRQAPGQGLEWMAWMNPNSGNTGYAQKFQGRVTMT RDTSTSTVYMESSLRSEDTAVYYCAREPYGDYGFQDYWGQGTITVTVSS

Table 5

Binding Agent	SEQ ID	VL
1	283	DIQMTQSPSSLSASVGDRV/TITCQASQDISNYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQTDSIPITFGGQTKVEIK
2	284	DIQMTQSPSSLSASVGDRV/TITCRASQYISSYLAWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFLTITIS LQPEDFATYYCQQSYSTPLTFGGGQTKVDIK
3	285	DIQMTQSPSSLSASVGDRV/TITCRASQNGISYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQTNSFPLTFGGGQTKVEIK
4	286	DIQMTQSPSSLSASVGDRV/TITCRASQSISSHLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFLTITIS LQPEDFATYYCQQSYSTPLTFGGGQTKVEIK
5	287	DIQMTQSPSSLSASVGDRV/TITCRASQSISSHLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCEQNYRLPITFGGQTRLEIK
6	288	DIQMTQSPSSLSASVGDRV/TITCQASQDISNYLNWYQQKPGKAPKLLIYAASSLHPGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQSDSFPLTFGGGQTKVEIK
7	289	DIQMTQSPSSLSASVGDRV/TITCQASQDISNYLNWYQQKPGKAPKLLIYAASNLESQVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQTNSFPIITFGGQTKLEIK
8	290	DIQMTQSPSSLSASVGDRV/TITCQASQDIRNYLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQSYSTPLTFGGGQTKVEIK
9	291	DIQMTQSPSSLSASVGDRV/TITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITIS LQPEDFATYYCQQSYSTPLTFGGGQTKVEIK
10	292	DIQMTQSPSSLSASVGDRV/TITCQASQDISNYLNWYQQKPGKAPKLLIYAASNLESQVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQAHSFPLTFGGGQTKVDIK
11	293	DIQMTQSPSSLSASVGDRV/TITCRASQSISSYLNWYQQKPGKAPKLLIYGASTLESQVPSRFSGSGSGTDFLTITIS LQPEDFATYYCQQSYSTPIITFGGQTKLEIK
12	294	DIVMTQSPDLSAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESQVPSRFSGSGSG TDFLTITISLQAEADVAVYCYQQYYSTPLTFGGGQTKVEIK
13	295	DIQMTQSPSSLSASVGDRV/TITCQASQDISNYLNWYQQKPGKAPKLLIYAATSLQSGVPSRFSGSGSGTDFLTITIS SLQPEDFATYYCQQAANSLPYSTFGGQTKLEIK

Binding Agent	SEQ ID	VL
14	296	DIQMTQSPSSLSASVGDRAVTITCRASENIGNWLAWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQYSTPTFTGGQTKLEIK
15	297	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLIYGASTRATGIPARFSGSGSGTEFTLTIS LQSEDFAVYYCQQYGTSPFTFGQTRLEIK
16	298	DIQMTQSPSSLSASVGDRAVTITCRASQGISNNLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQSYTTTLTFGPQTKVDIK
17	299	DIQMTQSPSSLSASVGDRAVTITCRASQISKFLNWYQQKPGKAPKLLIYASNLQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQANSFPLTFGGQTKVEIK
18	300	DIQMTQSPSSLSASVGDRAVTITCRASENIGNWLAWYHQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQYSTPTFTGGQTKLEIK
19	301	DIVMTQSPFLPVTPGEPASISCRSSQSLHSNGYNLDWYKQPGQSPQLLIYLGSNRASGVDPDRFSGSGSGTDF TLKISRVEAEDVGYYCMQGAHWPTFTGGQTKLEIK
20	302	DIQMTQSPSSLSASVGDRAVTITCRASQSIGSYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQSYSTPLTFGGQTKVEIK
21	303	DIQMTQSPSSLSASVGDRAVTITCQASQEIIGNYNWYQQKPGKAPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTPLTFGGQTKVEIK
22	304	DIVMTQSPFLPVTPGEPASISCRSSQSLHSNGYNLDWYKQPGQSPQLLIYAASLTQSGVPSRFSGSGSGTDF TLKISRVEAEDVGYYCMQALQTPFTFGGQTKVEIK
23	305	DIQMTQSPSSLSASVGDRAVTITCRASQISSYLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQSYGIPLTFGGQTKVEIK
23a	305	DIQMTQSPSSLSASVGDRAVTITCRASQISSYLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQSYGIPLTFGGQTKVEIK
23b	305	DIQMTQSPSSLSASVGDRAVTITCRASQISSYLNWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQSYGIPLTFGGQTKVEIK
24	306	DIQMTQSPSSLSASVGDRAVTITCQASQDISNYLNWYQQKPGKAPKLLIYKASSLESQVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQANTFPLTFGGQTKVEIK
25	307	DIQMTQSPSSLSASVGDRAVTITCQASQDITNFWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQSYSFPLTFGPQTKVDIK

Binding Agent	SEQ ID	VL
26	308	DIQMTQSPSSLSASVGDRV/TITCRASQSI TFLNWYQQKPGKAPKLLIYAASSLQTGVPSRFSGSGGTDFTLTIS LQPEDFATYYCQQSYSTPPFGPGTKVDIK
27	309	DIQMTQSPSSLSASVGDRV/TITCQASQDISKYNLWYQQKPGKAPKLLIYAASNLRKGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSPPTFGQGTKVEIK
28	310	DIQMTQSPSSLSASVGDRV/TITCQASQDISKYNLWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSPPTFGQGTKVEIK
29	311	DIQMTQSPSSLSASVGDRV/TITCRASQDIRNYLAWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQANSPPTFGQGTKVDIK
30	312	DIQMTQSPSSLSASVGDRV/TITCQASQDIRNYLAWYQQKPGKAPKLLIYDTSNLETGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQAYSLPWTFGQGTKLEIK
31	313	DIQMTQSPSSLSASVGDRV/TITCQASQDISNYLWYQQKPGKAPKLLIYASNLQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQSYTTPYTFGQGTKLEIK
32	314	DIQMTQSPSSLSASVGDRV/TITCRASQSISSYLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGGTDFTLTIS LQPEDFATYYCQQSDSPLTFGQGTKVEIK
33	315	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASFRSGVPPDRFSGSGSG TDFTLTISLQAEADVAVYCCQYYTTPFTFGGQGTKVEIK
34	316	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASARESGVPPDRFSGSGSG TDFTLTISLQAEADVAVYCCQYKSAFYTFGQGTKVEIK
35	317	DIQMTQSPSSLSASVGDRV/TITCRASQSISSYLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGGTDFTLTIS LQPEDFATYYCQQNSFPPLTFGPGTKVDIK
36	318	DIQMTQSPSSLSASVGDRV/TITCRASQSISSYLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGGTDFTLTIS LQPEDFATYYCQQSYQTPLTFGGGQGTKVEIK
37	319	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASIRESGVPPDRFSGSGSGT DFTLTISLQAEADVAVYCCQYYSSPFTFGQGTKLEIK
38	320	DIVMTQSPSLPVPTEPASISCRSSQSLHSNGYNYLDWYLYQKPGQSPQLLIYDASNLHAGVPPDRFSGSGSGTD FTLKISRVEADVGVYCYCMQALQAPVTFGQGTKLEIK
39	321	DIQMTQSPSSLSASVGDRV/TITCQASQDISKYNLWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGGTDFTLTIS SLQPEDFATYYCQQNSFPPLTFGGGQGTKLEIK

Binding Agent	SEQ ID	VL
40	322	DIQMTQSPSSLSASVGDRAVTITCRASQTVRSYLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQTYRTPLTFGGQTKVEIK

Table 6

Binding Agent	SEQ ID	Light Chain Sequence
1	325	DIQMTQSPSSLSASVGDRAVTITCRASQDISNYLNWYQQKPGKAPKLLIYAASLTQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQTDSIPITFGGQTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
20	326	DIQMTQSPSSLSASVGDRAVTITCRASQSIGSYLNWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQSYSTPLTFGGQTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
23a & 23b	327	DIQMTQSPSSLSASVGDRAVTITCRASQSISSYLNWYQQKPGKAPKLLIYLASSLTQSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQSYGIPLTFGGGQTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Table 7

Binding Agent	SEQ ID	Fc mod.	Heavy Chain Sequence
1	328	(none)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMQWVRQAPGQGLEWMGWINPKSGGTNYAQKFQ GRVTMTTRDTSTVYMESSLRSEDTAVYYCARGTYLRTGSSLSGYYYGMDVWGQGTITVTVSSASTK GPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPS SLGTQTYICNVNHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITLMISRTPETC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNK ALPAPIEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Binding Agent	SEQ ID	Fc mod.	Heavy Chain Sequence
1	329	SE	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMQWVRQAPGQGLEWMGWINPKSGGTNYAQKFQ GRVTMTRDTSTVYMELSSLRSEDTAVYFCARGTYLRTGSSLSGYYYGMDVWGQGTITVTVSSASTK GPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSS SLGTQTYICNVNHNKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDITLMISRTPEVTC VVVDVEHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPP VLDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
1	330	ER	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMQWVRQAPGQGLEWMGWINPKSGGTNYAQKFQ GRVTMTRDTSTVYMELSSLRSEDTAVYFCARGTYLRTGSSLSGYYYGMDVWGQGTITVTVSSASTK GPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSS SLGTQTYICNVNHNKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDITLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEK TISKAKGQPRRPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPP VLDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
1	331	SEER	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMQWVRQAPGQGLEWMGWINPKSGGTNYAQKFQ GRVTMTRDTSTVYMELSSLRSEDTAVYFCARGTYLRTGSSLSGYYYGMDVWGQGTITVTVSSASTK GPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSS SLGTQTYICNVNHNKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDITLMISRTPEVTC VVVDVEHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEK TISKAKGQPRRPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPP VLDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
1	332	NA	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMQWVRQAPGQGLEWMGWINPKSGGTNYAQKFQ GRVTMTRDTSTVYMELSSLRSEDTAVYFCARGTYLRTGSSLSGYYYGMDVWGQGTITVTVSSASTK GPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSS SLGTQTYICNVNHNKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDITLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPP VLDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

Binding Agent	SEQ ID	Fc mod.	Heavy Chain Sequence
1	333	GA	QVQLVQSGAEVKKPGASVKVSKASGYTFTSYMQWVRQAPGQGLEWMGWINPKSGGTNYAQKFQ GRVTMTRDTSTVYMELSSLRSEDTAVYYCARGTYLRTGSSLSGYGMDVWGQGTITVTVSSASTK GPSVFLAPSSKSTGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSS SLGTQTYICNVNHNKPSNTKVDKRVPEPKSCDKTHTCPPCPAPPELLAGPSVFLFPPKPKDITLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPA ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP VLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
20	334	(none)	QVQLVQSGAEVKKPGASVKVSKASGYFTNTYWIQWVRQAPGQGLEWMGWINPNSGGTRYARNFQ RVMTMTRDTSTVYMELSSLRSEDTAVYYCARGRYYYGSGSQYHAFDIWGQGTMTVTVSSASTKGPSV FPLAPSSKSTGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGT QTYICNVNHNKPSNTKVDKRVPEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDITLMISRTPEVTCVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPA PIEKTTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
20	335	GA	QVQLVQSGAEVKKPGASVKVSKASGYFTNTYWIQWVRQAPGQGLEWMGWINPNSGGTRYARNFQ RVMTMTRDTSTVYMELSSLRSEDTAVYYCARGRYYYGSGSQYHAFDIWGQGTMTVTVSSASTKGPSV FPLAPSSKSTGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGT QTYICNVNHNKPSNTKVDKRVPEPKSCDKTHTCPPCPAPPELLAGPSVFLFPPKPKDITLMISRTPEVTCVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPA PIEKTTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
20	336	LALA	QVQLVQSGAEVKKPGASVKVSKASGYFTNTYWIQWVRQAPGQGLEWMGWINPNSGGTRYARNFQ RVMTMTRDTSTVYMELSSLRSEDTAVYYCARGRYYYGSGSQYHAFDIWGQGTMTVTVSSASTKGPSV FPLAPSSKSTGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGT QTYICNVNHNKPSNTKVDKRVPEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDITLMISRTPEVTCVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPA PIEKTTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Binding Agent	SEQ ID	Fc mod.	Heavy Chain Sequence
20	337	NA	QVQLVQSGAEVKKPGASVKVCSKASGYFTNYWIQWVRQAPGQGLEWMGWINPNSGGTRYARNFQGRVMTMRDTSSTVYMELSSRLSEDTAVYYCARGRYYYGSGSQYHAFDIWGQGTMTVTVSSASTKGPSPV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGT QTYICNVNHHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDITLMISRTPETVTCVVV DVSHEDPEVKFNWYVDGVEVHNATKPREEQYASTYRVSVLTVLHQDWLNGKEYCKVSNKALPAP PIEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
20	338	CS (IgG2)	QVQLVQSGAEVKKPGASVKVCSKASGYFTNYWIQWVRQAPGQGLEWMGWINPNSGGTRYARNFQGRVMTMRDTSSTVYMELSSRLSEDTAVYYCARGRYYYGSGSQYHAFDIWGQGTMTVTVSSASTKGPSPV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSNFGT QTYTCNVVDHKPSNTKVDKTVVERKSCVECPAPPAAGPSVFLFPPKPKDITLMISRTPETVTCVVVSH EDPEVQFNWYVDGVEVHNATKPREEQFNSTFRVSVLTVVHQDWLNGKEYCKVSNKGLPAPIEKT ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSF FLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
20	339	ER	QVQLVQSGAEVKKPGASVKVCSKASGYFTNYWIQWVRQAPGQGLEWMGWINPNSGGTRYARNFQGRVMTMRDTSSTVYMELSSRLSEDTAVYYCARGRYYYGSGSQYHAFDIWGQGTMTVTVSSASTKGPSPV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGT QTYICNVNHHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDITLMISRTPETVTCVVV DVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPAP PIEKTIKAKGQPRRPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
23a	340	(none)	EVQLLESGGGLVQPGGSLRLSCAASGFTSSYSMNHWVRQAPGKGLWVAVISYDGRJKDYADSVKGR FTISRDNSKNTLYLQMNSLR AEDTAVYYCARVRGFSFWDPPWGQGTMTVTVSSASTKGPSPVFLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVN HKPSNTKVDKRVPEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDITLMISRTPETVTCVVVSHEDPE VKFNWYVDGVEVHNATKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFFLYS KLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

