ANTI-MARCO ANTIBODIES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. Application No. 63/115,272, filed November 18, 2020, and U.S. Application No. 63/244,662, filed September 15, 2021, each of which are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Month XX, 20XX, is named XXXXXUS_sequencelisting.txt, and is X,XXX,XXX bytes in size.

BACKGROUND

[0003] Myeloid populations of the tumor microenvironment prominently include monocytes and neutrophils (sometimes loosely grouped as myeloid-derived suppressor cells), macrophages, and dendritic cells. Although intra-tumoral myeloid populations, as a whole, have long been considered non-stimulatory or suppressive, it has more recently been appreciated that not all tumor-infiltrating myeloid cells are made equal.

[0004] Macrophage Receptor with Collagenous Structure (MARCO, also known as SCARA2; *See* HGNC: 6895 and NCBI: NM_006770.3 as available on May 8, 2020 via the NCBI website; herein incorporated by reference for all purposes) belongs to the class A scavenger receptor family and is expressed on peritoneal macrophages, as well as a subpopulation of macrophages in the spleen and lymph nodes (*see* Hirano S, PLoS ONE 2015: 10(11): e0142062). Recent studies have highlighted MARCO as a specific marker of TAMs in human cancer (Lavin et al., Cell; 2017: 169(4) 750-765). MARCO mediates macrophage internalization of unopsonized particles and microorganisms, such as bacteria (*see* Jing J, J Immunol 2013;190:(12) 6360-6367). Recently, MARCO has been shown to be involved in the TLR-induced gene expression response in dendritic cells and may play a role in the inflammatory immune response (Kissick HT, PLoS oNE 2014; 9(8):2104148).

[0005] An unmet need exists for novel cancer therapeutic approaches that involve selectively removing, or re-programming or activating myeloid cells that are ineffective at stimulating immune cell responses (e.g., T-cells or NK cells), thereby enhancing the immune response within the tumor microenvironment.

SUMMARY

[0006] In some aspects, provided herein are isolated antibodies or antigen binding fragments thereof that binds to human Macrophage Receptor with Collagenous Structure (MARCO) (SEQ ID NO: 384).

[0007] In some embodiments, the antibody or antigen binding fragment thereof binds to a Scavenger Receptor Cysteine-Rich (SRCR) domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

[0008] In some aspects, provided herein are isolated antibodies or antigen binding fragments thereof that binds to a Scavenger Receptor Cysteine-Rich (SRCR) domain (residues 424-519 of SEQ ID NO: 384) of human Macrophage Receptor with Collagenous Structure (MARCO) (SEQ ID NO: 384).

[0009] In some embodiments, the antibody comprises a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2), CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3), CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4), CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L) , CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

[0010] In some embodiments, the antibody or antigen binding fragment thereof binds to at least one of the following residues: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of MARCO (SEQ ID NO: 384).

[0011] In some embodiments, the antibody or antigen binding fragment comprises a chimeric, human, humanized, or rat antibody or antigen binding fragment.

[0012] In some embodiments, CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431).

[0013] In some embodiments, CDR-L1 comprises the sequence RASEGISNDLA (SEQ ID NO: 27).

[0014] In some embodiments, CDR-L1 comprises the sequence LASEGISNDLA (SEQ ID NO: 7).

[0015] In some embodiments, the VH sequence comprises the VH sequence set forth in SEQ ID NO: 61.

[0016] In some embodiments, the VH sequence comprises the VH sequence set forth in SEQ ID NO: 111.

[0017] In some embodiments, the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474.

[0018] In some embodiments, the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

[0019] In some embodiments, the VL sequence comprises the VL sequence set forth in SEQ ID NO: 116.

[0020] In some embodiments, the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

[0021] In some embodiments, the VH sequence comprises the VH sequence set forth in SEQ ID NO: 61; and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

[0022] In some embodiments, the VH sequence comprises the VH sequence set forth in SEQ ID NO: 111; and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 116.

[0023] In some embodiments, the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474 and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

[0024] In some embodiments, the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474 and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

[0025] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 65.

[0026] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 115.

[0027] In some embodiments, the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478.

[0028] In some embodiments, the antibody comprises a light chain sequence as set forth in SEQ ID NO: 70.

[0029] In some embodiments, the antibody comprises a light chain sequence as set forth in SEQ ID NO: 120.

[0030] In some embodiments, the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

[0031] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 65; and a light chain sequence as set forth in SEQ ID NO: 70.

[0032] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 115; and a light chain sequence as set forth in SEQ ID NO: 120.

[0033] In some embodiments, the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478; and a light chain sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

[0034] In some embodiments, the antibody comprises a heavy chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478; and/or a light chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

[0035] In some aspects, provided herein are isolated antibodies or antigen binding fragments thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence GYTFTDYAVN (SEQ ID NO: 232), CDR-H2 comprises the sequence WINTQTGKPT (SEQ ID NO: 233), CDR-H3 comprises the sequence DSYYYSSSLDY (SEQ ID NO: 234), CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432) or XASAGISNDLA (SEQ ID NO: 381), wherein X is arginine (R) or leucine (L), CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 238), and CDR-L3 comprises the sequence QQSYKYPWT (SEQ ID NO: 239).

[0036] In some embodiments, CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432).

[0037] In some embodiments, CDR-L1 comprises the sequence RASAGISNDLA (SEQ ID NO: 317).

[0038] In some embodiments, CDR-L1 comprises the sequence LASAGISNDLA (SEQ ID NO: 237).

[0039] In some embodiments, the VH sequence comprises the VH sequence as set forth in SEQ ID NO: 454.

[0040] In some embodiments, the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464.

[0041] In some embodiments, the VL sequence comprises the VL sequence as set forth in SEQ ID NO: 459.

[0042] In some embodiments, the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

[0043] In some embodiments, the VH sequence comprises the VH sequence as set forth in SEQ ID NO: 454; and the VL sequence comprises the VL sequence as set forth in SEQ ID NO: 459.

[0044] In some embodiments, the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464, and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

[0045] In some embodiments, the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464; and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

[0046] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 458.

[0047] In some embodiments, the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468.

[0048] In some embodiments, the antibody comprises a light chain sequence as set forth in SEQ ID NO: 463.

[0049] In some embodiments, the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

[0050] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 458; and a light chain sequence as set forth in SEQ ID NO: 463.

[0051] In some embodiments, the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468; and a light chain sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

[0052] In some embodiments, the antibody comprises a heavy chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468; and/or a light chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

[0053] In some aspects, provided herein are isolated antibodies or antigen binding fragments thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence KFTFSNYGMN (SEQ ID NO: 142), CDR-H2 comprises the sequence LIYYNSNNKY (SEQ ID NO: 143), CDR-H3 comprises the sequence SLTGGSDYFDS (SEQ ID NO: 144), CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433) or XASKSIGTFLA (SEQ ID NO: 382), wherein X is arginine (R) or lysine (K), CDR-L2 comprises the sequence SGSTLQS (SEQ ID NO: 148), and CDR-L3 comprises the sequence QQHDEYPFT (SEQ ID NO: 149).

[0054] In some embodiments, CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433).

[0055] In some embodiments, CDR-L1 comprises the sequence KASKSIGTFLA (SEQ ID NO: 147).

[0056] In some embodiments, CDR-L1 comprises the sequence RASKSIGTFLA (SEQ ID NO: 157).

[0057] In some embodiments, the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221.

[0058] In some embodiments, the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

[0059] In some embodiments, the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221 and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

[0060] In some embodiments, the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221 and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

[0061] In some embodiments, the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225.

[0062] In some embodiments, the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

[0063] In some embodiments, the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225 and a light chain sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

[0064] In some embodiments, the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225 and/or a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

[0065] In another aspect, provided herein are isolated antibodies or antigen binding fragments that bind to human MARCO (SEQ ID NO: 384), comprising a a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence GYTFTDYYLH (SEQ ID NO: 252), CDR-H2 comprises the sequence YINPNNAYTS (SEQ ID NO: 253), CDR-H3 comprises the sequence DTTDYYNLHFAY (SEQ ID NO: 254), CDR-L1 comprises the sequence LTSEGISNDLA (SEQ ID NO: 257), CDR-L2 comprises the sequence DASRLED (SEQ ID NO: 258), and CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 259).

[0066] In some embodiments, the VH sequence comprises a sequence as set forth in SEQ ID NO: 251 or 261.

[0067] In some embodiments, the VL sequence comprises a sequence as set forth in SEQ ID NO: 256 or 266.

[0068] In some embodiments, the VH sequence comprises a sequence as set forth in SEQ ID NO: 251 or 261, and the VL sequence comprises a sequence s set forth in SEQ ID NO: 256 or 266.

[0069] In some embodiments, the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence as set forth in SEQ ID NO: 251 or 261, and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence set forth in SEQ ID NO: 256 or 266.

[0070] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 255 or 265.

[0071] In some embodiments, the antibody comprises a light chain sequence as set forth in SEQ ID NO: 260 or 270.

[0072] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 255 or 265; and a light chain sequence as set forth in SEQ ID NO: 260 or 270.

[0073] In some embodiments, the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 255 or 265; and a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 260 or 270.

[0074] In another aspect, provided herein are isolated antibodies or antigen binding fragments that bind to human MARCO (SEQ ID NO: 384), comprising a a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence GFSLTSYTLS (SEQ ID NO: 362), CDR-H2 comprises the sequence AIWGGDNTD (SEQ ID NO: 363), CDR-H3 comprises the sequence ELGGSFDY (SEQ ID NO: 364), CDR-L1 comprises the sequence KTSQNINKKLD (SEQ ID NO: 367), CDR-L2 comprises the sequence YTNNLQT (SEQ ID NO: 368), and CDR-L3 comprises the sequence YQYDSGFT (SEQ ID NO: 369).

[0075] In some embodiments, the VH sequence comprises a sequence as set forth in SEQ ID NO: 361 or 371.

[0076] In some embodiments, the VL sequence comprises a sequence as set forth in SEQ ID NO: 366 or 376.

[0077] In some embodiments, the VH sequence comprises a sequence as set forth in SEQ ID NO: 361 or 371, and the VL sequence comprises a sequence s set forth in SEQ ID NO: 366 or 376.

[0078] In some embodiments, the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence as set forth in SEQ ID NO: 361 or 371, and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence set forth in SEQ ID NO: 366 or 376.

[0079] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 365 or 375; and a light chain sequence as set forth in SEQ ID NO: 370 or 380.

[0080] In some embodiments, the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 365 or 375; and a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 370 or 380.

[0081] In some embodiments, the antibody is a monoclonal antibody, a neutral antibody, an antagonistic antibody, an agonist antibody, a polyclonal antibody, an afucosylated antibody, a human antibody, a humanized antibody, a chimeric antibody, a full-length antibody, and an scFv.

[0082] In some embodiments, the antibody is an scFv.

[0083] In some embodiments, the antibody is a monoclonal antibody.

[0084] In some embodiments, the antibody is a humanized antibody.

[0085] In some embodiments, the antibody is a human antibody.

[0086] In some embodiments, the antibody comprises an Fc region.

[0087] In some embodiments, the Fc region comprises a human Fc region.

[0088] In some embodiments, the antibody comprises an active human Fc region.

[0089] In some embodiments, the antibody comprises a heavy chain human constant region of a class selected from IgG, IgA, IgD, IgE, and IgM.

[0090] In some embodiments, the antibody comprises a human heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4.

[0091] In some embodiments, the human Fc region comprises a wild-type, human IgG1 Fc region.

[0092] In some embodiments, the human Fc region comprises a wild-type, human IgG4 Fc region.

[0093] In some embodiments, the Fc region comprises one or more amino acid substitutions, wherein the one or more substitutions result in increased antibody half-life, increased ADCC activity, increased ADCP activity, increased CDC activity, decreased ADCC activity, decreased ADCP activity, or decreased CDC activity compared with an Fc region without the one or more substitutions.

[0094] In some embodiments, the Fc region binds an Fcγ Receptor selected from the group consisting of: FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb.

[0095] In some embodiments, the antibody binds to human MARCO with a KD of less than or equal to about 0.5, 1, 2, 3, 4, 5, 6, or 7x10-9 M, as measured by surface plasmon resonance (SPR) assay.

[0096] In some embodiments, binding of the antibody to human MARCO is divalent cation dependent.

[0097] In some embodiments, binding of the antibody to human MARCO is divalent cation independent.

[0098] In some embodiments, the divalent cation comprises Ca2+ or Mg2+.

[0099] In some embodiments, the antibody binds an extracellular domain of human MARCO.

[0100] In some embodiments, the antibody binds to soluble MARCO.

[0101] In some embodiments, the antibody binds the SRCR domain of human MARCO, cynomolgus MARCO, or human and cynomolgus MARCO.

[0102] In some embodiments, the antibody binds the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

[0103] In some embodiments, the antibody or antigen binding fragment thereof binds to at least one of: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of MARCO (SEQ ID NO: 384).

[0104] In some embodiments, the antibody has receptor-ligand blocking activity.

[0105] In some embodiments, the antibody induces increased expression of at least one cytokine or chemokine upon contact with a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

[0106] In some embodiments, the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

[0107] In some embodiments, upon cell contact the antibody induces increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

[0108] In some embodiments, upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

[0109] In some embodiments, upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

[0110] In some embodiments, upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

[0111] In some embodiments, upon cell contact the antibody induces repolarization of myeloid M2-like TAMS to M1-like tumor associated macrophages (TAMs), and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

[0112] In some embodiments, upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, MHCIIhigh monocytes, or MHCIImid monocytes as compared to an isotype control antibody.

[0113] In some embodiments, upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

[0114] In some embodiments, upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

[0115] In some embodiments, upon administration to a subject the antibody induces an increased anti-tumor memory response as compared to an isotype control antibody.

[0116] In some embodiments, a cell is a MARCO+ cell.

[0117] In some embodiments, the cell is a human MARCO+ cell.

[0118] In some embodiments, the MARCO + cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

[0119] In some embodiments, the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

[0120] In some embodiments, the antibody binds to MARCO on the cell surface of a MARCO+ cell.

[0121] In some embodiments, the antibody: competes for binding to human MARCO with humanized PI-HX-3011, PI-HX-3031, PI-HX-3043, PI-HX-3061, PI-HX-3092 antibody; binds to human MARCO; binds to cynomolgus MARCO; binds to human and cynomolgus MARCO; binds to the SRCR domain of human MARCO; binds to the SRCR domain of cynomolgus MARCO; binds to the SRCR domain of human and cynomolgus MARCO; binds to human or cynomolgus MARCO in a divalent cation dependent manner; binds to human or cynomolgus MARCO in a divalent cation independent manner; stimulates MARCO signaling upon binding to a MARCO+ cell; induces one or more immune signaling pathways upon binding to a MARCO+ cell; induces cytokine or chemokine secretion upon binding to a MARCO+ cell, optionally wherein the cytokine or chemokine is IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin; induces increased NK cell activation, B cell regulation, T cell proliferation, T cell activation, or T cell differentiation upon binding to a MARCO+ cell; induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response; decreases a cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway; induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis; induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes; modulates B cells in the spleen upon binding to a MARCO+ cell; increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, MHCIIhigh monocytes, and/or MHCIImid monocytes in the spleen and/or tumor; increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in

the spleen and/or tumor; decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages in the spleen and/or tumor; induces changes in cell adhesion, cytoskeletal, chemotaxis and cell migration upon binding to a MARCO+ cell; induces cell signaling pathways comprising adhesion, migration, chemotaxis cell cycle, T cell receptor, phagocytosis, autophagy, and wnt pathways upon binding to a MARCO+ cell; disables MARCO+ myeloid cells; or is capable of any combination above.

[0122] In some embodiments, the antibody is for use as a medicament.

[0123] In some embodiments, the antibody is for use in the treatment of a cancer or infection.

[0124] In some embodiments, the antibody is for use in the treatment of a cancer, wherein the cancer is selected from a solid tumor and a liquid tumor.

[0125] In another aspect, provided herein are isolated polynucleotides or sets of polynucleotides encoding the antibody described herein, a VH thereof, a VL thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof; optionally the isolated polynucleotide or set of polynucleotides is cDNA.

[0126] In another aspect, provided herein are vectors or set of vectors comprising the polynucleotide or set of polynucleotides.

[0127] In another aspect, provided herein are host cells comprising the polynucleotide or set of polynucleotides or the vector or set of vectors.

[0128] In another aspect, provided herein are methods of producing an antibody comprising expressing the antibody or antigen binding fragment thereof with the host cell and isolating the expressed antibody.

[0129] In another aspect, provided herein are pharmaceutical compositions comprising the isolated antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient.

[0130] In another aspect, provided herein are kits comprising the isolated antibody or antigen binding fragment thereof or a pharmaceutical composition and instructions for use.

[0131] In another aspect, provided herein are methods of increasing an immune response in a subject comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof.

[0132] In some embodiments, the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

[0133] In some embodiments, the composition comprises the isolated antibody or the pharmaceutical composition.

[0134] In some embodiments, the antibody has receptor-ligand blocking activity.

[0135] In some embodiments, the increased immune response is an adaptive immune response.

[0136] In some embodiments, the increased immune response is an innate immune response.

[0137] In some embodiments, the increased immune response comprises increased expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

[0138] In some embodiments, the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

[0139] In some embodiments, the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

[0140] In some embodiments, upon cell contact the antibody induces In some embodiments, upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

[0141] In some embodiments, upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

[0142] In some embodiments, upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

[0143] In some embodiments, upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

[0144] In some embodiments, upon cell contact the antibody increases increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, MHCIIhigh monocytes, or MHCIImid monocytes as compared to an isotype control antibody.

[0145] In some embodiments, upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

[0146] In some embodiments, upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

[0147] In some embodiments, the antibody induces an increased memory immune response.

[0148] In some embodiments, the cell is a MARCO+ cell.

[0149] In some embodiments, the cell is a human MARCO+ cell.

[0150] In some embodiments, the MARCO+ cells is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

[0151] In some embodiments, the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

[0152] In some embodiments, the antibody binds to MARCO on the cell surface of a MARCO + cell.

[0153] In some embodiments, the subject is human.

[0154] In some embodiments, the subject has cancer.

[0155] In some embodiments, the cancer is a solid cancer.

[0156] In some embodiments, the cancer is a liquid cancer.

[0157] In some embodiments, the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

[0158] In some embodiments, the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

[0159] In some embodiments, MARCO is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

[0160] In some embodiments, IL-10 is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

[0161] In another aspect, provided herein are methods of treating cancer in a subject, comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof.

[0162] In some embodiments, the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

[0163] In some embodiments, the composition comprises the antibody disclosed herein or the pharmaceutical composition thereof.

[0164] In another aspect, provided herein are methods of treating cancer in a subject, comprising administering to the subject a composition comprising the anti-human MARCO antibody or antigen binding fragment thereof or a pharmaceutical composition thereof.

[0165] In some embodiments, the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

[0166] In some embodiments, the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.

[0167] In some embodiments, the immunotherapy comprises an anti-PD1 antibody.

[0168] In another aspect, provided herein are methods of treating cancer in a subject, comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof and an immunotherapy.

[0169] In some embodiments, the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

[0170] In some embodiments, the composition comprises the antibody disclosed herein or the pharmaceutical composition thereof.

[0171] In some embodiments, the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.

[0172] In some embodiments, the immunotherapy comprises an anti-PD1 antibody.

[0173] In some embodiments, the subject is human.

[0174] In some embodiments, the cancer is a solid cancer.

[0175] In some embodiments, the cancer is a liquid cancer.

[0176] In some embodiments, the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like

breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

[0177] In some embodiments, the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

[0178] In some embodiments, MARCO is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

[0179] In some embodiments, IL-10 is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

[0180] In some embodiments, the antibody induces an increased anti-tumor memory response as compared to an isotype control antibody.

[0181] In some embodiments, the administration increases an immune response in the subject as compared to an isotype control antibody.

[0182] In some embodiments, the increased immune response is an adaptive immune response.

[0183] In some embodiments, the increased immune response is an innate immune response.

[0184] In some embodiments, the increased immune response comprises expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

[0185] In some embodiments, the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

[0186] In some embodiments, the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

[0187] In some embodiments, upon cell contact the antibody induces In some embodiments, upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2

signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

[0188] In some embodiments, upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

[0189] In some embodiments, upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

[0190] In some embodiments, upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

[0191] In some embodiments, upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, MHCIIhigh monocytes, or MHCIImid monocytes as compared to an isotype control antibody.

[0192] In some embodiments, upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

[0193] In some embodiments, upon cell contact the antibody decreases TAMs, tumor associated neutrophils (TANs), plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

[0194] In some embodiments, the cell is a MARCO+ cell.

[0195] In some embodiments, the cell is a human MARCO+ cell.

[0196] In some embodiments, the MARCO+ cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

[0197] In some embodiments, the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

[0198] In some embodiments, the antibody binds to MARCO on the cell surface of a MARCO + cell.

[0199] In another aspect, provided herein are methods of disabling myeloid cells that express MARCO on the cell surface, comprising contacting the myeloid cells with an anti-human MARCO antibody or antigen binding fragment thereof.

[0200] In another aspect, provided herein are methods of disabling myeloid cells that express MARCO on the cell surface, comprising contacting the myeloid cells with the antibody described herein or the pharmaceutical composition thereof.

[0201] In some embodiments, the antibody disables the myeloid cells by at least one of ADCC activity, CDC activity, or ADCP activity, optionally wherein the antibody disables the myeloid cells by ADCC activity, optionally wherein the antibody disables the myeloid cells by CDC activity, and optionally wherein the antibody disables the myeloid cells by ADCP activity.

[0202] In some embodiments, the myeloid cell is a MARCO+ cell.

[0203] In some embodiments, the myeloid cell is a human MARCO+ cell.

[0204] In some embodiments, the myeloid cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

[0205] In some embodiments, the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

[0206] In some embodiments, the myeloid cells are intratumoral or splenic myeloid cells.

[0207] In some embodiments, the contacting is in vitro or in vivo.

[0208] In some embodiments, the contacting occurs in vivo in a subject, optionally wherein the subject has cancer.

[0209] In some embodiments, the subject is a human.

[0210] In some embodiments, the cancer is a solid cancer.

[0211] In some embodiments, the cancer is a liquid cancer.

[0212] In some embodiments, the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

[0213] In some embodiments, the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

[0214] In some embodiments, the contacting increases an immune response in the subject as compared to an isotype control antibody.

[0215] In some embodiments, the increased immune response is an adaptive immune response.

[0216] In some embodiments, the increased immune response is an innate immune response.

[0217] In some embodiments, the increased immune response comprises expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

[0218] In some embodiments, the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

[0219] In some embodiments, the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

[0220] In some embodiments, upon cell contact the antibody IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

[0221] In some embodiments, upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia pathway, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

[0222] In some embodiments, upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or and IL-18 secretion and/or phagocytosis.

[0223] In some embodiments, upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes.

[0224] In some embodiments, upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, MHCIIhigh monocytes, or MHCIImid monocytes as compared to an isotype control antibody.

[0225] In some embodiments, upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

[0226] In some embodiments, upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

[0227] In some embodiments, the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

[0228] In some embodiments, the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.

[0229] In some embodiments, the immunotherapy comprises an anti-PD1 antibody.

[0230] In some embodiments, of determining an expression level of MARCO protein in a sample from a subject comprising contacting the sample with an anti-MARCO antibody and performing an immunohistochemistry assay or a soluble MARCO assay.

[0231] In some embodiments, the assay is an immunohistochemistry assay and the antibody comprises RDM5, RDM9, PI-3010.15, PI-3010.25, or PI-3030.41.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0232] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

[0233] **FIG. 1** shows the ordered MARCO mRNA expression in tumor (left bar) vs normal (right bar) tissue.

[0234] **FIG. 2** shows that MARCO RNA expression was induced by IL-10 in Human Monocyte-derived Macrophages (MDMs).

[0235] **FIG. 3A** shows the correlation of MARCO and IL-10 expression in various tumor types. **FIG. 3B** shows a heat map of the correlation between TREM2 expression, CD45 expression, IL-10 expression, and MARCO expression.

[0236] **FIG. 4A** shows that MARCO expression is inversely correlated with patient survival probability in CRC. **FIG. 4B** shows that MARCO expression is inversely correlated with patient survival probability in RCC. **FIG. 4C** shows that MARCO expression is inversely correlated with patient survival probability in neuroblastoma. **FIG. 4D** shows that MARCO expression increased as function of disease severity in neuroblastoma, according to INSS stage.

[0237] **FIG. 5** shows that MARCO is upregulated in basal-like breast cancer relative to other breast cancer subtypes.

[0238] **FIG. 6A** shows the binding of 33 anti-human MARCO antibodies to GFP-239T control cells (left bar), cells expressing human MARCO (middle bar), or cells expressing mouse MARCO (right bar). **FIG. 6B** shows flow cytometry histograms of one MARCO antibody, PI-M014, binding to cells expressing huMARCO, muMARCO, and CynoMARCO, as compared to control cells (GFP control). **FIG. 6C** shows a titration of PI-M014 and isotype control antibody binding to cells expressing huMARCO. **FIG. 6D** shows a flow cytometry histogram of PI-M014 binding to human monocyte-derived macrophages.

[0239] **FIG. 7** shows a summary of the binding competition assay and that PI-M015 and PI-M017 competed with each other for binding to the MARCO antigen, indicating they bound to the same MARCO epitope.

[0240] **FIG. 8A** shows that MARCO is expressed in human MDMs. **FIG. 8B** shows that MARCO is expressed in tumor associated macrophages (TAMs) from primary human tumor samples (gastric cancer and ovarian cancer).

[0241] **FIG. 9** shows that RDM-9514 also blocked LDL binding to MARCO in a dose dependent manner.

[0242] **FIG. 10A** shows that RDM-9514 bound to surface expressed MARCO on $MHCII^{high}$ TAMs and $MHCII^{low}$ TAMs isolated from CT26 tumors and Py8119 tumors. **FIG. 10B** shows that MARCO is expressed on TAMs and monocytes in the CT26 syngeneic tumor model.

[0243] **FIG. 11A** shows that anti-mouse MARCO antibodies PI-HX-3017 (left bar, renamed PI-3009), PI-HX-3016 (middle left bar, renamed PI-3008), PI-HX-3021 (middle right bar, renamed PI-3007) and PI-HX-3012 (right bar) each bound to mouse BMDMs. **FIG. 11B** shows that the same antibodies also bound to MARCO on TAMs (right bar) and monocytes (left bar) isolated from tumors in the CT26 syngeneic tumor model (n=2).

[0244] **FIG. 12** shows the tumor volume in mice groups treated with isotype antibody; PD-1 antibody only; or PI-3008 plus PD-1 antibodies, PI-3007 plus PD-1 antibodies, PI-3009 plus PD-1 antibodies, and PI-3007 plus PD-1 antibodies.

[0245] **FIG. 13A** shows the tumor volumes in individual mice treated with isotype control antibody. **FIG. 13B** shows the tumor volumes in individual mice treated with anti-PD-1 antibody. **FIG. 13C** shows the tumor volumes in individual mice treated with PI-3008 and anti-PD-1 antibody. **FIG. 13D** shows the tumor volumes in individual mice treated with PI-3009 and anti-PD-1 antibody. **FIG. 13E** shows the tumor volumes in individual mice treated

with isotype control antibody. **FIG. 13F** shows the tumor volumes in individual mice treated with fucosylated PI-3008. **FIG. 13G** shows the tumor volumes in individual mice treated with afucosylated PI-3008. **FIG. 13H** shows the tumor volumes in mice treated with the indicated antibody. **FIG. 13I** shows the shows the tumor volumes in mice treated with the indicated antibody **FIG. 13J** shows the percentage of tumor growth inhibition (%TGI) in mice treated with isotype control antibody (wt Fc) as compared to wt Fc PI-3008 and PD-1 antibody. **FIG. 13K** shows the shows the percentage of tumor growth inhibition (%TGI) in mice treated with isotype control antibody (effector dead Fc) as compared to dead Fc PI-3021 and PD-1 antibody.

[0246] **FIG. 14** shows the tumor volume of re-implanted CT26 tumor cells and EMT6 cells in mice that had been previously treated with anti-MARCO and anti-PD-1 antibodies.

[0247] **FIG. 15A** shows a timeline of the PD study. **FIG. 15B** shows CT26 tumor volume in mice treated with isotype antibody or PI-3008. **FIG. 15C** shows quantification of the PI-3008 antibody in the mice after the first and second dose.

[0248] **FIG. 16A** show pro-inflammatory molecule expression within the TME of CT26 mice treated with PI-3008. **FIG. 16B** shows a comparison of the genes upregulated in BMDMs and CT26 tumors after *in vitro* or *in vivo* treatment with PI-3008.

[0249] **FIG. 17A** shows a sequence comparison of PI-HX-3061 VH with a human VH framework sequence and three humanized VH sequences based on PI-HX-3061. **FIG. 17B** shows a sequence comparison of PI-HX-3061 VL with a human VL framework sequence and one humanized VL sequences based on PI-HX-3061.

[0250] **FIG. 18** shows a sequence comparison of PI-HX-3031 VL with a human VL framework sequence and 6 humanized VL sequences based on PI-HX-3031.

[0251] **FIG. 19** shows the geometric mean fluorescent intensity (gMFI) of cells incubated with anti-MARCO antibodies and AF488 fluorescent bacteria in a competition assay. Pre-incubation of the cells with anti-MARCO antibodies reduced the bacteria binding and fluorescent signal in a dose dependent manner.

[0252] **FIG. 20A** shows binding of the chimera antibodies bound to 293T cells overexpressing MARCO but not to the immune cells present in PBLs (peripheral blood leukocytes). The eosinophil binding was non-specific across all tested antibodies including the hIgG1 isotype control. PI-3010 is shown on the left, PI-3030 is shown on the left middle, PI-3031 is shown on the right middle, and isotype control hIgG1 is shown on the right. **FIG. 20B** shows binding of PI-HX-3031 on TAMs and monocytes from an endometrial cancer

(primary human tumor). Antibody binding is the right peak, isotype control binding is the left peak.

[0253] FIG. 21 shows a sequence comparison of the wild type SRCR domain in human and mouse MARCO and the mutations made in the indicated murine and human recombinant variant proteins.

[0254] FIG. 22 shows the amino acids residues of the wild type SRCR domain in human and mouse MARCO and the mutations made in the indicated recombinant variant proteins.

[0255] FIG. 23 shows binding of the indicated antibody to recombinant human SRCR MARCO hVar3 protein.

[0256] FIG. 24 shows the overlapping SRCR epitope residue (circled) in murine SRCR (left, Q452) and human SRCR (right, D452).

[0257] FIG. 25A shows the PK standard calibration curve for PI-3025. **FIG. 25B** shows the PK standard calibration curve for PI-3048.

[0258] FIG. 26A shows the concentration-time profile of PI-3025 and PI-3048 in the ligand binding PK assay. **FIG. 26B** shows the concentration-time profile of PI-3025 and PI-3048 in the total PK assay.

[0259] FIG. 27 provides cytokine and other relevant gene expression (MIP-1α, IL-27, LIF, IL-1β, IL-2, IL-4, IP-10, IL-6, IL-10, CD40, IL-12p70, G-CSF, IFNγ, GM-CSF, TNFα, MIP-1β, MCP-1, MIG, gro-alpha, IL-1α, IL-15, MCP-3, M-CSF, and VEGF-A) in hMDMs from two different donors after treatment with anti-MARCO antibody.

[0260] FIG. 28 provides the qPCR mRNA expression data for the indicated genes after treatment with PI-3010.15, PI-3010.25, PI-3030.41, or the hIgG1 control.

[0261] FIG. 29 shows that human and mouse MARCO mAbs drive similar pathway regulation.

[0262] FIG. 30 shows the top immune activation genes and pathways increased by anti-MARCO antibody in hDTCs include IL-2-STAT5 signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, the inflammatory response, IFNγ response, and IFNα response.

[0263] FIG. 31 shows that PI-3010.15 induced a pro-inflammatory signature in human suppressive macrophages (M2c).

[0264] FIG. 32 provides a comparison of the indicated cytokine expression fold change induced by PI-3010.15 and PI-3030.41.

[0265] FIG. 33A shows that PI-3008 induced statistically significant IL-1β secretion by the inflammasome in non-polarized macrophages from C57BL/6 mice. **FIG. 33B** shows that PI-3008 induced statistically significant IL-1β secretion by the inflammasome in IL-10 polarized

macrophages from C57BL/6 mice **FIG. 33C** shows that PI-3008 induced statistically significant IL-1β secretion by the inflammasome in non-polarized macrophages from Balb/c mice. **FIG. 33D** shows that PI-3008 induced statistically significant IL-1β secretion by the inflammasome in IL-10 polarized macrophages from Balb/c mice.

[0266] **FIG. 34A** shows that PI-3025 (IgG1 format) and PI-3048 (IgG4 format) induced statistically significant IL-1β secretion in IL-10 polarized macrophages after incubation with 0.1 μg/ml LPS+ATP and 1 μg/ml LSP+ATP. **FIG. 34B** shows that PI-3048 induced IL-1β secretion after treatment with 1 μg/ml LPS+ATP. Bars for PI-3025 are shown second from the left in each grouping, bars for PI-3048 are shown on the right in each grouping.

[0267] **FIG. 35** shows that of PI-3010.15, PI-3010.25, and PI-3030.41 induced IL-1β production when treated with LPS and ATP compared to the untreated condition

[0268] **FIG. 36** shows that PI-3008 demonstrated anti-tumor activity as a single agent in the EMT6 model. Tumor volumes in isotype control antibody treated mice are shown in the right panel, tumor volumes in PI-3008 antibody treated mice are shown in the left panel. The PI-3008 treated mice grouped into responders and non-responders.

[0269] **FIG. 37** shows that PI-3008 demonstrated anti-tumor activity as a single agent in the E0771 model. Tumor volumes in isotype control antibody treated mice are shown in the top right and bottom right panels, tumor volumes in PD-1 antibody treated mice are shown in the top left panel, and tumor volumes in PI-3008 antibody treated mice are shown in the bottom left panel.

[0270] **FIG. 38A** shows that the mice dosed with PI-3008 showed a statistically significant reduction in tumor volume as compared to isotype controls (p=0.0037). **FIG. 38B** shows the percentage of tumor growth inhibition (TGI) for isotype antibody and PI-3008. **FIG. 38C** shows that PI-3008 and effector dead PI-3021 both have anti-tumor activity in the E0771 model.

[0271] **FIG. 39A** provides a schematic of the E0771 PD/PK/efficacy study timeline. **FIG. 39B** shows the tumor volume in isotype control treated mice and PI-3008 treated mice over the course of the study. **FIG. 39C** provides individual tumor volumes in the isotype control mice. **FIG. 39D** provides individual tumor volumes in the PI-3008 mice. **FIG. 39E** provides the final tumor volumes at Day 28. **FIG. 39F** provides the serum levels of PI-3008.

[0272] **FIG. 40A** provides the PI-3008 serum concentrations in mono and combination experiments with PD-1 antibody. **FIG. 40B** provides the PD-1 antibody serum concentrations in combination experiments.

[0273] **FIG. 41A** provides IHC images of CD8 T cells and NCR1 (NK cells) stained with DAB after administration of isotype control or PI-3008. **FIG. 41B** provides quantification of inflammatory monocyte infiltration (CD8+ T cells, NCR1+ NK cells) by flow cytometry. **FIG. 41C** provides quantification of $MHCII^{High}$ Ly6C+ monocytes, DC infiltration, and NK1.1 NK cells by flow cytometry. **FIG. 41D** provides quantification of CD206+, cells, MARCO+ cells, NCR1+ cells, and CD8a+ cells at the indicated region.

[0274] **FIG. 42A** provides expression levels of the indicated proinflammatory cytokines and chemokines induced by PI-3008 in the E0771 model tumor supernatants. **FIG. 42B** provides expression levels of the indicated cytokines associated with T-cell activation and NK cells activation observed at Day 1 post-dose 2 in the tumor supernatants.

[0275] **FIG. 43** provides the results of the receptor occupancy assay.

[0276] **FIG. 44A** provides quantification of the indicated cell types in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 44B** provides quantification of the indicated cell types in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 44C** provides quantification of the indicated cell types in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 44D** provides quantification of the indicated cell types in the spleen after treatment with isotype control antibody or PI-3008. In each figure, isotype samples are shown on the left of the pairs, PI-3008 samples are shown on the right of the pairs.

[0277] **FIG. 45** provides quantification of the indicated immunoglobulin types in the spleen and serum after treatment with isotype control antibody or PI-3008.

[0278] **FIG. 46** provides quantification of MARCO positive cells in the spleens after the second dose and at the end of the study after treatment with isotype control antibody or PI-3008.

[0279] **FIG. 47A** provides quantification of the indicated cell type in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 47B** provides quantification of the indicated cell type in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 47C** provides quantification of the indicated cell type in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 47D** provides quantification of the indicated cell type in the spleen after treatment with isotype control antibody or PI-3008.

[0280] **FIG. 48A** provides quantification of the percentage positive cells per tissue compartment in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 48B** provides quantification of the percentage positive cells per tissue compartment in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 48C** provides

quantification of the percentage positive cells per tissue compartment in the spleen after treatment with isotype control antibody or PI-3008. **FIG. 48D** provides quantification of the percentage positive cells per tissue compartment in the spleen after treatment with isotype control antibody or PI-3008. In each figure, isotype samples are shown on the left of the pairs, PI-3008 samples are shown on the right of the pairs.

[0281] FIG. 49 shows that PI-3008 induced an increase in CD8+ T-cells and the cytotoxic marker granzyme B as measured by IHC compared to isotype control treated tumors.

[0282] FIG. 50 shows changes in MARCO levels on the marginal zone macrophages in the spleen, with noticeable gaps in the marginal zone area when stained with a non-PI-3008 competing anti-mouse MARCO IHC compatible antibody.

[0283] FIG. 51A shows representative images of colorectal tumor tissue (left) and lung tumor tissue (right) stained with 2.5 µg/mL RDM5 using high pH (ER2) epitope retrieval conditions on the top panels. The bottom panels provide representative images of normal tissue cores from lung, spleen, and liver, stained with 2.5 µg/ml RDM5 using high pH (ER2) epitope retrieval conditions. The dark gay color indicates positive staining of myeloid cells expressing MARCO. **FIG. 51B** shows the percentage of positive MARCO cancer cases in the indicated cancer type after IHC staining with the RDM5 antibody. **FIG. 51C** shows the IHC score in the indicated cancer type after IHC staining with the RDM5 antibody.

[0284] FIG. 52 shows that binding of some anti-MARCO antibodies to MARCO was calcium dependent.

[0285] FIG. 53 shows binding of the indicated MARCO antibody to human and cynomolgus MARCO expressing cell lines.

[0286] FIG. 54 shows binding of antibodies produced by the stable transfection method to MARCO expressing cells as compared to reference antibodies made via transient transfection.