Binding Agent	SEQ ID	Fc mod.	Heavy Chain Sequence
23a	341	ER	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYSMNWVRQAPGKGLEWVAVISYDGRKIDYADSVKGR FTISRDNSKNTLYLQMNSLR AEDTAVYYCARVRGFSWFDPWGQGT LVTSSASTKGPVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSVTVTPSSSLGTQTYICNVN HKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKA KGQPRRPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
23a	342	GA	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYSMNWVRQAPGKGLEWVAVISYDGRKIDYADSVKGR FTISRDNSKNTLYLQMNSLR AEDTAVYYCARVRGFSWFDPWGQGT LVTSSASTKGPVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSVTVTPSSSLGTQTYICNVN HKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
23a	343	CS	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYSMNWVRQAPGKGLEWVAVISYDGRKIDYADSVKGR FTISRDNSKNTLYLQMNSLR AEDTAVYYCARVRGFSWFDPWGQGT LVTSSASTKGPVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSVTVTPSSNFGTQTYTCNV DHKPSNTKVDKTVVERKSCVECPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYCKVSNKGLPAPIEKTISKTKGQ PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
23a	344	LALA	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYSMNWVRQAPGKGLEWVAVISYDGRKIDYADSVKGR FTISRDNSKNTLYLQMNSLR AEDTAVYYCARVRGFSWFDPWGQGT LVTSSASTKGPVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSVTVTPSSSLGTQTYICNVN HKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Binding Agent	SEQ ID	Fc mod.	Heavy Chain Sequence
23b	345	(none)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYSMNWVRQAPGKGLEWVAVISYDGRIKDYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRGFSWFEPWQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTVPSSSLGTQTYICNVN HKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSHFLYS KLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

[0146] As mentioned above, the binding agent can comprise an Ig heavy and/or light chain variable region with at least about 90% identity (e.g. at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identity) to a specific heavy or light chain variable region sequence provided herein. Similarly, the CDRs of the Ig heavy and/or light chain variable region can have at least about 90% identity (e.g. at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identity) to a specific CDR sequence provided herein. Thus, the Ig heavy and light chain variable region or CDR sequence can comprise at least one (e.g., 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, or 10 or more, etc., as applicable based on the length of the sequence) amino acid modification (e.g., substitution, addition, or deletion) as compared to the specific sequences provided herein, provided the binding agent maintains the ability to specifically bind Dectin-2, optionally wherein the binding agent maintains the affinity of a binding agent with the specified sequences and/or competes with a binding agent having the specified sequences for binding to Dectin-2.

[0147] The amino acids of the sequences provided can be substituted with any other amino acid. Amino acids include naturally-occurring α -amino acids and their stereoisomers, as well as non-naturally occurring amino acids and their stereoisomers. "Stereoisomers" of a given amino acid refer to isomers having the same molecular formula and intramolecular bonds but different three-dimensional arrangements of bonds and atoms (e.g., an L-amino acid and the corresponding D-amino acid). The amino acids can be glycosylated (e.g., N-linked glycans, O-linked glycans, phosphoglycans, C-linked glycans, or glypiation) or deglycosylated.

[0148] Naturally-occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Naturally-occurring α -amino acids include, without limitation, alanine (Ala), cysteine (Cys), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), arginine (Arg), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), serine (Ser), threonine (Thr), valine (Val), tryptophan (Trp), tyrosine (Tyr), and combinations thereof. Stereoisomers of naturally-occurring α -amino acids include, without limitation, D-alanine (D-Ala), D-cysteine (D-Cys), D-aspartic acid (D-Asp), D-glutamic acid (D-Glu), D-phenylalanine (D-Phe), D-histidine

(D-His), D-isoleucine (D-Ile), D-arginine (D-Arg), D-lysine (D-Lys), D-leucine (D-Leu), D-methionine (D-Met), D-asparagine (D-Asn), D-proline (D-Pro), D-glutamine (D-Gln), D-serine (D-Ser), D-threonine (D-Thr), D-valine (D-Val), D-tryptophan (D-Trp), D-tyrosine (D-Tyr), and combinations thereof.

[0149] Non-naturally occurring amino acids include, without limitation, amino acid analogs, amino acid mimetics, synthetic amino acids, *N*-substituted glycines, and *N*-methyl amino acids in either the L- or D-configuration that function in a manner similar to the naturally-occurring amino acids. For example, “amino acid analogs” can be unnatural amino acids that have the same basic chemical structure as naturally-occurring amino acids (i.e., a carbon that is bonded to a hydrogen, a carboxyl group, an amino group) but have modified side-chain groups or modified peptide backbones, e.g., homoserine, norleucine, methionine sulfoxide, and methionine methyl sulfonium. “Amino acid mimetics” refer to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally-occurring amino acid.

[0150] Amino acids may be referred to herein by either the commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission.

[0151] The amino acid substitution can be conservative, semi-conservative, or non-conservative with respect to the basic properties of the original amino acid residue. A “conservative” substitution refers to the replacement of one amino acid by another amino acid with a common property. A functional way to define common properties between individual amino acids is to analyze the normalized frequencies of amino acid changes between corresponding proteins of homologous organisms (Schulz and Schirmer, *Principles of Protein Structure*, Springer-Verlag, New York (1979)). According to such analyses, groups of amino acids may be defined where amino acids within a group exchange preferentially with each other, and therefore resemble each other most in their impact on the overall protein structure (Schulz and Schirmer, *supra*).

[0152] Amino acids are broadly grouped as “aromatic” or “aliphatic.” An aromatic amino acid includes an aromatic ring. Examples of “aromatic” amino acids include histidine (H or His), phenylalanine (F or Phe), tyrosine (Y or Tyr), and tryptophan (W or Trp). Non-aromatic amino acids are broadly grouped as “aliphatic.” Examples of “aliphatic” amino acids include glycine (G or Gly), alanine (A or Ala), valine (V or Val), leucine (L or Leu), isoleucine (I or Ile), methionine (M or Met), serine (S or Ser), threonine (T or Thr), cysteine (C or Cys),

proline (P or Pro), glutamic acid (E or Glu), aspartic acid (D or Asp), asparagine (N or Asn), glutamine (Q or Gln), lysine (K or Lys), and arginine (R or Arg).

[0153] Aliphatic amino acids may be sub-divided into four sub-groups. The “large aliphatic non-polar sub-group” consists of valine, leucine, and isoleucine. The “aliphatic slightly-polar sub-group” consists of methionine, serine, threonine, and cysteine. The “aliphatic polar/charged sub-group” consists of glutamic acid, aspartic acid, asparagine, glutamine, lysine, and arginine. The “small-residue sub-group” consists of glycine and alanine. The group of charged/polar amino acids may be sub-divided into three sub-groups: the “positively-charged sub-group” consisting of lysine and arginine, the “negatively-charged sub-group” consisting of glutamic acid and aspartic acid, and the “polar sub-group” consisting of asparagine and glutamine.

[0154] Aromatic amino acids may be sub-divided into two sub-groups: the “nitrogen ring sub-group” consisting of histidine and tryptophan and the “phenyl sub-group” consisting of phenylalanine and tyrosine.

[0155] Examples of conservative amino acid substitutions include substitutions of amino acids within the sub-groups described above, for example, lysine for arginine and vice versa such that a positive charge may be maintained, glutamic acid for aspartic acid and vice versa such that a negative charge may be maintained, serine for threonine such that a free -OH can be maintained, and glutamine for asparagine such that a free -NH₂ can be maintained.

[0156] “Semi-conservative mutations” include amino acid substitutions of amino acids within the same groups listed above, but not within the same sub-group. For example, the substitution of aspartic acid for asparagine, or asparagine for lysine, involves amino acids within the same group, but different sub-groups. “Non-conservative mutations” involve amino acid substitutions between different groups, for example, lysine for tryptophan, or phenylalanine for serine, etc.

[0157] In addition, one or more amino acids can be inserted into the aforementioned immunoglobulin heavy or light chain variable region polypeptides. Any number of any suitable amino acids can be inserted into the amino acid sequence of the immunoglobulin heavy or light chain variable region polypeptide. In this respect, at least one amino acid (e.g., 2 or more, 5 or more, or 10 or more amino acids), but not more than 20 amino acids (e.g., 18 or less, 15 or less, or 12 or less amino acids), can be inserted into the amino acid sequence of the immunoglobulin heavy or light chain variable region polypeptide. Preferably, 1-10 amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids) are inserted into the amino acid

sequence of the immunoglobulin heavy or light chain variable region polypeptide. In this respect, the amino acid(s) can be inserted into any one of the aforementioned immunoglobulin heavy or light chain variable region polypeptides in any suitable location. In some embodiments, the amino acid(s) are inserted into a CDR (e.g., CDR1, CDR2, or CDR3) of the immunoglobulin heavy or light chain variable region polypeptide; in other embodiments, the amino acids are inserted into a framework region.

[0158] Further provided is a Dectin-2 binding agent (e.g., antibody or antibody fragment) that competes with a Dectin-2 binding agent (e.g., antibody or antibody fragment) having an immunoglobulin heavy and light chain variable region specifically provided herein (e.g., one of the binding agents provided herein), and preferably retains the biological activity of the Dectin-2 binding agent.

[0159] The “biological activity” of a Dectin-2 binding agent refers to, for example, binding affinity for Dectin-2 or a particular Dectin-2 epitope, pharmacokinetics, and cross-reactivity (e.g., with non-human homologs or orthologs of the Dectin-2 protein, or with other proteins or tissues). In some embodiments, the biological activity of the Dectin-2 binding agent includes the ability to increase Dectin-2 activity *in vivo* and/or *in vitro*. Examples of Dectin-2 activity include increased or enhanced expression and/or production of pro-inflammatory cytokines, increased expression of costimulatory molecules, such as CD40, CD86, and major histocompatibility complex (MHC) molecules, and increased phagocytosis. Examples of pro-inflammatory cytokines include Tumor Necrosis Factor (TNF) alpha, IL-1 β , IL-2, IL-6, IL-23p19, IFN γ , IL-12p40, and IL-12p70.

[0160] The term “increase” or “enhance” as used in reference to Dectin-2 activity (e.g., Dectin-2 mediated signaling) means to increase or enhance such binding or signaling in any way and to any degree (e.g., act as an agonist). In some embodiments, Dectin-2 mediated signaling is increased sufficiently to reduce or alleviate any symptom of a disease or condition associated with deficient Dectin-2 activity, or which benefits from enhanced Dectin-2 activity, or to reverse, slow, or stop the progression or severity of such a disease or condition. The Dectin-2 binding agent of the invention preferably increases the activity of Dectin-2 by at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 100%, about 150%, about 200%, about 300%, or a range defined by any two of the foregoing values, as compared to the activity of Dectin-2 in Dectin-2 expressing cells in the absence of the Dectin-2 agent.

[0161] Other biological properties or characteristics of an antigen-binding agent recognized in the art include, for example, avidity, selectivity, solubility, folding, immunotoxicity, expression, and formulation. The aforementioned properties or characteristics can be observed, measured, and/or assessed using standard techniques including, but not limited to, ELISA, competitive ELISA, surface plasmon resonance analysis (BIAcore™), or KINEXA™, *in vitro* or *in vivo* neutralization assays, receptor-ligand binding assays, cytokine or growth factor production and/or secretion assays, and signal transduction and immunohistochemistry assays.

[0162] In some embodiments, the Dectin-2 binding agent (e.g., antibody or antibody fragment) increases or enhances Dectin-2 expression in cells of myeloid lineage, such as, for example, monocytes, macrophages, and dendritic cells, in comparison to Dectin-2 expression in cells of myeloid lineage not exposed to the Dectin-2 binding agent. This increase or enhancement in Dectin-2 expression can lead to an increased innate immune response. Without wishing to be bound by any particular theory, activation of the Dectin-2 signaling pathway is known to, for example, increase phagocytic activity and to activate MAPK and NF- κ B signaling pathways, leading to the production of pro-inflammatory cytokines such as, for instance, TNF α , IL-1 β , IL-2, IL-6, IL-23p19, IFN γ , IL-12p40, and IL-12p70.

[0163] In some embodiments, the Dectin-2 binding agent (e.g., antibody or antibody fragment) exhibits antibody dependent cell-mediated cytotoxicity (ADCC). ADCC is a mechanism of cell-mediated immune defense whereby an effector cell of the immune system lyses a target cell whose membrane-surface antigens have been bound by specific antibodies. ADCC is independent of the immune complement system that also lyses targets but does not require any other cell and is part of the adaptive immune response.

[0164] In some embodiments, the Dectin-2 binding agent (e.g., antibody or antibody fragment) promotes antibody dependent cell-mediated phagocytosis (ADCP). ADCP is a cellular process by which effector cells with phagocytic potential, such as monocytes and macrophages, can internalize target cells. Once phagocytosed, the target cell resides in a phagosome, which fuses with a lysosome to begin degradation of the target cell via an oxygen-dependent or independent mechanism. This function is dependent on opsonization, or identification of the target cell with a binding agent, which then also serves as a bridge between the target cell and the phagocytic cell. Mechanistically, the binding agent binds its cognate antigen on the target cell through its antigen recognition domain, and then recruits the phagocytic cell to the target with its Fc region. Once bound to the Fc receptor of the

phagocytic cell, the target cell is ingested and degraded. This process also leads to the production of soluble factors by the effector cells that help initiate and drive the immune response.

[0165] In some embodiments, the Dectin-2 binding agent (e.g., antibody or antibody fragment) exhibits complement dependent cytotoxicity (CDC). CDC is an effector function of IgG and IgM antibodies. When the binding agents are bound to surface antigen, the classical complement pathway is triggered, resulting in formation of a membrane attack complex (MAC) and target cell lysis.

[0166] In some embodiments, the binding agents comprise an Fc region containing one or more modifications (e.g., amino acid insertion, deletion, and/or substitution) in the Fc region that results in modulated binding (e.g., increased binding or decreased binding) to one or more Fc receptors (e.g., Fc γ RI (CD64), Fc γ RIIA (CD32A), Fc γ RIIB (CD32B), Fc γ RIIA (CD16a), and/or Fc γ RIIB (CD16b)) as compared to a binding agent or antibody with the native Fc region lacking the mutation. In some embodiments, the binding agents contain one or more modifications (e.g., amino acid insertion, deletion, and/or substitution) in the Fc region that reduce the binding of the Fc region to Fc γ RIIB. In some embodiments, the binding agents contain one or more modifications (e.g., amino acid insertion, deletion, and/or substitution) in the Fc region of the antibody that reduce the binding to Fc γ RIIB while maintaining the same binding or having increased binding to Fc γ RI (CD64), Fc γ RIIA (CD32A), and/or Fc γ RIIA (CD16a) as compared to a binding agent or antibody with a native Fc region lacking the mutation. In some embodiments, the binding agents contain one or more modifications in the Fc region that increase the binding of the Fc region to Fc γ RIIB. In some embodiments, the modifications substantially reduce or eliminate antibody effector functions.

[0167] The Fc region mutations can be in a CH2 domain, a CH3 domain, or a combination thereof. A “native Fc region” is synonymous with a “wild-type Fc region” and comprises an amino acid sequence that is identical to the amino acid sequence of an Fc region found in nature or identical to the amino acid sequence of the Fc region found in a native antibody. Native human Fc regions include a native sequence human IgG1 Fc region, native sequence human IgG2 Fc region, native sequence human IgG3 Fc region, and native sequence human IgG4 Fc region, as well as naturally occurring variants thereof. Native sequence Fc includes the various allotypes of Fcs (see, e.g., Jefferis et al., *mAbs*, 1(4): 332-338 (2009)).

[0168] In some embodiments, the Dectin-2 binding agent comprises an IgG (e.g., IgG1) Fc region or at least the CH2 domain thereof (e.g., a chimeric Fc comprising CH1, CH2, and CH3 regions of IgG1, but hinge region from a different Ig, such as IgG2). In some embodiments, the Dectin-2 binding agent comprises one or more of the following mutations or groups of mutations: SD (S239D), SDIE (S239D/I332E), SE (S267E), SEER (S267E/E345R), SELF (S267E/L328F), SDIEAL (S239D/I332E/A330L), GA (G236A), ALIE (A330L/I332E), GASDALIE (G236A/S239D/A330L/I332E), V9 (G237D/P238D/P271G/A330R), LALA (L234A/L235A), CS (C219S), NA (N297A), and V11 (G237D/P238D/H268D/P271G/A330R), and/or one or more mutations at the following amino acids: E345R, E233, G237, P238, H268, P271, N297, L328 and A330. All numbering refers to the EU numbering of human IgG (e.g., IgG1); however, the same mutations at corresponding positions of a different Ig (e.g., a chimeric Ig) can be used. In an embodiment, the mutation is SD. In an embodiment, the mutation is SDIE. In an embodiment, the mutation is SE. In an embodiment, the mutation is SELF. In an embodiment, the mutation is SDIEAL. In an embodiment, the mutation is GA. In an embodiment, the mutation is ALIE. In an embodiment, the mutation is GASDALIE. In an embodiment, the mutation is V9. In an embodiment, the mutation is LALA. In an embodiment, the mutation is CS. In an embodiment, the mutation is V11. In an embodiment, the mutation is E345R. In an embodiment, the mutation is NA. In an embodiment, the mutation is SEER. In an embodiment, the Dectin-2 binding agent comprises an Fc region with G236A, LALA and/or CS mutations, optionally wherein the Fc region is afucosylated (i.e., non-fucosylated). In some embodiments, the Dectin-2 binding agent comprises an Fc region with one or more of the above-listed mutations or groups of mutations, wherein the Fc region is afucosylated. Additional Fc region modifications for modulating Fc receptor binding are described in, for example, U.S. Patent Application Publication 2016/0145350 and U.S. Patents 7,416,726 and 5,624,821, which are hereby incorporated by reference in their entireties herein.

[0169] In an embodiment, the Dectin-2 binding agent is Binding Agent 1 disclosed herein (VH and VL regions respectively SEQ ID NOs: 243 and 283). In an embodiment, the Dectin-2 binding agent is Binding Agent 1 further comprising an Fc region. In another embodiment, the Dectin-2 binding agent is Binding Agent 1, wherein the Fc region is IgG1. In another embodiment, the Dectin-2 binding agent is Binding Agent 1, wherein the Fc region is IgG2. In another embodiment, the Dectin-2 binding agent is Binding Agent 1, wherein the Fc region is IgG1, and comprises the SE mutation. In another embodiment, the Dectin-2 binding agent

is Binding Agent 1, wherein the Fc region is IgG1, and comprises the E345R mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 1, wherein the Fc region is IgG1, and comprises the SEER mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 1, wherein the Fc region is IgG1, and comprises the NA mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 1, wherein the Fc region is IgG1, and comprises the GA mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 1, wherein the Fc region is IgG1, comprises the GA mutation, and is also afucosylated. In another embodiment, the Dectin-2 binding agent is Binding Agent 1, wherein the Fc region is IgG1, and is afucosylated.

[0170] In an embodiment, the Dectin-2 binding agent is Binding Agent 20 disclosed herein (VH and VL regions respectively SEQ ID NOs: 261 and 302). In an embodiment, the Dectin-2 binding agent is Binding Agent 20 further comprising an Fc region. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG1. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG2. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG1, and is afucosylated. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG1, and comprises the GA mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG1, and comprises the LALA mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG1, and comprises the NA mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG1, and comprises the CS mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG2, and comprises the CS mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region comprises the E345R mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 20, wherein the Fc region is IgG1, comprises the GA mutation, and is also afucosylated.

[0171] In an embodiment, the Dectin-2 binding agent is Binding Agent 23a disclosed herein (VH and VL regions respectively SEQ ID NOs: 265 and 305). In an embodiment, the Dectin-2 binding agent is Binding Agent 23a further comprising an Fc region. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a, wherein the Fc region is IgG1. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a, wherein the Fc region is IgG2. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a,

wherein the Fc region is IgG1, and is afucosylated. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a, wherein the Fc region is IgG1, and comprises the E345R mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a, wherein the Fc region is IgG1, and comprises the GA mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a, wherein the Fc region comprises the NA mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a, wherein the Fc region is IgG1, comprises the GA mutation, and is also afucosylated. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a, wherein the Fc region is IgG2, and comprises the CS mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 23a, wherein the Fc region comprises the LALA mutation. In another embodiment, the Dectin-2 binding agent is Binding Agent 23b disclosed herein (VH and VL regions respectively SEQ ID NOs: 324 and 305), wherein the Fc region is IgG1, and wherein the heavy chain variable region includes a D101E mutation (Kabat numbering).

[0172] In some embodiments, the Fc region of the binding agents are modified to have an altered glycosylation pattern of the Fc region compared to the native non-modified Fc region.

[0173] Human immunoglobulin is glycosylated at the Asn297 residue in the C γ 2 domain of each heavy chain. This N-linked oligosaccharide is composed of a core heptasaccharide, N-acetylglucosamine4Mannose3 (GlcNAc4Man3). Removal of the heptasaccharide with endoglycosidase or PNGase F is known to lead to conformational changes in the Fc region, which can significantly reduce binding affinity to activating Fc γ R and lead to decreased effector function. The core heptasaccharide is often decorated with galactose, bisecting GlcNAc, fucose, or sialic acid, which differentially impacts Fc binding to activating and inhibitory Fc γ R. Additionally, it has been demonstrated that α 2,6-sialylation enhances anti-inflammatory activity *in vivo*, while defucosylation leads to improved Fc γ RIIIa binding and a 10-fold increase in antibody-dependent cellular cytotoxicity and antibody-dependent phagocytosis. Specific glycosylation patterns, therefore, can be used to control inflammatory effector functions.

[0174] In some embodiments, the modification to alter the glycosylation pattern is a mutation. For example, a substitution at Asn297. In some embodiments, Asn297 is mutated to glutamine (N297Q). Methods for controlling immune response with antibodies that modulate Fc γ R-regulated signaling are described, for example, in U.S. Patent 7,416,726 and U.S. Patent Application Publications 2007/0014795 and 2008/0286819, which are hereby incorporated by reference in their entireties.

[0175] In some embodiments, the binding agents are modified to contain an engineered Fab region with a non-naturally occurring glycosylation pattern. For example, hybridomas can be genetically engineered to secrete afucosylated mAb, desialylated mAb or deglycosylated Fc with specific mutations that enable increased FcR γ IIIa binding and effector function. In some embodiments, the binding agents are engineered to be afucosylated.

[0176] In some embodiments, the entire Fc region is exchanged with a different Fc region, so that the Fab region is conjugated to a non-native Fc region. For example, the Fab region of atezolizumab, which normally comprises an IgG1 Fc region, can be conjugated to IgG2, IgG3, IgG4, or IgA, or the Fab region of nivolumab, which normally comprises an IgG4 Fc region, can be conjugated to IgG1, IgG2, IgG3, IgA1, or IgG2. In some embodiments, the Fc modified binding agent with a non-native Fc domain also comprises one or more additional amino acid modification, such as the S228P mutation within the IgG4 Fc, that modulate the stability of the Fc domain described. In some embodiments, the Fc modified binding agent with a non-native Fc domain also comprises one or more amino acid modifications described herein that modulate Fc binding to FcR.

[0177] In some embodiments, the modifications that modulate the binding of the Fc region to FcR do not alter the binding of the Fab region to its antigen when compared to the non-modified Fab. In other embodiments, the modifications that modulate the binding of the Fc region to FcR also increase the binding of the Fab region to its antigen when compared to the non-modified Fab.