[0287] FIG. 55A shows the sMARCO calibration curve for RG-3000A. **FIG. 55B** shows the sMARCO levels in normal and cancer serum samples.

[0288] FIG. 56 shows the tumor volumes in B-cell deficient mice after MARCO antibody, PD-1 antibody, combination, or isotype antibody treatment.

[0289] FIG. 57 shows the NF-kB reporter activity induced by PI-3010.15 or isotype antibody in combination with the indicated agonist at 4 hrs or 24 hrs.

[0290] FIG. 58 shows that PI-3008 treatment induced the indicated cytokines and chemokines in tumors in the E0771 model at early timepoints.

[0291] **FIG. 59** shows that PI-3008 treatment induced the indicated cytokines and chemokines in the spleen in the E0771 model at early timepoints.

[0292] **FIG. 60** provides quantification of the indicated tumor myeloid cell types at Day 2 and Day 5 post-administration of a isotype control antibody or PI-3008.

[0293] **FIG. 61** provides quantification of the indicated tumor myeloid cell types at Day 2 and Day 5 post-administration of a isotype control antibody or PI-3008.

[0294] **FIG. 62** provides quantification of the indicated tumor myeloid cell types at Day 2 and Day 5 post-administration of a isotype control antibody or PI-3008.

[0295] **FIG. 63** provides quantification of the indicated tumor lymphoid cell types at Day 2 and Day 5 post-administration of a isotype control antibody or PI-3008.

[0296] **FIG. 64** provides quantification of the indicated spleen lymphoid cell types at Day 5 post-administration of a isotype control antibody or PI-3008.

[0297] **FIG. 65** provides quantification of the indicated spleen lymphoid or myeloid cell types at Day 5 post-administration of a isotype control antibody or PI-3008.

[0298] **FIG. 66** provides quantification of the indicated spleen myeloid cell types at Day 5 post-administration of a isotype control antibody or PI-3008.

[0299] **FIG. 67** provides quantification of the indicated spleen myeloid cell types at Day 5 post-administration of a isotype control antibody or PI-3008.

[0300] **FIG. 68** provides quantification of the indicated spleen myeloid cell types at Day 5 post-administration of a isotype control antibody or PI-3008.

[0301] **FIG. 69** provides quantification of the indicated cell types in the blood at Day 5 post-administration of a isotype control antibody or PI-3008.

[0302] **FIG. 70** shows that Receptor Occupancy of the therapeutic MARCO antibody was achieved in the MARCO expressing cells in the spleen and tumors.

[0303] **FIG. 71** shows that PI-3010.15 induced expression of the indicated pro-inflammatory cytokines.

DETAILED DESCRIPTION

Definitions

[0304] Terms used in the claims and specification are defined as set forth below unless otherwise specified.

[0305] The term "ameliorating" refers to any therapeutically beneficial result in the treatment of a disease state, e.g., a cancer disease state, including prophylaxis, lessening in the severity or progression, remission, or cure thereof.

[0306] The term “in situ” refers to processes that occur in a living cell growing separate from a living organism, e.g., growing in tissue culture.

[0307] The term “in vivo” refers to processes that occur in a living organism.

[0308] The term “mammal” as used herein includes both humans and non-humans and include but is not limited to humans, non-human primates, canines, felines, murines, bovines, equines, and porcines.

[0309] The term percent "identity," in the context of two or more nucleic acid or polypeptide sequences, refer to two or more sequences or subsequences that have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned for maximum correspondence, as measured using one of the sequence comparison algorithms described below (e.g., BLASTP and BLASTN or other algorithms available to persons of skill) or by visual inspection. Depending on the application, the percent "identity" can exist over a region of the sequence being compared, e.g., over a functional domain, or, alternatively, exist over the full length of the two sequences to be compared.

[0310] For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0311] Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, Adv. Appl. Math. 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson & Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by visual inspection (see generally Ausubel et al., infra).

[0312] One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al., J. Mol. Biol. 215:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (ncbi.nlm.nih.gov/).

[0313] The term “sufficient amount” means an amount sufficient to produce a desired effect, e.g., an amount sufficient to modulate protein aggregation in a cell.

[0314] The term "therapeutically effective amount" is an amount that is effective to ameliorate a symptom of a disease. A therapeutically effective amount can be a "prophylactically effective amount" as prophylaxis can be considered therapy.

[0315] Abbreviations used in this application include the following: .

[0316] It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

Antibodies

Structure

[0317] The present application provides antibodies and compositions comprising an antibody which binds a MARCO protein. Such antibodies including antibodies that increase, enhance, or induce immune responses or kill, disable, or deplete myeloid cells.

[0318] The term "antibody" is used herein in its broadest sense and includes certain types of immunoglobulin molecules comprising one or more antigen-binding domains that specifically bind to an antigen or epitope. An antibody specifically includes intact antibodies (e.g., intact immunoglobulins), antibody fragments, and multi-specific antibodies.

[0319] The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. The "class" of an antibody or immunoglobulin refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG_2, IgG_3, IgG_4, IgA1, and IgA_2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively.

[0320] An exemplary immunoglobulin (antibody) structural unit is composed of two pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD), e.g., a homodimer of a paired light chain and heavy chain. The N-terminal domain of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL) and variable heavy chain (VH) refer to these light and heavy chain domains respectively. The IgG1 heavy chain comprises of the VH, CH1, CH2 and CH3 domains respectively from the N to C-terminus. The light chain comprises of the VL and CL domains from N to C terminus. The IgG1 heavy chain comprises a hinge between the CH1 and CH2 domains. In certain embodiments, the

immunoglobulin constructs comprise at least one immunoglobulin domain from IgG, IgM, IgA, IgD, or IgE connected to a therapeutic polypeptide. In some embodiments, the immunoglobulin domain found in an antibody provided herein, is from or derived from an immunoglobulin based construct such as a diabody, or a nanobody. In certain embodiments, the immunoglobulin constructs described herein comprise at least one immunoglobulin domain from a heavy chain antibody such as a camelid antibody. In certain embodiments, the immunoglobulin constructs provided herein comprise at least one immunoglobulin domain from a mammalian antibody such as a bovine antibody, a human antibody, a camelid antibody, a mouse antibody or any chimeric antibody.

[0321] In some embodiments, the antibodies provided herein comprise a heavy chain. In one embodiment, the heavy chain is an IgA. In one embodiment, the heavy chain is an IgD. In one embodiment, the heavy chain is an IgE. In one embodiment, the heavy chain is an IgG. In one embodiment, the heavy chain is an IgM. In one embodiment, the heavy chain is an IgG1. In one embodiment, the heavy chain is an IgG2. In one embodiment, the heavy chain is an IgG3. In one embodiment, the heavy chain is an IgG4. In one embodiment, the heavy chain is an IgA1. In one embodiment, the heavy chain is an IgA2.

[0322] The term "hypervariable region" or "HVR", as used herein, refers to each of the regions of an antibody variable domain which are hypervariable in sequence and/or form structurally defined loops ("hypervariable loops"). Generally, native four-chain antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). HVRs generally comprise amino acid residues from the hypervariable loops and/or from the complementarity determining regions (CDRs), the latter being of highest sequence variability and/or involved in antigen recognition. With the exception of CDR1 in VH, CDRs generally comprise the amino acid residues that form the hypervariable loops. Hypervariable regions (HVRs) are also referred to as "complementarity determining regions" (CDRs), and these terms are used herein interchangeably in reference to portions of the variable region that form the antigen-binding regions. This particular region has been described by Kabat et al., U.S. Dept. of Health and Human Services, Sequences of Proteins of Immunological Interest (1983) and by Chothia et al., J Mol Biol 196:901-917 (1987), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The exact residue numbers which encompass a particular CDR will vary depending on the sequence and

size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

[0323] The amino acid sequence boundaries of a CDR can be determined by one of skill in the art using any of a number of known numbering schemes, including those described by Kabat et al., *supra* ("Kabat" numbering scheme); Al-Lazikani et al., 1997, *J. Mol. Biol.*, 273:927-948 ("Chothia" numbering scheme); MacCallum et al., 1996, *J. Mol. Biol.* 262:732-745 ("Contact" numbering scheme); Lefranc et al., *Dev. Comp. Immunol.*, 2003, 27:55-77 ("IMGT" numbering scheme); and Honegge and Plückthun, *J. Mol. Biol.*, 2001, 309:657-70 ("AHo" numbering scheme); each of which is incorporated by reference in its entirety.

[0324] Table A provides the positions of CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and CDR-H3 as identified by the Kabat and Chothia schemes. For CDR-H1, residue numbering is provided using both the Kabat and Chothia numbering schemes.

[0325] CDRs may be assigned, for example, using antibody numbering software, such as Abnum, available at bioinf.org.uk/abs/abnum/, and described in Abhinandan and Martin, *Immunology*, 2008, 45:3832-3839, incorporated by reference in its entirety.

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

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

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

[0326] The "EU numbering scheme" is generally used when referring to a residue in an antibody heavy chain constant region (e.g., as reported in Kabat et al., *supra*). Unless stated otherwise, the EU numbering scheme is used to refer to residues in antibody heavy chain constant regions described herein.

[0327] As used herein, the term "single-chain" refers to a molecule comprising amino acid monomers linearly linked by peptide bonds. In a particular such embodiment, the C-terminus of the Fab light chain is connected to the N-terminus of the Fab heavy chain in the single-chain Fab molecule. As described in more detail herein, an scFv has a variable domain of light chain (VL) connected from its C-terminus to the N-terminal end of a variable domain of heavy chain (VH) by a polypeptide chain. Alternately the scFv comprises of polypeptide

chain where in the C-terminal end of the VH is connected to the N-terminal end of VL by a polypeptide chain.

[0328] The "Fab fragment" (also referred to as fragment antigen-binding) contains the constant domain (CL) of the light chain and the first constant domain (CH1) of the heavy chain along with the variable domains VL and VH on the light and heavy chains respectively. The variable domains comprise the complementarity determining loops (CDR, also referred to as hypervariable region) that are involved in antigen-binding. Fab′ fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region.

[0329] "$F(ab')_2$" fragments contain two Fab' fragments joined, near the hinge region, by disulfide bonds. $F(ab')_2$ fragments may be generated, for example, by recombinant methods or by pepsin digestion of an intact antibody. The F(ab') fragments can be dissociated, for example, by treatment with ß-mercaptoethanol.

[0330] "Fv" fragments comprise a non-covalently-linked dimer of one heavy chain variable domain and one light chain variable domain.

[0331] The "Single-chain Fv" or "scFv" includes the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. In one embodiment, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen-binding. For a review of scFv see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994). HER2 antibody scFv fragments are described in WO93/16185; U.S. Pat. No. 5,571,894; and U.S. Pat. No. 5,587,458.

[0332] "scFv-Fc" fragments comprise an scFv attached to an Fc domain. For example, an Fc domain may be attached to the C-terminal of the scFv. The Fc domain may follow the V_H or V_L, depending on the orientation of the variable domains in the scFv (i.e., V_H -V_L or V_L -V_H). Any suitable Fc domain known in the art or described herein may be used. In some cases, the Fc domain comprises an IgG4 Fc domain. In some cases, the Fc domain comprises an IgG1 Fc domain.

[0333] The term "single domain antibody" or "sdAb" refers to a molecule in which one variable domain of an antibody specifically binds to an antigen without the presence of the other variable domain. Single domain antibodies, and fragments thereof, are described in Arabi Ghahroudi et al., *FEBS Letters*, 1998, 414:521-526 and Muyldermans et al., *Trends in Biochem. Sci.*, 2001, 26:230-245, each of which is incorporated by reference in its entirety. Single domain antibodies are also known as sdAbs or nanobodies. Sdabs are fairly stable and

easy to express as fusion partner with the Fc chain of an antibody (Harmsen MM, De Haard HJ (2007). "Properties, production, and applications of camelid single-domain antibody fragments". Appl. Microbiol Biotechnol. 77(1): 13-22).

[0334] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a naturally occurring antibody structure and having heavy chains that comprise an Fc region. For example, when used to refer to an IgG molecule, a "full length antibody" is an antibody that comprises two heavy chains and two light chains.

[0335] The term "epitope" means a portion of an antigen that specifically binds to an antibody. Epitopes frequently consist of surface-accessible amino acid residues and/or sugar side chains and may have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter may be lost in the presence of denaturing solvents. An epitope may comprise amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding. The epitope to which an antibody binds can be determined using known techniques for epitope determination such as, for example, testing for antibody binding to MARCO variants with different point-mutations, or to chimeric MARCO variants. In some embodiments, the MARCO epitope is in the SRCR domain. In come embodiments, the MARCO epitope is in the collagen-like domain. In some embodiments, the anti-MARCO antibody or antigen binding fragment thereof binds the SRCR domain. In some embodiments, the anti-MARCO antibody or antigen binding fragment thereof binds the collagen-like domain.

[0336] A "multispecific antibody" is an antibody that comprises two or more different antigen-binding domains that collectively specifically bind two or more different epitopes. The two or more different epitopes may be epitopes on the same antigen (e.g., a single MARCO molecule expressed by a cell) or on different antigens (e.g., different MARCO molecules expressed by the same cell, or a MARCO molecule and a non- MARCO molecule). In some aspects, a multi-specific antibody binds two different epitopes (i.e., a "bispecific antibody"). In some aspects, a multi-specific antibody binds three different epitopes (i.e., a "trispecific antibody").

[0337] A "monospecific antibody" is an antibody that comprises one or more binding sites that specifically bind to a single epitope. An example of a monospecific antibody is a naturally occurring IgG molecule which, while divalent (i.e., having two antigen-binding

domains), recognizes the same epitope at each of the two antigen-binding domains. The binding specificity may be present in any suitable valency.

[0338] The term "monoclonal antibody" refers to an antibody from a population of substantially homogeneous antibodies. A population of substantially homogeneous antibodies comprises antibodies that are substantially similar and that bind the same epitope(s), except for variants that may normally arise during production of the monoclonal antibody. Such variants are generally present in only minor amounts. A monoclonal antibody is typically obtained by a process that includes the selection of a single antibody from a plurality of antibodies. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones, yeast clones, bacterial clones, or other recombinant DNA clones. The selected antibody can be further altered, for example, to improve affinity for the target ("affinity maturation"), to humanize the antibody, to improve its production in cell culture, and/or to reduce its immunogenicity in a subject.

[0339] "Effector functions" refer to those biological activities mediated by the Fc region of an antibody, which activities may vary depending on the antibody isotype. Examples of antibody effector functions include C1q binding to activate complement dependent cytotoxicity (CDC), Fc receptor binding to activate antibody-dependent cellular cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP), receptor ligand blocking, agonism, or antagonism. An active Fc region is one that is capable of Fc-based effector functions such as ADCC, CDC, and/or ADCP.

[0340] Anti-MARCO antibodies can include those described herein such as the clones set forth in the tables. In some embodiments, the antibody comprises an alternative scaffold. In some embodiments, the antibody consists of an alternative scaffold. In some embodiments, the antibody consists essentially of an alternative scaffold. In some embodiments, the antibody comprises an antibody fragment. In some embodiments, the antibody consists of an antibody fragment. In some embodiments, the antibody consists essentially of an antibody fragment. A "MARCO antibody," "anti-MARCO antibody," or "MARCO-specific antibody" is an antibody, as provided herein, which specifically binds to the antigen MARCO. In some embodiments, the antibody binds the extracellular domain of MARCO. In certain embodiments, a MARCO antibody provided herein binds to an epitope of MARCO that is conserved between or among MARCO proteins from different species.

[0341] The term "chimeric antibody" or "chimera antibody" refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0342] "Humanized" forms of non-human antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. A humanized antibody is generally a human antibody (recipient antibody) in which residues from one or more CDRs are replaced by residues from one or more CDRs of a non-human antibody (donor antibody). The donor antibody can be any suitable non-human antibody, such as a mouse, rat, rabbit, chicken, or non-human primate antibody having a desired specificity, affinity, or biological effect. The humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In some instances, selected framework region residues of the recipient antibody are replaced by the corresponding framework region residues from the donor antibody. Humanized antibodies may also comprise residues that are not found in either the recipient antibody or the donor antibody. Such modifications may be made to further refine antibody function. Examples of how to make humanized antibodies can be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293, each of which is incorporated by reference in its entirety. For further details, *see* Jones et al., *Nature*, 1986, 321:522-525; Riechmann et al., *Nature*, 1988, 332:323-329; and Presta, *Curr. Op. Struct. Biol.*, 1992, 2:593-596, each of which is incorporated by reference in its entirety.

[0343] In some embodiments, the antibody comprises a rat MARCO antibody. In some embodiments, the antibody comprises a chimeric MARCO antibody. In some embodiments, the antibody comprises a humanized MARCO antibody. In some embodiments, the antibody comprises a human MARCO antibody.

[0344] In some embodiments, the humanized MARCO antibody VH sequence comprises at least one of 16G, 19R, 23A, 37V, 42G, 48V, 49S, 82Q, 88A, 93V, 114T, 115L, S16G, K19R, V23A, I37V, K42G, I48V, A49S, E82Q, S88A, M93V, V114T, or M115L as compared to a rat VH sequence as shown in SEQ ID NO: 141. In some embodiments, the humanized MARCO antibody VH sequence comprises at least one of G16, R19, A23, V37, G42, V48, S49, Q82, A88, V93, T114, L115, numbering according to EU Index. In some embodiments, the humanized MARCO antibody VH sequence comprises at least one of I38, I48, A49, S54, Q54, A54, G56, S56, Q56, A56, S57, Q57, or A57, numbering according to EU Index.

[0345] In some embodiments, the humanized MARCO antibody VL sequence comprises at least one of 2I, 10S, 13S, 16V, 18D, 19R, 21T, 23T, 25R, 38Q, 41G, 43A, 44P, 50D, 51A, 53S, 55E, 58V, 76S, 77S, 79Q, 85T, 99Q, V2I, Y10S, A13S, P16V, E18D, S19R, S21T, S23T, K25R, E38Q, E41G, T43A, N44P, S50D, G51A, T53S, Q55E, T58V, R76S, N77S, E79Q, V85T, and S99Q, as compared to a rat VL sequence as shown in SEQ ID NO: 146. In

some embodiments, the humanized MARCO antibody VL sequence comprises at least one of I2, S10, S13, V16, D18, R19, T21, T23, R25, Q38, G41, A43, P44, D50, A51, S53, E55, V58, S76, S77, Q79, T85, or Q99, numbering according to EU Index. In some embodiments, the humanized MARCO antibody VL sequence comprises at least one of V2, R24, K24, Q38, E38, A43, T43, N44, or P44, numbering according to EU Index.

[0346] In some embodiments, the humanized MARCO antibody VH sequence comprises at least one of 2V, 9A, 11V, 16A, 20V, 38R, 43Q, 46E, 62Q, 63K, 65Q, 66G, 68V, 69T, 70M, 71T, 72R, 73D, 76T, 78A, 79Y, 80M, 81E, 82L, 83S, 84S, 86R, 87S, 92V, 94Y, 96A, 114T, 115L, I2V, P9A, L11V, E16A, I20V, K38R, N43Q, K46E, D62Q, D63K, K65Q, Q66G, F68V, V69T, F70M, S71T, L72R, E73D, A76T, S78A, F79Y, L80M, Q81E, I82L, N83S, N84S, N86R, I87S, T92V, F94Y, T96A, V114T, M115L as compared to a rat VH sequence as shown in SEQ ID NO: 231. In some embodiments, the humanized MARCO antibody VH sequence comprises at least one of V2, A9, V11, A16, V20, R38, Q43, E46, Q62, K63, Q65, G66G, V68, T69, M70, T71, R72, D73, T76, A78, Y79, M80, E81, L82, S83, S84, R86, S87, V92, Y94, A96, T114, L115, numbering according to EU index.

[0347] In some embodiments, the humanized MARCO antibody VL sequence at least one of 9S, 15V, 17D, 18R, 20T, 22T, 24R, 40P, 43A, 45K, 70D, 72T, 73T, 76S, 77L, 82F, 84T, 86Y, 100Q, 106I, A9S, L15V, E17D, T18R, S20T, E22T, L24R, S40P, S43A, Q45K, R70D, S72T, K73T, D76S, M77L, E82F, D84T, F86Y, G100Q, L106I, as compared to a rat VL sequence as shown in SEQ ID NO: 236. In some embodiments, the humanized MARCO antibody VL sequence at least one of S9, V15, D17, R18, T20, T22, R24, P40, A43, K45, D70, T72, T73, S76, L77, F82, T84, Y86, Q100, or I106, numbering according to EU index.

[0348] In some embodiments, the humanized MARCO antibody VH sequence comprises at least one of 1E, 5Q, 13K, 16E, 48I, 61P, 62S, 67V, 68T, 76N, 79S, 82L, 83S, 85V, 86T, 87A, 88A, 92V, 116T, 117L, Q1E, K5Q, Q13K, Q16E, M48I, S61P, L62S, L67V, S68T, S76N, F79S, M82L, N83S, L85V, Q86T, T87A, E88A, T92V, V116T, or M117L, as compared to a rat VH sequence as shown in SEQ ID NO: 1. In some embodiments, the humanized MARCO antibody VH sequence comprises at least one of E1, Q5, K13, E16, I48, P61, S62, V67, T68, N76, S79, L82, S83, V85, T86, A87, A88, V92, T116, or L117, numbering according to EU index.

[0349] In some embodiments, the humanized MARCO antibody VL sequence comprises at least one of 9S, 13A, 15V, 17D, 18R, 20T, 22T, 24R, 40P, 43A, 45K, 56S, 70D, 71F, 72T, 74T, 77S, 78L, 92F, 94T, 96Y, 100Q, 9S, T13A, L15V, E17D, T18R, S20T, E22T, L24R, S40P, S43A, Q45K, D56S, R70D, Y71F, S72T, K74T, G77S, M78L, E92F, D94T, F96Y, or

S100Q, as compared to a rat VL sequence as shown in SEQ ID NO: 6. In some embodiments, the humanized MARCO antibody VL sequence comprises at least one of S9, T13, A13, D17, R18, T20, T22, L24, R24, N31, S31, Q31, A31, D31, P40, A43, S43, I43, K45, D56, S56, D70, Y71, F71, T72, T74, S77, L78, M78, F83, E83, T85, Y87, F87, F92, T94, S100, or Q100, numbering according to EU index.

[0350] In one embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen.

[0351] A "human antibody" is one which possesses an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or derived from a non-human source that utilizes a human antibody repertoire or human antibody-encoding sequences (e.g., obtained from human sources or designed *de novo*). Human antibodies specifically exclude humanized antibodies. In one embodiment, all of the variable and constant domains are derived from human immunoglobulin sequences (a fully human antibody). These antibodies may be prepared in a variety of ways including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes.

[0352] In some embodiments, the antibodies provided herein comprise an antibody fragment. In some embodiments, the antibodies provided herein consist of an antibody fragment. In some embodiments, the antibodies provided herein consist essentially of an antibody fragment. In some embodiments, the antibody fragment is an Fv fragment. In some embodiments, the antibody fragment is a Fab fragment. In some embodiments, the antibody fragment is a $F(ab')_2$ fragment. In some embodiments, the antibody fragment is a Fab' fragment. In some embodiments, the antibody fragment is an scFv (sFv) fragment. In some embodiments, the antibody fragment is an scFv-Fc fragment. In some embodiments, the antibody fragment is a fragment of a single domain antibody.

Sequences of MARCO Antibodies

[0353] **Table B** provides the names and SEQ ID NOs of exemplary anti-MARCO antibodies provided herein.

	Table B		SEQ ID NOs
Name	**Revised Name (if applicable)**	**Description**	
PI-HX-3031		parental rat hybridoma	1-10
PI-3010-AB	PI-3010	hIgG1/ chimeric PI-HX- 3031	11-20
PI-3011-AB	PI-3010.11	humanized PI-HX- 3031 / 3031-1 hIgG1	21-30
PI-3012-AB	PI-3010.12	humanized PI-HX- 3031 / 3031-2 hIgG1	31-40
PI-3013-AB	PI-3010.13	humanized PI-HX- 3031 / 3031-3 hIgG1	41-50
PI-3014-AB	PI-3010.14	humanized PI-HX- 3031 / 3031-4 hIgG1	51-60
PI-3015-AB	PI-3010.15	humanized PI-HX- 3031 / 3031-5 hIgG1	61-70
PI-3020-AB	PI-3010.20	chimeric PI-HX- 3031 - hIgG4	71-80
PI-3022-AB	PI-3010.22	humanized PI-HX- 3031 / 3031-2 hIgG1	81-90
PI-3023-AB	PI-3010.23	humanized PI-HX- 3031 / 3031-2 hIgG1	91-100
PI-3024-AB	PI-3010.24	humanized PI-HX- 3031 / 3031-2 hIgG1	101-110
PI-3025-AB	PI-3010.25	humanized PI-HX- 3031 / 3031-2 hIgG1	434-443
PI-3026-AB	PI-3010.26	humanized PI-HX- 3031 / 3031-2 hIgG1	121-130
PI-3027-AB	PI-3010.27	humanized PI-HX- 3031 / 3031-2 hIgG1	131-140
PI-3046-AB	PI-3010.46	humanized PI-HX- 3031 / 3031-2 hIgG4	474-483
PI-3048-AB	PI-3010.48	humanized PI-HX- 3031 / 3031-2 hIgG4	444-453
PI-HX-3061		parental rat hybridoma	141-150
PI-3016-AB		humanized PI-HX- 3061 / 3061-1 hIgG1	151-160
PI-3017-AB		humanized PI-HX- 3061 / 3061-2 hIgG1	161-170
PI-3018-AB		humanized PI-HX- 3061 / 3061-3 hIgG1	171-180
PI-3019-AB		PI-HX-3061 mIgG2a chimera	181-190
PI-3028-AB		PI-HX-3061 hIgG1 chimera	191-200
PI-3029-AB		PI-HX-3061 hIgG4 chimera	201-210
PI-3032-AB		humanized PI-HX- 3061 / 3061-2 hIgG1	211-220
PI-3033-AB		humanized PI-HX- 3061 / 3061-2 hIgG1	221-230
PI-HX-3011		parental rat hybridoma	231-240
PI-3030-AB	PI-3030	HX3011-h1 Chimera hIgG1	241-250
PI-3036-AB	PI-3030.36	humanized PI-HX- 3011 / 3011-1 hIgG1	311-320
PI-3037-AB	PI-3030.37	humanized PI-HX- 3011 / 3011-2 hIgG1	321-330
PI-3038-AB	PI-3030.38	humanized PI-HX- 3011 / 3011-3 hIgG1	331-340
PI-3039-AB	PI-3030.39	humanized PI-HX- 3011 / 3011-4 hIgG1	341-350
PI-3040-AB	PI-3030.40	humanized PI-HX- 3011 / 3011-5 hIgG1	351-360
PI-3041-AB	PI-3030.41	humanized PI-HX- 3011 / 3011-5 hIgG1	454-463
PI-3047-AB	PI-3030.47	humanized PI-HX- 3011 / 3011-5 hIgG4	464-473

PI-HX-3043		parental rat hybridoma	251-260
PI-3031-AB		HX3043-h1 Chimera hIgG1	261-270
PI-HX-3092		parental rat hybridoma	361-370
PI-3035		HX3092 (A mutation) - mIgG2a	371-380

CDRs

[0354] In some embodiments, an isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2), CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3), CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4), CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L) , CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

[0355] In some embodiments, CDR-L1 comprises the sequence LASEGISNDLA (SEQ ID NO: 7). In some embodiments, CDR-L1 comprises the sequence RASEGISNDLA (SEQ ID NO: 27). In some embodiments, CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431).

[0356] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 4, a CDR-H2 of SEQ ID NO: 3, a CDR-H1 of SEQ ID NO: 2, a CDR-L3 of SEQ ID NO: 9, a CDR-L2 of SEQ ID NO: 8, and a CDR-L1 of SEQ ID NO: 7. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 4, a CDR-H2 of SEQ ID NO: 3, a CDR-H1 of SEQ ID NO: 2, a CDR-L3 of SEQ ID NO: 9, a CDR-L2 of SEQ ID NO: 8, and a CDR-L1 of SEQ ID NO: 27. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 4, a CDR-H2 of SEQ ID NO: 3, a CDR-H1 of SEQ ID NO: 2, a CDR-L3 of SEQ ID NO: 9, a CDR-L2 of SEQ ID NO: 8, and a CDR-L1 of SEQ ID NO: 431. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 4, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 3, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 2, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95%

identity with a CDR-L3 of SEQ ID NO: 9, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 8, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 431, 383, 7, or 27. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 4, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 3, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 2, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 9, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 8, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 431, 383, 7, or 27 with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions.

[0357] In some embodiments, an isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence GYTFTDYAVN (SEQ ID NO: 232), CDR-H2 comprises the sequence WINTQTGKPT (SEQ ID NO: 233), CDR-H3 comprises the sequence DSYYYSSSLDY (SEQ ID NO: 234), CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432) or XASAGISNDLA (SEQ ID NO: 381), wherein X is leucine (L) or arginine (R), CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 238), and CDR-L3 comprises the sequence QQSYKYPWT (SEQ ID NO: 239). In some embodiments, CDR-L1 comprises the sequence LASAGISNDLA (SEQ ID NO: 237). In some embodiments, CDR-L1 comprises the sequence RASAGISNDLA (SEQ ID NO: 317). In some embodiments, CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432).

[0358] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 234, a CDR-H2 of SEQ ID NO: 233, a CDR-H1 of SEQ ID NO: 232, a CDR-L3 of SEQ ID NO: 239, a CDR-L2 of SEQ ID NO: 238, and a CDR-L1 of SEQ ID NO: 237. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 234, a CDR-H2 of SEQ ID NO: 233, a CDR-H1 of SEQ ID NO: 232, a CDR-L3 of SEQ ID NO: 319, a CDR-L2 of SEQ ID NO: 318, and a CDR-L1 of SEQ ID NO: 317. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 234, a CDR-H2 of SEQ ID NO: 233, a CDR-H1 of SEQ ID NO: 232, a CDR-L3 of SEQ ID NO: 239, a CDR-L2 of SEQ ID NO: 238, and a CDR-L1 of SEQ ID NO: 432. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity

with a CDR-H3 of SEQ ID NO: 234, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 233, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 232, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 239, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 238, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 432, 237, 317, or 381. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 234, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 233, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 232, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 239, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 238, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 432, 237, 317, or 381 with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions.

[0359] In some embodiments, an isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 363), comprises a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence GYTFTDYYLH (SEQ ID NO: 252), CDR-H2 comprises the sequence YINPNNAYTS (SEQ ID NO: 253), CDR-H3 comprises the sequence DTTDYYNLHFAY (SEQ ID NO: 254), CDR-L1 comprises the sequence LTSEGISNDLA (SEQ ID NO: 257), CDR-L2 comprises the sequence DASRLED (SEQ ID NO: 258), and CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 259).

[0360] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 254, a CDR-H2 of SEQ ID NO: 253, a CDR-H1 of SEQ ID NO: 252, a CDR-L3 of SEQ ID NO: 259, a CDR-L2 of SEQ ID NO: 258, and a CDR-L1 of SEQ ID NO: 257. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 254, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 253, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 252, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 259, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 258, and the CDR-L1 has at least about 50%, 75%, 80%, 85%,

90%, or 95% identity with a CDR-L1 of SEQ ID NO: 257. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 254, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 253, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 252, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 259, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 258, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 257, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions.

[0361] In some embodiments, an isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 363), comprises a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence KFTFSNYGMN (SEQ ID NO: 142), CDR-H2 comprises the sequence LIYYNSNNKY (SEQ ID NO: 143), CDR-H3 comprises the sequence SLTGGSDYFDS (SEQ ID NO: 144), CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433) or XASKSIGTFLA (SEQ ID NO: 382), wherein X is lysine (K) or arginine (R), CDR-L2 comprises the sequence SGSTLQS (SEQ ID NO: 148), and CDR-L3 comprises the sequence QQHDEYPFT (SEQ ID NO: 149).

[0362] In some embodiments, CDR-L1 comprises the sequence KASKSIGTFLA (SEQ ID NO: 147). In some embodiments, CDR-L1 comprises the sequence RASKSIGTFLA (SEQ ID NO: 157). In some embodiments, CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433).

[0363] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 144, a CDR-H2 of SEQ ID NO: 143, a CDR-H1 of SEQ ID NO: 142, a CDR-L3 of SEQ ID NO: 149, a CDR-L2 of SEQ ID NO: 148, and a CDR-L1 of SEQ ID NO: 147. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 144, a CDR-H2 of SEQ ID NO: 143, a CDR-H1 of SEQ ID NO: 142, a CDR-L3 of SEQ ID NO: 149, a CDR-L2 of SEQ ID NO: 148, and a CDR-L1 of SEQ ID NO: 157. In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 144, a CDR-H2 of SEQ ID NO: 143, a CDR-H1 of SEQ ID NO: 142, a CDR-L3 of SEQ ID NO: 149, a CDR-L2 of SEQ ID NO: 148, and a CDR-L1 of SEQ ID NO: 433. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 144, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 143, the CDR-H1 has at least about

50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 142, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 149, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 148, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 433, 382, 147, or 157. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 144, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 143, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 142, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 149, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 148, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 433, 382, 147, or 157 with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions.

[0364] In some embodiments, an isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence GFSLTSYTLS (SEQ ID NO: 362), CDR-H2 comprises the sequence AIWGGDNTD (SEQ ID NO: 363), CDR-H3 comprises the sequence ELGGSFDY (SEQ ID NO: 364), CDR-L1 comprises the sequence KTSQNINKKLD (SEQ ID NO: 367), CDR-L2 comprises the sequence YTNNLQT (SEQ ID NO: 368), and CDR-L3 comprises the sequence YQYDSGFT (SEQ ID NO: 369).

[0365] In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 364, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 363, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 362, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 369, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 368, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 367. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 364, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 363, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H1 is a CDR-H1 of SEQ ID NO: 362, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L3 is a CDR-L3 of SEQ ID NO: 369, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 368, with up

to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 367 with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions.

[0366] In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described herein are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0367] In some embodiments, an antibody provided herein comprises a CDR-H3 selected of SEQ ID NO: 4, 14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, 204, 214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 437, 447, 457, 467, or 477. In some aspects, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 4, 14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, 204, 214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 437, 447, 457, 467, or 477. In some embodiments, the CDR-H3 is a CDR-H3 selected of SEQ ID NO: 4, 14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, 204, 214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 437, 447, 457, 467, or 477, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0368] In some embodiments, an antibody provided herein comprises a CDR-H2 of SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 513, 163, 173, 183, 193, 203, 213, 223, 233, 243, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 376, 436, 446, 456, 466, or 476. In some aspects, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 513, 163, 173, 183, 193, 203, 213, 223, 233, 243, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 376, 436, 446, 456, 466, or 476. In some embodiments, the CDR-H2 is a CDR-H2 of SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 513, 163, 173, 183, 193, 203, 213, 223, 233, 243, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 376, 436, 446, 456, 466, or 476, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0369] In some embodiments, an antibody provided herein comprises a CDR-H1 of SEQ ID NO: 2, 12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, 202, 212, 222, 232, 242, 252, 262, 272, 282, 292, 302, 312, 322, 332, 342, 352, 362, 372, 435, 445, 455, 465, or 475. In some aspects, the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 2, 12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, 202, 212, 222, 232, 242, 252, 262, 272, 282, 292, 302, 312, 322, 332, 342, 352, 362, 372, 435, 445, 455, 465, or 475. In some embodiments, the CDR-H1 is a CDR-H1 of SEQ ID NO: 2, 12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, 202, 212, 222, 232, 242, 252, 262, 272, 282, 292, 302, 312, 322, 332, 342, 352, 362, 372 435, 445, 455, 465, or 475, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0370] In some embodiments, an antibody provided herein comprises a CDR-H3 of SEQ ID NO: 4, 14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, 204, 214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 437, 447, 457, 467, or 477, a CDR-H2 of SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 513, 163, 173, 183, 193, 203, 213, 223, 233, 243, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 376, 436, 446, 456, 466, or 476, and a CDR-H1 of SEQ ID NO: 2, 12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, 202, 212, 222, 232, 242, 252, 262, 272, 282, 292, 302, 312, 322, 332, 342, 352, 362, 372 435, 445, 455, 465, or 475. In some embodiments, the CDR-H3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H3 of SEQ ID NO: 4, 14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, 204, 214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 437, 447, 457, 467, or 477, the CDR-H2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H2 of SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 513, 163, 173, 183, 193, 203, 213, 223, 233, 243, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 376, 436, 446, 456, 466, or 476, and the CDR-H1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-H1 of SEQ ID NO: 2, 12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, 202, 212, 222, 232, 242, 252, 262, 272, 282, 292, 302, 312, 322, 332, 342, 352, 362, 372 435, 445, 455, 465, or 475. In some embodiments, the CDR-H3 is a CDR-H3 of SEQ ID NO: 4, 14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, 204, 214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 437, 447, 457, 467, or 477,

with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; the CDR-H2 is a CDR-H2 of SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 513, 163, 173, 183, 193, 203, 213, 223, 233, 243, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 376, 436, 446, 456, 466, or 476, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions; and the CDR-H1 is a CDR-H1 of SEQ ID NO: : 2, 12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, 202, 212, 222, 232, 242, 252, 262, 272, 282, 292, 302, 312, 322, 332, 342, 352, 362, 372 435, 445, 455, 465, or 475, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0371] In some embodiments, an antibody provided herein comprises a CDR-L3 of SEQ ID NO: 9, 19, 29, 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 139, 149, 159, 169, 179, 189, 199, 209, 219, 229, 239, 249, 259, 269, 279, 289, 299, 309, 319, 329, 339, 349, 359, 369, 379, 442, 452, 462, 472, or 482. In some aspects, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 9, 19, 29, 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 139, 149, 159, 169, 179, 189, 199, 209, 219, 229, 239, 249, 259, 269, 279, 289, 299, 309, 319, 329, 339, 349, 359, 369, 379, 442, 452, 462, 472, or 482. In some embodiments, the CDR-L3 is a CDR-L3 of SEQ ID NO: 9, 19, 29, 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 139, 149, 159, 169, 179, 189, 199, 209, 219, 229, 239, 249, 259, 269, 279, 289, 299, 309, 319, 329, 339, 349, 359, 369, 379, 442, 452, 462, 472, or 482, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0372] In some embodiments, an antibody provided herein comprises a CDR-L2 of SEQ ID NO: 8, 18, 28, 38, 48, 58, 68, 78, 88, 98, 108, 218, 228, 238, 248, 258, 268, 278, 288, 298, 308, 318, 328, 338, 348, 358, 368, 378, 441, 451, 461, 471, or 481. In some aspects, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 8, 18, 28, 38, 48, 58, 68, 78, 88, 98, 108, 218, 228, 238, 248, 258, 268, 278, 288, 298, 308, 318, 328, 338, 348, 358, 368, 378, 441, 451, 461, 471, or 481. In some embodiments, the CDR-L2 is a CDR-L2 of SEQ ID NO: 8, 18, 28, 38, 48, 58, 68, 78, 88, 98, 108, 218, 228, 238, 248, 258, 268, 278, 288, 298, 308, 318, 328, 338, 348, 358, 368, 378, 441, 451, 461, 471, or 481, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0373] In some embodiments, an antibody provided herein comprises a CDR-L1 of SEQ ID NO: 7, 17, 27, 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 137, 147, 157, 167, 177, 187, 197, 207, 217, 227, 237, 247, 257, 267, 277, 287, 297, 307, 317, 327, 337, 347, 357, 367, 377,

381, 382, 383, 440, 450, 460, 470, or 480. In some aspects, the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 7, 17, 27, 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 137, 147, 157, 167, 177, 187, 197, 207, 217, 227, 237, 247, 257, 267, 277, 287, 297, 307, 317, 327, 337, 347, 357, 367, 377, 381, 382, or 383, 440, 450, 460, 470, or 480. In some embodiments, the CDR-L1 is a CDR-L1 of SEQ ID NO: 7, 17, 27, 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 137, 147, 157, 167, 177, 187, 197, 207, 217, 227, 237, 247, 257, 267, 277, 287, 297, 307, 317, 327, 337, 347, 357, 367, 377, 381, 382, 383, 440, 450, 460, 470, or 480, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions.