[0178] In some embodiments, the Fc region is modified by attachment or inclusion of a transforming growth factor beta 1 (TGF β 1) receptor, or a fragment thereof, that is capable of binding TGF β 1. For example, the receptor can be TGF β receptor II (TGF β RII) (see U.S. Patent 9,676,863, incorporated herein in its entirety). In some embodiments, the TGF β receptor is a human TGF β receptor. In some embodiments, the Fc region (e.g., IgG) has a C-terminal fusion to a TGF β receptor (e.g., TGF β RII) extracellular domain (ECD; e.g., amino acids 24-159 of SEQ ID NO: 9 of U.S. Patent 9,676,863). An "Fc linker" may be used to attach the TGF β R extracellular domain to the Fc region (e.g., IgG), for example, a G₄S₄G linker. The Fc linker may be a short, flexible peptide that allows for the proper three-dimensional folding of the molecule while maintaining the binding-specificity to the targets. In some embodiments, the N-terminus of the TGF β receptor is fused to the Fc region (with or without an Fc linker). In some embodiments, the C-terminus of the immunoglobulin heavy

chain is fused to the TGF β receptor (with or without an Fc linker), such as at the N-terminus of the TGF β receptor. In some embodiments, the C-terminal lysine residue of the antibody heavy chain is mutated to alanine.

[0179] The Dectin-2 binding agent can have any suitable affinity to a Dectin-2 protein or an epitope thereof. The term “affinity” refers to the equilibrium constant for the reversible binding of two agents and is expressed as the dissociation constant (K_D). Affinity of a binding agent to a ligand, such as affinity of an antibody for an epitope, can be, for example, from about 1 picomolar (pM) to about 1 micromolar (μ M) (e.g., from about 1 picomolar (pM) to about 1 nanomolar (nM), or from about 1 nM to about 1 micromolar (μ M)). In one embodiment, the Dectin-2 binding agent can bind to a human Dectin-2 protein with a K_D less than or equal to 1 micromolar (e.g., 0.9 μ M, 0.8 μ M, 0.7 μ M, 0.6 μ M, 0.5 μ M, 0.4 μ M, 0.3 μ M, 0.2 μ M, 0.1 μ M, 0.05 μ M, 0.025 μ M, 0.01 μ M, 0.001 μ M, or a range defined by any two of the foregoing values). In one embodiment, the Dectin-2 binding agent can bind to a human Dectin-2 protein with a K_D less than or equal to 200 nanomolar (e.g., 190 nM, 175 nM, 150 nM, 125 nM, 110 nM, 100 nM, 90 nM, 80 nM, 75 nM, 60 nM, 50 nM, 40 nM, 30 nM, 25 nM, 20 nM, 15 nM, 10 nM, 5 nM, 1 nM, or a range defined by any two of the foregoing values). In one embodiment, the Dectin-2 binding agent can bind to a human Dectin-2 protein with a K_D less than or equal to 1 nanomolar (e.g., 0.9 nM, 0.8 nM, 0.7 nM, 0.6 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, 0.1 nM, 0.05 nM, 0.025 nM, 0.01 nM, 0.001 nM, or a range defined by any two of the foregoing values). In another embodiment, the Dectin-2 binding agent can bind to human Dectin-2 with a K_D less than or equal to 200 pM (e.g., 190 pM, 175 pM, 150 pM, 125 pM, 110 pM, 100 pM, 90 pM, 80 pM, 75 pM, 60 pM, 50 pM, 40 pM, 30 pM, 25 pM, 20 pM, 15 pM, 10 pM, 5 pM, 1 pM, or a range defined by any two of the foregoing values).

[0180] In some embodiments, the Dectin-2 binding agent also binds to a non-human species of Dectin-2 protein that is useful for development in animal models (e.g., tox screens and the like). In some embodiments, the Dectin-2 binding agent has an affinity for human Dectin-2 as described above, and also has an affinity for cynomolgus monkey or rat Dectin-2 that is within the above-mentioned ranges of affinity for human Dectin-2.

[0181] Immunoglobulin affinity for an antigen or epitope of interest can be measured using any art-recognized assay. Such methods include, for example, fluorescence activated cell sorting (FACS), separable beads (e.g., magnetic beads), surface plasmon resonance (SPR), solution phase competition (KINEXA™), antigen panning, and/or ELISA (see,

Janeway et al. (eds.), *Immunobiology, 9th Ed.*, Garland Publishing, New York, NY (2017)). In some embodiments, the binding agent (e.g., an antibody or antigen-binding antibody fragment) has an affinity to human Dectin-2 as described above as determined by SPR or as determined by solution-phase competition assay. In some embodiments, the binding agent (e.g., an antibody or antigen-binding antibody fragment) has an affinity to human Dectin-2 as described above as determined by ELISA or as determined by FACs.

Nucleic Acids

[0182] The invention also provides nucleic acids that encode the immunoglobulin heavy chain polypeptide and/or the immunoglobulin light chain polypeptide of the Dectin-2 binding agent.

[0183] The term “nucleic acid sequence” is intended to encompass a polymer of DNA or RNA, i.e., a polynucleotide, which can be single-stranded or double-stranded and which can contain non-natural or altered nucleotides. The terms “nucleic acid” and “polynucleotide” as used herein refer to a polymeric form of nucleotides of any length, either ribonucleotides (RNA) or deoxyribonucleotides (DNA). These terms refer to the primary structure of the molecule, and thus include double- and single-stranded DNA, and double- and single-stranded RNA. The terms include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs and modified polynucleotides such as, though not limited to, methylated and/or capped polynucleotides. Nucleic acids are typically linked via phosphate bonds to form nucleic acid sequences or polynucleotides, though many other linkages are known in the art (e.g., phosphorothioates, boranophosphates, and the like).

[0184] The nucleic acid can be part of a vector. Thus, also provided is a vector comprising one or more nucleic acid sequences encoding the immunoglobulin heavy chain polypeptide, the immunoglobulin light chain polypeptide, or both, of the Dectin-2 binding agent. Any type of vector can be used, particularly an expression vector useful for expressing the polypeptides in a cell. The vector can be, for example, a plasmid, episome, cosmid, viral vector (e.g., retroviral or adenoviral), or phage. Suitable vectors and methods of vector preparation are well known in the art (see, e.g., Sambrook et al., *Molecular Cloning, a Laboratory Manual, 3rd edition*, Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (2001), and Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing Associates and John Wiley & Sons, New York, N.Y. (1994)).

[0185] The vector preferably comprises expression control sequences, such as promoters, enhancers, polyadenylation signals, transcription terminators, internal ribosome entry sites

(IRES), and the like, that provide for the expression of the coding sequence in a host cell. Exemplary expression control sequences are known in the art and described in, for example, Goeddel, *Gene Expression Technology: Methods in Enzymology*, Vol. 185, Academic Press, San Diego, Calif. (1990).

[0186] A large number of promoters, including constitutive, inducible, and repressible promoters, from a variety of different sources are well known in the art. Representative sources of promoters include for example, virus, mammal, insect, plant, yeast, and bacteria, and suitable promoters from these sources are readily available, or can be made synthetically, based on sequences publicly available, for example, from depositories such as the American Type Culture Collection (ATCC) as well as other commercial or individual sources. Promoters can be unidirectional (i.e., initiate transcription in one direction) or bi-directional (i.e., initiate transcription in either a 3' or 5' direction). Non-limiting examples of promoters include, for example, the T7 bacterial expression system, pBAD (araA) bacterial expression system, the cytomegalovirus (CMV) promoter, the SV40 promoter, the RSV promoter. Inducible promoters include, for example, the Tet system (U.S. Patents 5,464,758 and 5,814,618), the Ecdysone inducible system (No et al., *Proc. Natl. Acad. Sci.*, 93: 3346-3351 (1996)), the T-REX™ system (Invitrogen, Carlsbad, CA), LACSWITCH™ system (Stratagene, San Diego, CA), and the Cre-ERT tamoxifen inducible recombinase system (Indra et al., *Nuc. Acid. Res.*, 27: 4324-4327 (1999); *Nuc. Acid. Res.*, 28: e99 (2000); U.S. Patent 7,112,715; and Kramer & Fussenegger, *Methods Mol. Biol.*, 308: 123-144 (2005)).

[0187] The term “enhancer” as used herein, refers to a DNA sequence that increases transcription of, for example, a nucleic acid sequence to which it is operably linked. Enhancers can be located many kilobases away from the coding region of the nucleic acid sequence and can mediate the binding of regulatory factors, patterns of DNA methylation, or changes in DNA structure. A large number of enhancers from a variety of different sources are well known in the art and are available as or within cloned polynucleotides (from, e.g., depositories such as the ATCC as well as other commercial or individual sources). A number of polynucleotides comprising promoters (such as the commonly-used CMV promoter) also comprise enhancer sequences. Enhancers can be located upstream, within, or downstream of coding sequences.

[0188] The vector also can comprise a “selectable marker gene.” The term “selectable marker gene,” as used herein, refers to a nucleic acid sequence that allow cells expressing the nucleic acid sequence to be specifically selected for or against, in the presence of a

corresponding selective agent. Suitable selectable marker genes are known in the art and described in, e.g., International Patent Application Publications WO 1992/008796 and WO 1994/028143; Wigler et al., *Proc. Natl. Acad. Sci. USA*, 77: 3567-3570 (1980); O'Hare et al., *Proc. Natl. Acad. Sci. USA*, 78: 1527-1531 (1981); Mulligan & Berg, *Proc. Natl. Acad. Sci. USA*, 78: 2072-2076 (1981); Colberre-Garapin et al., *J. Mol. Biol.*, 150: 1-14 (1981); Santerre et al., *Gene*, 30: 147-156 (1984); Kent et al., *Science*, 237: 901-903 (1987); Wigler et al., *Cell*, 11: 223-232 (1977); Szybalska & Szybalski, *Proc. Natl. Acad. Sci. USA*, 48: 2026-2034 (1962); Lowy et al., *Cell*, 22: 817-823 (1980); and U.S. Patents 5,122,464 and 5,770,359.

[0189] In some embodiments, the vector is an "episomal expression vector" or "episome," which is able to replicate in a host cell, and persists as an extrachromosomal segment of DNA within the host cell in the presence of appropriate selective pressure (see, e.g., Conese et al., *Gene Therapy*, 11: 1735-1742 (2004)). Representative commercially available episomal expression vectors include, but are not limited to, episomal plasmids that utilize Epstein Barr Nuclear Antigen 1 (EBNA1) and the Epstein Barr Virus (EBV) origin of replication (oriP). The vectors pREP4, pCEP4, pREP7, and pcDNA3.1 from Invitrogen (Carlsbad, CA) and pBK-CMV from Stratagene (La Jolla, CA) represent non-limiting examples of an episomal vector that uses T-antigen and the SV40 origin of replication in lieu of EBNA1 and oriP.

[0190] Other suitable vectors include integrating expression vectors, which may randomly integrate into the host cell's DNA, or may include a recombination site to enable the specific recombination between the expression vector and the host cell's chromosome. Such integrating expression vectors may utilize the endogenous expression control sequences of the host cell's chromosomes to effect expression of the desired protein. Examples of vectors that integrate in a site specific manner include, for example, components of the flp-in system from Invitrogen (Carlsbad, CA) (e.g., pcDNATM5/FRT), or the cre-lox system, such as can be found in the pExchange-6 Core Vectors from Stratagene (La Jolla, CA). Examples of vectors that randomly integrate into host cell chromosomes include, for example, pcDNA3.1 (when introduced in the absence of T-antigen) from Invitrogen (Carlsbad, CA), UCOE from Millipore (Billerica, MA), and pCI or pFN10A (ACT) FLEXITM from Promega (Madison, WI).

[0191] Viral vectors also can be used. Representative commercially available viral expression vectors include, but are not limited to, the adenovirus-based Per.C6 system available from Crucell, Inc. (Leiden, The Netherlands), the lentiviral-based pLP1 from

Invitrogen (Carlsbad, CA), and the retroviral vectors pFB-ERV plus pCFB-EGSH from Stratagene (La Jolla, CA).

Cells

[0192] Nucleic acid sequences encoding the heavy and light chain immunoglobulin sequences can be provided to a cell on the same vector (i.e., in *cis*). A unidirectional promoter can be used to control expression of each nucleic acid sequence. In another embodiment, a combination of bidirectional and unidirectional promoters can be used to control expression of multiple nucleic acid sequences. Nucleic acid sequences encoding the inventive amino acid sequences alternatively can be provided to the population of cells on separate vectors (i.e., in *trans*). Each of the nucleic acid sequences in each of the separate vectors can comprise the same or different expression control sequences. The separate vectors can be provided to cells simultaneously or sequentially.

[0193] The vector(s) comprising the nucleic acid(s) encoding the inventive amino acid sequences can be introduced into a host cell that is capable of expressing the polypeptides encoded thereby, including any suitable prokaryotic or eukaryotic cell. As such, the invention provides an *in vitro* (isolated) cell or cell line comprising the inventive vector, which expresses the immunoglobulin heavy and light chain polypeptides. Preferred host cells are those that can be easily and reliably grown, have reasonably fast growth rates, have well characterized expression systems, and can be transformed or transfected easily and efficiently.

[0194] Examples of suitable prokaryotic cells include, but are not limited to, cells from the genera *Bacillus* (such as *Bacillus subtilis* and *Bacillus brevis*), *Escherichia* (such as *E. coli*), *Pseudomonas*, *Streptomyces*, *Salmonella*, and *Erwinia*. Particularly useful prokaryotic cells include the various strains of *Escherichia coli* (e.g., K12, HB101 (ATCC No. 33694), DH5 α , DH10, MC1061 (ATCC No. 53338), and CC102).

[0195] Preferably, the vector is introduced into a eukaryotic cell. Suitable eukaryotic cells are known in the art and include, for example, yeast cells, insect cells, and mammalian cells. Examples of suitable yeast cells include those from the genera *Kluyveromyces*, *Pichia*, *Rhizosporidium*, *Saccharomyces*, and *Schizosaccharomyces*. Preferred yeast cells include, for example, *Saccharomyces cerevisiae* and *Pichia pastoris*.

[0196] Suitable insect cells are described in, for example, Kitts et al., *Biotechniques*, 14: 810-817 (1993); Lucklow, *Curr. Opin. Biotechnol.*, 4: 564-572 (1993); and Lucklow et al., *J.*

Virol., 67: 4566-4579 (1993). Preferred insect cells include Sf-9 and HI5 (Invitrogen, Carlsbad, CA).

[0197] Preferably, mammalian cells are utilized in the invention. A number of suitable mammalian host cells are known in the art, and many are available from ATCC. Examples of suitable mammalian cells include, but are not limited to, Chinese hamster ovary cells (CHO) cells, such as CHO-K1 cells (ATCC No. CCL61), CHO DHFR-cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA*, 97: 4216-4220 (1980)), human embryonic kidney (HEK) 293 or 293T cells (ATCC No. CRL1573), and 3T3 cells (ATCC No. CCL92). Other suitable mammalian cell lines are the monkey COS-1 (ATCC No. CRL1650) and COS-7 cell lines (ATCC No. CRL1651), as well as the CV-1 cell line (ATCC No. CCL70). Further exemplary mammalian host cells include primate cell lines and rodent cell lines, including transformed cell lines. Normal diploid cells, cell strains derived from in vitro culture of primary tissue, as well as primary explants, are also suitable. Other suitable mammalian cell lines include, but are not limited to, mouse neuroblastoma N2A cells, HeLa, mouse L-929 cells, and BHK or HaK hamster cell lines, all of which are available from the ATCC. Suitable cell lines also include hybridomas. Methods for selecting suitable mammalian host cells and methods for transformation, culture, amplification, screening, and purification of cells are known in the art.

[0198] The mammalian cell can be a human cell. For example, the mammalian cell can be a human lymphoid or lymphoid derived cell line, such as a cell line of pre-B lymphocyte origin. Examples of human lymphoid cells lines include, without limitation, RAMOS (CRL-1596), Daudi (CCL-213), EB-3 (CCL-85), DT40 (CRL-2111), 18-81 (Jack et al., *Proc. Natl. Acad. Sci. USA*, 85: 1581-1585 (1988)), Raji cells (CCL-86), and derivatives thereof.

[0199] A nucleic acid sequence encoding the inventive amino acid sequence may be introduced into a cell by “transfection,” “transformation,” or “transduction.” “Transfection,” “transformation,” or “transduction,” as used herein, refer to the introduction of one or more exogenous polynucleotides into a host cell by using physical or chemical methods. Many transfection techniques are known in the art and include, for example, calcium phosphate DNA co-precipitation (see, e.g., Murray E.J. (ed.), *Methods in Molecular Biology*, Vol. 7, *Gene Transfer and Expression Protocols*, Humana Press (1991)); DEAE-dextran; electroporation; cationic liposome-mediated transfection; tungsten particle-facilitated microparticle bombardment (Johnston, *Nature*, 346: 776-777 (1990)); and strontium phosphate DNA co-precipitation (Brash et al., *Mol. Cell Biol.*, 7: 2031-2034 (1987)). Phage

or viral vectors can be introduced into host cells, after growth of infectious particles in suitable packaging cells, many of which are commercially available.

Compositions

[0200] The invention provides a composition comprising the Dectin-2 binding agent or nucleic acid(s) encoding same optionally in a vector. Preferably, the composition is a pharmaceutically acceptable (e.g., physiologically acceptable) composition, which comprises a carrier, preferably a pharmaceutically acceptable (e.g., physiologically acceptable) carrier, and the Dectin-2 binding agent or nucleic acid(s) encoding same. Any suitable carrier can be used within the context of the invention, and such carriers are well known in the art. The choice of carrier will be determined, in part, by the particular site to which the composition may be administered and the particular method used to administer the composition. The composition optionally can be sterile. The composition can be frozen or lyophilized for storage and reconstituted in a suitable sterile carrier prior to use. The compositions can be generated in accordance with conventional techniques described in, e.g., Remington: *The Science and Practice of Pharmacy, 21st Edition*, Lippincott Williams & Wilkins, Philadelphia, PA (2001).

[0201] The composition can be formulated for parenteral administration, such as IV administration or administration into a body cavity or lumen of an organ. Alternatively, the composition can be injected intra-tumorally. Compositions for injection will commonly comprise the active ingredient dissolved or suspended in a pharmaceutically acceptable carrier. Among the acceptable vehicles and solvents that can be employed are water and an isotonic solution of one or more salts such as sodium chloride, e.g., Ringer's solution. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed, including synthetic monoglycerides or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These compositions desirably are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well known sterilization techniques. The compositions can contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like.

[0202] The composition can contain any suitable concentration of the Dectin-2 binding agent or nucleic acid(s) encoding same optionally in a vector, in some embodiments, a

concentration effective to elicit a therapeutic response. The concentration can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. In certain embodiments, the concentration of the inventive immunoglobulin heavy chain polypeptide, the inventive immunoglobulin light chain polypeptide, the inventive Dectin-2 binding agent, the inventive nucleic acid sequence encoding any of the foregoing, or the inventive vector comprising the inventive nucleic acid sequence in a solution formulation for injection will range from about 0.1% (w/w) to about 10% (w/w).

Methods

[0203] The Dectin-2 binding agents provided herein can be used for any suitable purpose. For instance, the Dectin-2 binding agents can agonistically bind Dectin-2 expressing cells, and be used to activate or enhance Dectin-2 signaling therein (e.g., for therapeutic purposes). Accordingly, one aspect of the disclosure provides a method of treating a disease, condition, or disorder responsive to the activation and/or enhancement of Dectin-2 signaling in a mammal by administering a Dectin-2 binding agent, or composition comprising same, as described herein, to the mammal.

[0204] In some embodiments, the Dectin-2 binding agents can stimulate an antigen presenting cell (APC). Stimulation can occur by contacting an APC with a Dectin-2 binding agent at a dose and for a period of time sufficient to enhance Dectin-2 signaling in the APC, thereby generating a stimulated APC. In some embodiments, the APC is a cell of myeloid lineage. Examples of cells of myeloid lineage include monocytes, macrophages, and dendritic cells. In some embodiments, stimulated APCs produce at least one pro-inflammatory cytokine, examples of which include Tumor Necrosis Factor alpha, IL-1 β , IL-2, IL-6, IL-23p19, IFN γ , IL-12p40, and IL-12p70. In some embodiments, stimulated APCs exhibit increased phagocytosis in comparison to APCs that have not been contacted by a Dectin-2 binding agent. In some embodiments, the stimulated APC is contacted with a cancer antigen to produce an antigen-contacted APC. The cancer antigen can be, for example, present in a cancer cell lysate or be part of a cancer cell. The cancer cell lysate or cancer cell can be taken or derived from an individual. In some embodiments, the individual has cancer.

[0205] In some embodiments, the stimulated APC or the antigen-contacted APC is introduced into an individual. In embodiments wherein the antigen used to contact the APC is taken or derived from an individual to produce an antigen-contacted APC, the antigen-

contacted APC can be introduced into the individual. Such a stimulated APC or antigen-contacted APC can be autologous to the individual.

[0206] In some embodiments, the antigen-contacted APC is contacted with a T cell. The T cell can be introduced into an individual. The T cell and the antigen-contacted APC, with which the T cell is contacted, can each be autologous to the individual. In some embodiments, the individual has cancer.

[0207] As used herein, the terms “treat,” “treatment,” and “treating” refer to any indicia of success in the treatment or amelioration of an injury, pathology, condition (e.g., cancer), or symptom, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the symptom, injury, pathology, or condition more tolerable to the patient; reduction in the rate of symptom progression; decreasing the frequency or duration of the symptom or condition; or, in some situations, preventing the onset of the symptom. The treatment or amelioration of symptoms can be based on any objective or subjective parameter, including, for example, the result of a physical examination.

[0208] The terms “reduce” or “alleviate,” as used herein with respect to the activity of a Dectin-2 binding agent, refer to the ability to substantially prohibit, prevent, restrain, slow, disrupt, alter, eliminate, stop, or reverse the progression or severity of a disease or condition (e.g., cancer) associated with a Dectin-2 protein.

[0209] The terms “cancer,” “neoplasm,” and “tumor” are used herein to refer to cells which exhibit autonomous, unregulated growth, such that the cells exhibit an aberrant growth phenotype characterized by a significant loss of control over cell proliferation. Cells of interest for detection, analysis, and/or treatment in the context of the invention include cancer cells (e.g., cancer cells from an individual with cancer), malignant cancer cells, pre-metastatic cancer cells, metastatic cancer cells, and non-metastatic cancer cells. Cancers of virtually every tissue are known. The phrase “cancer burden” refers to the quantum of cancer cells or cancer volume in a subject. Reducing cancer burden accordingly refers to reducing the number of cancer cells or the cancer cell volume in a subject. The term “cancer cell” as used herein refers to any cell that is a cancer cell (e.g., from any of the cancers for which an individual can be treated, e.g., isolated from an individual having cancer) or is derived from a cancer cell, e.g., clone of a cancer cell. For example, a cancer cell can be from an established cancer cell line, can be a primary cell isolated from an individual with cancer, can be a progeny cell from a primary cell isolated from an individual with cancer, and the like. In

some embodiments, the term can also refer to a portion of a cancer cell, such as a sub-cellular portion, a cell membrane portion, or a cell lysate of a cancer cell. Many types of cancers are known to those of skill in the art, including solid tumors such as carcinomas, sarcomas, glioblastomas, melanomas, lymphomas, and myelomas, and circulating cancers such as leukemias.

[0210] As used herein, the term “cancer” includes any form of cancer, including but not limited to, solid tumor cancers (e.g., skin, lung, prostate, breast, gastric, bladder, colon, ovarian, pancreas, kidney, liver, glioblastoma, medulloblastoma, leiomyosarcoma, head & neck squamous cell carcinomas, melanomas, and neuroendocrine) and liquid cancers (e.g., hematological cancers); carcinomas; soft tissue tumors; sarcomas; teratomas; melanomas; leukemias; lymphomas; and brain cancers, including minimal residual disease, and including both primary and metastatic tumors.

[0211] Any cancer that can be influenced by cells expressing Dectin-2 is a suitable cancer to be treated by the subject methods and compositions. As used herein “Dectin-2 expression” refers to a cell that has a Dectin-2 receptor on the cell’s surface.

[0212] Carcinomas are malignancies that originate in the epithelial tissues. Epithelial cells cover the external surface of the body, line the internal cavities, and form the lining of glandular tissues. Examples of carcinomas include, but are not limited to, adenocarcinoma (cancer that begins in glandular (secretory) cells such as cancers of the breast, pancreas, lung, prostate, stomach, gastroesophageal junction, and colon); adrenocortical carcinoma; hepatocellular carcinoma; renal cell carcinoma; ovarian carcinoma; carcinoma in situ; ductal carcinoma; carcinoma of the breast; basal cell carcinoma; squamous cell carcinoma (e.g., head and neck squamous cell carcinoma); transitional cell carcinoma; colon carcinoma; nasopharyngeal carcinoma; multilocular cystic renal cell carcinoma; oat cell carcinoma; large cell lung carcinoma; small cell lung carcinoma; non-small cell lung carcinoma; and the like. Carcinomas may be found in prostate, pancreas, colon, brain (usually as secondary metastases), lung, breast, and skin.