[0374] In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, an antibody provided herein comprises a CDR-L3 of SEQ ID NO: 9, 19, 29, 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 139, 149, 159, 169, 179, 189, 199, 209, 219, 229, 239, 249, 259, 269, 279, 289, 299, 309, 319, 329, 339, 349, 359, 369, 379, 442, 452, 462, 472, or 482, and a CDR-L2 of SEQ ID NO8, 18, 28, 38, 48, 58, 68, 78, 88, 98, 108, 218, 228, 238, 248, 258, 268, 278, 288, 298, 308, 318, 328, 338, 348, 358, 368, 378, 441, 451, 461, 471, or 481. In some embodiments, an antibody provided herein comprises a CDR-L3 of SEQ ID NO: 9, 19, 29, 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 139, 149, 159, 169, 179, 189, 199, 209, 219, 229, 239, 249, 259, 269, 279, 289, 299, 309, 319, 329, 339, 349, 359, 369, 379, 442, 452, 462, 472, or 482, a CDR-L2 of SEQ ID NO: 8, 18, 28, 38, 48, 58, 68, 78, 88, 98, 108, 218, 228, 238, 248, 258, 268, 278, 288, 298, 308, 318, 328, 338, 348, 358, 368, 378, 441, 451, 461, 471, or 481, and a CDR-L1 of SEQ ID NO: 77, 17, 27, 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 137, 147, 157, 167, 177, 187, 197, 207, 217, 227, 237, 247, 257, 267, 277, 287, 297, 307, 317, 327, 337, 347, 357, 367, 377, 381, 382, or 383, 440, 450, 460, 470, or 480. In some embodiments, the CDR-L3 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L3 of SEQ ID NO: 9, 19, 29, 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 139, 149, 159, 169, 179, 189, 199, 209, 219, 229, 239, 249, 259, 269, 279, 289, 299, 309, 319, 329, 339, 349, 359, 369, 379, 442, 452, 462, 472, or 482, the CDR-L2 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L2 of SEQ ID NO: 8, 18, 28, 38, 48, 58, 68, 78, 88, 98, 108, 218, 228, 238, 248, 258, 268, 278, 288, 298, 308, 318, 328, 338, 348, 358, 368, 378, 441, 451, 461, 471, or 481, and the CDR-L1 has at least about 50%, 75%, 80%, 85%, 90%, or 95% identity with a CDR-L1 of SEQ ID NO: 7, 17, 27, 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 137, 147, 157, 167, 177, 187, 197, 207, 217, 227, 237, 247, 257, 267, 277, 287, 297, 307, 317, 327, 337, 347, 357, 367, 377, 381, 382, 383, 440, 450, 460, 470, or 480. In some embodiments, the CDR-L3 is a CDR-L3 of SEQ ID NO: 9, 19, 29, 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 139, 149, 159, 169, 179,

189, 199, 209, 219, 229, 239, 249, 259, 269, 279, 289, 299, 309, 319, 329, 339, 349, 359, 369, 379, 442, 452, 462, 472, or 482, with up to 1, 2, 3, 4, or 5 amino acid substitutions; the CDR-L2 is a CDR-L2 of SEQ ID NO: 8, 18, 28, 38, 48, 58, 68, 78, 88, 98, 108, 218, 228, 238, 248, 258, 268, 278, 288, 298, 308, 318, 328, 338, 348, 358, 368, 378, 441, 451, 461, 471, or 481, with up to 1, 2, 3, or 4 amino acid substitutions; and the CDR-L1 is a CDR-L1 of SEQ ID NO: 7, 17, 27, 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 137, 147, 157, 167, 177, 187, 197, 207, 217, 227, 237, 247, 257, 267, 277, 287, 297, 307, 317, 327, 337, 347, 357, 367, 377, 381, 382, 383, 440, 450, 460, 470, or 480, with up to 1, 2, 3, 4, 5, or 6 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions.

[0375] In some embodiments, an antibody provided herein comprises one to three CDRs of a V_H domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474. In some embodiments, an antibody provided herein comprises two to three CDRs of a V_H domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474. In some embodiments, an antibody provided herein comprises three CDRs of a VH domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

[0376] In some embodiments, the CDR-H1 is a CDR-H1 of a VH domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some embodiments, the CDR-H2 is a CDR-H2 of a VH domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some embodiments, the CDR-H3 is a CDR-H3 of a VH domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211,

221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474, with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated de novo according to the methods provided herein for obtaining antibodies.

[0377] In some embodiments, an antibody provided herein comprises one to three CDRs of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 434, 444, 454, 464, or 474. In some embodiments, an antibody provided herein comprises two to three CDRs of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 434, 444, 454, 464, or 474. In some embodiments, an antibody provided herein comprises three CDRs of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 434, 444, 454, 464, or 474. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

[0378] In some embodiments, the CDR-L1 is a CDR-L1 of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 434, 444, 454, 464, or 474, with up to 1, 2, 3, 4, or 5 amino acid substitutions. In some embodiments, the CDR-L2 is a CDR-L2 of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, or 376 with up to 1, 2, 3, 4, 5, 6, 7, or 8 amino acid substitutions. In some embodiments, the CDR-L3 is a CDR-L3 of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 434, 444, 454, 464, or 474 with up to 1, 2, 3, 4,

5, 6, 7, or 8 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated de novo according to the methods provided herein for obtaining antibodies.

[0379] In some embodiments, an antibody provided herein comprises one to three CDRs of a VH domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474, and one to three CDRs of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 434, 444, 454, 464, or 474. In some embodiments, an antibody provided herein comprises two to three CDRs of a VH domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474, and two to three CDRs of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 434, 444, 454, 464, or 474. In some embodiments, an antibody provided herein comprises three CDRs of a VH domain selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474, and three CDRs of a VL domain selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 434, 444, 454, 464, or 474. In some aspects, the CDRs are Kabat CDRs. In some aspects, the CDRs are Chothia CDRs. In some aspects, the CDRs are AbM CDRs. In some aspects, the CDRs are Contact CDRs. In some aspects, the CDRs are IMGT CDRs.

V_H Domains

[0380] In some embodiments, an antibody or antigen binding fragment thereof provided herein comprises a V_H sequence selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 1. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 121. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 181. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 191. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 221. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 241. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 261. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 351. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 371. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 434. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 444. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 454. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 464. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 474.

[0381] In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 1, wherein any variation from SEQ ID NO: 1 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 21, wherein any variation from SEQ ID NO: 21 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 121, wherein any variation from SEQ ID NO: 121 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 181, wherein any variation from SEQ ID NO: 181 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 191, wherein any variation from SEQ ID NO: 191 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or

90% identity with SEQ ID NO: 221, wherein any variation from SEQ ID NO: 221 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 241, wherein any variation from SEQ ID NO: 241 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 261, wherein any variation from SEQ ID NO: 261 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 351, wherein any variation from SEQ ID NO: 351 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 371, wherein any variation from SEQ ID NO: 371 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 434, wherein any variation from SEQ ID NO: 434 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 444, wherein any variation from SEQ ID NO: 444 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 454, wherein any variation from SEQ ID NO: 454 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 464, wherein any variation from SEQ ID NO: 464 does not occur within CDR-H1, CDR-H2, or CDR-H3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 474, wherein any variation from SEQ ID NO: 474 does not occur within CDR-H1, CDR-H2, or CDR-H3.

[0382] In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 1. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 21. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 121. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 181. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 191. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 221. In some embodiments, an antibody provided herein comprises a

V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 241. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 261. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 351. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 371. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 434. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 444. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 454. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 464. In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 474.

[0383] In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474. In some embodiments, an antibody provided herein comprises a V_H sequence provided in SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0384] In some embodiments, an antibody or antigen binding fragment as described herein is encoded by the polynucleotide sequence as shown in any one of SEQ ID NOs: 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, or 426.

V_L Domains

[0385] In some embodiments, an antibody or antigen binding fragment thereof provided herein comprises a V_L sequence selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 439, 449, 459, 469, or 479. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 6. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 26. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 126. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 186. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 196. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 226. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 246. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 266. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 356. In some embodiments, an antibody provided herein comprises a V_L sequence of SEQ ID NO: 376.

[0386] In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 6, wherein any variation from SEQ ID NO: 6 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 26, wherein any variation from SEQ ID NO: 26 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 126, wherein any variation from SEQ ID NO: 126 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 186, wherein any variation from SEQ ID NO: 186 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 196, wherein any variation from SEQ ID NO: 196 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90%

identity with SEQ ID NO: 226, wherein any variation from SEQ ID NO: 226 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 246, wherein any variation from SEQ ID NO: 246 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 266, wherein any variation from SEQ ID NO: 266 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 356, wherein any variation from SEQ ID NO: 356 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 376, wherein any variation from SEQ ID NO: 376 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 439, wherein any variation from SEQ ID NO: 439 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 449, wherein any variation from SEQ ID NO: 449 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 459, wherein any variation from SEQ ID NO: 459 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 469, wherein any variation from SEQ ID NO: 469 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_L sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 479, wherein any variation from SEQ ID NO: 479 does not occur within CDR-L1, CDR-L2, or CDR-L3.

[0387] In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 6. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 26. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 126. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 186. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 196. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 226. In some embodiments, an antibody provided herein comprises a

V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 246. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 266. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to SEQ ID NO: 356. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to V_L sequence of SEQ ID NO: 376. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to V_L sequence of SEQ ID NO: 439. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to V_L sequence of SEQ ID NO: 449. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to V_L sequence of SEQ ID NO: 459. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to V_L sequence of SEQ ID NO: 469. In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to V_L sequence of SEQ ID NO: 479.

[0388] In some embodiments, an antibody provided herein comprises a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_L sequence provided in SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 439, 449, 459, 469, or 479. In some embodiments, an antibody provided herein comprises a V_L sequence provided in SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 439, 449, 459, 469, or 479, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

V_H-V_L Combinations

[0389] In some embodiments, an antibody or antigen binding fragment thereof provided herein comprises a V_H sequence selected from SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474; and a V_L sequence selected from SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 439, 449, 459, 469, or 479.

[0390] In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 1 and a V_L sequence of SEQ ID NO: 6. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 21 and a V_L sequence of SEQ ID NO: 26. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 121 and V_L sequence of SEQ ID NO: 126. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 181 and a V_L sequence of SEQ ID NO: 186. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 191 and a V_L sequence of SEQ ID NO: 196. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 221 and a V_L sequence of SEQ ID NO: 226. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 241 and a V_L sequence of SEQ ID NO: 246. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 261 and a V_L sequence of SEQ ID NO: 266 In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 351 and a V_L sequence of SEQ ID NO: 356. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 371 and a V_L sequence of SEQ ID NO: 376. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 434 and a V_L sequence of SEQ ID NO: 439. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 444 and a V_L sequence of SEQ ID NO: 449. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 454 and a V_L sequence of SEQ ID NO: 459. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 464 and a V_L sequence of SEQ ID NO: 469. In some embodiments, an antibody provided herein comprises a V_H sequence of SEQ ID NO: 474 and a V_L sequence of SEQ ID NO: 479.

[0391] In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 1 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 6, wherein any variation from SEQ ID NO: 1 does not occur

within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 6 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 21 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 26, wherein any variation from SEQ ID NO: 21 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 26 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 121 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 126, wherein any variation from SEQ ID NO: 121 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 126 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 181 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 186, wherein any variation from SEQ ID NO: 181 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 186 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 191 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 196, wherein any variation from SEQ ID NO: 191 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 196 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 221 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 226, wherein any variation from SEQ ID NO: 221 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 226 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 241 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 246, wherein any variation from SEQ ID NO: 241 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 246 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 261 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 266, wherein any variation from SEQ ID NO: 261 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 266 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the

V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 351 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 356, wherein any variation from SEQ ID NO: 351 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 356 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 371 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 376, wherein any variation from SEQ ID NO: 371 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 376 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 434 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 439, wherein any variation from SEQ ID NO: 434 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 439 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 444 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 449, wherein any variation from SEQ ID NO: 444 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 449 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 454 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 459, wherein any variation from SEQ ID NO: 454 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 459 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 464 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 469, wherein any variation from SEQ ID NO: 464 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 469 does not occur within CDR-L1, CDR-L2, or CDR-L3. In some embodiments, the V_H sequence has at least 70%, 80%, or 90% identity with SEQ ID NO: 474 and wherein the variable region of the light chain has at least 70%, 80%, or 90% identity with SEQ ID NO: 479, wherein any variation from SEQ ID NO: 474 does not occur within CDR-H1, CDR-H2, or CDR-H3 and wherein any variation from SEQ ID NO: 479 does not occur within CDR-L1, CDR-L2, or CDR-L3.

[0392] In certain aspects, any of SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291,

301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474can be combined with any of SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 439, 449, 459, 469, or 479. For example, SEQ ID NO: 11 can be combined with any of SEQ ID NO: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 439, 449, 459, 469, or 479. As another example, SEQ ID NO: 16 can be combined with any of SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474.

[0393] In some embodiments, an antibody provided herein comprises a V_H sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, or 371; and a V_L sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative VL sequence provided in SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 439, 449, 459, 469, or 479. In some embodiments, an antibody provided herein comprises a VH sequence provided in SEQ ID NOs: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, 341, 351, 361, 371, 434, 444, 454, 464, or 474with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions, and a VL sequence provided in SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 256, 266, 276, 286, 296, 306, 316, 326, 336, 346, 356, 366, 376, 439, 449, 459, 469, or 479, with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions. In some aspects, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the antibodies described in this paragraph are referred to herein as "variants." In some embodiments, such variants are derived from a sequence provided herein, for example, by affinity maturation, site directed mutagenesis, random mutagenesis, or any other method known in the art or described herein. In some embodiments, such variants are not derived from a sequence provided herein and may, for example, be isolated *de novo* according to the methods provided herein for obtaining antibodies.

[0394] In some embodiments, the percent homology of the variable heavy or variable light chain is to be calculated outside the CDRs. For instance, the percent homology can be calculated in the framework regions

[0395] In some embodiments, an antibody or antigen binding fragment thereof comprises a heavy chain provided in SEQ ID NOs: 5, 15, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, 155, 165, 175, 185, 195, 205, 215, 225, 235, 245, 255, 265, 275, 285, 295, 305, 315, 325, 335, 345, 355, 365, 375, 438, 448, 458, 468 or 478.

[0396] In some embodiments, an antibody or antigen binding fragment thereof comprises a light chain provided in SEQ ID NOs: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 210, 220, 230, 240, 250, 260, 270, 280, 290, 310, 320, 330, 340, 350, 360, 370, 380, 443, 453, 463, 473, or 483.

[0397] In certain aspects, any of SEQ ID NOs: 5, 15, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, 155, 165, 175, 185, 195, 205, 215, 225, 235, 245, 255, 265, 275, 285, 295, 305, 315, 325, 335, 345, 355, 365, 375, 438, 448, 458, 468 or 478can be combined with any of SEQ ID NOs: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 210, 220, 230, 240, 250, 260, 270, 280, 290, 310, 320, 330, 340, 350, 360, 370, 380, 443, 453, 463, 473, or 483.

[0398] In some embodiments, an antibody provided herein comprises a heavy chain sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative V_H sequence provided in SEQ ID NOs: 5, 15, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, 155, 165, 175, 185, 195, 205, 215, 225, 235, 245, 255, 265, 275, 285, 295, 305, 315, 325, 335, 345, 355, 365, 375, 438, 448, 458, 468 or 478; and a light chain sequence having at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% identity to an illustrative VL sequence provided in SEQ ID NOs10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 210, 220, 230, 240, 250, 260, 270, 280, 290, 310, 320, 330, 340, 350, 360, 370, 380, 443, 453, 463, 473, or 483. In some embodiments, an antibody provided herein comprises a heavy chain sequence provided in SEQ ID NOs: : 5, 15, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, 155, 165, 175, 185, 195, 205, 215, 225, 235, 245, 255, 265, 275, 285, 295, 305, 315, 325, 335, 345, 355, 365, 375, 438, 448, 458, 468 or 478with up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions, and a light chain sequence provided in SEQ ID NOs: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 210, 220, 230, 240, 250, 260, 270, 280, 290, 310, 320, 330, 340, 350, 360, 370, 380, 443, 453, 463, 473, or 483, with up to 1, 2,

3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid substitutions.

[0399] In some embodiments, an antibody or antigen binding fragment polynucleotide sequence comprises a signal sequence as shown in SEQ ID NOs: 427 or 430. In some embodiments, an antibody or antigen binding fragment polypeptide sequence comprises a signal sequence as shown in SEQ ID NOs: 428 or 429.

Fc region

[0400] The term "Fc domain" or "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991. An "Fc polypeptide" of a dimeric Fc as used herein refers to one of the two polypeptides forming the dimeric Fc domain, i.e. a polypeptide comprising C-terminal constant regions of an immunoglobulin heavy chain, capable of stable self-association. For example, an Fc polypeptide of a dimeric IgG Fc comprises an IgG CH2 and an IgG CH3 constant domain sequence. An Fc can be of the class IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2.

[0401] The terms “Fc receptor” and “FcR” are used to describe a receptor that binds to the Fc region of an antibody. For example, an FcR can be a native sequence human FcR. Generally, an FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an “activating receptor”) and FcγRIIB (an “inhibiting receptor”), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Immunoglobulins of other isotypes can also be bound by certain FcRs (see, e.g., Janeway et al., Immuno Biology: the immune system in health and disease, (Elsevier Science Ltd., NY) (4th ed., 1999)). Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain (reviewed in Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol 9:457-92 (1991);

Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976); and Kim et al., J. Immunol. 24:249 (1994)).

[0402] In some embodiments, an antibody is an IgG1 antibody.

[0403] In some embodiments, an antibody is an IgG3 antibody.

[0404] In some embodiments, an antibody is an IgG2 antibody.

[0405] In some embodiments, an antibody is an IgG4 antibody.

[0406] Modifications in the CH2 domain can affect the binding of FcRs to the Fc. A number of amino acid modifications in the Fc region are known in the art for selectively altering the affinity of the Fc for different Fc-gamma (Fcγ) receptors. In one embodiment, the Fc comprises one or more modifications to promote selective binding of Fc-gamma receptors.

[0407] In some embodiments an antibody described herein includes modifications to improve its ability to mediate effector function. Such modifications are known in the art and include afucosylation, or engineering of the affinity of the Fc towards an activating receptor, mainly FCGR3a for ADCC, and towards C1q for CDC.

[0408] In certain embodiments, an antibody provided herein comprises an Fc region with one or more amino acid substitutions which improve ADCC.

[0409] In some embodiments, an antibody provided herein comprises one or more alterations that improves or diminishes C1q binding and/or CDC. *See* U.S. Pat. No. 6,194,551; WO 99/51642; and Idusogie et al., *J. Immunol.*, 2000, 164:4178-4184; each of which is incorporated by reference in its entirety.

[0410] Thus, in one embodiment, an antibody described herein can include a dimeric Fc that comprises one or more amino acid modifications that confer improved effector function. In another embodiment, the antibody can be afucosylated to improve effector function.

[0411] Fc modifications reducing FcγR and/or complement binding and/or effector function are known in the art. Recent publications describe strategies that have been used to engineer antibodies with reduced or silenced effector activity (see Strohl, WR (2009), Curr Opin Biotech 20:685-691, and Strohl, WR and Strohl LM, "Antibody Fc engineering for optimal antibody performance" In Therapeutic Antibody Engineering, Cambridge: Woodhead Publishing (2012), pp 225-249). These strategies include reduction of effector function through modification of glycosylation, use of IgG2/IgG4 scaffolds, or the introduction of

mutations in the hinge or CH2 regions of the Fc. For example, US Patent Publication No. 2011/0212087 (Strohl), International Patent Publication No. WO 2006/105338 (Xencor), US Patent Publication No. 2012/0225058 (Xencor), US Patent Publication No. 2012/0251531 (Genentech), and Strop et al ((2012) J. Mol. Biol. 420: 204-219) describe specific modifications to reduce FcγR or complement binding to the Fc.

[0412] Methods of producing antibodies with little or no fucose on the Fc glycosylation site (Asn 297 EU numbering) without altering the amino acid sequence are well known in the art. The GlymaxX® technology (ProBioGen AG) is based on the introduction of a gene for an enzyme which deflects the cellular pathway of fucose biosynthesis into cells used for antibody production. This prevents the addition of the sugar "fucose" to the N-linked antibody carbohydrate part by antibody-producing cells. (von Horsten et al. (2010) Glycobiology. 2010 Dec; 20 (12):1607-18.) Examples of cell lines capable of producing defucosylated antibody include CHO-DG44 with stable overexpression of the bacterial oxidoreductase GDP-6-deoxy-D-lyxo-4-hexylose reductase (RMD) (see Henning von Horsten et al., Glycobiol 2010, 20:1607-1618) or Lec13 CHO cells, which are deficient in protein fucosylation (see Ripka et al., Arch. Biochem. Biophys., 1986, 249:533-545; U.S. Pat. Pub. No. 2003/0157108; WO 2004/056312; each of which is incorporated by reference in its entirety), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene or FUT8 knockout CHO cells (see Yamane-Ohnuki et al., Biotech. Bioeng., 2004, 87: 614-622; Kanda et al., Biotechnol. Bioeng., 2006, 94:680-688; and WO 2003/085107; each of which is incorporated by reference in its entirety). Another approach to obtaining antibodies with lowered levels of fucosylation can be found in U.S. patent 8,409,572, which teaches selecting cell lines for antibody production for their ability to yield lower levels of fucosylation on antibodies.

[0413] Examples of cell lines capable of producing defucosylated antibody include CHO-DG44 with stable overexpression of the bacterial oxidoreductase GDP-6-deoxy-D-lyxo-4-hexylose reductase (RMD) (see Henning von Horsten et al., Glycobiol 2010, 20:1607-1618) or Lec13 CHO cells, which are deficient in protein fucosylation (see Ripka et al., Arch. Biochem. Biophys., 1986, 249:533-545; U.S. Pat. Pub. No. 2003/0157108; WO 2004/056312; each of which is incorporated by reference in its entirety), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene or FUT8 knockout CHO cells (see Yamane-Ohnuki et al., Biotech. Bioeng., 2004, 87: 614-622; Kanda et al., Biotechnol. Bioeng., 2006,

94:680-688; and WO 2003/085107; each of which is incorporated by reference in its entirety).

[0414] Antibodies can be fully afucosylated (meaning they contain no detectable fucose) or they can be partially afucosylated, meaning that the isolated antibody contains less than 95%, less than 85%, less than 75%, less than 65%, less than 55%, less than 45%, less than 35%, less than 25%, less than 15% or less than 5% of the amount of fucose normally detected for a similar antibody produced by a mammalian expression system.

[0415] In some aspects, an antibody provided herein comprises an IgG1 domain with reduced fucose content at position Asn 297 compared to a naturally occurring IgG1 domain. Such Fc domains are known to have improved ADCC. *See* Shields et al., *J. Biol. Chem.*, 2002, 277:26733-26740, incorporated by reference in its entirety. In some aspects, such antibodies do not comprise any fucose at position Asn 297. The amount of fucose may be determined using any suitable method, for example as described in WO 2008/077546, incorporated by reference in its entirety.

[0416] In some embodiments, an antibody provided herein comprises a bisected oligosaccharide, such as a biantennary oligosaccharide attached to the Fc region of the antibody that is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, for example, in WO 2003/011878; U.S. Pat. No. 6,602,684; and U.S. Pat. Pub. No. 2005/0123546; each of which is incorporated by reference in its entirety.

[0417] Other illustrative glycosylation variants which may be incorporated into the antibodies provided herein are described, for example, in U.S. Pat. Pub. Nos. 2003/0157108, 2004/0093621, 2003/0157108, 2003/0115614, 2002/0164328, 2004/0093621, 2004/0132140, 2004/0110704, 2004/0110282, 2004/0109865; International Pat. Pub. Nos. 2000/61739, 2001/29246, 2003/085119, 2003/084570, 2005/035586, 2005/035778; 2005/053742, 2002/031140; Okazaki et al., *J. Mol. Biol.*, 2004, 336:1239-1249; and Yamane-Ohnuki et al., *Biotech. Bioeng.*, 2004, 87: 614-622; each of which is incorporated by reference in its entirety.

[0418] In some embodiments, an antibody provided herein comprises an Fc region with at least one galactose residue in the oligosaccharide attached to the Fc region. Such antibody variants may have improved CDC function. Examples of such antibody variants are described, for example, in WO 1997/30087; WO 1998/58964; and WO 1999/22764; each of which his incorporated by reference in its entirety.

[0419] Examples of cell lines capable of producing defucosylated antibodies include CHO-DG44 with stable overexpression of the bacterial oxidoreductase GDP-6-deoxy-D-lyxo-4-hexylose reductase (RMD) (*see* Henning von Horsten et al., Glycobiol 2010, 20:1607-1618) or Lec13 CHO cells, which are deficient in protein fucosylation (*see* Ripka et al., *Arch. Biochem. Biophys.*, 1986, 249:533-545; U.S. Pat. Pub. No. 2003/0157108; WO 2004/056312; each of which is incorporated by reference in its entirety), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene or FUT8 knockout CHO cells (*see* Yamane-Ohnuki et al., *Biotech. Bioeng.*, 2004, 87: 614-622; Kanda et al., *Biotechnol. Bioeng.*, 2006, 94:680-688; and WO 2003/085107; each of which is incorporated by reference in its entirety).

[0420] In some embodiments, an antibody has antibody-dependent cellular phagocytosis (ADCP) activity. ADCP can occur when antibodies bind to antigens on the surface of pathogenic or tumorigenic target-cells. Phagocytic cells bearing Fc receptors on their cell surface, including monocytes and macrophages, recognize and bind the Fc region of antibodies bound to target-cells. Upon binding of the Fc receptor to the antibody-bound target cell, phagocytosis of the target cell can be initiated. ADCP can be considered a form of ADCC.

[0421] In some embodiments, the antibodies are capable of forming an immune complex. For example, an immune complex can be a tumor cell covered by antibodies.

[0422] In some aspects, an anti-MARCO antibody does not substantially bind myeloid cells present outside of cancer tissue. In some aspects, an anti-MARCO antibody does not substantially bind stimulatory myeloid cells present in cancer tissue.

[0423] In some embodiments the antibodies are monoclonal antibodies.

[0424] In some embodiments the antibodies are polyclonal antibodies.

[0425] In some embodiments the antibodies are produced by hybridomas. In other embodiments, the antibodies are produced by recombinant cells engineered to express the desired variable and constant domains.

[0426] In some embodiments the antibodies may be single chain antibodies or other antibody derivatives retaining the antigen specificity and the lower hinge region or a variant thereof.

[0427] In some embodiments the antibodies may be polyfunctional antibodies, recombinant antibodies, human antibodies, humanized antibodies, fragments or variants thereof. In particular embodiments, the antibody fragment or a derivative thereof is selected from a Fab fragment, a Fab'2 fragment, a CDR and ScFv.

[0428] In some embodiments, antibodies are specific for surface antigens, such as MARCO protein. In some embodiments, therapeutic antibodies are specific for tumor antigens (e.g.,

molecules specifically expressed by tumor cells). In particular embodiments, the therapeutic antibodies may have human or non-human primate IgG1 or IgG3 Fc portions.

Binding

[0429] With regard to the binding of an antibody to a target molecule, the terms "bind," "specific binding," "specifically binds to," "specific for," "selectively binds," and "selective for" a particular antigen (e.g., a polypeptide target) or an epitope on a particular antigen mean binding that is measurably different from a non-specific or non-selective interaction (e.g., with a non-target molecule). Specific binding can be measured, for example, by measuring binding to a target molecule and comparing it to binding to a non-target molecule. Specific binding can also be determined by competition with a control molecule that mimics the epitope recognized on the target molecule. In that case, specific binding is indicated if the binding of the antibody to the target molecule is competitively inhibited by the control molecule. Crosslinking of an antigen target is a type of binding. In some embodiments, an anti-MARCO antibody crosslinks MARCO to MARCO on a MARCO+ cell.

[0430] "Affinity" refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen or epitope). Unless indicated otherwise, as used herein, "affinity" refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen or epitope). The affinity of a molecule X for its partner Y can be represented by the dissociation equilibrium constant (K_D). The kinetic components that contribute to the dissociation equilibrium constant are described in more detail below. Affinity can be measured by common methods known in the art, including those described herein, such as surface plasmon resonance (SPR) technology (e.g., BIACORE®) or biolayer interferometry (e.g., FORTEBIO®).

[0431] The term "k_d" (sec^{-1}), as used herein, refers to the dissociation rate constant of a particular antibody - antigen interaction. This value is also referred to as the k_{off} value.

[0432] The term "k_a" ($M^{-1} \times sec^{-1}$), as used herein, refers to the association rate constant of a particular antibody -antigen interaction. This value is also referred to as the k_{on} value.

[0433] The term "K_D" (M), as used herein, refers to the dissociation equilibrium constant of a particular antibody -antigen interaction. $K_D = k_d/k_a$. In some embodiments, the affinity of an antibody is described in terms of the K_D for an interaction between such antibody and its antigen. For clarity, as known in the art, a smaller K_D value indicates a higher affinity interaction, while a larger K_D value indicates a lower affinity interaction.

[0434] The term "K_A" (M^{-1}), as used herein, refers to the association equilibrium constant of a particular antibody-antigen interaction. $K_A = k_a/k_d$.

[0435] When used herein in the context of two or more antibodies, the term "competes with" or "cross-competes with" indicates that the two or more antibodies compete for binding to an antigen (e.g., MARCO). In one exemplary assay, MARCO is coated on a surface and contacted with a first MARCO antibody, after which a second MARCO antibody is added. In another exemplary assay, a first MARCO antibody is coated on a surface and contacted with MARCO, and then a second MARCO antibody is added. If the presence of the first MARCO antibody reduces binding of the second MARCO antibody, in either assay, then the antibodies compete with each other. The term "competes with" also includes combinations of antibodies where one antibody reduces binding of another antibody, but where no competition is observed when the antibodies are added in the reverse order. However, in some embodiments, the first and second antibodies inhibit binding of each other, regardless of the order in which they are added. In some embodiments, one antibody reduces binding of another antibody to its antigen by at least 25%, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, or at least 95%. A skilled artisan can select the concentrations of the antibodies used in the competition assays based on the affinities of the antibodies for MARCO and the valency of the antibodies. The assays described in this definition are illustrative, and a skilled artisan can utilize any suitable assay to determine if antibodies compete with each other. Suitable assays are described, for example, in Cox et al., "Immunoassay Methods," in *Assay Guidance Manual [Internet]*, Updated December 24, 2014 (ncbi.nlm.nih.gov/books/NBK92434/; accessed September 29, 2015); Silman et al., *Cytometry*, 2001, 44:30-37; and Finco et al., *J. Pharm. Biomed. Anal.*, 2011, 54:351-358; each of which is incorporated by reference in its entirety.

[0436] In some embodiments, an antibody provided herein binds human MARCO. In some embodiments, an antibody provided herein binds mouse MARCO. In some embodiments, an antibody provided herein binds rhesus macaque MARCO. In some embodiments, an antibody provided herein binds cynomolgus MARCO. In some embodiments, an antibody provided herein binds human, rhesus macaque, and/or cynomolgus MARCO.

[0437] In some embodiments, an antibody provided herein binds human MARCO with a K_D of less than or equal to about 0.001, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.95, 2, 3, 4, 5, 6, 7, 8, 9, or 10×10^{-9} M , as measured by Biacore assay. In some embodiments, the K_D of the

antibody provided herein is between about 0.001-0.01, 0.01-0.1, 0.01-0.05, 0.05-0.1, 0.1-0.5, 0.5-1, 0.25-0.75, 0.25-0.5, 0.5-0.75, 0.75-1, 0.75-2, 1.1-1.2, 1.2-1.3, 1.3-1.4, 1.4-1.5, 1.5-1.6, 1.6-1.7, 1.7-1.8, 1.8-1.9, 1.9-2, 1-2, 1-5, 2-7, 3-8, 3-5, 4-6, 5-7, 6-8, 7-9, 7-10, or 5-10x10^{-9} M, as measured by Biacore assay.

[0438] In some embodiments, the antibody provided herein binds human MARCO with a K_D of less than or equal to about 2, 1.98, 1.95, 1.9, 1.85, 1.8, 1.75, 1.7, 1.65, 1.6, 1.55, 1.50, 1.45, or 1.4 x10^{-9} M, or less, as measured by Biacore assay. In some embodiments, the antibody provided herein binds human MARCO with a K_D between 1.9-1.8, 1.8-1.7, 1.7-1.6, 1.6-1.5, or 1.9-1.5x10^{-9} M as measured by Biacore assay. In some embodiments, the antibody provided herein binds human MARCO with a K_d of less than or equal to about 10, 9.56, 9.5, 9.0, 8.88, 8.84, 8.5, 8, 7.5, 7.32, 7, 6.5, 6, 5.5, 5, 4.5, 4, 3.5, 3, 2.5, 2, 1.5, or 1x10^{-4} (1/s), or less, as measured by Biacore assay. In some embodiments, the antibody provided herein binds human MARCO with a K_d between 7-10, 7-8, 8-9, 9-10, 7-7.5, 7.5-8, 8.-8.5, 8.5-9, 9-9,5, or 9.5-10x10^{-4} (1/s) as measured by Biacore assay. In some embodiments, the antibody provided herein binds human MARCO with a K_a of greater than or equal to about 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 45, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 7, 8, 9, or 10x10^{5} (1/Ms), or more, as measured by Biacore assay. In some embodiments, the antibody provided herein binds human MARCO with a K_a between 4-7, 4-4.5, 4.5-5, 5-5.5, 5.5-6, 6-6.5, or 6.5-7, 7-8, 8-9, or 9-10x10^{5} (1/Ms) as measured by Biacore assay.

[0439] In some embodiments, the antibody provided herein binds human MARCO with an EC50 of less than or equal to 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1 nM as measured by measured by flow cytometry. In some embodiments, the antibody binds human MARCO with an EC50 between 0.6-1.4 nM as measured by measured by flow cytometry. In some embodiments, the antibody binds human MARCO with an EC50 of about 0.5, 0.6, 0.9, 1.1, 1.2, 1.3, 1.4, or 1.5 nM as measured by measured by flow cytometry.

[0440] In some embodiments, the antibody provided herein binds mouse MARCO with an EC50 of less than or equal to 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1 nM as measured by measured by flow cytometry. In some embodiments, the antibody binds mouse MARCO with an EC50 between 0.6-1.4 nM as measured by measured by flow cytometry. In some embodiments, the antibody binds mouse MARCO with an EC50 of about 0.5, 0.6, 0.9, 1.1, 1.2, 1.3, 1.4, or 1.5 nM as measured by measured by flow cytometry.

[0441] In some embodiments, the antibody provided herein does not bind human MARCO with an EC50 great than or equal to 20 nM or more as measured by measured by flow cytometry. In some embodiments, the antibody provided herein does not bind mouse MARCO with an EC50 great than or equal to 3 nM or more as measured by measured by flow cytometry.

[0442] To screen for antibodies which bind to an epitope on a target antigen bound by an antibody of interest (e.g., MARCO), a routine cross-blocking assay such as that described in *Antibodies, A Laboratory Manual,* Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. Alternatively, or additionally, epitope mapping can be performed by methods known in the art.

[0443] Competition between antibodies can be determined by an assay in which an antibody under test inhibits or blocks specific binding of a reference antibody to a common antigen (see, e.g., Junghans et al., Cancer Res. 50:1495, 1990; Fendly et al. Cancer Research 50: 1550-1558; US 6,949,245). A test antibody competes with a reference antibody if an excess of a test antibody (e.g., at least 2x, 5x, 10x, 20x, or 100x) inhibits or blocks binding of the reference antibody by, e.g., at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% as measured in a competitive binding assay. Antibodies identified by competition assay (competing antibody) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur. For example, a second, competing antibody can be identified that competes for binding to MARCO with a first antibody described herein. In certain instances, the second antibody can block or inhibit binding of the first antibody by, e.g., at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% as measured in a competitive binding assay. In certain instances, the second antibody can displace the first antibody by greater than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%.

[0444] In some embodiments, the antibody binds to the Scavenger Receptor Cysteine-Rich (SRCR) domain of MARCO.

[0445] In some embodiments, the antibody binds to an epitope on SRCR comprising at least one of residues Q452, Y472, or K473 of wild type human MARCO (SEQ ID NO: 363). In some embodiments, the antibody binds to an epitope on SRCR comprising at least one of residues H505, D507, S509, or E511 of wild type human MARCO (SEQ ID NO: 363). In some embodiments, the antibody binds to an epitope on SRCR comprising at least one of residues E450, Q452, Q487, or T499 of wild type human MARCO (SEQ ID NO: 363). In

some embodiments, the antibody binds to an epitope on SRCR comprising at least one of residues E450, Q452, Q487, T499, H505, D507, S509, or E511 of wild type human MARCO (SEQ ID NO: 363).

[0446] In some embodiments, the antibody or antigen binding fragment thereof binds to at least one of the following residues: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of MARCO listed in SEQ ID NO: 363. In some embodiments, the antibody or antigen binding fragment thereof binds to at least two, three, four, five, six, seven, eight, nine, or ten of the following residues: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of SEQ ID NO: 363. In some embodiments, the antibody or antigen binding fragment thereof binds to at least two of the following residues: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of SEQ ID NO: 363. In some embodiments, the antibody or antigen binding fragment thereof binds to at least three of the following residues: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of SEQ ID NO: 363. In some embodiments, the antibody or antigen binding fragment thereof binds to at least four of the following residues: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of SEQ ID NO: 363.

[0447] In some embodiments, the antibody or antigen binding fragment thereof binds to at least Q452. In some embodiments, the antibody or antigen binding fragment thereof binds to at least Y472. In some embodiments, the antibody or antigen binding fragment thereof binds to at least K473. In some embodiments, the antibody or antigen binding fragment thereof binds to at least E450. In some embodiments, the antibody or antigen binding fragment thereof binds to at least Q487. In some embodiments, the antibody or antigen binding fragment thereof binds to at least T499. In some embodiments, the antibody or antigen binding fragment thereof binds to at least H505. In some embodiments, the antibody or antigen binding fragment thereof binds to at least D507. In some embodiments, the antibody or antigen binding fragment thereof binds to at least S509. In some embodiments, the antibody or antigen binding fragment thereof binds to at least E511.

Function

[0448] In some embodiments, the antibody has antibody-dependent cellular cytotoxicity (ADCC) activity. ADCC can occur when antibodies bind to antigens on the surface of pathogenic or tumorigenic target-cells. Effector cells bearing Fc gamma receptors (FcγR or FCGR) on their cell surface, including cytotoxic T-cells, natural killer (NK) cells, macrophages, neutrophils, eosinophils, dendritic cells, or monocytes, recognize and bind the

Fc region of antibodies bound to the target-cells. Such binding can trigger the activation of intracellular signaling pathways leading to cell death. In particular embodiments, the antibody's immunoglobulin Fc region subtypes (isotypes) include human IgG1 and IgG3. As used herein, ADCC refers to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) *(e.g.* Natural Killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and subsequently cause lysis of the target cell. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells in summarized is Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.*, in an animal model such as that disclosed in Clynes *et al., Proc. Natl. Acad. Sci. (USA)* 95:652-656 (1998).

[0449] In some embodiments, the antibody has complement-dependent cytotoxicity (CDC) activity. Antibody-induced CDC is mediated through the proteins of the classical complement cascade and is triggered by binding of the complement protein Clq to the antibody. Antibody Fc region binding to Clq can induce activation of the complement cascade. In particular embodiments, the antibody's immunoglobulin Fc region subtypes (isotypes) include human IgG1 and IgG3. As used herein, CDC refers to the ability of a molecule to lyse a target in the presence of complement. The complement activation pathway is initiated by the binding of the first component of the complement system (C1q) to a molecule (*e.g.* polypeptide (*e.g.*, an antibody)) complexed with a cognate antigen. To assess complement activation, a CDC assay, *e.g.* as described in Gazzano-Santoro *et al., J. Immunol. Methods* 202:163 (1996), may be performed.

[0450] In some embodiments, an antibody is an agonistic antibody. An agonistic antibody can induce (e.g., increase) one or more activities or functions of MARCO-expressing cells after the antibody binds a MARCO protein expressed on the cell. The agonistic antibody may bind to and activate MARCO-expressing cells, causing changes in proliferation of the cell or modifying antigen presentation capabilities. The agonistic antibody may bind to and activate MARCO-expressing cells, triggering intracellular signaling pathways that lead to modified cell growth or apoptosis.

[0451] In some embodiments, an antibody is an antagonistic antibody. An antagonistic antibody can block (e.g. decrease) one or more activities or functions of MARCO-expressing cells after the antibody binds a MARCO protein expressed on the cell. For example, the antagonist antibody may bind to and block ligand binding to one or more MARCO proteins, preventing differentiation and proliferation of the cell or modifying antigen presentation capabilities. The antagonist antibody may bind to and prevent activation of a MARCO protein by its ligand, modifying intracellular signaling pathways that contribute to cell growth and survival.

[0452] In some embodiments an antibody is a depleting antibody. A depleting antibody is one that would kill a MARCO-expressing cell upon contact through the antibody's interaction with other immune cells of molecules. For example, antibodies, when bound to cells bearing MARCO proteins, could engage complement proteins and induce complement-dependent cell lysis. Antibodies, when bound to cells bearing MARCO proteins, could also trigger neighboring cells bearing Fc receptors to kill them by antibody-dependent cellular cytotoxicity (ADCC).

[0453] In some embodiments, an antibody is a neutralizing antibody, and the antibody neutralizes one or more biological activities of MARCO-expressing cells. In some embodiments, MARCO protein is expressed on the surface of MARCO-expressing cells and the antibody recognizes the extracellular domain of MARCO protein.

[0454] In some embodiments an antibody is selective for MARCO-expressing cells (preferentially binds to MARCO). In certain embodiments, an antibody that selectively binds to MARCO-expressing cells has a dissociation constant (Kd) of range of 0.0001nM to 1μM. In certain embodiments, an antibody specifically binds to an epitope on a MARCO protein that is conserved among the protein from different species. In another embodiment, selective binding includes, but does not require, exclusive binding.

[0455] In one embodiment an anti-MARCO antibody bound to its target is responsible for causing the *in vivo* depletion of MARCO-expressing cells to which it is bound. In some embodiments, effector proteins induced by clustered antibodies can trigger a variety of responses, including release of inflammatory cytokines, regulation of antigen production, endocytosis, or cell killing. In one embodiment the antibody is capable of recruiting and activating complement or mediating antibody-dependent cellular cytotoxicity (ADCC) *in vivo*, or mediating phagocytosis by binding Fc receptors *in vivo*. The antibody may also deplete MARCO-expressing cells by inducing apoptosis or necrosis of the MARCO-expressing cell upon binding.

[0456] In some embodiments the disabling of MARCO-expressing cells is *in vitro* and is achieved: a) by killing of the MARCO-expressing cells; b) magnetic bead depletion of the MARCO-expressing cells; or c) Fluorescence-activated cell sorting (FACS) sorting of the MARCO-expressing cells.

[0457] In some embodiments, an antibody is bound to, or conjugated to an effector molecule. In particular embodiments, an antibody is conjugated to at least one therapeutic agent selected from the group consisting of a radionuclide, a cytotoxin, a chemotherapeutic agent, a drug, a pro-drug, a toxin, an enzyme, an immunomodulator, an anti-angiogenic agent, a pro-apoptotic agent, a cytokine, a hormone, an oligonucleotide, an antisense molecule, a siRNA, a second antibody and a second antibody fragment.

[0458] In certain embodiments an antibody is conjugated to a drug, e.g., a toxin, a chemotherapeutic agent, an immune modulator, or a radioisotope. Several methods of preparing ADCs (antibody drug conjugates) are known in the art and are described in US patents 8,624,003 (pot method), 8,163,888 (one-step), and 5,208,020 (two-step method), for example. An antibody or antigen-binding fragment thereof can be conjugated to at least one agent including a radionuclide, a cytotoxin, a chemotherapeutic agent, a drug, a pro-drug, a toxin, an enzyme, an immunomodulator, an anti-angiogenic agent, a pro-apoptotic agent, a cytokine, a hormone, an oligonucleotide, an antisense molecule, a siRNA, a second antibody, and a second antibody fragment that is antigen binding.

[0459] In some embodiments, an antibody modulates an immune response. In some embodiments, an antibody increases an immune response. In some embodiments, an antibody enhances or initiates an immune response.

Method of Treating Cancer

[0460] In another aspect, the invention provides methods of treating an immune-related condition (e.g., cancer) in an individual comprising administering to the individual an effective amount of a composition comprising an anti-MARCO antibody. In another aspect, the invention provides methods of enhancing an immune response in an individual comprising administering to the individual an effective amount of a composition comprising an anti-MARCO antibody.

[0461] In some embodiments, the methods provided herein are useful for the treatment of an immune-related condition in an individual. In one embodiment, the individual is a human.

[0462] In some embodiments, the methods provided herein (such as methods of enhancing an immune response) are useful for the treatment of cancer and as such an individual receiving

the anti-MARCO antibody has cancer. In some embodiments, the cancer is a solid cancer. In some embodiments, the cancer is a liquid cancer. In some embodiments, the cancer is immunoevasive. In some embodiments, the cancer is immunoresponsive. In some embodiments, the cancer expresses IL-10. In some embodiments, the cancer is a hypoxic cancer. In particular embodiments, the cancer is selected from the group consisting of lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancers. In some embodiments, the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

[0463] In some embodiments, the treatment results in a decrease in the cancer volume or size. In some embodiments, the treatment is effective at reducing a cancer volume as compared to the cancer volume prior to administration of the antibody. In some embodiments, the treatment results in a decrease in the cancer growth rate. In some embodiments, the treatment is effective at reducing a cancer growth rate as compared to the cancer growth rate prior to administration of the antibody. In some embodiments, the treatment is effective at eliminating the cancer.

[0464] In some embodiments, MARCO is expressed at a higher level in the cancer as compared to a non-cancer cell. In some embodiments, IL-10 is expressed at a higher level in the cancer as compared to a non-cancer cell. Levels of MARCO and/or IL-10 can be assessed by any technique known in the field, including, but not limited to, protein assays or nucleic assays such as FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, monoplex immunohistochemistry, multiplex immunohistochemistry, flow cytometry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, surface plasmon resonance, optical spectroscopy, mass spectrometry, HPLC, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, Luminex, MSD, and FISH, and combinations thereof.

Combination Therapies

[0465] For the treatment of cancer, the anti-MARCO antibody may be combined with one or more antibodies that inhibit immune checkpoint proteins. Of particular interest are immune checkpoint proteins displayed on the surface of a tumor cell. The immune-checkpoint receptors that have been most actively studied in the context of clinical cancer immunotherapy, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4; also known as CD152) and programmed cell death protein 1 (PD1; also known as CD279), are both inhibitory receptors. The clinical activity of antibodies that block either of these receptors implies that antitumor immunity can be enhanced at multiple levels and that combinatorial strategies can be intelligently designed, guided by mechanistic considerations and preclinical models.

[0466] The two ligands for PD-1 are PD-1 ligand 1 (PD-L1; also known as B7-H1 and CD274) and PD-L2 (also known as B7-DC and CD273). PD-L1 is expressed on cancer cells and through binding to its receptor PD-1 on T cells it inhibits T cell activation/function. Inhibitors that block the interaction of PD-1 with its cognate ligands on the cancer cells, PD-L1 and PD-L2, can result in both increased T cell activation and function, and prevent cancer cells from evading the immune system.

[0467] In some embodiments, the immunotherapy is an agent that interferes with PD-1 and PD-L1 or PD-L2 binding. In some embodiments, the immunotherapy is an anti-PD1 antibody. In some embodiments, the immunotherapy is an anti-PD-L1 antibody. In some embodiments, the immunotherapy is an anti-PD-L2 antibody.

[0468] Various PD-1, PD-L1, and PD-L2 antibodies are known in the art. In some embodiments, the additional therapeutic agent is at least one of: Atezolizumab (PD-L1), Avelumab (PD-L1), Durvalumab (PD-L1), Nivolumab (PD-1), Pembrolizumab (PD-1), Cemiplimab (PD-1), Ipilimumab (CTLA-4), Tremelimumab (CTLA-4), or any combination thereof.

[0469] The additional therapeutic agent can be administered by any suitable means. In some embodiments, an antibody provided herein and the additional therapeutic agent are included in the same pharmaceutical composition. In some embodiments, an antibody provided herein and the additional therapeutic agent are included in different pharmaceutical compositions.

[0470] In embodiments where an antibody provided herein and the additional therapeutic agent are included in different pharmaceutical compositions, administration of the antibody

can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent.

Method of Immune Modulation

[0471] Immunosuppressive M2-like MARCO expressing cells, such as MARCO+ tumor associated macrophages (TAMs), and MARCO+ mMDSCs, are upregulated in IL-10 enriched and hypoxic tumor micro environments (TME). These cells suppress immune cytotoxic activity. Immunosuppression also leads to increased angiogenesis and metastasis.

[0472] Anti-MARCO antibodies can activate intra-tumor immunity at least by mediating repolarization of MARCO+ myeloid M2-like TAMs to M1-like TAMs, and repolarization of mMDSCs to pro-inflammatory monocytes. This repolarization can lead to production of cytokines, chemokines, and activation receptors, which in turn leads to activation of T cells, B cells, and NK cells. The repolarization of myeloid M2-like TAMs and mMDSCs can activate T cells, B cells, and NK cells. Once activated, these NK cells, CD8+ T cells, M1-like TAMs and inflammatory monocytes can induce tumor destruction. In addition, the anti-tumor immunity can be modulated by decreasing the M2-like TAMs and immunosuppressive mMDSCs. Anti-tumor immunity may also be mediated by increased antigen presentation and activation of cells in the spleen and lymph nodes. Binding of the anti-MARCO antibody to medullary cord macrophages (MCMs) can induce changes in adhesion and motility in the lymph node, and binding of the anti-MARCO antibody to marginal zone macrophages (MZMs) in the spleen can lead to changes in adhesion and motility, leading to potential B cell activation.

[0473] In some embodiments, repolarization of MARCO+ cells is observed by rapid modulation of phospho-signaling cascades involved in molecular association, enzymatic activity, transcription, translation, and pro-inflammatory signaling (Src, SYK, NF-kB, PI3K/AKT, TLR, STAT6, IL2RA, CAMK, PKC, Raf1, TPL2, MAPKs, cell cycle, survival, cell adhesion and migration, cytoskeletal rearrangement); changes in phagocytosis, adhesion, motility, and chemotaxis; activation of NF-kB reporter activity as single agent and in combination with TLRs agonists; induction of secretion of pro-inflammatory cytokines and chemokines, including but not limited to, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, eotaxin; and increasing inflammasome activation and phagocytosis.

[0474] Methods of administration of a MARCO antibody as described herein can result in modulation of an immune response. Modulation can be an increase or decrease in an immune response. In some embodiments, modulation is an increase in an immune response.

[0475] In one aspect, administration of a MARCO antibody as described herein can result in induction of pro-inflammatory molecules, such as cytokines, chemokines, or expression of myeloid activation receptors by myeloid cells. Generally, induced pro-inflammatory molecules are present at levels greater than that achieved with isotype control. In some embodiments, the myeloid cells are MARCO-expressing (MARCO+) cells. In some embodiments, the MARCO+ myeloid cell is a monocyte or a macrophage. In some embodiments, the MARCO+ macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM). Such pro-inflammatory molecules in turn result in activation of anti-tumor immunity, including, but not limited to, T cell activation, T cell proliferation, T cell differentiation, M1-like macrophage activation, B cell regulation, and NK cell activation. Thus, the administration of an anti-MARCO antibody can induce multiple anti-tumor immune mechanisms that lead to tumor destruction.

[0476] In another aspect, provided herein are methods of increasing an immune response in an individual comprising administering to the individual an effective amount of a composition comprising an anti-MARCO antibody or antigen-binding fragment thereof. In some embodiments, the method of increasing an immune response in a subject comprises administering to the subject an antibody that binds to the SRCR domain of human MARCO (SEQ ID NO: 363). In some embodiments, the method of increasing an immune response in a subject comprises administering to the subject an antibody that competes for binding to human MARCO (SEQ ID NO: 363) with a reference antibody. In some embodiments, the method of increasing an immune response in a subject comprises comprising administering to the subject an antibody that competes for binding to human MARCO (SEQ ID NO: 363), wherein the antibody binds at least one of residues Q452, Y472, and K473 of human MARCO (SEQ ID NO: 363). In some embodiments, the method of increasing an immune response in a subject comprises comprising administering to the subject an antibody that competes for binding to human MARCO (SEQ ID NO: 363), wherein the antibody binds at least one of residues E450, Q452, Q487, and T499 of human MARCO (SEQ ID NO: 363). In some embodiments, the method of increasing an immune response in a subject comprises comprising administering to the subject an antibody that competes for binding to human MARCO (SEQ ID NO: 363), wherein the antibody binds at least one of residues H505, D507, S509, or E511 of human MARCO (SEQ ID NO: 363).

[0477] In some embodiments, the antibody is present in a pharmaceutical composition further comprising a pharmaceutically acceptable excipient.

[0478] In any and all aspects of increasing an immune response as described herein, any increase or decrease or alteration of an aspect of characteristic(s) or function(s) is as compared to a cell not contacted with an anti-MARCO antibody.

[0479] Increasing an immune response can be both enhancing an immune response or inducing an immune response. For instance, increasing an immune response encompasses both the start or initiation of an immune response, or ramping up or amplifying an on-going or existing immune response. In some embodiments, the treatment induces an immune response. In some embodiments, the induced immune response is an adaptive immune response. In some embodiments, the induced immune response is an innate immune response. In some embodiments, the treatment enhances an immune response. In some embodiments, the enhanced immune response is an adaptive immune response. In some embodiments, the enhanced immune response is an innate immune response. In some embodiments, the treatment increases an immune response. In some embodiments, the increased immune response is an adaptive immune response. In some embodiments, the increased immune response is an innate immune response. In some embodiments, the immune response is started or initiated by administration of an anti-MARCO antibody. In some embodiments, the immune response is enhanced by administration of an anti-MARCO antibody.

[0480] In another aspect, the present application provides methods of contacting a cell with an anti-MARCO antibody, which results in the modulation of the immune function of the cell. The modulation can be increasing an immune response or reprogramming of MARCO-expressing cells. In some embodiments, the modulation is an increase in immune function. In some embodiments, the modulation of function leads to the activation of MARCO-expressing myeloid cells. In some embodiments, the modulation of function leads to the reprogramming of MARCO-expressing myeloid cells.

[0481] In some embodiments, the cells are myeloid cells. In some embodiments, the cells are MARCO-expressing cells (MARCO+ cells). In some embodiments, the MARCO+ cells are one or more of monocytes, macrophages, tumor associated macrophage (TAM), and monocyte-derived macrophages (MDM). In some embodiments, the MARCO+ cell is a monocyte. In some embodiments, the MARCO+ cell is a macrophage. In some embodiments, the MARCO+ cell is a tumor associated macrophage (TAM). In some embodiments, the MARCO+ cell is a monocyte-derived macrophage (MDM). In some embodiments, contacting a MARCO-expressing cell with a MARCO antibody induces activation of the cell.

[0482] In some embodiments, the modulation of function of the MARCO+ cells leads to an increase in the cells' abilities to stimulate both native and activated CD8+ T-cells, for example, by increasing the ability of MARCO-expressing cells to cross-present tumor antigen on MHCI molecules to naive CD8+ T-cells or by increasing cytokine or chemokine secretion by the MARCO-expressing cells. In some embodiments, the modulation of function of the MARCO+ cells leads to an increase in the cells' abilities to stimulate both native and activated CD4+ T-cells, for example, by increasing the ability of MARCO-expressing cells to cross-present tumor antigen on MHCII molecules to naive CD4+ T-cells. In some embodiments, the modulation of function enhances or increases the cells' ability to produce cytokines, chemokines, or costimulatory or activating receptors. In some embodiments, the modulation increases the T-cell stimulatory function of the MARCO+ cell, including, for example, the cells' abilities to trigger T-cell receptor (TCR) signaling, T-cell proliferation, or T-cell cytokine production.

[0483] In some embodiments, the increased immune response is secretion of cytokines and chemokines. In some embodiments, the MARCO antibody has agonist activity. In some embodiments, the MARCO antibody induces increased expression of at least one cytokine or chemokine in a cell as compared to an isotype control antibody. In some embodiments, the MARCO antibody induces increased expression of at least one pro-inflammatory cytokine or chemokine in a cell as compared to an isotype control antibody. In some embodiments, the at least one cytokine or chemokine is selected from the group consisting of: IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin. In some embodiments, the cytokine or chemokine is IL-2. In some embodiments, the cytokine or chemokine is IL-12. In some embodiments, the cytokine or chemokine secretion is increased between about 1-100-fold 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 1-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, or 90-100 fold as compared to an untreated cell or a cell treated with an isotype control antibody. In some embodiments, the chemokine is IL-2 and the secretion is increased between about 1-100-fold, 1-fold, 5-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 1-10-fold, 10-20-fold, 20-30-fold, 30-40-fold, 40-50-fold, 50-60-fold, 60-70-fold, 70-80-fold, 80-90-fold, or 90-100-fold as compared to an untreated cell or a cell treated with an isotype control antibody. In some embodiments, the cytokine is IL-12 and the secretion is increased between about 1-100-fold, 1-fold, 5-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold,

70-fold, 80-fold, 90-fold, 100-fold, 1-10-fold, 10-20-fold, 20-30-fold, 30-40-fold, 40-50-fold, 50-60-fold, 60-70-fold, 70-80-fold, 80-90-fold, or 90-100-fold as compared to an untreated cell or a cell treated with an isotype control antibody.

[0484] In some embodiments, the MARCO antibody induces decreased expression of at least one gene in a cell as compared to an isotype control antibody. In some embodiments, the at least one gene is ALK, MPB, TMEM37, NHSL2, or SLC46A2. In some embodiments, the gene is decreased between about 1-100-fold 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 1-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, or 90-100 fold as compared to an untreated cell or a cell treated with an isotype control antibody.

[0485] In some embodiments, the MARCO antibody induces inflammasome activation as compared to an isotype control antibody. Inflammasome activation can be determined by measuring IL-1β and/or IL-18 secretion.

[0486] In some embodiments, the MARCO antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

[0487] In some embodiments, the MARCO antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, $MHCII^{high}$ monocytes, $MHCII^{mid}$ monocytes, marginal zone macrophages, follicular B cells, and/or red pulp macrophages as compared to an isotype control antibody.

[0488] In some embodiments, upon cell contact the antibody decreases TAMs, neutrophils, marginal zone B cells, CD19+ B cells, and/or MHCII- monocytes, as compared to an isotype control antibody.

[0489] In some embodiments, the MARCO antibody modulates motility and/or phagocytosis changes by altering cytoskeletal, actin and muscles, and cell-adhesion related pathways in the tumor. In some embodiments, the MARCO antibody results in a pro-inflammatory activation within the TME, comprising M2 to M1 macrophage reprogramming, an increase in the phagocytosis and/or inflammasome, activation of NK cells, and/or activation of T cells.

[0490] In some embodiments, the MARCO antibody modulates cell signaling, cell adhesion, cytoskeletal, and motility changes in the lymph nodes. In some embodiments, the MARCO antibody binds to medullary cord macrophages in the lymph nodes and modulates cell adhesion and motility.

[0491] In some embodiments, the MARCO antibody modulates cell adhesion, cytoskeletal, migration, motility, cell signaling, and B cell activation in the spleen. In some embodiments,

the MARCO antibody binds to marginal zone macrophages in the spleen and modulates cell adhesion, motility, and B cell activation.

[0492] In some embodiments, the modulation increases cell adhesion, cytoskeletal, and cell migration as compared to an isotype control antibody. In some embodiments, the modulation induces B cell maturation in the spleen as compared to an isotype control antibody. In some embodiments, the modulation induces cell signaling pathways comprising cell cycle, T cell receptor, phagocytosis, autophagy, and wnt pathways as compared to an isotype control antibody.

[0493] In some embodiments, the enhanced immune response is anti-tumor immune cell recruitment and activation.

[0494] In some embodiments, the antibody induces a memory immune response as compared to an isotype control antibody. In general, a memory immune response is a protective immune response upon a subsequent exposure to pathogens or antigens that the immune system encountered previously. Exemplary memory immune responses include the immune response after infection or vaccination with an antigen. In general, memory immune responses are mediated by lymphocytes such as T cells or B cells. In some embodiments, the memory immune response is a protective immune response to cancer, including cancer cell growth, proliferation, or metastasis. In some embodiments, the memory immune response inhibits, prevents, or reduces cancer cell growth, proliferation, or metastasis.

[0495] In some embodiments, the MARCO antibody induces or increases at least one of the following pathways or a gene associated with: B cell maturation in the spleen, the actin mediated cell contraction pathway, the kinase activation and activity pathway, the Toll-like receptor signaling pathway, the TLR 4 and 9 pathways, GTPase binding and activity, and/or the RAS-Rho signal transduction pathways, as compared to isotype antibody. In some embodiments, the MARCO antibody induces or increases at least one of the following pathways or a gene associated with: the humoral immune response, NK mediated immunity, NK activation, IL-2 and IL-12 production, cell killing, regulation of effector process, T cell proliferation, activation, differentiation, chemotaxis and migration, cell – cell adhesion, phagocytosis, and/or myeloid differentiation, as compared to isotype antibody.

[0496] In some embodiments, the MARCO antibody induces or increases at least one of the following pathways or a gene associated with: Natural Killer cell mediated cytotoxicity, T cell receptor signaling pathway, JAK/STAT signaling pathway, cytokine-cytokine receptor interaction, Intestinal immune network for IgA production, leukocyte trans-endothelial migration, chemokine signaling pathway, hematopoietic cell lineage, type II diabetes

mellitus, and Fc-epsilon RI signaling pathway, as compared to isotype antibody. In some embodiments, the MARCO antibody decreases or suppresses at least one of the following pathways or a gene associated with: homologous recombination, Alzheimer's disease, RNA polymerase, arginine and proline metabolism, citrate cycle (TCA cycle), porphyrin and chlorophyll metabolism, valine, leucine, and isoleucine degradation, biosynthesis of unsaturated fatty acids, N-glycan biosynthesis, and aminoacyl tRNA biosynthesis, as compared to isotype antibody.

[0497] In some embodiments, the MARCO antibody induces or increases at least one of the following pathways or a gene associated with: cytokine-cytokine receptor interaction, Natural Killer cell mediated cytotoxicity, primary immunodeficiency, chemokine signaling pathway, hematopoietic cell lineage, JAK/STAT signaling pathway, T cell receptor signaling pathway, Intestinal immune network for IgA production, neuroactive ligand receptor interaction, and Fc-epsilon RI signaling pathway, as compared to isotype antibody. In some embodiments, the MARCO antibody decreases or suppresses at least one of the following pathways or a gene associated with: glycolysis gluconeogenesis, propanoate metabolism, proteasome, citrate cycle TCA cycle, cardiac muscle contraction, Alzheimer's disease, Huntington's disease, oxidative phosphorylation, ribosome, and Parkinson's disease, as compared to isotype antibody.

[0498] In some embodiments, the MARCO antibody induces or increases at least one of the following pathways or a gene associated with: phosphatidylinositol signaling system, focal adhesion, inositol phosphate metabolism, axon guidance, adherens junction, pathways in cancer, regulation of actin cytoskeleton, progesterone mediated oocyte maturation, ERBB signaling pathway, and Wnt signaling pathway, as compared to isotype antibody. In some embodiments, the MARCO antibody decreases or suppresses at least one of the following pathways or a gene associated with: aminoacyl tRNA biosynthesis, lysosome, histidine metabolism, drug metabolism cytochrome p450, proteasome, Alzheimer's disease, Huntington's disease, Parkinson disease, oxidative phosphorylation, and ribosome, as compared to isotype antibody.

[0499] In some embodiments, the MARCO antibody induces or increases at least one of the following pathways or a gene associated with: focal adhesion, phosphatidylinositol signaling system, neurotrophin signaling pathway, insulin signaling pathway, inositol phosphate metabolism, MAPK signaling pathway, pathways in cancer, regulation of actin cytoskeleton, ERBB signaling pathway, and adherens junction, as compared to isotype antibody. In some embodiments, the MARCO antibody decreases or suppresses at least one of the following

pathways or a gene associated with: metabolism of xenobiotics by cytochrome p450, hematopoietic cell lineage, lysosome, Alzheimer's disease, proteasome, cytokine-cytokine receptor interaction, Huntington's disease, Parkinson's disease, oxidative phosphorylation, and ribosome, as compared to isotype antibody.

[0500] In some embodiments, the MARCO antibody induces or increases at least one of the following pathways or a gene associated with: ECM receptor interaction, focal adhesion, tight junction, adheres junction, proteasome, complement and coagulation cascades, cell adhesion molecules and CAMs, pathways in cancers, arrhythmogenic right ventricular cardiomyopathy ARVC, Wnt signaling pathway, regulation of actin skeleton, axon guidance, Huntington's disease, pathogenic Escherichia coli infection, Alzheimer's disease, leukocyte transendothelial migration, cytokine-cytokine receptor interaction, basal cell carcinoma, melanogenesis, and hedgehog signaling pathway, as compared to isotype antibody. In some embodiments, the MARCO antibody decreases or suppresses at least one of the following pathways or a gene associated with: cell cycle, aminoacyl tRNA biosynthesis, mismatch repair, glycosylphosphatidylinositol GPI anchor biosynthesis, glycerophospholipid metabolism, and homologous recombination, as compared to isotype antibody.

[0501] In some embodiments, the MARCO antibody induces or increases at least one of the following pathways or a gene associated with: cell cycle, proteasome, T cell receptor signaling pathway, DNA replication, ubiquitin mediated proteolysis, regulation of actin cytoskeleton, adherens junction, pathogenic Escherichia coli infection, basal transcription factors, pentose phosphate pathway, Fc gamma R mediated phagocytosis, neurotrophin signaling pathway, regulation of autophagy, glycolysis gluconeogenesis, oocyte meiosis, chronic myeloid leukemia, citrate cycle TCA cycle, Wnt signaling pathway, P53 signaling pathway, and natural killer cell mediated cytotoxicity, as compared to isotype antibody. In some embodiments, the MARCO antibody decreases or suppresses at least one of the following pathways or a gene associated with: ABC transporters, glycosylphosphatidylinositol GPI anchor biosynthesis, RNA polymerase, ribosome, arachidonic acid metabolism, glycerophospholipid metabolism, as compared to isotype antibody.

[0502] In some embodiments, the MARCO antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response, an

complement, inflammatory response pathway, or allograft rejection pathways as compared to an isotype control antibody.

[0503] In some embodiments, the MARCO antibody decreases oxidative phosphorylation, mTOR signaling, unfolded protein response, cholesterol homeostasis, fatty acid metabolism, myc targets, glycolysis pathways, a cell cycle pathway, cell survival, cell adhesion, E2F targets pathway, hypoxia, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathways as compared to an isotype control antibody.

[0504] In some embodiments, the MARCO antibody induces increased expression of at least one pro-inflammatory or activation gene in a cell in the tumor as compared to an isotype control antibody. In some embodiments, the MARCO antibody induces or increases expression of at least one of the following genes: Klrk1, Nrc1, Prf1, Cd40, Cd8α, Nod2, Tlr4, Tnf, Nlrp3, Cd274, Clec9α, Cd200r3, Il-27, Cxcl9, Cxcl10, or Cxcl12.

[0505] In some embodiments, the MARCO antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, MHCIIhigh monocytes, and/or MHCIImid monocytes in the spleen and/or tumor.

[0506] In some embodiments, the MARCO antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen and/or tumor.

[0507] In some embodiments, the MARCO antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages in the spleen and/or tumor.

[0508] In some embodiments, the expression level of the chemokine, cytokine, gene, or pathway is detected by a nucleic acid or protein assay. Exemplary nucleic acid or protein assays include, but are not limited to, FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, monoplex immunohistochemistry, multiplex immunohistochemistry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometry, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, Luminex, MSD, and FISH, and combinations thereof.

[0509] In some embodiments, the MARCO antibody induces changes in cell adhesion, cytoskeletal, chemotaxis and cell migration upon binding to a MARCO+ cell.

[0510] In some embodiments, the antibody crosslinks MARCO to MARCO on the cell surface of a MARCO+ cell. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*. In some particular embodiments, the contacting is *in*

vivo in a human. In some embodiments, the contacting is effected by administering an anti-MARCO antibody. In some embodiments, the individual receiving the antibody (such as a human) has cancer.

Methods of Disabling, Killing, or Depleting MARCO-Expresssing cells

[0511] In one aspect, the present application provides methods of contacting cells with an anti-MARCO antibody, such as a human or humanized antibody, which results in the disabling of the MARCO-expressing cells. Disabling MARCO-expressing cells also encompasses killing and/or depleting MARCO-expressing cells.

[0512] In another aspect, the present application provides methods of contacting MARCO-expressing cells with an anti-MARCO antibody, which results in the disabling of the MARCO-expressing cells.

[0513] In some embodiments, the MARCO-expressing are myeloid cells. In some embodiments, the MARCO-expressing are one or more of monocytes or macrophages. In some embodiments, the MARCO-expressing cells are one or more of TAM cells and monocyte-derived macrophages (MDM). In some embodiments, the MARCO-expressing cells are monocytic Myeloid Derived Suppressor Cells (mMDSC).

[0514] In some embodiments, the present application provides methods of disabling MARCO-expressing cells, comprising contacting the MARCO-expressing cells with a MARCO antibody, thereby killing the MARCO-expressing cells. Disabling refers to rendering a cell partially or completely non-functional. In some embodiments, the disabling of the cells leads to inducing growth arrest in the cells. In some embodiments, the disabling of the cells leads to apoptosis in the cells. In some embodiments, the disabling of the cells leads to lysis of the cells, as for example by complement dependent cytotoxicity (CDC) or antibody-dependent cell cytotoxicity (ADCC). In some embodiments, the disabling of the MARCO-expressing cells leads to necrosis in the cells. In some embodiments, the disabling of the MARCO-expressing cells leads to inducing growth arrest in the cells. In some embodiments, the disabling of the MARCO-expressing cells leads to inactivating the cells. In some embodiments, the disabling of the MARCO-expressing cells leads to neutralizing the activity of a MARCO protein in the cells. In some embodiments, the disabling of the MARCO-expressing cells leads to reduction in proliferation of the cells. In some embodiments, the disabling of MARCO-expressing cells leads to differentiation of the cells. In some embodiments, the disabling of the MARCO-expressing leads to a decrease in the cells' ability to act as inhibitory antigen presenting cells or leads to an increase in the cells'

ability to act as activating antigen-presenting cells. In some embodiments, the disabling of the MARCO-expressing cells leads to the mislocalization of the cells within tumor tissue or tumor microenvironment (TME). In some embodiments, the disabling of the MARCO-expressing cells leads to an altered spatial organization of the cells within tumor tissue or tumor microenvironment. In some embodiments, the disabling of the MARCO-expressing cells leads to an altered temporal expression of the cells within tumor tissue or TME. In some embodiments, the method further comprises removing the MARCO-expressing cells.

[0515] In any and all aspects of disabling MARCO-expressing cells as described herein, any increase or decrease or alteration of an aspect of characteristic(s) or function(s) is as compared to a cell not contacted with an anti-MARCO antibody.

[0516] In another aspect, the present application provides methods of contacting MARCO-expressing cells with an anti-MARCO antibody, which results in the modulation of function of the MARCO-expressing cells. The modulation can be any one or more of the following. In some embodiments the MARCO-expressing cells are one or more of monocytes, macrophages, TAMs, and MDMs. In some embodiments, the modulation of function of the cells leads to an increase in the cells' abilities to stimulate both native and activated CD8+ T-cells, for example, by increasing the ability of MARCO-expressing cells to cross-present tumor antigen on MHCI molecules to naive CD8+ T-cells. In some embodiments, the modulation of function of the MARCO-expressing cells leads to an increase in the cells' abilities to stimulate both native and activated CD4+ T-cells, for example, by increasing the ability of MARCO-expressing cells to cross-present tumor antigen on MHCII molecules to naive CD4+ T-cells. In some embodiments, the modulation increases the T-cell stimulatory function of the myeloid cells, including, for example, the cells' abilities to trigger T-cell receptor (TCR) signaling, T-cell proliferation, or T-cell cytokine production. In some embodiments, the modulation of function enhances or increases the cells' ability to produce cytokines, chemokines, or costimulatory or activating receptors.

[0517] In any and all aspects of decreasing the function of MARCO-expressing cells as described herein, any increase or decrease or alteration of an aspect of characteristic(s) or function(s) is as compared to a cell not contacted with an anti-MARCO antibody.

[0518] In some embodiments, the present application provides methods of killing (also referred to as inducing cell death) MARCO-expressing cells, comprising contacting the MARCO-expressing cells with an anti-MARCO antibody, thereby killing the MARCO-expressing cells. In some embodiments the killing is increased relative to MARCO-expressing cells that have not been contacted with an anti-MARCO antibody. In some

embodiments, the contacting induces apoptosis in the MARCO-expressing cells. In some embodiments, the MARCO-expressing cells are in a population of immune cells comprising MARCO-expressing cells and non-MARCO expressing cells. In some embodiments, the method further comprises removing the MARCO-expressing cells. In some embodiments, 10%-100% of the cells are killed. In some embodiments, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the cells are killed.

[0519] In some embodiments, the MARCO-expressing cells are reduced in number. In some embodiments, the MARCO-expressing cells are killed, for example by necrosis, or apoptosis. In some embodiments, the MARCO-expressing cells are induced to undergo growth arrest. In some embodiments, the MARCO-expressing cells no longer proliferate. In some embodiments the spatial localization of the MARCO-expressing cells is altered, and the ratio is increased in a particular region of the TME. In some embodiments the temporal expression of the MARCO-expressing cells is altered, and the ratio is increased during a particular time during the development of the tumor.

Additional Methods

Determining Expression of MARCO

[0520] Also provided herein are methods of treating a cancer or modulating an immune response in an individual comprising: determining or having determined the expression of MARCO in the subject; and administering or having administered to the subject an isolated antibody or antigen binding fragment that binds to MARCO.

[0521] In some embodiments, the method further comprises determining or having determined the expression level of MARCO in a biological sample from the individual. In some embodiments the biological sample includes, but is not limited to a body fluid, a tissue sample, an organ sample, urine, feces, blood, saliva, CSF and any combination thereof. In some embodiments the biological sample is derived from a tumor tissue. In some embodiments, the expression level of MARCO comprises the mRNA expression level of MARCO. In some embodiments, the expression level of MARCO comprises the protein expression level of MARCO. In some embodiments the expression level of MARCO is detected in the sample using a method selected from the group consisting of FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, monoplex immunohistochemistry, multiplex immunohistochemistry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometry, qPCR, RT-qPCR, multiplex qPCR or

RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, Luminex, MSD, and FISH, and combinations thereof.

[0522] In some aspects, provided herein are methods of determining an expression level of MARCO protein in a sample from a subject comprising contacting the sample with an anti-MARCO antibody and performing an immunohistochemistry assay. In some embodiments, the antibody comprises RDM5, RDM9, PI-3010.15, PI-3010.25, or PI-3030.41.

[0523] In embodiments described herein for detection and/or quantification, the anti-MARCO antibody binds to the MARCO protein, but does not necessarily have to effect a biological response, such as ADCC, although it may have an effect on a biological response. In some embodiments, the antibody binds to soluble MARCO.

[0524] In another aspect, the present invention provides methods for identifying an individual who may respond to immunotherapy (e.g. with an anti-MARCO antibody) for the treatment of an immune-related condition (e.g. cancer) comprising: detecting the expression level of MARCO in a biological sample from the individual; and determining based on the expression level of MARCO, whether the individual may respond immunotherapy, wherein an elevated level of MARCO in the individual relative to that in a healthy individual indicates that the individual may respond to immunotherapy. In some embodiments, the MARCO expression in the individual has already been determined. In some embodiments, these methods may also be used for diagnosing an immune-related condition (e.g. cancer) in the individual and are based the expression level of MARCO, wherein an elevated level of MARCO in the individual relative to that in a healthy individual indicates that the individual suffers from cancer. In some embodiments, the expression level of MARCO comprises the mRNA expression level of MARCO. In other embodiments, the expression level of MARCO comprises the protein expression level of MARCO. In some embodiments the expression level of MARCO is detected in the sample using a nucleic acid or protein assay. Exemplary a nucleic acid or protein assays include, but are not limited to, FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, monoplex immunohistochemistry, multiplex immunohistochemistry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometry, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, Luminex, MSD, and FISH, and combinations thereof. In these embodiments, the anti-MARCO antibody binds to the MARCO protein, but does not necessarily have to effect a biological response, such as ADCC. In some embodiments the biological sample is derived from a tumor tissue. In some embodiments the

biological sample includes, but is not limited to a body fluid, a tissue sample, an organ sample, urine, feces, blood, saliva, CSF and any combination thereof.