[0213] Soft tissue tumors are a highly diverse group of rare tumors that are derived from connective tissue. Examples of soft tissue tumors include, but are not limited to, alveolar soft part sarcoma; angiomatoid fibrous histiocytoma; chondromyxoid fibroma; skeletal chondrosarcoma; extraskeletal myxoid chondrosarcoma; clear cell sarcoma; desmoplastic small round-cell tumor; dermatofibrosarcoma protuberans; endometrial stromal tumor; Ewing’s sarcoma; fibromatosis (Desmoid); fibrosarcoma, infantile; gastrointestinal stromal

tumor; bone giant cell tumor; tenosynovial giant cell tumor; inflammatory myofibroblastic tumor; uterine leiomyoma; leiomyosarcoma; lipoblastoma; typical lipoma; spindle cell or pleomorphic lipoma; atypical lipoma; chondroid lipoma; well-differentiated liposarcoma; myxoid/round cell liposarcoma; pleomorphic liposarcoma; myxoid malignant fibrous histiocytoma; high-grade malignant fibrous histiocytoma; myxofibrosarcoma; malignant peripheral nerve sheath tumor; mesothelioma; neuroblastoma; osteochondroma; osteosarcoma; primitive neuroectodermal tumor; alveolar rhabdomyosarcoma; embryonal rhabdomyosarcoma; benign or malignant schwannoma; synovial sarcoma; Evan's tumor; nodular fasciitis; desmoid-type fibromatosis; solitary fibrous tumor; dermatofibrosarcoma protuberans (DFSP); angiosarcoma; epithelioid hemangioendothelioma; tenosynovial giant cell tumor (TGCT); pigmented villonodular synovitis (PVNS); fibrous dysplasia; myxofibrosarcoma; fibrosarcoma; synovial sarcoma; malignant peripheral nerve sheath tumor; neurofibroma; pleomorphic adenoma of soft tissue; and neoplasias derived from fibroblasts, myofibroblasts, histiocytes, vascular cells/endothelial cells, and nerve sheath cells.

[0214] A sarcoma is a rare type of cancer that arises in cells of mesenchymal origin, e.g., in bone or in the soft tissues of the body, including cartilage, fat, muscle, blood vessels, fibrous tissue, or other connective or supportive tissue. Different types of sarcoma are based on where the cancer forms. For example, osteosarcoma forms in bone, liposarcoma forms in fat, and rhabdomyosarcoma forms in muscle. Examples of sarcomas include, but are not limited to, askin's tumor; sarcoma botryoides; chondrosarcoma; ewing's sarcoma; malignant hemangioendothelioma; malignant schwannoma; osteosarcoma; and soft tissue sarcomas (e.g., alveolar soft part sarcoma; angiosarcoma; cystosarcoma phyllodesdermatofibrosarcoma protuberans (DFSP); desmoid tumor; desmoplastic small round cell tumor; epithelioid sarcoma; extraskkeletal chondrosarcoma; extraskkeletal osteosarcoma; fibrosarcoma; gastrointestinal stromal tumor (GIST); hemangiopericytoma; hemangiosarcoma (more commonly referred to as "angiosarcoma"); kaposi's sarcoma; leiomyosarcoma; liposarcoma; lymphangiosarcoma; malignant peripheral nerve sheath tumor (MPNST); neurofibrosarcoma; synovial sarcoma; and undifferentiated pleomorphic sarcoma).

[0215] A teratoma is a type of germ cell tumor that may contain several different types of tissue (e.g., can include tissues derived from any and/or all of the three germ layers: endoderm, mesoderm, and ectoderm), including, for example, hair, muscle, and bone.

Teratomas occur most often in the ovaries in women, the testicles in men, and the tailbone in children.

[0216] Melanoma is a form of cancer that begins in melanocytes (cells that make the pigment melanin). Melanoma may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines.

[0217] Merkel cell carcinoma is a rare type of skin cancer that usually appears as a flesh-colored or bluish-red nodule. It frequently appears on the face, head or neck. Merkel cell carcinoma is also called neuroendocrine carcinoma of the skin. In some embodiments, the Merkel cell carcinoma has metastasized when administration occurs.

[0218] Leukemias are cancers that start in blood-forming tissue, such as the bone marrow, and cause large numbers of abnormal blood cells to be produced and enter the bloodstream. For example, leukemias can originate in bone marrow-derived cells that normally mature in the bloodstream. Leukemias are named for how quickly the disease develops and progresses (e.g., acute versus chronic) and for the type of white blood cell that is affected (e.g., myeloid versus lymphoid). Myeloid leukemias are also called myelogenous or myeloblastic leukemias. Lymphoid leukemias are also called lymphoblastic or lymphocytic leukemia. Lymphoid leukemia cells may collect in the lymph nodes, which can become swollen. Examples of leukemias include, but are not limited to, Acute myeloid leukemia (AML), Acute lymphoblastic leukemia (ALL), Chronic myeloid leukemia (CML), and Chronic lymphocytic leukemia (CLL).

[0219] Lymphomas are cancers that begin in cells of the immune system. For example, lymphomas can originate in bone marrow-derived cells that normally mature in the lymphatic system. There are two basic categories of lymphomas. One category of lymphoma is Hodgkin lymphoma (HL), which is marked by the presence of a type of cell called the Reed-Sternberg cell. There are currently 6 recognized types of HL. Examples of Hodgkin lymphomas include nodular sclerosis classical Hodgkin lymphoma (CHL), mixed cellularity CHL, lymphocyte-depletion CHL, lymphocyte-rich CHL, and nodular lymphocyte predominant HL.

[0220] The other category of lymphoma is non-Hodgkin lymphomas (NHL), which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course. There are currently 61 recognized types of NHL. Examples of non-Hodgkin lymphomas include, but are not limited to, AIDS-related Lymphomas, anaplastic large-cell lymphoma, angioimmunoblastic lymphoma, blastic NK-

cell lymphoma, Burkitt's lymphoma, Burkitt-like lymphoma (small non-cleaved cell lymphoma), chronic lymphocytic leukemia/small lymphocytic lymphoma, cutaneous T-Cell lymphoma, diffuse large B-Cell lymphoma, enteropathy-type T-Cell lymphoma, follicular lymphoma, hepatosplenic gamma-delta T-Cell lymphomas, T-Cell leukemias, lymphoblastic lymphoma, mantle cell lymphoma, marginal zone lymphoma, nasal T-Cell lymphoma, pediatric lymphoma, peripheral T-Cell lymphomas, primary central nervous system lymphoma, transformed lymphomas, treatment-related T-Cell lymphomas, and Waldenstrom's macroglobulinemia.

[0221] Brain cancers include any cancer of the brain tissues. Examples of brain cancers include, but are not limited to, gliomas (e.g., glioblastomas, astrocytomas, oligodendrogliomas, ependymomas, and the like), meningiomas, pituitary adenomas, and vestibular schwannomas, primitive neuroectodermal tumors (medulloblastomas).

[0222] The “pathology” of cancer includes all phenomena that compromise the well-being of the patient. This includes, without limitation, abnormal or uncontrollable cell growth, metastasis, interference with the normal functioning of neighboring cells, release of cytokines or other secretory products at abnormal levels, suppression or aggravation of inflammatory or immunological response, neoplasia, premalignancy, malignancy, and invasion of surrounding or distant tissues or organs, such as lymph nodes.

[0223] As used herein, the phrases “cancer recurrence” and “tumor recurrence,” and grammatical variants thereof, refer to further growth of neoplastic or cancerous cells after diagnosis of cancer. Particularly, recurrence may occur when further cancerous cell growth occurs in the cancerous tissue. “Tumor spread,” similarly, occurs when the cells of a tumor disseminate into local or distant tissues and organs, therefore, tumor spread encompasses tumor metastasis. “Tumor invasion” occurs when the tumor growth spread out locally to compromise the function of involved tissues by compression, destruction, or prevention of normal organ function.

[0224] As used herein, the term “metastasis” refers to the growth of a cancerous tumor in an organ or body part, which is not directly connected to the organ of the original cancerous tumor. Metastasis will be understood to include micrometastasis, which is the presence of an undetectable amount of cancerous cells in an organ or body part that is not directly connected to the organ of the original cancerous tumor. Metastasis can also be defined as several steps of a process, such as the departure of cancer cells from an original tumor site, and migration and/or invasion of cancer cells to other parts of the body.

[0225] As used herein the phrases “effective amount” and “therapeutically effective amount” refer to a dose of a substance such as a binding agent that produces therapeutic effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); Goodman & Gilman’s *The Pharmacological Basis of Therapeutics*, 11th Edition (McGraw-Hill, 2006); and Remington: *The Science and Practice of Pharmacy*, 22nd Edition, (Pharmaceutical Press, London, 2012)).

[0226] As used herein, the terms “recipient,” “individual,” “subject,” “host,” and “patient” are used interchangeably and refer to any mammalian subject for whom diagnosis, treatment, or therapy is desired (e.g., humans). “Mammal” for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, goats, pigs, camels, etc. In certain embodiments, the mammal is human.

[0227] As used herein, the term “administering” refers to parenteral, intravenous, intraperitoneal, intramuscular, intratumoral, intralesional, intranasal, or subcutaneous administration, oral administration, administration as a suppository, topical contact, intrathecal administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to the subject.

[0228] Administration of a composition comprising the inventive immunoglobulin heavy chain polypeptide, the inventive immunoglobulin light chain polypeptide, the inventive Dectin-2 binding agent, the inventive nucleic acid sequence encoding any of the foregoing, or the inventive vector comprising the inventive nucleic acid sequence induces an immune response against a cancer in a mammal. An “immune response” can entail, for example, activation (induction) of one or more Dectin-2-associated pathways (signaling) in Dectin-2 expressing cells, which can lead to the expression of pro-inflammatory cytokines and/or increased phagocytosis in Dectin-2 expressing cells.

[0229] The inventive methods comprise administering a “therapeutically effective amount” of the binding agent. A “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. The therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the binding agent to elicit a desired

response in the individual. For example, a therapeutically effective amount of a binding agent of the invention is an amount enhances the immune response against a cancer.

[0230] Alternatively, the pharmacologic and/or physiologic effect may be prophylactic, i.e., the effect completely or partially prevents a disease or symptom thereof. In this respect, the inventive method comprises administering a “prophylactically effective amount” of the binding agent. A “prophylactically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired prophylactic result (e.g., prevention of disease onset).

[0231] A typical dose can be, for example, in the range of 1 pg/kg to 20 mg/kg of animal or human body weight; however, doses below or above this exemplary range are within the scope of the invention. The daily parenteral dose can be about 0.00001 µg/kg to about 20 mg/kg of total body weight (e.g., about 0.001 µg /kg, about 0.1 µg /kg , about 1 µg /kg, about 5 µg /kg, about 10 µg/kg, about 100 µg /kg, about 500 µg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, or a range defined by any two of the foregoing values), preferably from about 0.1 µg/kg to about 10 mg/kg of total body weight (e.g., about 0.5 µg/kg, about 1 µg/kg, about 50 µg/kg, about 150 µg/kg, about 300 µg/kg, about 750 µg/kg, about 1.5 mg/kg, about 5 mg/kg, or a range defined by any two of the foregoing values), more preferably from about 1 µg/kg to 5 mg/kg of total body weight (e.g., about 3 µg/kg, about 15 µg/kg, about 75 µg/kg, about 300 µg/kg, about 900 µg/kg, about 2 mg/kg, about 4 mg/kg, or a range defined by any two of the foregoing values), and even more preferably from about 0.5 to 15 mg/kg body weight per day (e.g., about 1 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 6 mg/kg, about 9 mg/kg, about 11 mg/kg, about 13 mg/kg, or a range defined by any two of the foregoing values). Therapeutic or prophylactic efficacy can be monitored by periodic assessment of treated patients. For repeated administrations over several days or longer, depending on the condition, the treatment can be repeated until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful and are within the scope of the invention. The desired dosage can be delivered by a single bolus administration of the composition, by multiple bolus administrations of the composition, or by continuous infusion administration of the composition.

[0232] The composition comprising an effective amount of the inventive immunoglobulin heavy chain polypeptide, the inventive immunoglobulin light chain polypeptide, the inventive binding agent, the inventive nucleic acid sequence encoding any of the foregoing, or the inventive vector comprising the inventive nucleic acid sequence can be

administered to a mammal using standard administration techniques, including oral, intravenous, intraperitoneal, subcutaneous, pulmonary, transdermal, intramuscular, intranasal, buccal, sublingual, or suppository administration. The composition preferably is suitable for parenteral administration. The term “parenteral,” as used herein, includes intravenous, intramuscular, subcutaneous, rectal, vaginal, and intraperitoneal administration. More preferably, the composition is administered to a mammal using peripheral systemic delivery by intravenous, intraperitoneal, or subcutaneous injection.