[0525] In some embodiments, the assay is an immunohistochemistry assay and the antibody comprises RDM5, RDM9, PI-3010.15, PI-3010.25, or PI-3030.41.

Method of Administration

[0526] In some embodiments, the anti-MARCO antibody is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. An effective amount of the anti-MARCO antibody may be administered for the treatment of cancer. The appropriate dosage of the anti-MARCO antibody may be determined based on the type of cancer to be treated, the type of the anti-MARCO antibody, the severity and course of the cancer, the clinical condition of the individual, the individual's clinical history and response to the treatment, and the discretion of the attending physician.

Method of Preparation

[0527] Antibodies described herein can be produced using recombinant methods and compositions, e.g., as described in U.S. Pat. No. 4,816,567.

[0528] In one embodiment, isolated nucleic acid encoding an antibody described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chains of the antibody) or an amino acid sequence comprising the VHH of a single domain antibody. In a further embodiment, one or more vectors (e.g., expression vectors) comprising such nucleic acid are provided. In one embodiment, the nucleic acid is provided in a multicistronic vector. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antigen-binding polypeptide construct, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antigen-binding polypeptide construct and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antigen-binding polypeptide construct. In one embodiment, the host cell is eukaryotic, e.g. a Chinese Hamster Ovary (CHO) cell, or human embryonic kidney (HEK) cell, or lymphoid cell (e.g., Y0, NS0, Sp20 cell). In one embodiment, a method of making an

antibody is provided, wherein the method comprises culturing a host cell comprising nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[0529] For recombinant production of the antibody, nucleic acid encoding an antibody, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0530] The term "substantially purified" refers to a construct described herein, or variant thereof that may be substantially or essentially free of components that normally accompany or interact with the protein as found in its naturally occurring environment, i.e. a native cell, or host cell in the case of recombinantly produced heteromultimer that in certain embodiments, is substantially free of cellular material includes preparations of protein having less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% (by dry weight) of contaminating protein. When the heteromultimer or variant thereof is recombinantly produced by the host cells, the protein in certain embodiments is present at about 30%, about 25%, about 20%, about 15%, about 10%, about 5%, about 4%, about 3%, about 2%, or about 1% or less of the dry weight of the cells. When the heteromultimer or variant thereof is recombinantly produced by the host cells, the protein, in certain embodiments, is present in the culture medium at about 5 g/L, about 4 g/L, about 3 g/L, about 2 g/L, about 1 g/L, about 750 mg/L, about 500 mg/L, about 250 mg/L, about 100 mg/L, about 50 mg/L, about 10 mg/L, or about 1 mg/L or less of the dry weight of the cells. In certain embodiments, "substantially purified" heteromultimer produced by the methods described herein, has a purity level of at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, specifically, a purity level of at least about 75%, 80%, 85%, and more specifically, a purity level of at least about 90%, a purity level of at least about 95%, a purity level of at least about 99% or greater as determined by appropriate methods such as SDS/PAGE analysis, RP-HPLC, SEC, and capillary electrophoresis.

[0531] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein.

[0532] A "recombinant host cell" or "host cell" refers to a cell that includes an exogenous polynucleotide, regardless of the method used for insertion, for example, direct uptake, transduction, f-mating, or other methods known in the art to create recombinant host cells. The exogenous polynucleotide may be maintained as a nonintegrated vector, for example, a plasmid, or alternatively, may be integrated into the host genome. Host cells can include CHO, derivatives of CHO, NS0, Sp2O, CV-1, VERO-76, HeLa, HepG2, Per.C6, or BHK.

[0533] As used herein, the term "eukaryote" refers to organisms belonging to the phylogenetic domain Eucarya such as animals (including but not limited to, mammals, insects, reptiles, birds, etc.), ciliates, plants (including but not limited to, monocots, dicots, algae, etc.), fungi, yeasts, flagellates, microsporidia, protists, etc.

[0534] As used herein, the term "prokaryote" refers to prokaryotic organisms. For example, a non-eukaryotic organism can belong to the Eubacteria (including but not limited to, Escherichia coli, Thermus thermophilus, Bacillus stearothermophilus, Pseudomonas fluorescens, Pseudomonas aeruginosa, Pseudomonas putida, etc.) phylogenetic domain, or the Archaea (including but not limited to, Methanococcus jannaschii, Methanobacterium thermoautotrophicum, Halobacterium such as Haloferax volcanii and Halobacterium species NRC-1, Archaeoglobus fulgidus, Pyrococcus furiosus, Pyrococcus horikoshii, Aeuropyrum pernix, etc.) phylogenetic domain.

[0535] For example, antibody may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, Methods in Molecular Biology, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 245-254, describing expression of antibody fragments in E. coli.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0536] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been “humanized,” resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, Nat. Biotech. 22:1409-1414 (2004), and Li et al., Nat. Biotech. 24:210-215 (2006).

[0537] Suitable host cells for the expression of glycosylated antibodies are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may

be used in conjunction with insect cells, particularly for transfection of Spodoptera frugiperda cells.

[0538] Plant cell cultures can also be utilized as hosts. See, e.g., U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0539] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., J. Gen Virol. 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, Biol. Reprod. 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., Annals N.Y. Acad. Sci. 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR− CHO cells (Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, Methods in Molecular Biology, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J.), pp. 255-268 (2003).

[0540] In one embodiment, the antibodies described herein are produced in stable mammalian cells, by a method comprising: transfecting at least one stable mammalian cell with: nucleic acid encoding the antibody, in a predetermined ratio; and expressing the nucleic acid in the at least one mammalian cell. In some embodiments, the predetermined ratio of nucleic acid is determined in transient transfection experiments to determine the relative ratio of input nucleic acids that results in the highest percentage of the antibody in the expressed product.

[0541] In some embodiments is the method of producing an antibody in stable mammalian cells as described herein wherein the expression product of the at least one stable mammalian cell comprises a larger percentage of the desired glycosylated antibody as compared to the monomeric heavy or light chain polypeptides, or other antibodies.

[0542] In some embodiments is the method of producing a glycosylated antibody in stable mammalian cells described herein, said method comprising identifying and purifying the

desired glycosylated antibody. In some embodiments, the said identification is by one or both of liquid chromatography and mass spectrometry.

[0543] If required, the antibodies can be purified or isolated after expression. Proteins may be isolated or purified in a variety of ways known to those skilled in the art. Standard purification methods include chromatographic techniques, including ion exchange, hydrophobic interaction, affinity, sizing or gel filtration, and reversed-phase, carried out at atmospheric pressure or at high pressure using systems such as FPLC and HPLC. Purification methods also include electrophoretic, immunological, precipitation, dialysis, and chromatofocusing techniques. Ultrafiltration and diafiltration techniques, in conjunction with protein concentration, are also useful. As is well known in the art, a variety of natural proteins bind Fc and antibodies, and these proteins can find use in the present invention for purification of antibodies. For example, the bacterial proteins A and G bind to the Fc region. Likewise, the bacterial protein L binds to the Fab region of some antibodies. Purification can often be enabled by a particular fusion partner. For example, antibodies may be purified using glutathione resin if a GST fusion is employed, Ni+2 affinity chromatography if a His-tag is employed or immobilized anti-flag antibody if a flag-tag is used. For general guidance in suitable purification techniques, see, e.g. incorporated entirely by reference Protein Purification: Principles and Practice, 3rd Ed., Scopes, Springer-Verlag, NY, 1994, incorporated entirely by reference. The degree of purification necessary will vary depending on the use of the antibodies. In some instances no purification is necessary.

[0544] In certain embodiments the antibodies are purified using Anion Exchange Chromatography including, but not limited to, chromatography on Q-sepharose, DEAE sepharose, poros HQ, poros DEAF, Toyopearl Q, Toyopearl QAE, Toyopearl DEAE, Resource/Source Q and DEAE, Fractogel Q and DEAE columns.

[0545] In specific embodiments the proteins described herein are purified using Cation Exchange Chromatography including, but not limited to, SP-sepharose, CM sepharose, poros HS, poros CM, Toyopearl SP, Toyopearl CM, Resource/Source S and CM, Fractogel S and CM columns and their equivalents and comparables.

[0546] In addition, antibodies described herein can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W. H. Freeman & Co., N.Y and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide

sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4diaminobutyric acid, alpha-amino isobutyric acid, 4aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, alanine, fluoro-amino acids, designer amino acids such as methyl amino acids, C-methyl amino acids, N-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

Pharmaceutical compositions

[0547] Methods for treatment of immune-related diseases (e.g., cancer) are also encompassed by the present invention. Said methods of the invention include administering a therapeutically effective amount of an anti-MARCO antibody or antigen-binding fragment. The MARCO antibody or antigen-binding fragment can be formulated in pharmaceutical compositions. These compositions can comprise, in addition to one or more of the anti-MARCO antibodies or antigen-binding fragments, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material can depend on the route of administration, e.g. oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraperitoneal routes.

[0548] Pharmaceutical compositions for oral administration can be in tablet, capsule, powder or liquid form. A tablet can include a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol can be included.

[0549] For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives can be included, as required.

[0550] Whether it is a polypeptide, antibody, or antigen-binding fragment or other pharmaceutically useful compound according to the present invention that is to be given to an individual, administration is preferably in a "therapeutically effective amount" or "prophylactically effective amount"(as the case can be, although prophylaxis can be considered therapy), this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of protein aggregation disease being treated. Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980.

[0551] A composition can be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

Kits and Articles of Manufacture

[0552] The present application provides kits comprising any one or more of the antibody compositions described herein. In some embodiments, the kits further contain a component selected from any of secondary antibodies, reagents for immunohistochemistry analysis, pharmaceutically acceptable excipient and instruction manual and any combination thereof. In one specific embodiment, the kit comprises a pharmaceutical composition comprising any one or more of the antibody compositions described herein, with one or more pharmaceutically acceptable excipients.

[0553] The present application also provides articles of manufacture comprising any one of the antibody compositions or kits described herein. Examples of an article of manufacture include vials (including sealed vials).

Additional Embodiments

[0554] In one aspect, provided herein are isolated antibodies or antigen binding fragments thereof that binds to human Macrophage Receptor with Collagenous Structure (MARCO) (SEQ ID NO: 384) and competes for binding with a reference antibody, wherein the reference antibody comprises a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2),

CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3),

CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4),

CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L),

CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and

CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

[0555] In some embodiments, CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431).

[0556] In some embodiments, CDR-L1 comprises the sequence RASEGISNDLA (SEQ ID NO: 27).

[0557] In some embodiments, the VH sequence comprises the VH sequence set forth in SEQ ID NO: 61 ; and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

[0558] In some embodiments, the VH sequence comprises the VH sequence set forth in SEQ ID NO: 111; and the and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 116.

[0559] In some embodiments, the VH sequence comprises the VH sequence set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, or 474.

[0560] In some embodiments, the VL sequence comprises the VL sequence set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96, 106, 116, 126, 136, 439, 449, or 479.

[0561] In some embodiments, the VH sequence comprises the VH sequence set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, or 474; and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96, 106, 116, 126, 136, 439, 449, or 479.

[0562] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 65 ; and a light chain sequence as set forth in SEQ ID NO: 70.

[0563] In some embodiments, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 115; and a light chain sequence as set forth in SEQ ID NO: 120.

[0564] In some embodiments, the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478 and a light chain sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

[0565] In some embodiments, the VH sequence consists of the VH sequence set forth in SEQ ID NO: 61 ; and the VL sequence consists of the VL sequence set forth in SEQ ID NO: 66.

[0566] In some embodiments, the VH sequence consists of the VH sequence set forth in SEQ ID NO: 111; and the and the VL sequence consists of the VL sequence set forth in SEQ ID NO: 116.

[0567] In some embodiments, the VH sequence consists of the VH sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, or 474; and the VL sequence consists of the VL sequence selected from the sequences set forth in SEQ ID NOs: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96, 106, 116, 126, 136, 439, 449, or 479.

[0568] In some embodiments, the antibody comprises a heavy chain and a light chain, wherein the sequence of the heavy chain consists of the heavy chain sequence set forth in SEQ ID NO: 65 and the sequence of the light chain consists of the light chain sequence set forth in SEQ ID NO: 70.

[0569] In some embodiments, the antibody comprises a heavy chain and a light chain, wherein the sequence of the heavy chain consists of the heavy chain sequence set forth in SEQ ID NO: 115 and the sequence of the light chain consists of the light chain sequence set forth in SEQ ID NO: 120.

[0570] In some embodiments, the antibody comprises a human Fc region.

[0571] In some embodiments, the human Fc region is a wild-type human IgG1 Fc.

[0572] In some embodiments, the antibody comprises a wild type human IgG1 Fc, and wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 61, and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

[0573] In some embodiments, the antibody comprises a wild type human IgG1 Fc, and wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 111, and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 116.

[0574] In some embodiments, the antibody binds to human MARCO with a KD of less than or equal to about 0.5, 1, 2, 3, 4, 5, 6, or 7x10-9 M, as measured by surface plasmon resonance (SPR) assay.

[0575] In some embodiments, the antibody is humanized.

[0576] In one aspect, provided herein are methods of producing an antibody comprising expressing the antibody as disclosed herein from a host cell and isolating the expressed antibody.

[0577] In one aspect, provided herein are pharmaceutical compositions comprising the antibody as disclosed herein and a pharmaceutically acceptable excipient.

[0578] In one aspect, provided herein are kits comprising the antibody as disclosed herein and instructions for use.

[0579] In one aspect, provided herein are isolated antibodies or antigen binding fragments thereof that binds to human MARCO (SEQ ID NO: 384) and competes for binding with a reference antibody, wherein the reference antibody comprises a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

CDR-H1 comprises the sequence GYTFTDYAVN (SEQ ID NO: 232),

CDR-H2 comprises the sequence WINTQTGKPT (SEQ ID NO: 233),

CDR-H3 comprises the sequence DSYYYSSSLDY (SEQ ID NO: 234),

CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432) or XASAGISNDLA (SEQ ID NO: 381), wherein X is arginine (R) or leucine (L),

CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 238), and

CDR-L3 comprises the sequence QQSYKYPWT (SEQ ID NO: 239).

[0580] In one aspect, provided herein are methods of treating cancer in a subject, comprising administering to the subject an antibody that competes for binding to human MARCO (SEQ ID NO: 384) with a reference antibody, wherein the reference antibody comprises a heavy chain comprising a variable heavy (VH) chain sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a light chain comprising a variable light (VL) chain sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2),

CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3),

CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4),

CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L),

CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and

CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

[0581] In some embodiments, the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy, wherein the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; anti-PD1 antibody; anti-PDL1 antibody; anti-CTLA4 antibody; adoptive T cell therapy; CAR-T cell therapy; a dendritic cell vaccine; a monocyte vaccine; an antigen binding protein that binds both a T cell and an

antigen presenting cell; a BiTE dual antigen binding protein; a toll-like receptor ligand; a cytokine; a cytotoxic therapy; a chemotherapy; a radiotherapy; a small molecule inhibitor; a small molecule agonist; an immunomodulator; and an epigenetic modulator.

[0582] In some embodiments, the immunotherapy is an anti-PD1 antibody, an anti-PDL1 antibody, or an anti-CTLA4 antibody.

[0583] In one aspect, provided herein are methods of increasing an immune response in a subject, comprising administering to the subject an antibody that competes for binding to human MARCO (SEQ ID NO: 384) with a reference antibody, wherein the reference antibody comprises a heavy chain comprising a variable heavy (VH) chain sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a light chain comprising a variable light (VL) chain sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2),

CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3),

CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4),

CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L) ,

CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and

CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

EXAMPLES

[0584] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

[0585] The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., T.E. Creighton, *Proteins: Structures and Molecular Properties* (W.H. Freeman and Company, 1993); A.L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition); Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989); *Methods In Enzymology* (S. Colowick and N. Kaplan eds., Academic Press, Inc.); *Remington's Pharmaceutical Sciences*, 18th Edition (Easton, Pennsylvania: Mack Publishing

Company, 1990); Carey and Sundberg *Advanced Organic Chemistry 3rd Ed.* (Plenum Press) Vols A and B(1992).

Example 1: MARCO is expressed in multiple tumor types

[0586] MARCO bulk RNA expression in multiple cancer types

[0587] MARCO mRNA expression in tumor and normal tissues across all indications in The Cancer Genome Atlas (TCGA) was generated by the BROAD Institute gene expression viewer on *firebrowse.org*.

[0588] Ordered MARCO mRNA expression in tumor (left bar) vs normal (right bar) tissue is shown in **FIG. 1.** The x-axis lists the following tumor types: ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; COADREAD, colon adenocarcinoma and rectum adenocarcinoma; DLBC, diffuse large b-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; GBMLGG, glioblastoma multiforme and lower grade glioma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; KIPAN, pan-kidney cohort (KICH+KIRC+KIRP); LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; STES, stomach and esophageal cancer; TGCT, testicular germ cell tumors; THYM, thymoma; THCA, thyroid carcinoma; UCS, uterine carcinosarcoma; UCEC, uterine corpus endometrial carcinoma; UVM, uveal melanoma. The y-axis represents log2-transformed values of transcript abundance from RNA-seq data, quantified using RNAseq by Expectation-Maximization (RSEM).

[0589] MARCO expression in primary tumors by scRNA-seq

[0590] Single Cell RNA Sequencing (scRNA-Seq)

[0591] 1 mL of frozen, dissociated tumor cells from various tumors were purchased from Discovery Life Sciences. The frozen pellet was thawed in a 37C water bath and gradually diluted with 25 mL of warm RPMI containing 10% FBS and 10mM HEPES, and centrifuged for 5 min at 550 rcf. The cell pellet was stained with anti-CD45-PE (clone HI30, Biolegend).

DAPI$^-$, CD45$^+$ cells were sorted on a BD FACSAria Fusion. After sorting, cells were washed with 3 mL of 0.04% BSA/PBS three times and resuspended at 5 x 10^5 cells/mL. The cells were loaded into a Chromium Chip B for a targeted cell encapsulation of 10,000 cells, and placed into the Chromium Controller (10X Genomics, Single Cell 3' v3 Reagent Kit). Post GEM-RT cleanup, cDNA amplification and library construction were performed according to the Single Cell 3' v3 user manual from 10X Genomics. The libraries were sequenced on a NovaSeq by MedGenome Inc.

[0592] Single Cell Data Processing

[0593] Sequencing data was processed using 10X Genomics Cell Ranger v3.0.2 pipeline. MedGenome Inc. provided fastq files for each sample by converting raw, Illumina bcl files into fastq files using the Cell Ranger subroutine *mkfastq*. Afterwards, Cell Ranger *count* was run, which utilizes STAR (Dobin et al., 2013) to align reads against the GRCh38 human reference genome. After filtering reads with redundant unique molecular identifiers (UMI), *count* generated gene-cellular barcode files (filtered_feature_bc_matrix folder consisting of barcodes.tsv, features.tsv, and matrix.mtx). Both *mkfastq* and *count* were run with default parameters.

[0594] Cellular Identification, Clustering, and Visualization

[0595] For each sample, the filtered_feature_bc_matrix files were passed to the R (v. 3.6.0) software package Seurat (Satija et al., 2015) (https://satijalab.org/seurat) (v2.3.4) for all downstream analyses. The features.tsv file was renamed to genes.tsv to be compatible with the *Read10X* function. Data was filtered for cells that expressed a minimum of 200 genes, all genes were expressed in at least 3 cells, and had no more than 8500 UMI. Cells that contained >20% of reads associated with mitochondrial genes and >45% of reads associated with ribosomal genes were removed. Count data was then log transformed and scaled using each remaining cell's UMI count and proportion of mitochondrial and ribosomal genes as nuisance factors (implemented in Seurat's *ScaleData* function) to correct for any remaining unwanted effects in downstream clustering and differential expression analyses. For each sample, principal component (PC) analysis was performed on a set of highly variable genes defined by Seurat's *FindVariableGenes* function. Genes associated with the resulting top PCs (chosen by visual inspection of scree plots) were then used for graph-based cluster identification and subsequent dimensionality reduction using t-distributed stochastic neighbor embedding (tSNE). Cluster-based marker identification and differential expression were performed using Seurat's *FindAllMarkers* for all between-cluster comparisons. Graphs were plotted using built-in visualization functions in Seurat (*TSNEPlot*, *FeaturePlot*).

[0596] MARCO is predominantly expressed in human tumor monocytes and macrophages as determined by the scRNA-seq analysis (data not shown). Tumor cells from lung cancer, kidney (RCC) cancer, ovarian cancer, colorectal cancer, and head and neck cancer all showed expression of MARCO on monocytes and macrophages.

[0597] MARCO RNA expression is induced by IL-10

[0598] Differentiated human macrophages were polarized by adding the following cytokines to the media for 24 hours at 37 C: 50 ng/ml lipopolysaccharide (LPS) (InvivoGen), 25 ng/ml recombinant human IFN-γ (PeproTech), LPS+ IFN-γ, IL-4, IL-10, TGF-β, TGF-β+, or IL-10. The media was then removed and macrophages lysed in 300µl of RLT buffer + BME, followed by RNA extraction using the Qiagen kit. The mRNA quantity and quality were assessed by Nanodrop and the Agilent Bioanalyzer before sending the samples to Medgenome for library preparation and RNAseq. MARCO mRNA expression in each of the polarization conditions was then extracted from the RNAseq analysis and plotted in log2 CPM units.

[0599] As shown in **FIG. 2**, MARCO RNA expression was induced by IL-10 in Human Monocyte-derived Macrophages (MDMs)

[0600] IL10 and MARCO expression correlate across indications

[0601] All single indication, Level 2, RNAseq data from TCGA were downloaded from the Broad Institute using *firehose_get*. RSEM values for MARCO, IL-10, PTPRC (CD45), and TREM2 expression from tumor samples were converted to log 2 counts per million. Per-indication, median values for MARCO and IL10 expression were plotted in R. Dot size was scaled by the degree of IL10-MARCO Spearman rank correlation. The matrix of per-indication, median expression values for the genes listed above was transformed into a matrix of Spearman correlations and plotted as a heatmap using the *pheatmap* package in R.

[0602] **FIG. 3A** shows the correlation of MARCO and IL-10 expression in various tumor types, and **FIG. 3B** shows a heat map of the correlation between TREM2 expression, CD45 expression, IL-10 expression, and MARCO expression. As shown in **FIGs. 3A** and **3B**, IL10 and MARCO expression are well correlated across cancer indications.

[0603] MARCO expression and correlation with patient survival in different indications

[0604] In colorectal cancer (CRC)

[0605] Prenormalized MARCO expression profiles and associated clinical data across 55 colorectal tumors were downloaded from NCBI's GEO website (accession GSE17537). Expression profiles were divided into two cohorts based on median level of MARCO. Kaplan-Meier survival curves were plotted for each cohort and the associated logrank test

was carried using the *survival* and *survminer* packages in R. As shown in **FIG. 4A**, MARCO expression inversely correlated with patient survival probability in CRC; higher MARCO expression correlated with lower patient survival probability and lower MARCO expression correlated with higher patient survival probability.

[0606] In Renal Cell Carcinoma (RCC)

[0607] Survival associations of two cohorts of kidney cancer (renal cell carcinoma) from TCGA based on median split of MARCO mRNA expression generated by the Gene Expression Profiling Interactive Analysis (GEPIA2) viewer at *http://gepia2.cancer-pku.cn/#index.*

[0608] As shown in **FIG. 4B**, MARCO expression is inversely correlated with patient survival probability in RCC; higher MARCO expression correlated with lower patient survival probability and lower MARCO expression correlated with higher patient survival probability in RCC.

[0609] In Neuroblastoma

[0610] Pre-normalized MARCO expression profiles and associated clinical data across 498 neuroblastoma tumors were downloaded from NCBI's GEO website (accession GSE62564). Expression profiles were divided into two cohorts based on median level of MARCO. Kaplan-Meier survival curves were plotted for each cohort and the associated logrank test was carried using the *survival* and *survminer* packages in R.

[0611] As shown in **FIG. 4C**, MARCO expression is inversely correlated with patient survival probability in neuroblastoma; higher MARCO expression correlated with lower patient survival probability and lower MARCO expression correlated with higher patient survival probability in neuroblastoma.

[0612] Prenormalized MARCO expression profiles and associated clinical data across 394 neuroblastoma tumors were downloaded from NCBI's GEO website (accession GSE120572). MARCO expression profiles were plotted for all samples with an identified INSS Stage. Statistics for paired comparisons were generated using the Wilcoxon Rank Sum Test in R. As shown in **FIG. 4D**, MARCO expression increased as function of disease severity in neuroblastoma, according to INSS stage.

[0613] In Basal-Like Breast cancer

[0614] MARCO expression from TCGA across PAM50 subtyping of human breast cancer generated by the Gene Expression Profiling Interactive Analysis (GEPIA2) viewer at *gepia2.cancer-pku.cn/#index*. METABRIC expression profiling and associated clinical data was downloaded from cBioPortal at *cbioportal.org*. Normalized MARCO expression profiles

were plotted in R across cohorts based on PAM50 subtyping. Statistics for paired comparisons were generated using the Wilcoxon Rank Sum Test in R.

[0615] As shown in **FIG. 5**, MARCO is upregulated in basal-like breast cancer relative to other breast cancer subtypes. The left panel shows the MARCO expression from TCGA, the right panel shows the MARCO expression from METABRIC.

[0616] MARCO is highly expressed on a population of intratumoral intermediate monocytes. Gene signatures of immune desert and exclusion were upregulated in the MARCO+ cluster. Aggregated TAMs and monocytes derived from single cell sequencing of human immune cells from bladder, breast, colorectal, endometrial, gastric, head and neck, kidney, lung, and ovarian tumors yielded a single cluster with substantially elevated MARCO expression in transitioning monocytes (cluster 2). Gene Set Enrichment Analysis (GSEA) of Hallmark pathways (MARCO-rich cluster 2 vs. all other macrophages and monocytes) showed that MARCO expression was associated with immunosuppressive, matrix-associated gene sets (e.g., angiogenesis, EMT) and downregulated for inflammatory, interferon-based pathways. Significant (FDR < 0.05) pathways identified that were upregulated in MARCO+ cells were glycolysis, oxidative phosphorylation, epithelial mesenchymal transition, hypoxia, xenobiotic metabolism, angiogenesis, cholesterol homeostasis, adipogenesis, fatty acid metabolism, reactive oxygen species pathway, and mTORC1 signaling. Significant (FDR < 0.05) pathways identified that were downregulated in MARCO+ cells were allograft rejection, TGF-b signaling, KRAS signaling DN, TNFα signaling vi NF-kB, IFNγ response, and IFNα response.

Example 2: Production and characterization of anti-human MARCO antibodies

[0617] *First generation of Hybridomas*

[0618] An antibody campaign was performed at Antibody Solutions (Sunnyvale, CA) with two Rapid campaigns on 3 Balb/c mice each and one standard campaign on 4 Balb/c mice using a human MARCO His-tagged extracellular domain (His-ECD 147-520, using residues 147-419 of the Collagen-like domain (CLD) and residues 424-520 of the Scavenger Receptor Cysteine-Rich (SRCR) domain, Pi-114) as the immunogen. The rapid immunization program consisted of 10 injections, 2x a week, utilizing the footpad as the route. The standard immunization program consisted of 5 injections over the course of 12 weeks, utilizing the subQ as the route. Rapid 1 campaign included TLR + anti-CTLA4 for adjuvants while Rapid 2 campaign included TLR + anti-GITR. The mouse serum was tested at different timepoints for antigen titer by ELISA. Spleen and lymph nodes from the mouse from Rapid 1 campaign

with the highest titer were fused and the hybridoma library was created to provide an immortal population of antibody producing cells representing the stimulated B-cell population responding to the antigen. Single cell cloning by FACS sorting was performed to generate single clones hybridomas for monoclonal antibody cultures. 2,880 clones were then screened by dual flow cytometry for binding to mouse and human 293T overexpressing MARCO cell lines and using a GFP expressing cell line (GFP-293T) as the negative control for no binding. 33 clones were identified from the primary screen with cross-reactivity to both human and mouse MARCO and with no to low background binding and were additionally screened by ELISA on the MARCO human antigen Pi-114. Hybridoma supernatants from the 33 clones were checked for cell binding by flow cytometry.

[0619] *Generation of stably overexpressing cell lines*

[0620] Mouse and human MARCO DNA sequences were cloned in the pLenti-GIII-CMV-GFP-2A-Puro lentiviral vector at Abmgood (Vancouver, Canada) and amplified using standard bacterial transformation protocols using *E.coli* DH5-alpha strains to produce high yields of plasmid for lentiviral packaging. Viral particles from the empty GFP control vector, Human MARCO, and mouse MARCO cloned lentiviral vectors were produced and packaged in 293T cells and concentrated for high titers. 293T cells were used as the target cells for infection using the virus provided by Abmgood following their protocols and guidelines. Puromycin was used to select for infected pools and single clones expressing homogeneous high levels of Mouse MARCO (293T_MuMARCO), human MARCO (293T_HuMARCO), and GFP (293T_GFP) were expanded.

[0621] pD2109-CMV-puromycin lentiviral backbone was subsequently generated to clone additional MARCO plasmids without and with IRES-GFP: Human MARCO full length with GFP (plasmid 3012) and without GFP (plasmid 3010), Mouse MARCO full length with GFP (plasmid 3013) and without GFP (plasmid 3011), Cynomolgus MARCO (cyno MARCO) full length with GFP (plasmid 3021) and without GFP (plasmid 3014), Human MARCO CLD only (1-419, plasmid 3022), and the chimera Mouse MARCO CLD – human MARCO SRCR with IRES- GFP (plasmid 3020). 293FT cells from Sigma were transfected with the above constructs using Fugene to produce lentiviral particles and subsequently transduce 293T cells. Puromycin was used to select the positive clones, which were expanded to generate the following stable pools of cells for in vitro use: 3010 (Hu_MARCO), 3012 (Hu_MARCO_GFP), 3011 (Mu_MARCO), 3013 (Mu_MARCO_GFP), 3014 (Cy_MARCO), 3021 (Cy_MARCO_GFP), 3020 (MuCLD_HuSRCR_GFP), and 3022 (Hu_MARCO_CLD).

[0622] *Characterization of binding of the anti-MARCO hybridomas and anti-MARCO antibodies to cell surface expressed MARCO*

[0623] HEK293T cells expressing human MARCO (293T_HuMARCO), mouse MARCO (293T_MuMARCO), cyno MARCO (CyMARCO), and GFP-expressing control cell line (293T_GFP) were maintained in DMEM (Gibco) with 10% FBS at 37°C. Cells were counted and then harvested by centrifugation at 400xg for 5 minutes (min). Supernatants were removed and cell pellets were resuspended in Ca^{2+}+ and Mg^{2+}+ Dulbecco's phosphate-buffered saline (D-PBS) at $1x10^6$ cells/ml. 100,000 cells/well were plated onto U-bottom 96-well plates for staining and all centrifugation steps were performed at 1500rpm at 4°C for 5 min and samples were kept protected from light throughout the protocol. Cells were pelleted and resuspended in 100 µl of Zombie NIR viability dye (BioLegend) prepared by diluting Zombie NIR dimethyl sulfoxide (DMSO) stock 1000-fold in D-PBS. Cells were stained by incubation for 10 min at room temperature (RT) in the dark, followed by quenching the staining reaction with the addition of 100 µl of Staining Medium (D-PBS containing 2% FBS and 2 mM ethylenediaminetetraacetic acid (EDTA). Cells were pelleted and resuspended in 100 µl of the different antibodies and hybridomas supernatants needed for screening and corresponding isotype controls in freshly prepared staining medium, such as PI-M014 and mIgG2b isotype. All mAbs were tested at the final top concentration of 100 nM (15µg/ml) followed by an 8-point three-fold serial dilution, including 0 mg/ml control. Staining was carried out for 1 hour (hr) on ice, followed by 2 washes in Staining Medium. Cells were then pelleted and resuspended in 100 ul of allophycocyanin (APC)-conjugated goat anti-mouse IgG (Fc-specific) secondary antibody, prepared by 500-fold dilution of the antibody stocks in Staining Medium, and incubated for 30 min on ice. Plates were then washed two times with Staining Medium, followed by resuspension in 150ul of the same buffer for acquisition on the flow cytometer (Attune NxT, Life Technologies). Flow cytometry data were analyzed using FlowJo software (version 10.6.1) and data were processed and further analyzed in Microsoft Excel and GraphPad Prism software (version 8). Half-maximal effective concentrations (EC_{50}) were calculated based on geometric mean fluorescence intensities (gMFI). In case when the plates were not able to be analyzed on the cytometer, cells were pelleted after the washes and fixed in 100 µl of 2% paraformaldehyde (PFA), prepared by diluting the 16% (w/v) stock (Thermo Fisher) in DPBS, for 15 min at RT. Cells were then pelleted and the fixative was removed, followed by resuspension in 150 µl of Staining Medium and stored at 4°C until acquisition on the flow cytometer.

[0624] **FIG. 6A** shows the binding of the 33 antibodies to GFP-239T control cells (left bar), or cells expressing human MARCO (middle bar) or mouse MARCO (right bar). **FIG. 6B** shows flow cytometry histograms of one MARCO antibody, PI-M014, binding to cells expressing huMARCO, muMARCO, and CynoMARCO, as compared to control cells (GFP control). **FIG. 6C** shows a titration of PI-M014 and isotype control antibody binding to cells expressing huMARCO. PI-M014 bound to huMARCO with an EC50 of 1.37nM.

[0625] Characterization of binding of the anti-MARCO hybridomas and anti-MARCO antibodies to recombinant MARCO by ELISA

[0626] Hybridomas from Antibody Solutions or the anti-MARCO antibodies were screened by enzyme-linked immunosorbent assay (ELISA) on recombinant human MARCO protein (Pi-114 His tag). Briefly, 96-well plates (Biolegend) were coated with 1 ug/well of recombinant MARCO protein, overnight in D-PBS. Plates were washed 3X with PBS/0.1% TWEEN-20/2mM EDTA (ELISA wash buffer) and blocked with 1% BSA for 2 hrs at RT. Antibodies were incubated for 1h at RT at the final top concentration of 5μg/ml followed by an 8-point three-fold serial dilution in PBS, including 0 mg/ml control. Plates were washed as above and incubated with goat anti-mouse IgG F(ab')2 Fragment-HRP conjugated secondary antibody (Jackson Immuno) at 1:5000 dilution for 1 hr at room temperature. Plates were washed 4 times in the above ELISA wash buffer and developed with TMB substrate for 10 min (Thermo) and stopped with TMB Stop Solution (1M H_3PO_4 Phosphoric Acid), and the A450 determined using a plate reader (SpectraMax i3x).

[0627] *MARCO antibody kinetics characterization by SPR*

[0628] Surface plasmon resonance (SPR) was performed on the BIAcore™ T200 (GE Healthcare) instrument and all data were collected at 25°C using multi cycle kinetics. An anti-mouse Fc mAb (GE Healthcare) was immobilized on a CM4 biosensor chip (GE Healthcare) using amine coupling chemistry with 4500 RUs as target for immobilization of the mAb. Serial dilution of were made in mobile buffer containing 10 mM HEPES pH 7.4, 150 mM NaCl, 3mM EDTA and 0.05% (v/v) surfactant P20. Anti-mouse Fc mAb was used to capture select monoclonal antibodies against human MARCO antigen (ligand). The anti-MARCO antibodies tested were PI-M014, PI-M015, PI-M017, and PI-M018. The interacting analyte used was N-terminally polyhistidine tagged human MARCO ECD (147-520) termed PI-RG-3000 The following range of antibody concentrations was injected into flow cells: 0.625 nM, 1.25 nM, 2.5 nM, 5 nM and 10nM. A flow rate of 30μL/min, with an association and dissociation time of 90 and 600 seconds, respectively. After each cycle (comprising of

the antigen capture, antibody association and dissociation phases), the cell surface was regenerated by injecting 10 mM glycine HCl buffer pH 1.7 for 100 seconds at 50µL/min flowrate. Kinetic evaluation was performed using BIAevaluation 3.1 software to determine single cycle and multi cycle kinetics.

[0629] PI-M014 monomer had a K_D of 3.91 nM in a single SPR cycle, and a K_D of 1.32 nM in a multi cycle assay. PI-M015 monomer had a K_D of 0.39 nM in a multi cycle assay. PI-M017 monomer had a K_D of 0.96 nM in a multi cycle assay. PI-M018 monomer had a K_D of 1.65 nM in a multi cycle assay.

[0630] *MARCO cell surface expression on human monocyte derived macrophages*

[0631] Frozen human peripheral blood $CD14^+$ monocytes isolated from peripheral blood mononuclear cells using negative immunomagnetic selection (StemCell Technologies) were thawed and cultured in RPMI 1640 medium supplemented with 10% (v/v) heat-inactivated FBS (HyClone), 1 mM sodium pyruvate, non-essential amino-acids, 2 mM L-glutamine, 55 uM 2-mercaptoethanol and antimycotic antibiotic (all from Gibco). Monocytes were differentiated into macrophages by culturing in complete RPMI 1640 medium in the presence of 50 ng/ml human macrophage colony-stimulating factor (M-CSF) (PeproTech) at a density of 12-15x10^6 cells in 15cm dish. At day 3 of differentiation, media was replenished with the addition of fresh M-CSF. After 7 days of differentiation, macrophages were gently harvested non-enzymatically using a sterile cell scraper (Nunc) into FACS buffer (D-PBS containing 2 mM EDTA and 0.5% (w/v) bovine serum albumin (BSA) (Sigma)) followed by centrifugation at 400xg for 5 min at ~20°C.

[0632] Cells were counted and seeded onto 96-well plates at 250,000 cells per well. 100 ul of Zombie NIR viability dye (BioLegend), prepared by diluting the stock 1000-fold in D-PBS, was added to each well and incubated for 10 min at RT in the dark. The reaction was quenched by addition of 150 ul of FACS buffer, followed by centrifugation at 400xg for 5 min at 4°C. Cells were then incubated in 100 ul of blocking solution, containing 2.5% mouse and 2.5% rat serum and human TruStain FcX (BioLegend) diluted 50-fold in Fc receptor blocker (Innovex Biosciences), for 20 min in the dark. Cells were then washed and resuspended in 100 µl of the different antibodies needed for screening and corresponding isotype controls in freshly prepared in FACS buffer (PI-M014, PI-M015, PI-M017, PI-M018, mouse IgG2a and mouse IgG2b all APC-conjugated with the Thermo Fisher conjugation kit). mAbs were tested in single point concentrations (3.33µg/ml for PI-M014 or 5µg/ml for the other mAbs) and primary incubation was carried out for 20-30 min on ice, followed by 2

washes in FACS buffer. Cells were resuspended in 150ul of the same buffer for acquisition on the flow cytometer (Attune NxT, Life Technologies). Flow cytometry data were analyzed using FlowJo software and data were processed and further analyzed in Microsoft Excel and GraphPad Prism software.