[0233] Once administered to a mammal (e.g., a human), the biological activity of the inventive binding agent can be measured by any suitable method known in the art. For example, the biological activity can be assessed by determining the stability of a particular binding agent. In one embodiment of the invention, the binding agent (e.g., an antibody) has an *in vivo* half life between about 30 minutes and 45 days (e.g., about 30 minutes, about 45 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, about 10 hours, about 12 hours, about 1 day, about 5 days, about 10 days, about 15 days, about 25 days, about 35 days, about 40 days, about 45 days, or a range defined by any two of the foregoing values). In another embodiment, the Dectin-2 binding agent has an *in vivo* half life between about 2 hours and 20 days (e.g., about 5 hours, about 10 hours, about 15 hours, about 20 hours, about 2 days, about 3 days, about 7 days, about 12 days, about 14 days, about 17 days, about 19 days, or a range defined by any two of the foregoing values). In another embodiment, the binding agent has an *in vivo* half life between about 10 days and about 40 days (e.g., about 10 days, about 13 days, about 16 days, about 18 days, about 20 days, about 23 days, about 26 days, about 29 days, about 30 days, about 33 days, about 37 days, about 38 days, about 39 days, about 40 days, or a range defined by any two of the foregoing values).

[0234] In addition to therapeutic uses, the binding agent described herein can be used in diagnostic or research applications. In this respect, the binding agent can be used in a method to diagnose a cancer. In a similar manner, the binding agent can be used in an assay to monitor Dectin-2 protein levels in a subject being tested for a disease or disorder that is associated with abnormal Dectin-2 expression. Research applications include, for example, methods that utilize the binding agent and a label to detect a Dectin-2 protein in a sample, e.g., in a human body fluid or in a cell or tissue extract. The binding agent can be used with or without modification, such as covalent or non-covalent labeling with a detectable moiety. For example, the detectable moiety can be a radioisotope (e.g., ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I), a fluorescent or chemiluminescent compound (e.g., fluorescein isothiocyanate, rhodamine, or

luciferin), an enzyme (e.g., alkaline phosphatase, beta-galactosidase, or horseradish peroxidase), or prosthetic groups. Any method known in the art for separately conjugating an antigen-binding agent (e.g., an antibody) to a detectable moiety may be employed in the context of the invention (see, e.g., Hunter et al., *Nature*, 194: 495-496 (1962); David et al., *Biochemistry*, 13: 1014-1021 (1974); Pain et al., *J. Immunol. Meth.*, 40: 219-230 (1981); and Nygren, *J. Histochem. and Cytochem.*, 30: 407-412 (1982)).

[0235] Dectin-2 protein levels can be measured using the inventive binding agent by any suitable method known in the art. Such methods include, for example, immunohistochemistry, immunofluorescence, radioimmunoassay (RIA), and FACS. Normal or standard expression values of Dectin-2 protein can be established using any suitable technique, e.g., by combining a sample comprising, or suspected of comprising, a Dectin-2 polypeptide with a Dectin-2 specific antibody under conditions suitable to form an antigen-antibody complex. The antibody is directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, and radioactive materials (see, e.g., Zola, *Monoclonal Antibodies: A Manual of Techniques*, CRC Press, Inc. (1987)). The amount of Dectin-2 polypeptide expressed in a sample is then compared with a standard value.

Kits

[0236] The binding agent can be provided in a kit, i.e., a packaged combination of reagents in predetermined amounts with instructions for performing a diagnostic assay. If the binding agent is labeled with an enzyme, the kit desirably includes substrates and cofactors required by the enzyme (e.g., a substrate precursor which provides a detectable chromophore or fluorophore). In addition, other additives may be included in the kit, such as stabilizers, buffers (e.g., a blocking buffer or lysis buffer), and the like. The relative amounts of the various reagents can be varied to provide for concentrations in solution of the reagents which substantially optimize the sensitivity of the assay. The reagents may be provided as dry powders (typically lyophilized), including excipients which on dissolution will provide a reagent solution having the appropriate concentration.

Examples of Non-Limiting Aspects of the Disclosure

[0237] Aspects, including embodiments, of the invention described herein may be beneficial alone or in combination, with one or more other aspects or embodiments. Without

limiting the foregoing description, certain non-limiting aspects of the disclosure numbered (1)-(33) are provided below. As will be apparent to those of skill in the art upon reading this disclosure, each of the individually numbered aspects may be used or combined with any of the preceding or following individually numbered aspects. This is intended to provide support for all such combinations of aspects and is not limited to combinations of aspects explicitly provided below:

[0238] (1) A Dectin-2 binding agent comprising an immunoglobulin heavy chain variable region polypeptide and an immunoglobulin light chain variable region polypeptide, wherein:

the immunoglobulin heavy chain variable region polypeptide comprises a complementarity determining region 1 (HCDR1) comprising any one of SEQ ID NOs: 1-30, a complementarity determining region 2 (HCDR2) comprising any one of SEQ ID NOs: 31-64, and a complementarity determining region 3 (HCDR3) comprising any one of SEQ ID NOs: 65-103 or 323; or

the immunoglobulin light chain variable region polypeptide comprises a complementarity determining region 1 (LCDR1) comprising any one of SEQ ID NOs: 104-125, a complementarity determining region 2 (LCDR2) comprising any one of SEQ ID NOs: 126-148, and a complementarity determining region 3 (LCDR3) comprising any one of SEQ ID NOs: 149-181.

[0239] (2) A Dectin-2 binding agent comprising an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 243-282 or 324, or at least the CDRs thereof; and an immunoglobulin light chain variable region of any one of SEQ ID NOs: 283-322 or at least the CDRs thereof.

[0240] (3) A Dectin-2 binding agent comprising an immunoglobulin heavy chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 243-282 or 324, and an immunoglobulin light chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 284-322.

[0241] (4) The Dectin-2 binding agent of any one of aspects 1-3, which comprises the heavy and light chain immunoglobulin polypeptides, or at least the CDRs thereof, of a Dectin-2 binding agent of Table 1.

[0242] (5) The Dectin-2 binding agent of any one of aspects 1-4, wherein the binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.

- [0243] (6) The Dectin-2 binding agent of aspect 5, wherein the binding agent is an antibody fragment selected from F(ab')₂, Fab', Fab, Fv, scFv, dsFv, dAb, and a single chain binding polypeptide.
- [0244] (7) The Dectin-2 binding agent of aspect 5, wherein the binding agent is an antibody.
- [0245] (8) The Dectin-2 binding agent of any one of aspects 5-7, wherein the antibody is an IgG, IgM, IgA, IgD or IgE antibody.
- [0246] (9) The Dectin-2 binding agent of any one of aspects 5-8, wherein the antibody is an IgG antibody.
- [0247] (10) The Dectin-2 binding agent of aspect 9, wherein the IgG antibody comprises one or more mutations in the Fc region that result in modulated binding to one or more Fc receptors.
- [0248] (11) The Dectin-2 binding agent of any one of aspects 7-10, wherein the antibody exhibits antibody dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), or complement dependent cytotoxicity (CDC).
- [0249] (12) The Dectin-2 binding agent of any of aspects 1-11, wherein the binding agent is part of a bispecific antibody, chimeric antigen receptor, chimeric T cell receptor, or bispecific T-cell engager.
- [0250] (13) A nucleic acid encoding the heavy chain immunoglobulin polypeptide of the Dectin-2 binding agent of any one of aspects 1-12.
- [0251] (14) A nucleic acid encoding the light chain immunoglobulin polypeptide of the Dectin-2 binding agent of any one of aspects 1-12.
- [0252] (15) A nucleic acid encoding the heavy chain immunoglobulin polypeptide and the light chain immunoglobulin polypeptide of the Dectin-2 binding agent of any one of aspects 1-12.
- [0253] (16) A vector comprising the nucleic acid sequence of any one of aspects 13-15.
- [0254] (17) An isolated cell comprising the nucleic acid of any one of aspects 13-15, optionally in a vector.
- [0255] (18) A method of providing a Dectin-2 binding agent of any of aspects 1-12, the method comprising expressing in a cell *in vitro* one or more nucleic acids encoding the immunoglobulin heavy and light chain polypeptides thereof.

[0256] (19) A composition comprising the Dectin-2 binding agent of any one of aspects 1-12 or nucleic acid of any one of aspects 13-15, optionally in a vector, and a pharmaceutically acceptable carrier.

[0257] (20) The Dectin-2 binding agent of any one of aspects 1-12 or conjugate comprising same, or the composition of claim 19, for use as a medicament for treating a disease, disorder, or condition in a mammal that is responsive to Dectin-2 inhibition or binding.

[0258] (21) The Dectin-2 binding agent or composition of claim 20, wherein the disease, disorder, or condition is cancer.

[0259] (22) The Dectin-2 binding agent of any one of aspects 1-12 or the composition of claim 19 for use as a medicament for enhancing an immune response in a mammal.

[0260] (23) The Dectin-2 binding agent for use according to claim 22, wherein the immune response is an anti-tumor immune response.

[0261] (24) A method for treating a disease, disorder, or condition in a mammal that is responsive to Dectin-2 binding or inhibition, the method comprising administering the Dectin-2 binding agent of any one of aspects 1-12 or conjugate comprising same, or the composition of claim 19, to the mammal.

[0262] (25) The method of claim 24, wherein the disease, disorder, or condition is cancer.

[0263] (26) A hybridoma or cell line that expresses a Dectin-2 binding agent of any of aspects 1-12.

[0264] (27) A method of stimulating an antigen presenting cell (APC), the method comprising contacting an APC with a Dectin-2 binding agent of aspects 1-12 at a dose and for a period of time sufficient to enhance Dectin-2 signaling in the APC, thereby generating a stimulated APC.

[0265] (28) The method according to claim 27, wherein the APC is a cell of myeloid lineage.

[0266] (29) The method according to claim 28, wherein the myeloid cell is a monocyte, macrophage, or a dendritic cell.

[0267] (30) The method according to aspects 27-29, wherein the stimulated APC produces at least one pro-inflammatory cytokine and/or exhibits increased phagocytosis as compared to an APC that has not been contacted by a Dectin-2 binding agent.

[0268] (31) The method according to claim 30, wherein the at least one pro-inflammatory cytokine is selected from the group consisting of TNF α , IL-1 β , IL-2, IL-6, IL-23p19, IFN γ , IL-12p40, and IL-12p70.

[0269] (32) The method according to any of aspects 27-31, comprising contacting the stimulated APC with a cancer antigen to produce an antigen-contacted APC.

[0270] (33) The method according to any of aspects 28-32, wherein the cancer antigen is present in a cancer cell lysate or is part of a cancer cell.

EXAMPLES

[0271] Human monocytes were isolated from LRS chambers obtained from the Stanford Blood Center (Palo Alto, CA; chamber is a byproduct from leukapheresis) using RosetteSep™ Human Monocyte Enrichment Cocktail (STEMCELL Technologies Inc.) followed by the EasySep™ Human Monocyte Enrichment Kit without CD16 Depletion (STEMCELL Technologies Inc.) according to the manufacturer's instructions. The isolated human monocytes were used in the following experiments.

Example 1

[0272] In a first experiment, the isolated human monocytes were cultured in complete RPMI medium (10% FBS, P/S, glutamine) supplemented with 100 ng/mL hGM-CSF (PeproTech, Inc.). Following two days' incubation, the treated monocytes were harvested with a cell scraper and added to TC-treated 96-well plates (Corning Inc., Corning, NY) which were pre-coated with one of the antibody clones listed in Figure 1. The antibody-coated 96-well plates used in this experiment were prepared by diluting the indicated antibody to 25 μ g/mL in PBS, and incubating overnight at 4 °C, followed by several PBS washes. After an 18 hour incubation, supernatants were collected and TNF α levels were measured by ELISA according to the manufacturer's instructions (Invitrogen eBioscience Human TNF alpha ELISA Ready-SET-Go!). The results of the first experiment are shown in Figure 1. As can be seen in Figure 1, a number of the tested antibodies triggered a significant increase in TNF α expression.