[0633] PI-M014 bound to human monocyte-derived macrophages, as shown in **FIG. 6D**.

[0634] *Mouse Antibody-Dependent Cellular Phagocytosis (ADCP) Assay*

[0635] Bone marrow derived macrophages were generated as demonstrated previously, using 25 ng/ml of murine CSF-1 (Peprotech) for differentiation. On day 6 of culture, 25ng/ml of murine IFN-γ (peprotech) was added to the BMDM culture for 18 hours. The following day, cells were stimulated with 200ng/ml LPS (invivogen) for 2 hours before use in ADCP assay. IFN-γ/LPS-induced BMDM served as effector cells and the GFP+ HEK293T cells transduced with human MARCO (293T Hu_MARCO) or control (293T_GFP) were targets. After harvest, effector BMDM were stained with Cell-Trace Violet dye (invitrogen) for 20 minutes at 37°C. 50,000 target cells were plated in 96-well U-bottom plates and co-incubated with anti-MARCO mAbs or corresponding isotype (PI-M014 to PI-M018). Antibodies were serially diluted and prepared in media for 30 minutes at 37°C. Effector cells were then added to Antibody-Target plates at a 3:1 ratio (150,000 effectors to 50,000 targets) and incubated for 2 hours at 37°C. Following incubation, cells were viability stained using Zombie NIR (BioLegend) then fixed using 2% Paraformaldehyde (Invitrogen) for 20 minutes at room temperature prior to being run on an Attune NXT flow cytometer (ThermoFisher). ADCP activity was assessed based on double-positivity of Cell Trace Violet and GFP levels, gated downstream of live cells.

[0636] Incubation of target cells with PI-M015 and PI-M017 both induced ADCP activity by effector cells. The results are summarized in **Table 1**, below.

[0637] *HuMARCO Antibody Epitope Binning*

[0638] The ForteBio Blitz label free system was used to analyze the epitopes for the anti-MARCO antibodies.

[0639] For the tandem format, N-terminal his-tagged MARCO protein was loaded onto the ForteBio anti-his probe followed by baseline and then association with the first antibody. Following binding of the first antibody, a second antibody was added and the association of the second set of antibodies was measured. Any additional binding observed for the second antibody, measured as an increased signal indicates that the second antibody bound to a different epitope than the first antibody.

[0640] PI-M015 and PI-M017 competed with each other for binding to the MARCO antigen, indicating they bind to the same MARCO epitope (**FIG. 7**). All other antibodies bound to different epitopes and did not compete with any other antibody for binding to MARCO. However, the antibodies only bound to the CLD domain of human MARCO and did not bind to the SRCR domain of human MARCO.

[0641] *MARCO expression on primary human DTCs tumors and Peripheral Blood Leukocytes (PBLs)*

[0642] MARCO expression was assessed in the microenvironment of human tumors from three indications by flow cytometry, ovarian cancer and gastric cancer, using the newly developed human MARCO antibodies. Tumor tissues were previously dissociated as "dissociate tumor cells" (DTCs) and snap frozen (Folio Conversant). DTCs were thawed following the manufacturer's guidelines and were counted to assess total viable cells. PBLs were isolated from buffy coats (two donors from Stanford Blood Center). The single cell suspensions from DTCs and PBLs were diluted in PBS (Gibco), washed once, and stained with Zombie NIR (Biolegend) to determine cell viability. Fc receptors were also blocked with a combination of human serum (Jackson Immunoresearch), human FcX (Biolegend), and a peptide-based FcR block solution (Innovex Biosciences). After incubation with FcR blocking reagents, surface receptors on the DTCs were stained with a flow cytometry cocktail encompassing markers for major intratumoral immune subsets as well as isotypes control (5µg/ml mIgG2a or mIgG2b or Rat IgG2a) and anti-human MARCO antibodies directly conjugated (5µg/ml PI-M017 or PI-M018 or PI-HX-3031). Cells were also fixed and permeabilized (True-Nuclear Transcription Buffer Set, Biolegend) in order to determine intracellular CD68 expression. PBLs were stained with a flow cytometry cocktail encompassing markers for major blood immune subsets as well as the isotype control (10µg/ml hIgG1-conjugated with PE Zenon labeling) and anti-human MARCO antibodies (10µg/ml PI-3010, PI-3030, and PI-3031- conjugated with PE Zenon labeling). Data from DTCs and PBLs was acquired using an Attune NxT analyzer (ThermoFisher) and analyzed using FlowJo (BD Biosciences).

[0643] **FIGs. 8A** and **8B** show that MARCO is expressed in human MDMs (**FIG. 8A**) and tumor associated macrophages (TAMs) from primary human tumor samples (gastric cancer and ovarian cancer, **FIG. 8B**). In **FIG. 8A** and **8B**, the right peak(s) indicates MARCO antibody PI-M018 or PI-M017 binding and staining, while the left peak indicates isotype mIgG2a binding.

[0644] A summary of the binding and functional characterization of selected antibodies from the first antibody campaign is shown in **Table 1**.

Table 1

Anti-huMARCO mAb	Isotype	Epitope bin and map	K_D (nM)	Endogenous cell binding	Human EC_{50} 293T (HuMARCO) (nM)	Cyno EC_{50} 293T (CyMARCO) (nM)	Mouse EC_{50} 293T (MuMARCO) (nM)	ADCP/ADCC in BMDM assay in vitro
PI-M014	mIgG2b	4 (CLD)	1.32	+	7.861	11.07	41.57	No
PI-M015 (RDM1)	mIgG2a	1 (CLD)	0.39	+	1.606	1.206	NB	Yes
PI-M017 (RDM7)	mIgG2a	1 (CLD)	0.96	+	1.59	1.522	NB	Yes
PI-M018 (RDM9)	mIgG2b	3 (CLD)	1.65	+	1.851	45.4	NB	No

[0645] *NB: No binding

Example 3: Production and characterization of anti-mouse MARCO antibodies

[0646] Materials and Methods

[0647] *Immunization for generating anti-mouse MARCO antibodies*

[0648] Rat anti-mouse MARCO hybridomas were generate by immunizing Sprague Dawley rats with recombinant N-terminal-his-tagged mouse MARCO protein produced at Pionyr, using Sigma Adjuvant System (SAS) alone or alternating with mouse MARCO expressing HEK293 cells, also in SAS. The sequence of the recombinant N-terminal-his-tagged mouse MARCO protein used is shown below. Recombinant mouse MARCO protein was analyzed by SDS-PAGE and using size exclusion chromatography to confirm that the protein molecular weight was correct.

[0649] Rats were immunized twice weekly in the hock at Antibody Solutions (Santa Clara, CA) and serum titers tested at day 21 by ELISA. Rats with sufficient serum antibody titers to mouse MARCO were chosen for electrofusion to generate hybridomas. Two final boosts were given on days -3 and -2 prior to harvest in phosphate buffered saline (PBS).

[0650] The mouse MARCO mAb RDM-9514 was purchased from R&D biosystems (CUST017 MABP, Clone 57914) as a custom purified hybridoma clone, raised in rat against NS0-derived recombinant mouse MARCO Gln70-Ser518.

[0651] *Hybridoma Generation*

[0652] Lymph node cells were harvested from immunized rats and single cell suspensions generated. Lymphocytes were fused with the myeloma cell line, SP2/0-Ag 14 (ATCC) using electrofusion with the BTX EC2000+ electrofusion apparatus (Harvard Bioscience). Fused

cells were plated into 96-well flat-bottom plates (Corning) and recovered overnight in Clona-Cell Medium E containing HT (Stem Cell Technologies). The following day, aminopterin (Sigma) was added to the cultures to a 1X final concentration. Fusions were fed on day 6 and day 8, and screened on day 11.

[0653] *Hybridoma screening*

[0654] Hybridomas were screened by enzyme-linked immunosorbent assay (ELISA) on either recombinant mouse MARCO protein or recombinant human MARCO protein depending on the immunization. Briefly, 96-well Maxisorp plates (Nunc) were coated with 0.1 ug/well of recombinant MARCO protein, overnight in DPBS containing Ca2+ and Mg2+ (Gibco Cat#14040117)-. Plates were washed 3X with PBS/0.05% TWEEN-20 and blocked with PBS/Ca2+ containing 2% fetal bovine serum. Hybridoma supernatants were added 1:1 to the wells with PBS/Ca2+/2% FBS buffer and incubated at room temperature for 1 hour. Plates were washed as above and incubated with goat anti-rat IgG -HRP conjugated secondary antibody (Jackson Immuno) or mouse anti-rat IgG (1, 2a, 2b) HRP conjugated antibodies (Southern Biotech) for 1 hr at room temperature. Plates were washed and developed with TMB substrate (Thermo) and stopped with TMB Stop Solution (Suromodics), and the A450 determined using a platereader (Tecan). Hybridomas producing anti-MARCO antibodies were transferred to a 24-well plate and the supernatant from positive clones re-tested for MARCO reactivity and further tested in additional binding assays. Hybridomas were screened on recombinant human MARCO, recombinant mouse MARCO, and control recombinant his-tagged protein to eliminate any non-specific or his-tag specific clones and also tested on mouse MSR1 (R&D Systems) or human MSR1 (R&D Systems) to check for cross-reactivity to related scavenger receptor proteins. Hybridomas were also tested for binding to two chimeric proteins, N-terminal recombinant human MARCO SRCR/mouse CLD protein and N-terminal recombinant mouse MARCO SRCR/human CLD protein to determine the domain on the MARCO protein for which antibodies were specific. The sequences for the recombinant proteins used in these studies is below:

[0655] N-terminal his-tagged mouse MARCO protein:

[0656] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG

QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGR
ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS

[0657] N-terminal his tagged chimeric MARCO protein (human SRCR/mouse CLD domains):

[0658] HHHHHHHHKGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQ
GPQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGD
KGDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGK
PGVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQ
KGTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEK
GQKGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGYSKGRA
LYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV

[0659] N-terminal his tagged chimeric MARCO protein (mouse SRCR/human CLD domains):

[0660] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLG
YSRGRALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS

[0661] *Cell Binding*

[0662] Clones positive for binding to MARCO by ELISA were tested for binding to cell surface MARCO by staining human MARCO -293 cells, mouse MARCO-293 cells, or control 293 cells and testing by flow cytometry using the Intellicyt iQue flow cytometer. Hybridomas that were positive for binding to MARCO by ELISA and to cell surface MARCO by flow cytometry were chosen for subcloning and purification.

[0663] *Hybridoma subcloning and purification*

[0664] Subcloning of parental hybridomas was performed by single cell sorting on the FACSAria. Single cells were sorted into flat-bottom 96-well tissue culture plates into Clona-Cell Medium E. Single cells were cultured for 7-9 days and then assayed for anti-MARCO specific clones by ELISA, as described above.

[0665] Monoclonal hybridomas were then culture for purification by growth in serum-free expansion medium (AOF, Stem Cell Technologies) and purified using either protein A or protein G.

[0666] *Hybridoma antibody variable region sequences generation*

[0667] Total RNA was extracted from (104 to 106) monoclonal hybridoma cells using the RNeasy purification kit (Qiagen Cat#74134), then reverse transcription (RT)was performed to synthesize cDNA using Maxima H Minus First Strand cDNA Synthesis Kit (Thermofisher Cat# K1651) and reverse gene specific primers(GSP1). cDNA was purified to remove GSP and enzymes in the RT reaction using the QIAquick PCR Purification Kit (Qiagen Cat# 28104). Terminal Deoxynucleotidyl Transferase was used to add a string of oligo-dA to the 3' end of the cDNA (Thermo Scientific Cat#10533065), the product was purified again (QIAquick PCR Purification Kit Cat# 28104) before amplification. PCR was then carried out using a second gene specific primer (GSP2) and the Oligo-dT forward primer that binds the Oligo-dA tail previously added to the 3' ends of the cDNAs. PCR products were sequenced. In cases where sequences of insufficient quality were generated from PCR products, the PCR products were TOPO cloned and transformed into E. coli, and single colonies processed for sequencing.

[0668] The primers used are listed below:

[0669] GSP1-mk: TTGTCGTTCACTGCCATCAATC

[0670] GSP2-mk: ACATTGATGTCTTTGGGGTAGAAG

[0671] GSP1- mHC: AGCTGGGAAGGTGTGCACAC

[0672] GSP2-mHC: GGGATCCAGAGTTCCAGGTC

[0673] GSP1-rk: GT GAG GAT GAT GTC TTA TGA ACA

[0674] GSP2-rk: GCCATCAATCTTCCACTTGACAC

[0675] GSP1-rHC: GAG ATG STT TTC TCG ATG GG

[0676] GSP2-rHC: GS GGG AAG ATG AAG ACA GAT G

[0677] *Calcium dependency ELISA assay*

[0678] The purpose of this assay was to determine the calcium dependency for binding to MARCO by the anti-MARCO antibodies. This assay can apply to both hybridoma supernatant and purified antibodies.

[0679] 0.05μg/ml of the human or mouse MARCO recombinant proteins were coated on 4 Nunc-Immuno™ MicroWell plates using the following conditions: in DPBS with Ca2+ (Gibco Cat#14040117), in DPBS without Ca2+ (Gibco Cat#14190136) with 2mM EDTA (Invitrogen Cat# 15575020) -Plate B, in DPBS without Ca2+ with 10mM EDTA , and in DPBS without Ca2+ with 50mM EDTA.

[0680] After the plates were incubated at room temperature for 1 hour or 4°C overnight, the plates were wash 3 times with ELISA wash buffer (PBS/0.05% TWEEN-20), then

hybridoma supernatant (1:5 dilution) or purified antibody (1ug) was diluted in DPBS /Ca2+ /2% FBS, DPBS without Ca2+ /2mM EDTA/2% FBS, DPBS without Ca2+/10mM EDTA/2% FBS, and DPBS without Ca2+/50mM EDTA/2% FBS. Plates again were incubated at room temperature for 1 hour.

[0681] Plates were washed as above and incubated with goat anti-mouse IgG -HRP (Jackson) or a mixture of mouse anti-rat IgG-HRP (1+2a+2b) 1:1:1 (SouthernBiotech Cat# 3060-05, 3065-05, 3070-05) diluted 1:5000 for 1 hr at room temperature in the 4 different buffers as above. Plates were then washed and developed with TMB substrate (Thermofisher) and stopped with TMB Stop Solution (Surmodics), and read at A450 using a Tecan plate reader.

[0682] *Kinetics and epitope binning using the ProbeLife Gator instrument*

[0683] The Probe-Life Gator™label free system was used to analyze binding kinetics and epitopes for the anti-MARCO antibodies.

[0684] The kinetics assay used either anti-mouse Fc or anti-human Fc probes to capture the anti-MARCO antibodies onto the probe, and then a five-step kinetic protocol was used to measure the affinity of the antibodies to the antigen, including the following steps: baseline, loading, baseline, association, and dissociation. The kinetics buffer (K buffer) provided by ProbeLife was used to establish the baseline for 60 seconds, and then the anti-mFc or anti-hFc probes were loaded with 200nM of the antibodies for 120s until the capture reached saturation, measurement of the baseline in K buffer was performed for another 60s, followed by the association step using 200nM antigen (human MARCO, mouse MARCO or cyno MARCO), and the dissociation step performed in K buffer for 5-10 minutes. The assay was done at 37°C to maximize antibody:antigen dissociation.

[0685] For epitope binning of the antibodies, both tandem and sandwich formats were used.

[0686] For tandem format, 200nM of the N-terminal his-tagged MARCO protein was loaded onto ProbeLife anti-his probe for 120s or until binding reached saturation, followed by baseline for 60s and then association with the first set of saturating antibodies loaded at 200nM. Following binding of the first antibody, a second antibody was added at 100-200nM) and the association of the second set of antibodies was measured. Any additional binding observed for the second antibody, measured as an increased signal indicates that the second antibody bound to a different epitope than the first antibody.

[0687] For sandwich assay format, the first antibody at 200nM was loaded onto anti-mFc or anti-hFc probes for 120s, followed by a baseline step, and then association with MARCO antigen (200nM) for 120s. Association of the second antibody at 200nM was then measured for 120s to determine if there was additional binding. In this format, where the first antibody

was at low concentration, additional isotype control antibody was added after the first association in order to saturate free binding sites on the probe. All probes and buffers were directly ordered from ProbeLife.

[0688] *MARCO staining on BMDMs with the anti-mouse MARCO hybridomas*

[0689] Femurs and tibias from three female C57BL/6 mice (Jackson Laboratories) were cleaned and crushed in Staining Medium (0.5% (w/v) BSA (Sigma) and 2 mM EDTA in D-PBS) using a mortar and pestle. Samples were then passed through a 40 um filter, washed with D-PBS and pelleted at 400xg for 5 min at RT. Cell pellets were resuspended in 5 ml of BD Pharm Lyse buffer (BD Biosciences) and red blood cell lysis was carried out at RT for 5 min, followed by quenching with 10 volumes of Staining Medium. Cells were pelleted at 400xg for 5 min at RT and resuspended in Macrophage Medium composed of Iscove's modified Dulbecco Medium supplemented with 10% (v/v) fetal bovine serum (FBS) (HyClone) and antibiotic-antimycotic solution (Gibco), at the density of 15x106 cells/ml in 15 cm plates. These bone marrow mononuclear cells were stimulated with 25 ng/ml of mouse macrophage colony-stimulating factor (M-CSF) (PeproTech) for 7 days to generate M0-macrophages and differentiated into M1-like by supplementing the medium with LPS at 100ng/ml on day 6 and into M2-like macrophages by adding 20ng/ml of IL-10. After 18 hours of incubation at 37C with polarizing cytokines, M0, M1, and M2-like macrophages were rinsed with DPBS and incubated in 6 ml of 2 mM EDTA for 10 minutes to promote cell detachment. Cells were gently scraped into an additional 6 ml of the Staining Medium described above, counted and seeded onto 96-well plates at 250,000 cells per well. 100 ul of Zombie NIR viability dye (BioLegend), prepared by diluting the stock 1000-fold in D-PBS, was added to each well and incubated for 10 min at RT in the dark. The reaction was quenched by addition of 150 ul of Staining Medium, followed by centrifugation at 400xg for 5 min at 4°C. Cells were then incubated in 100 ul of blocking solution, containing 2.5% mouse and 2.5% rat serum and mouse TruStain FcX PLUS (BioLegend) diluted 50-fold in Fc receptor blocker (Innovex Biosciences), for 20 min in the dark. Cells were then washed and resuspended in 100 µl of the different antibodies and hybridomas needed for screening and corresponding isotype controls in freshly prepared FACS buffer containing 2% FBS in DPBS with Ca2+ (RDM-9514, HX-3012, HX-3014, HX-3016, HX-3017, Rat IgG2a and Rat IgG1 all PE-conjugated with the PE Lightning kit). RDM-9514 was tested at the final top concentration of 10µg/ml followed by an 8-point three-fold serial dilution in PBS the highest dose of 10µg/ml. The internal hybridomas were tested at the single point concentrations of 5µg/ml. Staining was carried out for 20-30 min on ice, followed by 2 washes in FACS buffer.

Cells were resuspended in 150ul of the same buffer for acquisition on the flow cytometer (Attune NxT, Life Technologies). Flow cytometry data were analyzed using FlowJo software (version 10.6.1) and data were processed and further analyzed in Microsoft Excel and GraphPad Prism software (version 8). Data was plotted as Delta gmfi between the antibody and corresponding isotype. In case when the plates were not able to be analyzed on the cytometer, cells were pelleted after the washes and fixed in 100 µl of 2% paraformaldehyde (PFA), prepared by diluting the 16% (w/v) stock (Thermo Fisher) in DPBS, for 15 min at RT. Cells were then pelleted and the fixative was removed, followed by resuspension in 150 µl of Staining Medium and stored at 4°C until acquisition on the flow cytometer.

[0690] *MARCO staining on tumors with anti-mouse MARCO PE conjugated mAbs*

[0691] Py8119 and CT26 tumors were harvested from mice when they reached a volume of ~ 400mm3. Fat and fibrous material were removed from the tumors by dissection. The tumors were then weighed and processed for single-cell suspension by a combination of mechanical and enzymatic dissociation. After mincing the tissues, tumors were enzymatically digested using an optimized enzyme cocktail (Miltenyi Biotec, Tumor Dissociation Kit, mouse 130-096-830) with gentleMACS C tubes (Miltenyi Biotec, 130-093-235) in a gentleMACS Octo Dissociator (Miltenyi Biotec, 130-095-937). After dissociation, the sample was applied to a filter to remove any remaining larger particles. Single cell suspension of tumor tissues was surface stained using a panel of antibodies for flow cytometry. The antibody panel for evaluating myeloid subsets included antibodies specific for CD45, XCR1, F4/80, CD64, CD11c, Ly6C, CD11b, Ly6G, CD24, MHC class II as well as lineage markers in the dump channel (CD45R, CD90.2, CD3e, NKp46, CD19, Siglec F). The antibody panel for evaluating lymphoid subsets included antibodies specific for CD45, CD4, CD25, B220, NKp46, CD44, CD90.2, CD8a, CD11b, and CD49b. The anti-MARCO antibodies used to stain the mouse tumors were RDM-9514, PI-HX-3012, PI-HX-3021, PI-HX-3016, PI-HX-3017, rat IgG1 and rat IgG2a isotypes at 5µg/ml. All data were collected on an Attune flow cytometer (Thermo Fisher) and analyzed using FlowJo software.

[0692] *LDL competition assay on mouse and human recombinant MARCO*

[0693] A high-binding, 96-well MSD plate was coated with 4 µg/ml mouse MARCO or 4µg/ml human MARCO (R&D biosystems). After the plate was blocked with PBST and 5% BSA for an hour, titrated anti-mouse or anti-human MARCO antibodies were added to the plate and incubated for 30 minutes. Biotinylated hLDL (860pM or 2µg/ml) were added to the antibody, and the antibody/LDL mixture was incubated for an hour to allow the mixture to reach binding equilibrium. The plates were washed and bound biotinylated LDL was detected

with Sulfo-tagged streptavidin that generates an electrocheminlumenscent signal when read buffer is added and electricity is applied to the electrodes in the MSD plate. IC50 's were calculated using a 4-parameter curve fit in GraphPad Prism software.

[0694] Results

[0695] Multiple antibodies that bound to the SRCR domain of mouse MARCO were generated and characterized. 909 candidate antibodies were identified in the primary ELISA screen using purified mouse MARCO, human MARCO, mouse CLD-human SRCR, human-CLD-mouse-SRCR, and mouse MSR1. Secondary screening of binding to 293T cells expressing mouse MARCO or GFP control resulted in 275 candidates. Screening of binding on endogenous mouse BMDMs resulted in 40 candidates. A final screen for just SRCR binders resulted in 20 candidates. The candidates were screened for additional biophysical characteristics. The biophysical characterization of the top anti-mouse MARCO antibodies generated is shown in **Table 2**. These antibodies showed no binding to 293T HuMARCO cells or 293T CyMARCO cells. The sequences of selected mouse MARCO antibodies are shown in the sequence listing table. The CDRs were defined using the AbM definition.

Anti-muMARCO mAb	Isotype	SRCR Bin (CDR3 sequence)	Epitope Bin	Biacore K_{on} (1/Ms)	Biacore K_{off} (1/s)	Mouse EC_{50} 293T (MuMAR (nM)	EC_{50} LDL competition assay (nM)	MSR1 binding	Binding to BMDM
RDM-9514	Rat IgG1	11	2	1.36E+05	6.95E-07	0.83 - 0.86	0.38	-	+
PI-HX-3001 (PI-3006)	Rat IgG2a	1	2	1.88E+05	7.89E-07	0.48 - 1.09	0.4	-	NA
PI-HX-3003	Rat IgG2a	8	2	2.16E+05	5.40E-07	1.00	0.23	+/-	+
PI-HX-3004	Rat IgG2a	10	2	3.45E+05	3.58E-08	0.92	0.17	+/-	NA
PI-HX-3012	Rat IgG2a	1	2	1.54E+05	2.48E-07	0.80	0.17	-	+
PI-HX-3013	Rat IgG2a	2	2	2.40E+05	4.50E-07	0.34	0.36	+/-	+
PI-HX-3021 (PI-3007)	Rat IgG2a	3	2	1.91E+05	2.11E-05	0.47 – 0.75	0.25	-	+
PI-HX-3016 (PI-3008)	Rat IgG1	1	2	1.84E+05	1.27E-06	0.36 - 0.59	0.34	-	+
PI-HX-3017 (PI-3009)	Rat IgG1	6	2	1.55E+05	2.35E-07	0.66 - 1.30	0.14	-	+

[0696] RDM-9514 bound to the SRCR domain of MARCO. RDM-9514 also blocked LDL binding to MARCO in a dose dependent manner (**FIG. 9**) and bound to surface expressed MARCO on $MHCII^{high}$ TAMs and $MHCII^{low}$ TAMs isolated from CT26 tumors and Py8119 tumors (**FIG. 10A**). Staining with mouse antibody RDM-9514 also showed that MARCO is expressed on TAMs and monocytes in the CT26 syngeneic tumor model (**FIG. 10B**).

[0697] MARCO expression on mouse BDMDs after macrophage and IL-10 polarization was also assessed with the newly generated mouse MARCO antibodies. PI-HX-3017 (left bar, renamed PI-3009), PI-HX-3016 (middle left bar, renamed PI-3008), PI-HX-3021 (middle right bar, renamed PI-3007) and PI-HX-3012 (right bar) each bound to mouse BMDMs (**FIG. 11A**). The same antibodies also bound to MARCO on TAMs (right bar) and monocytes (left bar) isolated from tumors in the CT26 syngeneic tumor model (**FIG. 11B**, n=2).

Example 4: In vivo efficacy of anti-mouse MARCO antibodies in mono and combination therapy

[0698] Materials and Methods

[0699] *In vivo combination therapy with PD-1 antibody in CT26 syngeneic model*

[0700] Antibodies for in vivo use were all tested for endotoxin and used at or below 0.2 EU/mg protein. Anti-PD-1 [clone RMP1-14] in a mouse IgG1 D265A format was obtained. Mouse IgG1 [clone MOPC-21] and mouse IgG2a [clone C1.18.4] isotype controls were obtained. PI-3006, PI-3007, PI-3008, and PI-3009 were produced in HEK293 cells and evaluated for monodispersity and purity by SEC and CE-SDS as well as endotoxin tested. Antibodies were also tested for binding to mouse MARCO overexpressing 293T cells and for lack of binding to the parental 293T cells by flow cytometry.

[0701] Female BALB/c mice at about eight weeks of age were obtained from Taconic Biosciences (Rensselaer, NY). Mouse tumor cell line CT26.WT (CRL-2638) was obtained from American Type Culture Collection (ATCC), and cultured according to their guidelines. Low passage cells were resuspended at $1x10^7$ cells/ml in serum-free 1x DPBS (Gibco). The tumor cell suspension was subcutaneously injected on the shaved lower right ventral flank of BALB/c mice under isoflurane anesthesia. Tumor volume growth was monitored twice a week via perpendicular tumor diameter measurements and calculated using the formula $(mm^3) = 0.5x(length) \times (width)^2$. Six treatment groups were randomly assigned with 10 animals each when tumors reached an average of 97 mm^3. For drug treatments, mice were dosed intraperitoneally once every 5 days for 4 doses total (Q5Dx 4) with anti-mouse isotype control IgG2a (Clone C1.18.4) at 15mg/kg, anti-mouse isotype control IgG1 (Clone MOPC-21) at 5mg/kg, anti-mouse PD-1 (clone RMP1-14 recombinantly produced as mouse IgG1

D265A format and called PI-0004-AB) at 5mg/kg alone or in combination with the anti-mouse MARCO antibodies (PI-3006, PI-3007, PI-3008, and PI-3009) at 10 mg/kg. All studies were conducted in accordance with the Explora Biolabs institutional animal care and use committee under the protocol EB17-010. Mice were housed under conditions outlined in the NIH Guide for Care and Use of Laboratory Animals in compliance with the USDA Laboratory Animal Welfare Act. The animals were allowed ad libitum access to Lab Diet rodent chow and water. Mice were monitored a minimum of twice per week by the investigator or veterinary staff for clinical abnormalities which may require euthanasia. Mice showing a net body weight loss >20% compared to baseline weight measurement were euthanized.

[0702] *Anti-tumor immune memory assay*

[0703] BALB/c mice that were tumor-free from the CT26 tumor model study with the anti-MARCO antibodies plus anti-PD-1 antibody treatment as described above were re-challenged with $1x10^6$ CT26 tumor cells on the left ventral flank. EMT6 cells were injected subcutaneously on the opposite right ventral flank as a control cell line to track for tumor growth during the study period. No additional treatment was provided to the mice during the study period. Tumor volume was measured for 35 days after the re-challenge implant.

[0704] *Pharmacodynamics (PD) and in vivo anti-MARCO antibody single agent efficacy in CT26 model*

[0705] Female BALB/c mice at about eight weeks of age were obtained from Taconic Biosciences (Rensselaer, NY). Mouse tumor cell line CT26.WT (CRL-2638) was obtained from American Type Culture Collection (ATCC), and cultured according to their guidelines. Low passage cells were resuspended at 1x107 cells/ml in serum-free 1x DPBS (Gibco). The tumor cell suspension was subcutaneously injected on the shaved lower right ventral flank of BALB/c mice under isoflurane anesthesia. Tumor volume growth was monitored twice a week via perpendicular tumor diameter measurements and calculated using the formula $(mm^3) = 0.5x(length) \times (width)^2$. Two treatment groups were randomly assigned with 10 animals each when tumors reached an average of 109 mm^3. For drug treatments, mice were dosed iv once every 7 days (Q7D) with anti-mouse isotype control IgG2a (Clone C1.18.4) and anti-mouse MARCO antibody (PI-3008) at 10 mg/kg. All studies were conducted in accordance with the Explora Biolabs institutional animal care and use committee under the protocol EB17-010. Mice were housed under conditions outlined in the NIH Guide for Care and Use of Laboratory Animals in compliance with the USDA Laboratory Animal Welfare Act. The animals were allowed ad libitum access to Lab Diet rodent chow and water. Mice

were monitored a minimum of twice per week by the investigator or veterinary staff for clinical abnormalities which may require euthanasia. Mice showing a net body weight loss >20% compared to baseline weight measurement were euthanized. A schematic of the study time line is shown in **FIG. 15A**.

[0706] *Pharmacokinetics (PK) assay*

[0707] The mouse MARCO PK assay was used for quantification of drug antibody levels in mouse serum. A high-binding 96-well MSD plate was coated with 2 µg/ml mMARCO (PI-RG-3016). After blocking for an hour with blocking buffer (PBST, 5% BSA (PBS, 0.01% Tween-20, BSA), a standard curve and diluted serum samples were added to the plate and incubated for 2 hours on a plate shaker. Both the samples and the standard curve were normalized to a final concentration of 5% mouse serum. The plate was washed in DPBS++ (Gibco), 0.05% Tween-20, 1 % BSA, and the bound MARCO antibody was detected using a sulfo-tagged anti-mouse IgG2a (Jackson Immuno). The sulfo tagged antibody generates an electrochemiluminescent signal when read buffer was added and electricity was applied to the electrodes in the MSD plate. Antibody levels in the serum samples are quantitated by interpolating from the standard curve using a 4-parameter curve fit in the MSD software.

[0708] *RNAseq and Pathway analysis of the tumors, LNs, and spleens from the CT26 PD study*

[0709] The first timepoint for PD takedown was 4h following iv dosing of the antibodies. Blood (serum), spleen, tumor, and tumor draining lymph nodes from each mouse was harvested and tissues snap frozen in liquid nitrogen. The second timepoint was 4h after the second iv dosing of the antibodies, which occurred 6 days after the first iv dose. Blood (serum), spleen, tumor, and tumor draining lymph nodes from each mouse was harvested and tissues snap frozen in liquid nitrogen. Snap frozen samples were shipped to Medgenome Inc. for tissue homogenization using the Biospec Beadbeater in buffer RLT + BME and RNA extraction using the Qiagen All Prep kit and Biospec Beadbe. The mRNA quantity and quality were assessed by Nanodrop and the Agilent Bioanalyzer before moving to library preparation and RNAseq analysis to determine changes in gene expression induced by MARCO at the early and late PD timepoints. Differentially expressed genes (upregulated and downregulated) with FDR (<0.05) and cpm>2 cutoffs were generated and GSEA pathway analysis was performed and plotted using Cytoscape, KEGG, and Hallmarks analyses. The IgV genes observed in the differentially expressed gene list from the spleens treated with PI-3008 at 4h were plotted using a heatmap.

[0710] *Afucosylated antibody assay*

[0711] Afucosylated PI-3008 with an mIgG2a mouse Fc was generated and tested *in vivo*. Fucosylated PI-3008 antibody and an mIgG2a isotype antibody were used as controls.

[0712] CT26 tumor cells (1x10^6 cells per mouse) were implanted on Day 0. Afucosylated PI-3008 antibody IV (10mg/kg; Q7dx3) dosing was initiated when tumors reached an average of ~100 mm3 in volume.

[0713] *Effector dead antibody assay*

[0714] An N297A mutation was engineered in the mouse IgG2a Fc of PI-3008 to generate an effector dead mAb, PI-3021. PI-3008 and effector dead PI-3021 were tested alone and in combination with anti-PD-1 antibody in the CT26 mouse model. Balb/c female mice were inoculated subcutaneously with syngeneic CT26 tumor cells (1x10^6 cells per mouse) on Day 0, and dosed with PI-3008 (WT Fc; 10mg/kg), PI-3021 (Effector dead; 10mg/kg), anti-PD-1 (5mg/kg), and appropriate isotype controls (10mg/kg) as single agent or in combination. with anti-PD1 (N=10/group) was initiated when tumor volumes reached an average of ~100 mm3. Animals were dosed intraperitoneally every 5 days, for total of four doses. Tumor volumes were monitored over time and presented as averages per group, individual tumor volumes at the end of study, or as %TGI.

[0715] **Results**

[0716] The mouse anti-MARCO antibodies demonstrated significant anti-tumor efficacy in the CT26 model in combination with an anti-PD-1 antibody. **FIG. 12** shows the tumor volume in mice groups treated with isotype antibody; PD-1 antibody only; or PI-3008 plus PD-1 antibodies, PI-3007 plus PD-1 antibodies, PI-3009 plus PD-1 antibodies, and PI-3007 plus PD-1 antibodies. PI-3006 and PD-1 antibodies resulted in 10% cancer remission (CR), while PI-3007 and PI-3009 in combination with PD-1 antibodies resulted in 20% CR. PI-3008 had the best response and TGI overall. **FIG. 13A-D** show the responses in the individual mice after treatment with isotype control, anti-PD-1, PI-3008 + PD-1 antibodies, or PI-3009 + PD-1 antibodies. PI-3008 (**FIG. 13C**) and PI-3009 (**FIG. 13D**) demonstrated the best ant-tumor efficacy in combination with the anti-PD-1 antibody.

[0717] *Afucosylated antibody assay*

[0718] PI-3008 demonstrated better single agent (monotherapy) anti-tumor activity than the Fc enhanced variant (PI-3008-Afuc). Afucosylated PI-3008 did not show appreciable monotherapy when compared to fucosylated PI-3008 (**FIG. 13E**, **13F**, and **13G**). Without wishing to be bound by theory, this data suggests that enhanced Fc mediated engagement is not required for monotherapy

[0719] *Effector dead antibody assay*

[0720] The effector dead PI-3008 (PI-3021) also did not result in increased anti-tumor efficacy. Anti-tumor efficacy of PI-3008 in combination with anti-PD-1 was robust and more pronounced than that of PI-3021/anti-PD-1 combination (**FIG. 13H**). In the CT26 model, PI-3021 in combination with anti-PD1 did not lead to same level anti-tumor activity as observed with PI-3008 (**FIG. 13H**). At the end of study, day 22, PI-3008 had significant reduction in tumor volume compared to anti-PD-1 alone while PI-3021 did not reach statistical significance (**FIG. 13I**). In addition, percentage of tumor growth inhibition (%TGI) was higher in PI-3008 compared to PI-3021 in individual mice treated with combination therapy (**FIG. 13J** and **13K**). Finally, mouse BMDMs treated *in vitro* with PI-3021 did not show activation of the pro-inflammatory pathways as seen with PI-3008 after 4 hr of treatment (data not shown). Without wishing to be bound by theory, this data suggests that PI-3008 with a fucosylated Fc is the optimal Fc format for the desired anti-tumor activity *in vivo* in in the anti-PD-1 resistant CT26 mouse model. However, PI-3021 demonstrated equal anti-tumor activity as PI-3008 in the E0771 anti-PD1 sensitive model (**Example 11** and **FIG. 38**), suggesting that anti-MARCO antibody activity could also be due to target activity on MARCO in addition to Fc-mediated signaling.

[0721] Anti-MARCO and PD-1 combination treatment also resulted in long-term, anti-tumor immune memory after CT26 tumor challenge (**FIG. 14**). The mice that were tumor free after the first treatment of anti-MARCO antibodies were re-implanted with CT26 tumor cells, or EMT6 tumor cells. As shown in **FIG. 14**, no growth of the re-implanted CT26 tumor cells was observed in the mice that had been previously treated with anti-MARCO and anti-PD-1 antibodies.

[0722] The pharmacodynamics (PD) and anti-tumor efficacy of one anti-MARCO antibody, PI-3008, was also assessed in the CT26 colorectal tumor model as single agent monotherapy (**FIG. 15A-15C**). The PI-3008 anti-MARCO antibody demonstrated significant monotherapy in the CT26 model. **FIG. 15A** shows a timeline of the PD study. **FIG. 15B** shows that treatment with PI-3008 reduced mouse tumor size 6 days after the first dose, as compared to isotype control antibody. **FIG. 15C** shows quantification of the PI-3008 antibody in the mice after the first and second dose.

[0723] Molecular profiling analysis of CT26 tumors was also performed on samples taken 4 hours after the first and second dose of PI-3008 and isotype antibodies. The anti-MARCO antibody activated multiple immune pathways. After dose 1, genes in the actin mediated cell contraction pathway were upregulated, with a pathway FDR<0.1. 4 hours after the second dose, genes in kinase activation and activity pathway, Toll-like receptor signaling pathway,

TLR 4 and 9 pathways, GTPase binding and activity, and RAS-Rho signal transduction pathways were upregulated. After both the first and second dose, the following pathways were upregulated: humoral immune response, NK mediated immunity, NK activation, IL-2 and IL-12 production, cell killing, regulation of effector process, T cell proliferation, activation, differentiation, chemotaxis and migration, cell – cell adhesion, phagocytosis, and myeloid differentiation.

[0724] The KEGG pathways induced by anti-MARCO antibody in the CT26 tumors *in vivo* were determined. After dose 1, the top 10 most differentially upregulated pathways were: Natural Killer cell mediated cytotoxicity, T cell receptor signaling pathway, JAK/STAT signaling pathway, cytokine-cytokine receptor interaction, Intestinal immune network for IgA production, leukocyte trans-endothelial migration, chemokine signaling pathway, hematopoietic cell lineage, type II diabetes mellitus, and Fc-epsilon RI signaling pathway. After dose 1, the top 10 most differentially downregulated pathways were: homologous recombination, Alzheimer's disease, RNA polymerase, arginine and proline metabolism, citrate cycle (TCA cycle), porphyrin and chlorophyll metabolism, valine, leucine, and isoleucine degradation, biosynthesis of unsaturated fatty acids, N-glycan biosynthesis, and aminoacyl tRNA biosynthesis.

[0725] After dose 2, the top 10 most differentially upregulated pathways in the CT26 tumors were: cytokine-cytokine receptor interaction, Natural Killer cell mediated cytotoxicity, primary immunodeficiency, chemokine signaling pathway, hematopoietic cell lineage, JAK/STAT signaling pathway, T cell receptor signaling pathway, Intestinal immune network for IgA production, neuroactive ligand receptor interaction, and Fc-epsilon RI signaling pathway. After dose 2, the top 10 most differentially downregulated pathways were: glycolysis gluconeogenesis, propanoate metabolism, proteasome, citrate cycle TCA cycle, cardiac muscle contraction, Alzheimer's disease, Huntington's disease, oxidative phosphorylation, ribosome, and Parkinson's disease.

[0726] The KEGG pathways induced by anti-MARCO antibody in the tumor draining lymph nodes *in vivo* were also determined. After dose 1, the top 10 most differentially upregulated pathways were: phosphatidylinositol signaling system, focal adhesion, inositol phosphate metabolism, axon guidance, adherens junction, pathways in cancer, regulation of actin cytoskeleton, progesterone mediated oocyte maturation, ERBB signaling pathway, and Wnt signaling pathway. After dose 1, the top 10 most differentially downregulated pathways were: aminoacyl tRNA biosynthesis, lysosome, histidine metabolism, drug metabolism cytochrome

p450, proteasome, Alzheimer's disease, Huntington's disease, Parkinson disease, oxidative phosphorylation, and ribosome.

[0727] After dose 2, the top 10 most differentially upregulated pathways in the tumor draining lymph nodes were: focal adhesion, phosphatidylinositol signaling system, neurotrophin signaling pathway, insulin signaling pathway, inositol phosphate metabolism, MAPK signaling pathway, pathways in cancer, regulation of actin cytoskeleton, ERBB signaling pathway, and adherens junction. After dose 2, the top 10 most differentially downregulated pathways were: metabolism of xenobiotics by cytochrome p450, hematopoietic cell lineage, lysosome, Alzheimer's disease, proteasome, cytokine-cytokine receptor interaction, Huntington's disease, Parkinson's disease, oxidative phosphorylation, and ribosome.

[0728] The KEGG pathways induced by anti-MARCO antibody in the spleen *in vivo* were also determined. After dose 1, upregulated pathways included: ECM receptor interaction, focal adhesion, tight junction, adheres junction, proteasome, complement and coagulation cascades, cell adhesion molecules and CAMs, pathways in cancers, arrhythmogenic right ventricular cardiomyopathy ARVC, Wnt signaling pathway, regulation of actin skeleton, axon guidance, Huntington's disease, pathogenic Escherichia coli infection, Alzheimer's disease, leukocyte transendothelial migration, cytokine-cytokine receptor interaction, basal cell carcinoma, melanogenesis, and hedgehog signaling pathway. Downregulated pathways included: cell cycle, aminoacyl tRNA biosynthesis, mismatch repair, glycosylphosphatidylinositol GPI anchor biosynthesis, glycerophospholipid metabolism, and homologous recombination.

[0729] After dose 2, upregulated pathways in the spleen included: cell cycle, proteasome, T cell receptor signaling pathway, DNA replication, ubiquitin mediated proteolysis, regulation of actin cytoskeleton, adherens junction, pathogenic Escherichia coli infection, basal transcription factors, pentose phosphate pathway, Fc gamma R mediated phagocytosis, neurotrophin signaling pathway, regulation of autophagy, glycolysis gluconeogenesis, oocyte meiosis, chronic myeloid leukemia, citrate cycle TCA cycle, Wnt signaling pathway, P53 signaling pathway, and natural killer cell mediated cytotoxicity. Downregulated pathways included: ABC transporters, glycosylphosphatidylinositol GPI anchor biosynthesis, RNA polymerase, ribosome, arachidonic acid metabolism, glycerophospholipid metabolism.

[0730] A more in depth analysis of the differentially expressed genes in the PI-3008-treated CT26 tumors after dose 1 and dose 2 was also performed. Genes associated with NK cells, such as Klrk1, Nrc1, and Prf1; genes associated with pro-inflammatory and immune

activation, such as Cd40, Cd8α, Nod2, Tlr4, Tnf, Nlrp3, Cd274, Clec9α, and Cd200r3; and pro-inflammatory cytokines, such as Il-27, Cxcl9, Cxcl10, and Cxcl12 were upregulated. **FIG. 16A** shows the expression levels of Klrk1, Nrc1, Tlr4, Il-27, Cd8α, Cxcl9, Cxcl10, and Tnf in the CT26 tumor microenvironment after treatment with PI-3008 or an isotype control antibody. In each case, treatment with PI-3008 increased expression of the gene. **FIG. 16B** shows a comparison of the genes upregulated in BMDMs and CT26 tumors after treatment with PI-3008.

[0731] In addition, anti-Marco antibody 3008 upregulated IG-V genes in CT26 spleens after the first dose. 154 annotated IG-V genes with CPM > 1 are known. All of the 154 annotated IG-V genes were upregulated with PI-3008 treatment, while 138/154 were differentially expressed with an FDR<0.05. Thus, polyclonal expansion of plasma cells or activated B-cells in the Marginal Zone in the spleen may be occurring upon anti-MARCO antibody treatment to activate self-antigens or tumor antigens, such as NK activation.

Example 5: Production and characterization of additional anti-human MARCO antibodies

[0732] Materials and methods

[0733] A further antibody campaign to develop antibodies that bind to the SRCR domain of human MARCO was performed.

[0734] *Immunization for generating anti-human MARCO antibodies*

[0735] Rat anti-human MARCO hybridomas were generated by immunizing Sprague Dawley rats with recombinant N-terminal-his tagged human MARCO protein in Sigma Adjuvant System (SAS) alone or alternating with human MARCO expressing HEK 293 cells. The recombinant N-terminal his-tagged human MARCO protein comprised residues 147-520 of human MARCO. The recombinant human MARCO protein was quality control for proper folding and trimer formation. In contrast, the human MARCO protein (Pi 114) previously used for the unsuccessful anti-human MARCO campaign described in **Example 2** consisted of a modified MARCO ECD domain comprising residues 147-419 of the CLD domain and residues 424-520 of the SRCR domain.

[0736] Rats were immunized twice weekly in the hock and serum titers tested at day 21 at Antibody Solutions (Santa Clara, CA). Rats with sufficient serum antibody titers to human MARCO were chosen for electrofusion to generate hybridomas. Two final boosts were given on days -3 and -2 prior to harvest Immunizations in phosphate buffered saline (PBS).

[0737] *Hybridoma Generation and screening*

[0738] Hybridoma generation and screening assays for human MARCO antibodies were performed as described in **Example 3**.

[0739] *Cell Binding*

[0740] Cell binding assays for human MARCO antibodies were performed as described in **Example 3**.

[0741] *Hybridoma subcloning and purification*

[0742] Hybridoma subcloning and purification for human MARCO antibodies were performed as described in **Example 3**.

[0743] *Hybridoma antibody variable region sequences generation*

[0744] Hybridoma antibody variable region sequences for human MARCO antibodies were generated as described in **Example 3**.

[0745] *Chimeric and humanized antibody generation*

[0746] Chimeric antibodies were made by replacing the rat IgG1 or IgG2a Fc domain with human IgG1 or IgG4 domains.

[0747] Humanized antibodies were also synthesized from the rat parental hybridomas.

[0748] The VH and VL sequences of the rat hybridomas were compared to libraries of known human germline sequences on the NCBI website (ncbi.nlm.nih.gov/igblast/; Ye, J. et al. Nucleic Acids Research 41:W34-W40 (2013)). The databases used were IMGT human VH genes (F+ORF, 273 germline sequences) and IMGT human VLkappa genes (F+ORF, 74 germline sequences) as used by the NCBI IgBLAST program. The acceptor human germline was chosen from those closest in sequence to the parental antibody.

[0749] Human germline IGHV1-46(allele 1) was chosen as the acceptor sequence and the human heavy chain IGHJ4(allele 1) joining region (J gene) was chosen from human joining region sequences compiled at IMGT® the international ImMunoGeneTics information system® imgt.org (founder and director: Marie-Paule Lefranc, Montpellier, France).

[0750] Human germline IGKV1-39(allele 1) was chosen as the acceptor sequence and human light chain IGKJ2(allele 1) joining region (J gene) was chosen from human joining region sequences compiled at IMGT® the international ImMunoGeneTics information system® imgt.org (founder and director: Marie-Paule Lefranc, Montpellier, France). Sequence alignments of the HX-3061 rat parental and humanized VH and VL sequences are shown in **FIG. 17A** and **17B**, respectively. Sequence alignments of the HX-3031 rat parental and humanized VL sequences are shown in **FIG. 18**.

[0751] Additional back mutations were made in the humanized antibody VH derived from the HX-3061 hybridoma and the VL derived from the HX-3031 hybridoma. The back

mutations made in the HX-3061 VH were: V37I, V48I, and S49A, based on the human framework VH sequence. The back mutations made in the HX-3031 VL were: A13T, A43P, S56D, F71Y, L78M, F83E, and Y87F, based on the human framework VL sequence.

[0752] CDRs were defined according to the AbM definition (bioinf.org.uk/abs/ for a table comparing CDR definitions).

[0753] *Calcium dependency ELISA assay*

[0754] The calcium dependency ELISA assay was performed as described in **Example 3**.

[0755] *Kinetics and epitope binning using the ProbeLife Gator instrument*

[0756] Kinetics and epitope binning analysis of the newly generated anti-human MARCO antibodies was performed as described in **Example 3**.

[0757] *LDL competition assay on mouse and human recombinant MARCO*

[0758] LDL competition assay on mouse and human recombinant MARCO was performed as described in **Example 3**.

[0759] *MARCO bacteria competition assay*

[0760] 293T cells expressing human or mouse MARCO were harvested along with the parental 293T cells. Zombie NIR viability dye (BioLegend) was prepared by diluting the stock 1000-fold in D-PBS and added to the cells. The cells were incubated with the dye for 10 min at RT in the dark. The reaction was quenched by adding 1m of 4x Staining buffer (2% FBS in DBPS containing Ca^{2+}), followed by centrifugation at 400xg for 5 min at 4°C. Cells were then plated in V- shaped 96 well plates at a density of 100,000 cells. A488-fluorescently labeled bacteria (E.coli from Invitrogen) was added at 10μg/ml with the anti-human or anti-mouse antibodies of interest for a 30 min incubation at 37 C. Plates were then washed twice followed by resuspension in 100ul of staining buffer for acquisition on the flow cytometer (Attune NxT, Life Technologies). Flow cytometry data were analyzed using FlowJo software (version 10.6.1) and data were processed and further analyzed in Microsoft Excel and GraphPad Prism software (version 8).

[0761] **Results**

[0762] Primary screening of anti-human MARCO antibodies via ELISA screening for binding to human MARCO resulted in 304 candidates. A secondary screening

[0763] 304 candidate antibodies were identified in the primary ELISA screen using purified human MARCO. Secondary screening of binding to 293T cells expressing human, cyno, and mouse MARCO or GFP control cells resulted in 138 candidates. An additional secondary screen for SRCR verus CLD binding was also performed via ELISA. 90 SRCR binding antibodies and 47 CLD binding antibodies were identified. Candidate antibodies were then

screened for binding on endogenous cells, binding kinetics, LDL competition, and binding to human MSR1. 42 candidate antibodies were identified, 37 SRCR binding antibodies and 5 CLD binding antibodies. Of these, 11 candidate anti-human MARCO antibodies were identified with good binding characteristics. The sequences of selected human MARCO antibodies are shown in the sequence listing table. The CDRs are defined using the AbM definition.

[0764] The characterization of the rat hybridoma anti-human MARCO antibodies generated are shown in **Table 3**.

Table 3

Anti-huMARCO mAb	Isotype	Bin	Ca2+ /Mg2+ req for binding	K_{on} (1/Ms)	K_{off} (1/s)	Human EC_{50} 293T(HuMARCO) (nM)	Cyno EC_{50} 293T(CyMARCO) (nM)	EC_{50} LDL competition assay (nM)	MSR1 binding
PI-HX-3011	Rat IgG2a	3	+	4.01E+05	9.14E-04	0.096	0.094	NA	-
PI-HX-3023	Rat IgG2a	2	+/-	2.27E+05	4.75E-04	0.451	0.071	1.5	-
PI-HX-3026	Rat IgG2a	2	+	2.42E+05	6.01E-04	0.23	0.162	1.3	-
PI-HX-3028	Rat IgG2a	2	+/-	2.42E+05	4.79E-04	0.332	0.144	1.5	-
PI-HX-3031	Rat IgG2a	3	+	4.43E+05	7.98E-04	0.141	0.046	NA	-
PI-HX-3033	Rat IgG2a	2	+	2.70E+05	8.07E-04	0.272	0.067	NA	-
PI-HX-3040	Rat IgG2a	3	+	2.41E+05	6.72E-04	0.229	0.107	2.9	-
PI-HX-3041	Rat IgG2a	3	+	3.08E+05	7.96E-04	0.215	0.110	NA	-
PI-HX-3043	Rat IgG2a	3	+	2.33E+05	8.49E-04	0.438	0.067	3.4	-
PI-HX-3047	Rat IgG2a	1	-	4.84E+05	6.55E-04	0.326	0.100	NA	-
PI-HX-3061	Rat IgG2a	4	-			0.49	0.45	8.2	-

[0765] Five of the eleven candidate anti-MARCO antibodies were selected for further development based on CDR sequence analysis: PI-HX-3011, PI-HX-3031, PI-HX-3043, PI-

HX-3061, and PI-HX-3092. Human chimeric antibodies were made by exchanging the rat IgG2a Fc region with human IgG1 (for PI-HX-3011 and PI-HX-3043) or both IgG1 and IgG4 (for PI-3031 ad PI-HX-3061). Additional chimeric antibodies were also made by exchanging the rat IgG2a Fc region with mouse IgG2a (for PI-HX-3036, and PI-HX-3092). Further humanization of the VH and VL frameworks was performed on antibodies derived from the PI-HX-3011, PI-HX-3031, and PI-HX-3061 rat parental antibodies.

[0766] Table 4 provides a summary of the selected rat parental antibodies, the chimeric antibodies, and the humanized antibodies generated.

	Table 4		SEQ ID NOs
Name	**Revised Name (if applicable)**	**Description**	
PI-HX-3031		parental rat hybridoma	1-10
PI-3010-AB	PI-3010	hIgG1/ chimeric PI-HX- 3031	11-20
PI-3011-AB	PI-3010.11	humanized PI-HX- 3031 / 3031-1 hIgG1	21-30
PI-3012-AB	PI-3010.12	humanized PI-HX- 3031 / 3031-2 hIgG1	31-40
PI-3013-AB	PI-3010.13	humanized PI-HX- 3031 / 3031-3 hIgG1	41-50
PI-3014-AB	PI-3010.14	humanized PI-HX- 3031 / 3031-4 hIgG1	51-60
PI-3015-AB	PI-3010.15	humanized PI-HX- 3031 / 3031-5 hIgG1	61-70
PI-3020-AB	PI-3010.20	chimeric PI-HX- 3031 - hIgG4	71-80
PI-3022-AB	PI-3010.22	humanized PI-HX- 3031 / 3031-2 hIgG1	81-90
PI-3023-AB	PI-3010.23	humanized PI-HX- 3031 / 3031-2 hIgG1	91-100
PI-3024-AB	PI-3010.24	humanized PI-HX- 3031 / 3031-2 hIgG1	101-110
PI-3025-AB	PI-3010.25	humanized PI-HX- 3031 / 3031-2 hIgG1	434-443
PI-3026-AB	PI-3010.26	humanized PI-HX- 3031 / 3031-2 hIgG1	121-130
PI-3027-AB	PI-3010.27	humanized PI-HX- 3031 / 3031-2 hIgG1	131-140
PI-3046-AB	PI-3010.46	humanized PI-HX- 3031 / 3031-2 hIgG4	474-483
PI-3048-AB	PI-3010.48	humanized PI-HX- 3031 / 3031-2 hIgG4	444-453
PI-HX-3061		parental rat hybridoma	141-150
PI-3016-AB		humanized PI-HX- 3061 / 3061-1 hIgG1	151-160
PI-3017-AB		humanized PI-HX- 3061 / 3061-2 hIgG1	161-170
PI-3018-AB		humanized PI-HX- 3061 / 3061-3 hIgG1	171-180
PI-3019-AB		PI-HX-3061 mIgG2a chimera	181-190
PI-3028-AB		PI-HX-3061 hIgG1 chimera	191-200
PI-3029-AB		PI-HX-3061 hIgG4 chimera	201-210
PI-3032-AB		humanized PI-HX- 3061 / 3061-2 hIgG1	211-220
PI-3033-AB		humanized PI-HX- 3061 / 3061-2 hIgG1	221-230
PI-HX-3011		parental rat hybridoma	231-240
PI-3030-AB	PI-3030	HX3011-h1 Chimera hIgG1	241-250
PI-3036-AB	PI-3030.36	humanized PI-HX- 3011 / 3011-1 hIgG1	311-320

PI-3037-AB	PI-3030.37	humanized PI-HX- 3011 / 3011-2 hIgG1	321-330
PI-3038-AB	PI-3030.38	humanized PI-HX- 3011 / 3011-3 hIgG1	331-340
PI-3039-AB	PI-3030.39	humanized PI-HX- 3011 / 3011-4 hIgG1	341-350
PI-3040-AB	PI-3030.40	humanized PI-HX- 3011 / 3011-5 hIgG1	351-360
PI-3041-AB	PI-3030.41	humanized PI-HX- 3011 / 3011-5 hIgG1	454-463
PI-3047-AB	PI-3030.47	humanized PI-HX- 3011 / 3011-5 hIgG4	464-473
PI-HX-3043		parental rat hybridoma	251-260
PI-3031-AB		HX3043-h1 Chimera hIgG1	261-270
PI-HX-3092		parental rat hybridoma	361-370
PI-3035		HX3092 (A mutation) - mIgG2a	371-380

[0767] The newly generated rat hybridoma anti-human MARCO antibodies were characterized as previously described. The characterization of the rat parental antibodies HX-3031 and HX-3061 is shown in **Table 5.** Neither antibody bound to MSR1. Binding kinetics were determined via Multi Cycle Kinetics analysis using the huMARCO antigen as previously described.

Table 5

Anti-hu MARCO mAb	Bin	Ca2+/ Mg2+ req for binding	EC_{50} (raIgG2a) ELISA (hu/SRCR/cyn)	K_D (M) Hu	K_D (M) Cyno	Human EC_{50} 293T (Hu MARCO) (nM)	Cyno EC_{50} 293T (Cy MARCO) (nM)	Mouse EC_{50} 293T (Mu MARCO) (nM)	EC_{50} Bac comp-etition assay (nM)	EC_{50} LDL comp-etition assay (nM)
PI-HX-3031	3	+	0.13/0.15/0.14	9.13E-11	1.09E-10	0.56	0.51	nb	0.18	6.2
PI-HX-3061	4	-	0.24/0.24/0.23	2.56E-10	1.19E-10	0.49	0.45	1.52	0.52	8.2

[0768] One anti-huMARCO antibody (PI-HX-3061) was determined to be cross reactive with human and mouse MARCO.

[0769] Three antibodies, two anti-mouse MARCO antibodies, PI-3008 and PI-3009, and the cross reactive anti-human MARCO antibody PI-HX-3061, were further characterized in a bacterial binding assay. As shown in **FIG. 19**, incubation of muMARCO 293T cells with increasing concentrations of each of PI-3008, PI-3009, or PI-HX-3061 decreased bacterial binding in a dose dependent manner, while incubation with isotype controls rat IgG1 or mouse IgG2a did not affect bacteria binding to the cells.

[0770] A comparison of the physical properties of PI-3008, PI-3009, and PI-HX-3061 is provided in **Table 6**.

Table 6

Anti-muMARCO mAb	Mouse bin	Ca2+/Mg2+ req for binding	Biacore K_D (nM)	Mouse EC_{50} 293T(muMARCO) (nM)	EC_{50} Bac competition assay (nM)	MSR1 binding	Binding to BMDM	Binding to TAMs in vivo
PI-3008	2	Yes	<0.02	1.097	1.81	-	+	+
PI-3009	4	Yes	<0.02	TBD	3.84	-	+	+
PI-HX-3061 (Cross-reactive)	5	No	<0.02	2.526	0.85	-	+	TBD

[0771] ELISA screening of selected rat hybridoma parental antibodies with 4 EDTA concentrations on recombinant human MARCO showed differential dependency on divalent cations for binding to MARCO with the various anti-MARCO antibodies and different epitopes. The results are shown in **Table 7**.

Table 7

	Clone ID	EDTA [Conc]			
		0	2mM	10mM	50mM
SRCR	PI-HX-3010	0.9525	0.8158	0.101	0.1055
	PI-HX-3011	1.1743	0.0636	0.0811	0.082
	PI-HX-3047	0.9688	1.2065	0.9205	0.9986
	PI-HX-3031	1.3709	0.0678	0.0589	0.0754
	PI-HX-3043	1.1971	0.0595	0.06	0.1002
CLD	PI-HX-3049	1.1909	1.1447	1.0708	1.1915
	PI-HX-3048	1.1987	1.2159	1.0695	1.2002

[0772] Select human chimera and further humanized antibodies were also characterized for species binding specificity, divalent cation binding requirement, SRCR and CLD domain binding kinetics, and cell binding.

[0773] As shown in **FIG. 52**, binding of some anti-MARCO antibodies to MARCO was calcium dependent. Addition of 2 mM EDTA abrogated binding of PI-3010.15, PI-3010.25, and PI-3030.41 to MARCO while the binding of a calcium independent mAb, PI-3032 was not affected. The surrogate anti-mouse MARCO mAb, PI-3008-AB also bound to mouse MARCO in a calcium dependent manner. Addition of 2 mM EDTA abrogated binding, while a calcium independent anti-mouse MARCO mAb, PI-3000 was not affected.

[0774] A summary of the characterization results for PI-3010 (hIgG1), PI-3030 (hIgG1), and PI-3031 (hIgG1) are shown in **Table 8**.

Table 8

Anti-huMARCO mAb	Specificity	Ca^{2+} dependent binding	K_D (nM) Human	K_D (nM) Cyno	K_{off} (1/s) ProbeLife	EC_{50} (nM) OVX Human	EC_{50} (nM) OVX HuSRCR-mouse CLD	EC_{50} (nM) OVX Cyno	Binding to PBLs
PI-3010-AB (hIgG1)	hu/cy	Yes	0.43-0.64	0.26	2.34E-03	0.68	0.25	0.34	No
PI-3030-AB (hIgG1)	hu/cy	Yes	0.44	n.d.	3.51E-03	0.55	0.17	0.38	No
PI-3031-AB (hIgG1)	hu/cy	Yes	0.60	n.d.	2.81E-03	1.6	1.071	1.092	No

[0775] Results for the PI-3031 (hIgG1) chimera and two further humanized antibodies based on the PI-3031 chimera are shown in **Table 9**.

Table 9

mAb	SRCR Epitope	Ca^{2+} dep	EC_{50} (raIgG2a) ELISA (hu/SRCR/cyn)	K_D (M; sc) Human	K_D (M; sc) Cyno	EC_{50} (nM) OVX Human	EC_{50} (nM) OVX Cyno	EC_{50} Bac (nM) Cell-based	MSR1 Binding
PI-3031-chi (PI-3010)	Bin 3	Yes	0.04/0.12/0.07	4.30E-10	2.59E-10	0.68	1.48	0.44	-
PI-3031-h2 (PI-3012)	Bin 3	Yes	0.08/0.27/0.07	1.13E-09	7.35E-10	0.57	1.40	0.12	-
PI-3031-h5 (PI-3015)	Bin 3	Yes	0.08/0.25/0.09	9.11E-10	6.11E-10	0.86	1.73	0.50	-

[0776] The chimera antibodies PI-3010, PI-3030, and PI-3031 were also assessed for PBL binding. As shown in **FIG. 20A**, the chimera antibodies bound to 293T cells overexpressing MARCO but not to the immune cells present in PBLs. The binding to eosinophils was non-specific across all tested antibodies including the hIgG1 isotype control. PI-3010 is shown on the left, PI-3030 is shown on the left middle, PI-3031 is shown on the right middle, and isotype control hIgG1 is shown on the right. Binding of PI-HX-3031 in immune cells from Endometrial cancer (primary human tumor) was also assessed. As shown in **FIG. 20B**, the antibody bound to TAMs and monocytes from the tumor sample. Antibody binding is the right peak, isotype control binding is the left peak.

Example 6: Epitope Mapping by Surface Residues Swapping

[0777] Materials and methods

[0778] Mouse MARCO SRCR crystal structure (PDB Entry 2OY3) was used to design the constructs. Mouse and human MARCO SRCR sequences were aligned and different residues on the protein surface were swapped with each other in clusters. N-term his tag and CLD domain were added to the SRCR sequences to produce recombinant proteins. The sequences for the recombinant proteins used in these studies are listed below. Bold and underlined residues are the swapped epitope residues:

[0779] hMARCO(His-CLD-SRCR) (RG3033)

[0780] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV*

[0781] hVar1 (RG3034)

[0782] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYY**NNE**WGTICDDEWQNSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV*

[0783] hVar2 (RG3035)

[0784] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDD**D**W**D**N**N**DAIVFCRMLGYS
RGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV*

[0785] hVar3 (RG3036)

[0786] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD

QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEW**D**NSDAIVFCRMLGYS
KGRAL**SS**VGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV*

[0787] hVar4 (RG3037)

[0788] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNVQCRGTE**NS**LW**D**C**S**KNSWGHHDCSHEEDAGVECSV*

[0789] hVar5 (RG3038)

[0790] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWG**N**H**N**C**V**H**N**EDAGVECSV
*

[0791] hVar6 (RG3039)

[0792] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDD**D**W**D**NSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNV**N**CRGTESTLWSC**S**KNSWGHHDCSHEEDAGVECSV*

[0793] hVar7 (RG3040)

[0794] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG

LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGE**SFQR**VRIVG**GT**NRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGY
SKGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV
*

[0795] mMARCO (RG3016)

[0796] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG
PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK
GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG
QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGR
ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS

[0797] mVar1 (RG3026)

[0798] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG
PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK
GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG
QKGESFQRVRIMGGTNRGRAEVYY**SGT**WGTICDDDWDNNDATVFCRMLGYSRGR
ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS*

[0799] mVar2 (RG3027)

[0800] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG
PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK
GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG
QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDD**E**W**Q**N**S**DATVFCRMLGYS**K**GR
ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS*

[0801] mVar3 (RG3028)

[0802] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG
PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK
GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG

QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDW**Q**NNDATVFCRMLGYSRGR
AL**YK**YGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS*

[0803] mVar4 (RG3029)

[0804] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG
PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK
GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG
QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGR
ALSSYGGGSGNIWLDNVNCRGTE**ST**LW**S**C**T**KNSWGNHNCVHNEDAGVECS*

[0805] mVar5 (RG3030)

[0806] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG
PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK
GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG
QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGR
ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWG**HH**D**C**S**H**EEDAGVECS*

[0807] mVar6 (RG3031)

[0808] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG
PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK
GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG
QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDD**E**W**Q**NNDATVFCRMLGYSRGR
ALSSYGGGSGNIWLDNV**Q**CRGTENSLWDC**T**KNSWGNHNCVHNEDAGVECS*

[0809] mVar7 (RG3032)

[0810] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG
PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK
GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG
QKGE**NSVS**VRIMG**SS**NRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGRA
LSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS*

[0811] Sequence comparisons of the wild type human and mouse SRCR domain, and the mouse and human variant sequences made are shown in **FIG. 21**.

[0812] *Binding Kinetics using the ProbeLife Gator instrument*

[0813] The Probe-Life Gator™label free system was used to analyze binding of the top anti-human and anti-mouse antibodies to the mouse/human SRCR antigen variants.

[0814] The kinetics assay used either anti-mouse Fc or anti-human Fc probes to capture the anti-MARCO antibodies onto the probe, and then a five-step kinetic protocol was used to measure the affinity of the antibodies to the different variant antigens described above, including the following steps: baseline, loading, baseline, association, and dissociation. The kinetics buffer (K buffer) provided by ProbeLife was used to establish the baseline for 60 seconds, and then the anti-mFc or anti-hFc probes were loaded with 200nM of the antibodies for 120s until the capture reached saturation, measurement of the baseline in K buffer was performed for another 60s, followed by the association step using 200nM antigen (human SRCR MARCO variants and mouse SRCR MARCO variants), and the dissociation step performed in K buffer for 5-10 minutes. The assay was done at 37°C to maximize antibody:antigen dissociation.

[0815] Antibodies used for loading were PI-3010, PI-3008, PI-3019, PI-3030, PI-3031, and PI-3035. PI-3008, PI-3010, and PI-3030 are $Ca2^+$ dependent binders, while PI-3019, and PI-3035 are $Ca2^+$ independent binders. PI-3019 and PI-3035 also have cross reactivity with both human and mouse MARCO.

[0816] Results

[0817] PI-3008 binding to mMARCO was most affected by the mutations in mVar2, mVar 3, mVar 4, mVar, 5, and mVar6 (data not shown). However, binding of PI-3008 to mMARCO SRCR was the most affected by the mutations in mVar6, and thus the altered residues in mVar6 are likely part of the mMARCO epitope (D450, D452, N487, S499 of mouse MARCO). The mutations in mVar 1 and mVar 7 had minimal adverse effect on PI-3008 binding to mMARCO. A sequence comparison of wild type (wt) mMARCO SRCR domain and the mVar6 sequence is shown in **FIG. 22**.

[0818] The cross reactive antibodies with Ca2+ independent binding, PI-3019 and PI-3035, were tested with both the mouse and human MARCO variants. PI-3019 was most adversely affected by the mutations in hVar3 (Q452D, Y472S, and K473S of human MARCO), while PI-3035 was adversely affected by hVar5 and hVar6 (data not shown). Similar binding reductions were seen with mVar3 for PI-3019 and mVar 3 and mVar 5 for PI-3035. A sequence comparison of wild type (wt) hMARCO SRCR domain and the hVar3, hVar5, and

hVar6 sequences are shown in **FIG. 22**. The bolded and underlined amino acids were mutated as compared to wild type human or mouse MARCO.

[0819] The human-only and Ca2+ dependent antibodies PI-3010, PI-3030, and PI-3031 all showed significantly reduced binding with hVar3 (data not shown). Thus, hVar3 affected binding of PI-3010, PI-3030, PI-3031 and PI-3019, while hVar5 and hVar6 affected binding of PI-3035.

[0820] A summary of the antibody binding and cation dependence is shown in **Table 10**.

Table 10

Antibody	Variant Reduced Binding	Species binding	Ca+ Dependent?
PI-3010 (HX-3031)	hVar3	Human/Cyno	+
PI-3030 (HX-3011)	hVar3	Human/Cyno	+
PI-3033 (HX-3043)	hVar3	Human/Cyno	+
PI-3019 (HX-3061)	hVar3	Human/Cyno/Mouse	- (independent)
PI-3035 (HX-3092)	hVar5, hVar6	Human/Cyno/Mouse	- (independent)
PI-3008	mVar6	Mouse	+

[0821] Binding of various human antibodies to hVar3 as measured by ELISA are shown in **FIG. 23**. hIgG1 and mIgG2a were used as antibody controls. PI-3008 and PI-300 were used as negative controls. Antibodies with single reactivity to human MARCO (PI-3010, PI-3020, PI-3030, PI-3031) did not bind to hVar3, while antibodies derived from the cross reactive HX-3061 hybridoma (PI-3028, PI-3029, PI-319) or HX-3092 (PI-3035) bound to hVar3.

[0822] To confirm the importance of the residues identified in hVar3 (Q452, Y472, and K473) as the binding epitope for the single reactive hMARCO antibodies, PI-3010 was bound to both hVar3, which has mutant Q452D, Y472S, and K473S residues, and mVar3, which has the same residues as the wild type human MARCO, Q452, Y472, and K473. The binding of PI-3010 was lost on the hVar3, but restored on mVar3 (data not shown). This confirmed that at least one, some, or all of residues Q452, Y472, and K473 are likely part of the MARCO epitope for the antibodies generated against human MARCO derived from HX-3011, HX-3043, HX-3031, and HX-3061 (e.g., those including, but not limited to, PI-3010, PI-3020, PI-3030, PI-3031, PI-3019, and PI-3033). These residues are also near the D447 D448 E511 acidic cluster on MARCO.

[0823] The residues that were mutated in hVar5 that affected binding of PI-3035 were H505, D507, S509, and E511. The residues that were mutated in hVar6 that affected binding of PI-3035 were E450, Q452, Q487, and T499. Thus, at least one, some, or all of residues E450, Q452, Q487, T499, H505, D507, S509, and E511 likely represent another binding epitope for antibodies derived from HX-3092 (e.g., those including, but not limited to, PI-3035).

[0824] The mouse and human antibodies have overlapping epitopes in the SRCR domain, with one overlapping residue, Q452 for the human SRCR and D452 for mouse SRCR, shown in **FIG. 24.** The overlapping residue is circled on both the mouse SRCR domain on the left and the human SRCR domain on the right.

Example 7: Non-Human Primate Pharamacokinetics Study

[0825] To assess drug exposure and safety of the humanized drug candidates, two pharmacokinetic (PK) assays, total and free (ligand binding), were developed to quantify PI-3025-AB2 (IgG1 format) and PI-3048-AB (IgG4 format) antibody concentrations in an exploratory single dose non-human primate (NHP) PK and tolerability study. The single dose study consisted of four animals (1 male and 1 female per group) dosed at 10 mg/kg with PI-3025-AB2 (IgG1) and PI-3048-AB (IgG4). **Table 11** shows the study design.

Table 11

Group	Test Material	Dose Level (mg/kg)	Dose Vol. (ml/kg)	Dose Conc. (mg/ml)	No. animals	
					Males	Females
1	Control Article	0	2	0	1	1
2	PI-3025-AB2	10	2	5	1	1
3	PI-3048-AB	10	2	5	1	1

[0826] Ligand binding assay

[0827] A standard MSD Plate (Meso Scale Discovery, Catalog # L15XA-3) was coated with recombinant human MARCO protein at 1 µg/mL. The plate was incubated at room temperature for 60 min and then washed. The plate was then blocked with 5% bovine serum albumin (BSA) for 60 min at room temperature.

[0828] PI-3025-AB2 and PI-3048-AB protein standards and quality control samples, and animal samples were diluted in buffer (PBS/0.5%BSA/0.05%Tween + Ca2+/Mg2+) and added to the coated plate in salt buffer. The plate was incubated for 60 min at room temperature and washed. 0.5 µg/mL of the detection antibody, anti-human IgG CH2 (Thermo Fisher, Catalog # MA5-16929) was added and the plate incubated for 60 min at room temperature. The plate was washed and 1x Read Buffer (Meso Scale Discovery, Catalog # R92TC-1) was added to the MSD plate. The plate was read on an MSD Sector Imager.

[0829] Total PK Assay Format

[0830] A streptavidin MSD plate (Meso Scale Discovery, Catalog # L15SA-1) was coated with biotinylated anti-human kappa antibody (Invitrogen, Catalog # SA1-19155) at 1 µg/mL. The plate was incubated at room temperature for 60 min and then washed. PI-3025-AB2 and PI-3048-AB protein standards and quality control samples, and animal samples were diluted in buffer (PBS/0.5%BSA/0.05%Tween + Ca2+/Mg2+) and added to the coated plate in salt buffer. The plate was incubated for 60 min at room temperature and washed. 0.5 µg/mL of the detection antibody, anti-human IgG CH2 (Thermo Fisher, Catalog # MA5-16929) was added and the plate incubated for 60 min at room temperature. The plate was washed and 1x Read Buffer (Meso Scale Discovery, Catalog # R92TC-1) was added to the MSD plate. The plate was read on an MSD Sector Imager.

[0831] Results

[0832] The single dose study demonstrated that PI-3025 and PI-3048 antibodies have an acceptable PK and were well tolerated. Both total and free assay formats measured similar drug concentrations for each antibody.

[0833] The PK calibration curve for PI-3025-AB2 is shown in **FIG. 25A** and **Table 12**.

Table 12

	LBA Assay Format			**Total Assay Format**		
Nominal Conc. ng/ml	Detected Mean Conc. (ng/ml)	Calc. Mean Conc. CV	% Recovery Mean	Detected Mean Conc. (ng/ml)	Calc. Mean Conc CV	% Recovery Mean
240	233	5	94	280	10	116
100	109	5	106	120	3	120
50	46	5	96	56	0	111
10	9	5	89	10	5	100
5	4	3	77	5	6	91

[0834] The PK calibration curve for PI-3048-AB is shown in **FIG. 25B** and **Table 13.**

Table 13

	LBA Assay Format			**Total Assay Format**		
Nominal Conc. ng/ml	Detected Mean Conc. (ng/ml)	Calc. Mean Conc. CV	% Recovery Mean	Detected Mean Conc. (ng/ml)	Calc. Mean Conc CV	% Recovery Mean
240	217	4.1	88	295	0	123
100	98	0.8	97	88	21	88
50	47	2.2	94	58	9	116
10	10	1.8	99	10	16	104
5	4	2.4	85	6	3	129

[0835] The PK assays were successfully developed to measure drug concentrations in the exploratory NHP study. The PK assay range was 1.85 ng/mL to 300 ng/mL (in assay) with a minimum required dilution (MRD) of 20. The LLOQ was 1.85 ng/mL and the ULOQ was 240 ng/mL. The quality controls (QCs) ranged from 5 ng/mL to 240 ng/mL.