[0273] The tested antibodies correspond to Binding Agents 1-40 disclosed herein, as follows:

Table 8

Tested Antibody	Binding Agent (VH and VL SEQ ID NOs)	Tested Antibody	Binding Agent (VH and VL SEQ ID NOs)
R3H-P1C02	1 (SEQ ID NOs: 243 and 283)	R3H-P1E01	21 (SEQ ID NOs: 262 and 303)
R3H-P3A02	2 (SEQ ID NOs: 244 and 284)	R3C-P2B08	22 (SEQ ID NOs: 263 and 304)
R3H-P3H07	3 (SEQ ID NOs: 245 and 285)	R3C-P1G05	23 (SEQ ID NOs: 264 and 305)
R3M-P2C06	4 (SEQ ID NOs: 246 and 286)	R3H-P1B11	24 (SEQ ID NOs: 266 and 306)
R3C-P1E10	5 (SEQ ID NOs: 247 and 287)	R3H-P2B10	25 (SEQ ID NOs: 267 and 307)
R3H-P1D01	6 (SEQ ID NOs: 248 and 288)	R3C-P3C07	26 (SEQ ID NOs: 268 and 308)
R3H-P1C10	7 (SEQ ID NOs: 249 and 289)	R3H-P3A06	27 (SEQ ID NOs: 269 and 309)
R3H-P2D03	8 (SEQ ID NOs: 250 and 290)	R3H-P3D01	28 (SEQ ID NOs: 270 and 310)
R4H-P1G05	9 (SEQ ID NOs: 251 and 291)	R3M-P2D05	29 (SEQ ID NOs: 271 and 311)
R3M-P1C03	10 (SEQ ID NOs: 252 and 292)	R3C-P2D05	30 (SEQ ID NOs: 272 and 312)
R3H-P2G03	11 (SEQ ID NOs: 253 and 293)	R3H-P2D12	31 (SEQ ID NOs: 273 and 313)
R4H-P1G11	12 (SEQ ID NOs: 254 and 294)	R3H-P2A09	32 (SEQ ID NOs: 274 and 314)
R3H-P1B01	13 (SEQ ID NOs: 255 and 295)	R3H-P2G01	33 (SEQ ID NOs: 275 and 315)
R3C-P1C09	14 (SEQ ID NOs: 256 and 296)	R3M-P3E03	34 (SEQ ID NOs: 276 and 316)
R3H-P1G03	15 (SEQ ID NOs: 257 and 297)	R3H-P3B09	35 (SEQ ID NOs: 277 and 317)
R3M-P3B04	16 (SEQ ID NOs: 258 and 298)	R4C-P1F06	36 (SEQ ID NOs: 278 and 318)
R3H-P2F02	17 (SEQ ID NOs: 259 and 299)	R3H-P2D07	37 (SEQ ID NOs: 279 and 319)
R3M-P3B11	18 (SEQ ID NOs: 256 and 300)	R3M-P3C04	38 (SEQ ID NOs: 280 and 320)
R3M-P1D05	19 (SEQ ID NOs: 260 and 301)	R3H-P1C12	39 (SEQ ID NOs: 281 and 321)
R3H-P1F05	20 (SEQ ID NOs: 261 and 302)	R3C-P1C01	40 (SEQ ID NOs: 282 and 322)

Example 2

[0274] In a second experiment, isolated human monocytes were cultured in complete RPMI medium (10% FBS, P/S, glutamine) supplemented with 200 ng/mL hGM-CSF (PeproTech, Inc.). Following three days' incubation, the treated monocytes were harvested with a cell scraper and added to TC-treated 96 well plates (Corning Inc., Corning, NY), wherein the monocytes were stimulated with one of the antibody clones listed in Figure 2 (in soluble form) at 100 µg/mL. After an 18 hour incubation, supernatants were collected and TNFα levels were measured by ELISA according to the manufacturer's instructions (Invitrogen eBioscience Human TNF alpha ELISA Ready-SET-Go!). The results of the first experiment are shown in Figure 2. As can be seen in Figure 2, a number of the tested

antibodies triggered a significant increase in TNF α expression. The tested antibodies correspond to the Binding Agents disclosed herein as shown in Table 8.

Example 3

[0275] In a third experiment, isolated human monocytes were cultured in complete RPMI medium (10% FBS, P/S, glutamine) supplemented with human GM-CSF (PeproTech, Inc.). Following 6 days of incubation, macrophages were harvested and added to TC-treated 96 well plates (Corning Inc., Corning, NY), wherein the macrophages were stimulated with a dose titration of each of the indicated antibodies. After an 18 hour incubation, supernatants were collected and TNF α levels were measured by ELISA according to the manufacturer's instructions (Invitrogen eBioscience Human TNF alpha ELISA Ready-SET-Go!). As can be seen in Figure 3, a number of the tested antibodies triggered a significant increase in TNF α expression. The tested antibodies were each R3H-P1F05 (corresponding to Binding Agent 20 disclosed herein, (i.e., comprising VH and VL regions respectively SEQ ID NOs: 261 and 302)), each with or without certain modifications to the Fc region of the antibody as shown on Figure 3, including, for example, use of an IgG2 Fc domain instead of an IgG1 Fc domain.

[0276] Specifically, R3H-P1F05 comprises SEQ ID NOs: 326 and 334, R3H-P1F05 hIgG1-G236A comprises SEQ ID NOs 326 and 335, R3H-P1F05 hIgG1-LALA comprises SEQ ID NOs: 326 and 336, R3H-P1F05 hIgG1-N297A comprises SEQ ID NOs: 326 and 337, and R3H-P1F05 hIgG1-C219S comprises SEQ ID NOs: 326 and 338.

Example 4

[0277] In a fourth experiment, isolated human monocytes were cultured in complete RPMI medium (10% FBS, P/S, glutamine) supplemented with human GM-CSF (PeproTech, Inc.). Following 5 days of incubation, macrophages were harvested and added to TC-treated 96 well plates (Corning Inc., Corning, NY), wherein the macrophages were stimulated with a dose titration of each of the indicated antibodies. After a 20 hour incubation, supernatants were collected and TNF α levels were measured by ELISA according to the manufacturer's instructions (Invitrogen eBioscience Human TNF alpha ELISA Ready-SET-Go!). As can be seen in Figure 4, a number of the tested antibodies triggered a significant increase in TNF α expression. The tested antibodies were each R3H-P1F05 (corresponding to Binding Agent 20 disclosed herein (VH and VL regions respectively SEQ ID NOs: 261 and 302)), or an antibody corresponding to Binding Agent 23a disclosed herein (i.e., comprising VH and VL

regions respectively SEQ ID NOs: 265 and 305), each with or without certain modifications to the Fc region of the antibody as shown in Figure 4.

[0278] Specifically, R3H-P1F05 comprises SEQ ID NOs: 326 and 334, R3H-P1F05-E345R comprises SEQ ID NOs: 326 and 339, R3H-P1F05 hIgG1-G236A comprises SEQ ID NOs 326 and 335, Binding Agent 23a hIgG1 comprises SEQ ID NOs: 327 and 340, Binding Agent 23a hIgG1-E345R comprises SEQ ID NOs: 327 and 341, and Binding Agent 23a hIgG1-G236A comprises SEQ ID NOs: 327 and 342.

Example 5

[0279] In a fifth experiment, isolated human monocytes were cultured in complete RPMI medium (10% FBS, P/S, glutamine) supplemented with human M-CSF (PeproTech, Inc.). Following 6 days incubation, macrophages were harvested and added to TC-treated 96 well plates (Corning Inc., Corning, NY), wherein the macrophages were stimulated with a dose titration of each of the indicated antibodies. After a 20 hour incubation, supernatants were collected and TNF α levels were measured by ELISA according to the manufacturer's instructions (Invitrogen eBioscience Human TNF alpha ELISA Ready-SET-Go!). As can be seen in Figures 5A and 5B, a number of the tested antibodies triggered a significant increase in TNF α expression. The tested antibodies were each R3H-P1F05 (Figure 5A) (corresponding to Binding Agent 20 disclosed herein (i.e., comprising VH and VL regions respectively SEQ ID NOs: 261 and 302)), or Binding Agent 23a disclosed herein (Figure 5B) (i.e., comprising VH and VL regions respectively SEQ ID NOs: 265 and 305), each with or without certain modifications to the Fc region of the antibody as shown in Figures 5A and 5B, wherein "nf" stands for non-fucosylated (i.e., afucosylated).

[0280] Specifically, in Figure 5A, R3H-P1F05 and R3H-P1F05-nf each comprise SEQ ID NOs: 326 and 334, and R3H-P1F05 hIgG1-G236A and R3H-P1F05 hIgG1-G236A-nf each comprise SEQ ID NOs 326 and 335. In Figure 5B, Binding Agent 23a hIgG1 and Binding Agent 23a hIgG1-nf each comprise SEQ ID NOs: 327 and 340, and Binding Agent 23a hIgG1-G236A and Binding Agent 23a hIgG1-G236A-nf each comprise SEQ ID NOs: 327 and 342.

Example 6

[0281] In a sixth experiment, isolated human monocytes were cultured in complete RPMI medium (10% FBS, P/S, glutamine) supplemented with human M-CSF (PeproTech, Inc.). Following 5 days incubation, macrophages were harvested and added to TC-treated 96 well

plates (Corning Inc., Corning, NY), wherein the macrophages were stimulated with a dose titration of each of the indicated antibodies. After a 20 hour incubation, supernatants were collected and TNF α levels were measured by ELISA according to the manufacturer's instructions (Invitrogen eBioscience Human TNF alpha ELISA Ready-SET-Go!). As can be seen in Figure 6, a number of the tested antibodies triggered a significant increase in TNF α expression. The tested antibodies were each an antibody corresponding to Binding Agent 23a disclosed herein (i.e., comprising VH and VL regions respectively SEQ ID NOs: 265 and 305), or an antibody corresponding to Binding Agent 23b disclosed herein (i.e., comprising VH and VL regions respectively SEQ ID NOs: 324 and 305), each with or without certain modifications to the Fc region of the antibody as shown in Figure 6, including use of an IgG2 domain instead of an IgG1 domain.

[0282] Specifically, Binding Agent 23a hIgG1 comprises SEQ ID NOs: 327 and 340, Binding Agent 23a hIgG1-G236A comprises SEQ ID NOs: 327 and 342, Binding Agent 23b hIgG1 comprises SEQ ID NOs: 327 and 345, Binding Agent 23a hIgG2-C219S comprises SEQ ID NOs: 327 and 343, and Binding Agent 23a hIgG1-LALA comprises SEQ ID NOs: 327 and 344.

Example 7

[0283] In a seventh experiment, isolated human monocytes were cultured in complete RPMI medium (10% FBS, P/S, glutamine) supplemented with human GM-CSF (PeproTech, Inc.). Following 3 days incubation, macrophages were harvested and added to TC-treated 96 well plates (Corning Inc., Corning, NY), which were pre-coated with the indicated antibodies. The antibody-coated 96-well plates used in this experiment were prepared by diluting the indicated antibody in PBS and incubating overnight at 4 °C, followed by several PBS washes. After a 20 hour incubation, supernatants were collected and TNF α levels were measured by ELISA according to the manufacturer's instructions (Invitrogen eBioscience Human TNF alpha ELISA Ready-SET-Go!). As can be seen in Figure 7, a number of the tested antibodies triggered a significant increase in TNF α expression. The tested antibodies were each R3H-P1C02 (corresponding to Binding Agent 1 disclosed herein (i.e., comprising VH and VL regions respectively SEQ ID NOs: 243 and 283)), with or without certain modifications to the Fc region of the antibody as shown in Figure 7, wherein "nf" stands for non-fucosylated (i.e., afucosylated).

[0284] Specifically, each of R3H-P1C02 hIgG1 and R3H-P1C02 hIgG1nf comprises SEQ ID NOs: 325 and 328, R3H-P1C02 hIgG1-S267E comprises SEQ ID NOs: 325 and 329,

R3H-P1C02 hIgG1-E345R comprises SEQ ID NOs: 325 and 330, R3H-P1C02 hIgG1-SEER comprises SEQ ID NOs: 325 and 331, R3H-P1C02 hIgG1-N297A comprises SEQ ID NOs: 325 and 332, and each of R3H-P1C02 hIgG1-G236A and R3H-P1C02 hIgG1nf-G236A comprises SEQ ID NOs: 325 and 333.

[0285] The terms “about” and “around,” as used herein to modify a numerical value, indicate a close range surrounding the numerical value. Thus, if “X” is the value, “about X” or “around X” indicates a value of from 0.9X to 1.1X, e.g., from 0.95X to 1.05X or from 0.99X to 1.01X. A reference to “about X” or “around X” specifically indicates at least the values X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, and 1.05X. Accordingly, “about X” and “around X” are intended to teach and provide written description support for a claim limitation of, e.g., “0.98X.”

[0286] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0287] The use of the terms “a” and “an” and “the” and “at least one” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term “at least one” followed by a list of one or more items (for example, “at least one of A and B”) is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the

specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0288] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.