[0836] The *in vivo* ligand binding PK assay results are shown in **FIG. 26A**. PI-3025-AB2 showed no detectable drug levels post Day 21 (504 hr) in the ligand binding assay (**FIG. 26A**). PI-3048-AB was detected up to Day 28 (672 hr) in the ligand binding assay (**FIG. 26A**). The *in vivo* total PK assay results are shown in **FIG. 26B**. PI-3025-AB2 was detected up to Day 21 (504 hr) and Day 28 (672 hr) (**FIG. 26B**). PI-3048-AB was detected up to Day 28 (672 hr) (**FIG. 26B**). Animals dosed with PI-3048-AB showed slightly better exposure than dosed with PI-3025-AB2.

[0837] The PK results for PI-3025-AB2 and PI-3048-AB were comparable using both the total and free assay. PI-3025-AB2 and PI-3048-AB antibodies had an acceptable tolerability and good exposure following the single dose study.

Example 8: Additional characterization of anti-human MARCO antibodies

[0838] Materials and methods

[0839] Anti-MARCO antibody cell binding, SPR binding kinetics (K_D) and macrophage binding were performed as previously described in **Examples 2** and **5**.

[0840] *Ligand Binding Block Assay*

[0841] 293T cells expressing human MARCO were harvested along with the parental 293T cells. Zombie NIR viability dye (BioLegend), prepared by diluting the stock 1000-fold in D-PBS, was added to the cells and incubated for 10 min at RT in the dark. The reaction was quenched by adding 1m of 4x Staining buffer (2% FBS in DBPS containing Ca2+), followed by centrifugation at 400xg for 5 min at 4°C. Cells were then plated in V- shaped 96 well plates at a density of 100,000 cells. A488-fluorescently labeled bacteria (E.coli from Invitrogen) was added at 10μg/ml with the anti-human MARCO antibodies of interest for a 30 min incubation at 37 C. Plates were then washed twice followed by resuspension in 100ul of staining buffer for acquisition on the flow cytometer (Attune NxT, Life Technologies). Flow cytometry data were analyzed using FlowJo software (version 10.6.1) and data were processed and further analyzed in Microsoft Excel and GraphPad Prism software (version 8).

[0842] *T-cell binding assay*

[0843] A standard flow binding assay using Jurkat T-cells obtained from ATCC was performed. 100,000 cells/well of Jurkat T cells were plated onto U-bottom 96-well plates for staining and all centrifugation steps were performed at 1500rpm at 4°C for 5 min and samples were kept protected from light throughout the protocol. Cells were pelleted and resuspended in 100 μl of Zombie NIR viability dye (BioLegend) prepared by diluting Zombie NIR dimethyl sulfoxide (DMSO) stock 1000-fold in D-PBS. Cells were stained by incubation for

10 min at room temperature (RT) in the dark, followed by quenching the staining reaction with the addition of regular Medium containing 10% FBS. Cells were pelleted and resuspended in 100 µl of the different anti-human MARCO antibodies and the corresponding hIgG1 and hIgG4 isotype controls in freshly prepared staining medium (2% FBS in DBPS containing Ca2+). All mAbs were tested at the final top concentration of 100 nM (15µg/ml) followed by an 8-point three-fold serial dilution, including 0 mg/ml control. Staining was carried out for 1 hour (hr) on ice, followed by 2 washes in Staining Medium. Cells were then pelleted and resuspended in 100 ul of allophycocyanin (APC)-conjugated goat anti-mouse IgG (Fc-specific) secondary antibody, prepared by 500-fold dilution of the antibody stocks in Staining Medium, and incubated for 30 min on ice. Plates were then washed two times with Staining Medium, followed by resuspension in 150ul of the same buffer for acquisition on the flow cytometer (Attune NxT, Life Technologies). Flow cytometry data were analyzed using FlowJo software (version 10.6.1) and data were processed and further analyzed in Microsoft Excel and GraphPad Prism software (version 8). Half-maximal effective concentrations (EC50) were calculated based on geometric mean fluorescence intensities (gMFI).

[0844] *mAb Thermal stability assessment using Dynamic Light Scattering (DLS)*

[0845] Dynamic light scattering takes advantage of the Brownian motion of particles in solution or suspension to measure their size. The rate of fluctuation corresponds directly to the diffusion rate of the scattering particles. Larger particles diffuse more slowly, leading to slow optical fluctuations, while smaller particles diffuse more rapidly, leading to fast optical fluctuations. The diffusion coefficient of the particles can be determined from the autocorrelation analysis on the raw optical signals and fitting the resulting autocorrelation function. The particle size is then determined from the diffusion coefficient using the Stokes-Einstein equation.

[0846] DLS measurements were made using the Dynapro plate reader III (Wyatt Technology). Antibodies to be evaluated were diluted in 1x PBS (Gibco catalog # 14190-144), filtered through a 0.02 um filter to remove particulate matter and large aggregates, to a final concentration of 1-2 mg/mL. Twenty-five microliters of the antibody solution was added to wells of a 384 well plate (Aurora catalog # ABA210100A), followed by 5 uL of silicone oil (Alfa Aesar catalog # A12728). The plate was covered and centrifuged at 1000 x g for 1 min to ensure removal of air bubbles. The plate was then loaded on the DLS instrument, and data collected using the following setup along with default instrument settings.

[0847] The initial temperature was set at 25°C, followed by a steady increase in temperature by 1°C/min up to 85°C with enabled auto attenuation of laser intensity. Continuous measurements were made for each well to determine the diffusion coefficient and hydrodynamic radii. The temperature onset for aggregation (Tagg) value was obtained by using the integrated Dynamics7.1 software, which analyzed changes in radii corresponding to change in temperature and identified the temperature corresponding to increase in hydrodynamic radius as the Tagg.

[0848] *mAb Thermal stability assessment using Differential Scanning Fluorimetry (DSF)*

[0849] DSF was carried out with the QuantStudio5 real-time PCR instrument (Life Technologies) using the protein thermal shift Protein Thermal Shift™ Dye Kit (Life Technologies Catalog # 4461146) following manufacturer protocols. MicroAmp 384-well plates (Thermo Fisher catalog # AB1384/W) were used with 20 µL sample per well. Monoclonal antibodies were diluted to a 1 mg/mL concentration in the respective formulation buffer, and samples were prepared as follows: five microliters of Protein Thermal Shift™ Buffer, 12.5 µL of the antibody (1 mg/mL) or buffer (negative control), and 2.5 µL of Diluted Protein Thermal Shift™ Dye (8x) were added together for a total volume of 20.0 µL for each reaction. SYPRO Orange was diluted 125-fold from the 1000× concentrated stock solution to the working dye solution in the provided thermal shift buffer prior to addition to the reaction mixture. To prevent bleaching, the working solution of SYPRO Orange was added to the reaction mixture just prior to the experiment. Each sample was measured in quadruplicate. Thermal denaturation was carried out by increasing the temperature from 25 °C to 95 °C at a rate of 0.017 °C per second. Fluorescence intensity (excitation at 490 nm and emission with the use of a ROX filter at 600 to 630 nm) was collected at 0.07 °C intervals and analyzed with Protein Thermal Shift Software (Life Technologies), using the first derivative approach to calculate Tm. In this method, Tm is the temperature corresponding to the maximum value of the first derivative of the DSF melting curve.

[0850] *Immune Pathway Activation in Human Dissociated Tumor Cells (DTCs)*

[0851] Dissociated Tumor Cells (DTCs) from four NSCLC patients were purchased from DLS and thawed per manufacturer's recommendation. Cells were counted and plated at around 2M cells per 24 well in 3 wells in Ex vivo media with anti-anot but no serum. 5µg/ml of R&D, RDM5 and RDM9, PI-3030, and hIgG1 (ultra-LEAF) were added to each well containing 1ml of media. Four hours later at 37 C, cells were collected in 15ml canonical tubes and centrifuged at 400xg for 5 min at 4°C. Each pellet was resuspended in 600ul of RLT buffer with B-mercapthoethanol (at 1:100 dilution).

[0852] Total RNA was isolated from the above DTCs samples using the Qiagen RNeasy Mini kit and control treated human and submitted for high-throughput RNA sequencing. Libraries were prepared using Illumina's TruSeq Stranded mRNA kit and sequenced on an Illumina Novaseq 6000. Subsequent data was aligned to the human genome (GRCh38.p12) and per-gene expression values were tabulated using the STAR aligner. The resulting expression matrices were used as input for differential expression analysis using DESeq2. Resulting fold changes from PI-3010 vs control comparisons for all protein coding genes were submitted to Gene Set Enrichment Analysis (GSEA) software, using the preRanked test, available from the Broad Institute at https://www.gsea-msigdb.org/gsea/index.jsp. MSigDB's Hallmark pathways were assessed and resulting Normalized Enrichment Scores were plotted using ggplot2 in R. FDR values were determined via permutation test implanted within GSEA using standard parameters.

[0853] *Proinflammatory Signature in Human Suppressive Macrophages (M2c)*

[0854] Four Frozen human peripheral blood CD14+ monocytes isolated from peripheral blood mononuclear cells using negative immunomagnetic selection (StemCell Technologies) were thawed and cultured in RPMI 1640 medium supplemented with 10% (v/v) heat-inactivated FBS (HyClone), 1 mM sodium pyruvate, non-essential amino-acids, 2 mM L-glutamine, 55 uM β-mercaptoethanol and antimycotic antibiotic (all from Gibco). Monocytes were differentiated into macrophages by culturing in complete RPMI 1640 medium in the presence of 50 ng/ml human macrophage colony-stimulating factor (M-CSF) (PeproTech) at a density of 500,000 cells per well in 24 well plates. At day 3 of differentiation, media was replenished with the addition of fresh M-CSF. Differentiated human macrophages were polarized by adding the following cytokines to the media for 24 hours at 37 C: M0 (no cytokine addition) and 25ng/ml of recombinant human IL-10 (M2 condition) for 24 hours at 37 C. On day 7, the media was aspirated and cells washed gently. Fresh complete RPMI 1640 medium macrophage medium with 5μg/ml of PI-3010.15, PI-3030.41, and hIgG1 (Ultra-LEAF from Biolegend) were added to each well from the above 2 conditions. 4 hours later, media was aspirated and cells lysed in RLT buffer with β-mercapthoethanol (at 1:100 dilution).

[0855] Total RNA was isolated from the IL-10 polarized hMDMs using Qiagen RNeasy Mini kit and submitted for high-throughput RNA sequencing. Libraries were prepared using Illumina's TruSeq Stranded mRNA kit and sequenced on an Illumina Novaseq 6000. Subsequent data was aligned to the human genome (GRCh38.p12) and per-gene expression values were tabulated for all MDM using the STAR aligner. The resulting expression

matrices were used as input for differential expression analysis using DESeq2. Resulting fold changes from PI-3010.15 vs control comparisons for all protein coding genes were submitted to Gene Set Enrichment Analysis (GSEA) software, using the preRanked test, available from the Broad Institute at www.gsea-msigdb.org/gsea/index.jsp. MSigDB's Hallmark pathways were assessed and resulting Normalized Enrichment Scores were plotted using ggplot2 in R. FDR values were determined via permutation test implanted within GSEA using standard parameters.

[0856] *Hallmark Pathways: PI-3008 Treated BMDMs vs PI-3008 Treated CT26 Tumors*

[0857] Individual femurs and tibias from four females BALB/c mice were cleaned and crushed in Macrophage Medium composed of Iscove's modified Dulbecco Medium supplemented with 10% (v/v) fetal bovine serum (FBS) (HyClone) and antibiotic-antimycotic solution (Gibco), using a mortar and pestle. Samples were then passed through a 40 um filter, washed with media and pelleted at 400xg for 5 min at RT. Cell pellets were resuspended in 5 ml of BD Pharm Lyse buffer (BD Biosciences) and red blood cell lysis was carried out at RT for 5 min, followed by quenching with 10 volumes of Macrophage Medium. Cells were pelleted at 400xg for 5 min at RT and resuspended in Macrophage Medium at the density of 500,000 cells per well in 24 well plates. These bone marrow mononuclear cells were stimulated with 25 ng/ml of mouse macrophage colony-stimulating factor (M-CSF) (PeproTech) for 6 days to generate M0- macrophages and polarized into M1-like and M2-like macrophages by supplementing the medium with LPS (1ng/ml) and mouse IL-10 at 20 ng/ml respectively for 24 hours at 37C.

[0858] On day 7, the media was aspirated and cells washed gently with macrophage medium. Fresh media with 5ug/ml of PI-3008 or its mIgG2a isotype control was added to each well from the three conditions: M0, M1, and M2. 4 hours later, media was aspirated and cells lysed in RLT buffer with B-mercapthoethanol (at 1:100 dilution).

[0859] Total RNA was isolated from these BMDMs using the Qiagen RNeasy Mini kit and CT26 tumors (previously described for figures 12C-12H) and submitted for high-throughput RNA sequencing. Libraries were prepared using Illumina's TruSeq Stranded mRNA kit and sequenced on an Illumina Novaseq 6000. Subsequent data was aligned to the murine genome (GRCm38.p6) and per-gene expression values were tabulated for all BMDM samples and CT26 samples, respectively, using the STAR aligner. The resulting expression matrices were used as input for differential expression analysis using DESeq2. Resulting fold changes from PI3008 vs control comparisons (from both BMDM and CT26 subsets) for all protein coding genes were submitted to Gene Set Enrichment Analysis (GSEA) software, using the

preRanked test, available from the Broad Institute at gsea-msigdb.org/gsea/index.jsp. MSigDB's Hallmark pathways were assessed for both the BMDM and CT26 comparisons and resulting Normalized Enrichment Scores were plotted using ggplot2 in R.

[0860] *Cytokine qPCR Assay*

[0861] Two frozen human peripheral blood CD14+ monocytes isolated from peripheral blood mononuclear cells using negative immunomagnetic selection (StemCell Technologies) were thawed and cultured in RPMI 1640 medium supplemented with 10% (v/v) heat-inactivated FBS (HyClone), 1 mM sodium pyruvate, non-essential amino-acids, 2 mM L-glutamine, 55 uM β-mercaptoethanol and antimycotic antibiotic (all from Gibco). Monocytes were differentiated into macrophages by culturing in complete RPMI 1640 medium in the presence of 50 ng/ml human macrophage colony-stimulating factor (M-CSF) (PeproTech) at a density of 500,000 cells per well in 24 well plates. At day 3 of differentiation, media was replenished with the addition of fresh M-CSF. Differentiated human macrophages were polarized on day 6 by adding 25ng/ml of recombinant human IL-10 (M2 condition) for 24 hours at 37 C. On day 7, the media was aspirated and cells washed gently. Fresh complete RPMI 1640 macrophage medium with 5μg/ml of PI-3010.15 (PI-3015), PI-3010.25 (PI-3025), PI-3030.41 (PI-3041), or hIgG1 isotype control (Ultra-LEAF from Biolegend) and 5μg/ml of PI-3010.46 (PI-3046), PI-3030.47 (PI-3047), PI-3010.48 (PI-3048), or hIgG4 isotype control (Ultra-LEAF from Biolegend) were added to the corresponding wells. 4 hours later, media was collected into 96 well plates for Luminex cytokine secretion and cells lysed in RLT buffer with β-mercapthoethanol (at 1:100 dilution). Total RNA was isolated from the IL-10 polarized hMDMs using Qiagen RNeasy Mini kit and 250ng of RNA was made into single strand DNA using the High-capacity cDNA Reverse Transcription kit (Applied Biosystems). qPCR was performed using the 5ul of SYBR green mix and primers specific to IL-6, IL-1b, IL10, TNFa, CXCL10, IL18, CCL20, CCL24, IL1A. The endogenous housekeeping primers tested were GAPDH and RPL37A. The plates were ran on the QuantStudio 5 qPCR machine from Thermo Fisher.

[0862] This cytokine expression qPCR assay was repeated in multiple hMDMs donors and different runs with titrating down the concentration of the hIgG1 lead antibodies to be 1 ug/ml compared to hIgG1 isotype (PI-0003). In addition, this assay was used to confirm the activation of the pro-inflammatory gene signature The expression of IL-6, TNFa, IL-1b, IL10, IL18, CCL20, CCL24, CXCL8, IL1A was assessed for pro-inflammatory activation was tested in all assays.

[0863] In addition this assay was used to confirm the activation of the pro-inflammatory gene signature downstream of PI-3010.15-AB in THP-1 monocytic cells overexpressing human full length MARCO.

[0864] The qPCR analysis was done by calculating the fold changes of the treated samples over the corresponding isotype control using the 2^-(ddCT). Each gene CT value was normalized to the CT value of the endogenous control used (such as GAPDH or RPL37A).

[0865] Human Cytokine and chemokines secretion by MSD

[0866] 200ul of Supernatant collected from hMDMs cells treated with the human anti-MARCO PI-3010.15, PI-3010.25, and PI-3030.41 and isotype were evaluated for cytokine levels using the V-PLEX human proinflammatory panel 1 human kit measuring 10 cytokines (MSD, Cat. No. K15049D) and the V-PLEX human chemokine panel 1 human kit measuring 10 chemokines (MSD, Cat. No. K15049D) from Meso Scale Discovery (MSD, Cat. No. K15047D) or a customized human PrecartaPlex 26-plex kit from Thermo Fisher (Cat. No. PPX-26-MX-3222A). The MSD multiplex assay plates were precoated with capture antibodies. Samples for analysis or kit standards were added at a volume of 50 µl per well after pre-diluting the original sample with assay diluent. The plates were washed after a two-hour incubation at room temperature with agitations.

[0867] For the V-PLEX assay, sulfo-tagged detection antibodies were added and incubated for another two hours at room temperature with agitations. Following the incubation, plates were washed once again. 2X Read Substrate was added and plates were read on MSD reader. All data were analyzed by MSD Discovery Workbench® Software 4.0.

[0868] For the customized human 26-plex kit, biotinylated labeled detection antibodies were added and incubated for one hour at room temperature with agitations. Plates were washed. PE(Phycoerythrin)-labeled Streptavidin were added and incubated for 30 min at room temperature with agitations. After the plates were washed, Luminex reading buffer was added and plates were read on Luminex 200 analyzer. All data were analyzed by xPONENT Software.

[0869] Results

[0870] DNA sequences for the heavy and light chain of antibodies PI-3010.15, PI-3010.25, and PI-3030.41 were codon optimized and incorporated into proprietary vectors at Atum (Newark, CA). The heavy and light chain encoding vectors were transfected in CHO cells at 2 L scale, followed by purification using MabSelect Sure Protein A resin. Both candidates showed high titers and <5% aggregates post Protein A purification. Data are summarized in **Table 14**.

Table 14					
Antibody	Germline	Isotype	Expression CHO - transient (mg/L)	Theoretical pI	% Monomer (post Protein A)
PI-3010.15-H1	IGHV1-46 IGKV1-39	hIgG1	585	8.45	>95
PI-3010.25-H1	IGHV1-46 IGKV1-39	hIgG1	818	8.11	>95
PI-3030.41-H1	IGHV1-59 IGKV1-39	hIgG1	868	8.44	>95

[0871] Binding of PI-3010.15, PI-3010.25, and PI-3030.41 was assessed by Biacore on recombinant human and cynomolgus MARCO protein and demonstrated high affinity binding to both human and cynoMARCO, with the affinity of binding to cynoMARCO within 2-3 fold of the human MARCO affinity.

[0872] Flow cytometry was used to assess the binding of the antibodies to human and cynomolgus MARCO expressing cell lines, including MARCO transfectants in HEK 293T cells and human monocyte derived macrophages (MDM) expressing endogenous MARCO. The antibodies bound to human and cynoMARCO with comparable EC50s and bound to endogenous MARCO on human MDMs with high affinity. No off-target binding was observed to parental HEK 293T cells that did not express MARCO or to Jurkat T cells by flow cytometry (**Table 15** and **FIG. 53**).

Table 15							
Humanized mAb	**EC50 OVX Cell binding (nM) (hu/cyn)**	**K_D(nM) Human**	**K_D(nM) Cyno**	**K_{off} (1/s) Human**	**Binding on human macrophages**	**Block ligand(s) binding**	**Binding to T-cells**
PI-3010.15 PI-3015 (hIgG1)	0.798/1.16	0.51	1.65	2.94E-04	+	+	-
PI-3010.46 PI-3046 (hIgG4)	0.821/1.07	0.78	1.10	3.71E-04	+		-
PI-3010.25 PI-3025 (hIgG1)	0.790/1.01	1.09	1.79	4.30E-04	+	+	-
PI-3010.48 PI-3048 (hIgG4)	0.721/2.39	1.05	1.81	3.86E-04	+		-
PI-3030.41 PI-3041 (hIgG1)	0.704/1.028	0.82	1.12	3.34E-04	+	+	-
PI-3030.47 PI-3047 (hIgG4)	0.796/1.39	0.72	0.79	3.37E-04	+		-

[0873] Thermal stability assessment to determine the temperature for melting (Tm1) and aggregation (Tagg) using differential scanning fluorimetry (DSF) and dynamic light scattering (DLS) respectively showed that all 3 antibodies have acceptable and similar

properties. In addition, all 3 antibodies were soluble and stable up to 30 mg/ml as determined by size exclusion chromatography (SEC) and DLS in citrate and histidine buffers ranging between pH 5.0-6.5. A summary of the data is shown in **Table 16** below.

Table 16

	Analysis Method	PI-3010.25 (PI-3025) (hIg1)	PI-3010.48 (PI-3048) (hIg4)	PI-3010.15 (PI-3015) (hIg1)	PI-3010.46 (PI-3046) (hIg4)	PI-3030.41 (PI-3041) (hIg1)	PI-3030.47 (PI-3047) (hIg4)
Binding affinity to human MARCO (KD)	**Biacore (SPR, nM)**	1.09	1.05	0.51	0.78	0.82	0.72
Thermal Stability (PBS)	**Tm1 (DSF, °C)**	68	65	68	64	68	64
Thermal Stability (PBS)	**Tagg (DLS, °C)**	83	73	78	72	78	71
Solubility (30 mg/mL)	**SEC, DLS**	Soluble and stable up to 30 mg/mL in citrate and acetate buffers, pH 5.0-6.0					

[0874] Cytokine expression induced by human anti-MARCO antibodies in hMDMs was also assessed. As shown in **Table 17**, all of PI-3010.15, PI-3010.46, PI-3010.25, PI-3010-48, PI-3030-41, and PI-3030.47 induced expression of the indicated cytokine genes in Donor 1. Cytokine and other relevant gene expression (MIP-1α, IL-27, LIF, IL-1β, IL-2, IL-4, IP-10, IL-6, IL-10, CD40, IL-12p70, G-CSF, IFNγ, GM-CSF, TNFα, MIP-1β, MCP-1, MIG, gro-alpha, IL-1α, IL-15, MCP-3, M-CSF, and VEGF-A) in hMDMs from two different donors (Donor 1 and Donor 2) is also shown in **FIG. 27**.

Table 17. Gene fold induction over corresponding isotype

Donor 1	IL-6	TNFα	CXCL10	IL18	CCL20	IL1A
PI-3010.15 IgG1	1.3	2.2	1.5	1.8	1.4	2.4
PI-3010.46 IgG4	1.8	1.9	1	1.8	1.7	3.6
PI-3010.25 IgG1	1.2	2.5	1.5	3.9	1.5	4.1
PI-3010.48 IgG4	1	2.1	0.9	1.5	1.3	3.6
PI-3030.41 IgG1	1.3	3.2	1.9	4.3	1.6	7.8
PI-3030.47 IgG4	2	3.2	1.8	1.3	1.8	6.6

[0875] **FIG. 28** provides the qPCR mRNA data (TNFα, IL-1 β, IL-18, and CXCL8) and MSD cytokine data (TNFα, IL-1β, IL-6, MIP1-α) for PI-3010.15, PI-3010.25, and PI-3030.41 as well as the hIgG1 control. qPCR mRNA analysis of pro-inflammatory genes was plotted as fold induction over the hIgG1 control isotype of one representative donor (top row). Data is presented as mean values of technical duplicates ± standard deviation (SD). Cytokine secretion was also measured by MSD and data plotted for the levels (pg/ml) of representative pro-inflammatory cytokines and chemokines levels (bottom row). Data is presented as mean values of technical duplicates of the same representative donor ± standard deviation (SD).

[0876] PI-3010.15 hIgG1 control treated human disassociated tumor cells and PI3008/control treated CT26 tumors were processed as described above (**FIG. 16B**). GSEA derived Normalized Enrichment Scores from both experiments were plotted using ggplot2 in R. As shown in **FIG. 29**, human and mouse MARCO mAbs drive similar pathway regulation.

[0877] PI-3010.15 activated anti-tumor immune pathways in human dissociated tumor cells (DTCs) (**FIG. 30**). The top immune activation genes and pathways increased by anti-MARCO antibody in hDTCs including IL-2-STAT5 signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, the inflammatory response, IFNγ response, and IFNα response (**FIG. 30**). These pathways were also upregulated by PI-3008 in mouse tumor cells and BMDMs as shown in **Example 4**. The pathways decreased by anti-MARCO antibody in hDTCs included hypoxia, apical junctions, Myc targets, PI3K-AKT-mTOR, E2F targets and oxidative phosphorylation. These pathways were also downregulated by PI-3008 in mouse tumor cells and BMDMs as shown in **Example 4**. Pathways were defined using the Hallmark pathway set.

[0878] PI-3010.15 also induced a pro-inflammatory signature in human suppressive macrophages (M2c) (**FIG. 31**). Upregulated cytokines and genes were CXCL3, CXCL8, TNFα, CCL3, IL7R, CCL4, CCL5, CCL24, CCL20, IL-1α, IL-6, IDO, CD274, SF2, LAMP3, CCR7, CXCL11, and CXCL9. Down regulated cytokines and genes were ALK, MPB, TMEM37, NHSL2, SLC46A2. Upregulated pathways were TNFa signaling via NF-kB, inflammatory response, INFg response, Myc targets, hypoxia, IL6/JAK/STAT3 signaling, IFNa response, unfolded protein response, IL2/STAT5 signaling, UV response, allograft rejection, epithelial mesenchymal rejection, apoptosis, mTORC1 signaling, estrogen response early, KRAS signaling up, cholesterol homeostasis, notch signaling, apical junction, wnt beta catenin signaling, oxidative phosphorylation, complement, PI3k Akt mTOR signaling, reactive oxygen species pathway, hedgehog signaling, angiogenesis, glycolysis, KRAS signaling DN, DNA repair, p53 pathway, myogenesis, coagulation, apical surface, androgen response, TGFβ signaling, fatty acid metabolism, and xenobiotic metabolism.

[0879] Pathways down regulated were bile acid metabolism, estrogen response late, adipogenesis, peroxisome, heme metabolism, UV response DN, mitotic spindle, protein secretion, spermatogenesis, G2M checkpoint, and E2F targets. The key pro-inflammatory genes and pathways induced by PI-3010.15 in M2c hMDMs included IL-2-STAT5 signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, the inflammatory response, IFNγ response, and IFNα response. Pathways were defined using the Hallmark pathway set. Similar pathways were induced in BMDMs treated with PI-3008.

[0880] A comparison of the fold change induced in cytokine expression by PI-3010.15 and PI3030.41 is shown in **FIG. 32**. PI-3010.15 induced higher levels of IL-1β, CSF3, CSF2, IL-1α, IL-6, TNFα, CCL4, CXCL1, CCL3, and CXCL10 as compared to PI-3030.41.

[0881] **Tables 18** and **19** provide a comparison summary of a selection of anti-MARCO antibodies and characteristics. (-) indicates no difference between antibodies, (+) indicates an advantage.

Table 18

Criteria/Test	PI-3010.15	P-3010.25	P-3030.41
K_D human (avid)	-	-	-
K_D cyno (avid)	-	-	-
ELISA binding	-	-	-
Calculated (In silico) sequence liability	Oxidation (low) Deamidation (low) +	Deamidation (low) Isomerization (high)	Deamidation (low) Isomerization (high)
Observed liabilities (forced degradation)	Oxidation (low) +	Isomerization (low)	Deamidation (lhigh) Isomerization (high)
Aggregation (SEC, DLS, HIC from transient expression)	+	+	
Aggregation (SEC from Lonza stable pooled transfected materials)	+	+	
Thermal Stress (DLS, DSF)	-	-	-
Stability over time (DLS, SEC, SPR)	+		
Deamidation and Isomerization Risk	+		
Functional in vitro assays	+		

Table 19

In vitro assays	PI-3010.15	PI-3010.25	PI-3030.41
Binding to overexpressed cells and absence of binding on negative cells	-	-	-
Compete for the binding of ligands to the SRCR domain	-	-	-
Cell surface expression in hMDMs and THP1 cells polarized with IL-10	+		
RNAseq in DTCs	+	+	
RNAseq in hMDMs	+	Not tested	
qPCR for gene expression in hMDMs	-	-	-

Cytokine secretion assay by MSD and/or Luminex	-	-	-
Increase Inflammasome in hMDMs	+		
NF-κB reporter assay in THP1-Blue™ NF-κB Cells	+	+	
Mild Increase in Phagocytosis	+	+	

[0882] In order to determine if any potential liabilities exist in the sequences of three selected antibodies, Sentinel APART algorithm (Lonza) was used for *in-silico* sequence analysis of the candidates. Points of concern that were flagged by *in-silico* analysis were: increased hydrophobicity, aggregation propensity, aspartate isomerization, and oxidation liability. Previous *in silico* assessment showed similar liabilities that were flagged but proved to be minor liabilities when tested under various stress conditions and forced degradation assays. **Table 20** below shows a summary of the experimental data in comparison with the theoretical data.

Table 20

Antibody	**Aggregation**		**Deamidation**		**Isomerization/ Fragmentation**		**Oxidation**	
	Calculated (in silico)	**Observed (HIC)**	**Calculated (in silico)**	**Observed (HIC)**	**Calculated (in silico)**	**Observed (HIC)**	**Calculated (in silico)**	**Observed (HIC)**
PI-3010.15	High	Low	0 (1)	0 (0)	0 (0)	0 (0)	0 (2)	0 (2)
PI-3010.25	High	Low	0 (1)	0 (0)	1 (0)	0 (1)	0 (1)	0 (0)
PI-3030.41	High	Low	0 (2)	1 (1)	2 (0)	1 (1)	0 (3)	0 (0)

[0883] Total hydrophobicity of lead candidates was evaluated using hydrophobic interaction chromatography (HIC). Longer retention time indicates more hydrophobicity. An anti-TREM1 antibody was used as a positive control in this assay. The PI-3010.15, PI-3010.25 and PI-3030.41 antibodies all showed hydrophobicity in the range expected for antibodies (**Table 21**). High levels of main peak % indicate fewer modifications and lower retention time corresponds to lower hydrophobicity.

Table 21

Sample Number	**Main Peak (%)**	**Retention Time (min)**
PI-3010.15	88.7	15.7
PI-3010.25	95.8	15.6
PI-3030.41	70.7	11.5

[0884] A forced degradation study to understand liabilities of selected antibodies was conducted. PI-3010.15-H1, PI-3010.25-H1 and PI-3030.41-H1 samples were incubated under stress conditions (oxidation, low pH, and high pH) and analyzed by peptide mapping (LC-MS/MS) to identify protein modifications in the mAbs. The focus was on the analysis of

isomerization and oxidation liabilities. In addition, other parameters were used to assess the stability of each antibody at the various stress conditions (Table 22).

Table 22

Sample	Source	Isoytpe	Conc (mg/mL)	Condition	Time	Readout
PI-3010.25	CHO-ATUM	hIgG1	8.4	4°C (PBS control 40°C (PBS) 40°C (pH 5.5) 40°C (pH 8.5) 40°C (PBS) + AAPH (6hrs) 25°C (pH 3.5)	2 weeks	Nanodrop (A280) SEC (aggregation) DLS (Tagg, size) DSF (domain stability) LC-MS (peptide mapping to detect modifications) Charge variant analysis Biacore (binding)
PI-3010.41	CHO-ATUM	hIgG1	9.5			
PI-3010.15	CHO-ATUM	hIgG1	10.5			

[0885] Isomerization

[0886] PI-3010.15 was incubated at the following conditions: 40°C in PBS for 2 weeks, control in PBS at -80°C, 40°C (PBS) + 1mM AAPH for 6 h, and 40°C in pH 5.5 sodium acetate for 2 weeks. Post treatment the samples were analyzed by LC-MS/MS which identified the % modification on isolated peptides derived from the antibody after trypsin digest.

[0887] LC/MS peptide mapping was done on PI-3010.15 after incubation at low pH for extended periods to identify potential hotspots. PI-3010.15 did not show any Isoaspartate (IsoAsp), deamidation or succinimide formation. PI-3010.25 showed IsoAsp formation in residue D56 of light chain (>2%, only under pH 5.5, 40°C) and D72 of heavy chain (3.7% at pH 3.5) while PI-3030.41 showed IsoAsp in D56 of light chain (>2.7%, under pH 5.5, 40°C) and succinimide at residue N52 of heavy chain (6-9% under all conditions, including control).

[0888] Oxidation:

[0889] PI-3010.15 was incubated at the following conditions: control in PBS at -80°C, 40°C (PBS) + 1mM AAPH for 6 h, 0.5 and 1.5 % H2O2 in PBS for 24 h, which was compared to a previous experiment at 40°C (PBS) + 1mM AAPH for 6 h. Post treatment the samples were analyzed by LC-MS/MS which identified the % modification on isolated peptides derived from the antibody after trypsin digest.

[0890] PI-3010.15 showed oxidation of Met-48 and Trp-52 with AAPH and H2O2 treatment. Trp-52 was flagged as a potential liability in the in-silico assessment. Met-48 residue is expected to be buried in the structure, and not solvent accessible. It was not possible to

unambiguously assign oxidation liability to either residue as they are found as part of the same peptide during LC-MS/MS analysis.

[0891] Binding of the stressed samples to recombinant human MARCO was assessed by Biacore. The binding of the stressed samples had similar KDs and Rmax levels compared to the control conditions suggesting that binding potency was not significantly affected (**Table 23**), including various oxidized stress samples from PI-3010.15 (**Table 24**).

Table 23

Binding to MARCO

Antibody	Control		40°C 2 week		Deamidation (40°C 2 week)		Isomerization/ Fragmentation		Oxidation (1mM AAPH, 6hrs)	
	K_D (nM)	Rmax	K_D (nM)	Rmax	K_D (nM)	Rmax	K_D (nM)	Rmax	K_D (nM)	Rmax
PI-3010.15	1.2	131.7	1.2	103.8	1.24	111.3	1.24	108.6	1.29	104.5
PI-3010.25	0.54	63.2	0.58	62.2	0.66	62.4	0.66	62.4		
PI-3030.41	0.24	62	0.36	54.3	0.39	54.8	0.34	48.9		

Table 24

Oxidation

Antibody	Control		0.5% H2O2 (24 hr, RT)		1.5% H2O2 (24 hr, RT)		1mM AAPH, 6hrs 40°C)	
	K_D (nM)	Rmax	K_D (nM)	Rmax	K_D (nM)	Rmax	K_D (nM)	Rmax
PI-3010.15	0.97	111.7	1.05	97.1	1.07	109.5	1.10	97.6

[0892] The 3 antibodies (PI-3010.15, PI-3010.25, and PI-3030.41) were successfully concentrated up to 30 mg/mL in the following buffers in pH range 5.0-6.0 without any other excipients. PBS was used a control. The antibodies were incubated at 4oC overnight prior to the following analyses: % aggregation by SEC-HPLC; Size (radius) and polydispersity using DLS; Thermal stability [Tagg (DLS), Tm (DSF)]; Colloidal stability (kd) by SLS.

[0893] PI-3010.25 was concentrated in the following buffers (**Table 25**).

Table 25

Buffer	pH	mAb Concentration (mg/mL) for PI-3010.25
10 mM Histidine HCl	6.0	27.1
10 mM Histidine HCl	5.5	36.4
10 mM Sodium Citrate	6.0	33.2
10 mM Sodium Citrate	5.5	35.8
10 mM Sodium Citrate	5.0	29.7
10 mM Sodium Acetate	5.5	33.4
10 mM Sodium Acetate	5.0	36.1
PBS (control)	7.4	30.4

[0894] PI-3010.25 could be concentrated to 30 mg/mL without increase in HMW aggregates.

Example 9: Anti-MARCO Antibody Induces Inflammasome Activation

[0895] Materials and Methods

[0896] *Inflammasome Assay in mBMDMs*

[0897] Femurs and tibias from three females C57BL/6 mice and three females BALB/c were cleaned and crushed in Staining Medium (0.5% (w/v) BSA (Sigma) and 2 mM EDTA in D-PBS) using a mortar and pestle. Samples were then passed through a 40 um filter, washed with D-PBS and pelleted at 400xg for 5 min at RT. Cell pellets were resuspended in 5 ml of BD Pharm Lyse buffer (BD Biosciences) and red blood cell lysis was carried out at RT for 5 min, followed by quenching with 10 volumes of Staining Medium. Cells were pelleted at 400xg for 5 min at RT and resuspended in Macrophage Medium composed of Iscove's modified Dulbecco Medium supplemented with 10% (v/v) fetal bovine serum (FBS) (HyClone) and antibiotic-antimycotic solution (Gibco), at the density of 15x10^6 cells/ml in 15 cm plates. These bone marrow mononuclear cells were stimulated with 25 ng/ml of mouse macrophage colony-stimulating factor (M-CSF) (PeproTech) for 7 days to generate M0-macrophages and differentiated into M2-like by supplementing the medium with mouse IL-1b at 20 ng/ml on day 6 for 24 hours at 37C. On day 7, macrophages were rinsed with DPBS and incubated in 6 ml of 2 mM EDTA for 10 minutes to promote cell detachment. Cells were gently scraped into an additional 6 ml of the Staining Medium described above, counted and seeded onto 96-well plates at 100,000 cells per well.

[0898] After 30 minutes to 1h at 37C to allow the cells to attach, BMDMs were treated with 5 μg/ml of the anti-mouse MARCO antibody PI-3008 and its corresponding isotype control mIgG2a. After 3 hours of incubation with the antibodies, LPS (tested 0.5 and 50 ng/ml) was added to prime the inflammasome pathway for an additional 2.5 hours. ATP (5mM) was then added for 30 minutes to activate the inflammasome and induce cytokine secretion of IL-1β that was measured by MSD. Sidak's multiple comparisons test was used to calculate statistical significance of secreted IL-1β fold change over untreated isotype (no LPS and no ATP). Sidak's multiple comparisons test, **P<0.01.

[0899] *Inflammasome Assay in hMDMs*

[0900] Frozen human peripheral blood CD14+ monocytes isolated from peripheral blood mononuclear cells using negative immunomagnetic selection (StemCell Technologies) were thawed and cultured in RPMI 1640 medium supplemented with 10% (v/v) heat-inactivated FBS (HyClone), 1 mM sodium pyruvate, non-essential amino-acids, 2 mM L-glutamine, 55 uM 2-mercaptoethanol and antimycotic antibiotic (all from Gibco). Monocytes were differentiated into macrophages by culturing in complete RPMI 1640 medium in the presence of 50 ng/ml human macrophage colony-stimulating factor (M-CSF) (PeproTech) at a density of 12-15x10^6 cells in 15cm dish. At day 3 of differentiation, media was replenished with the

addition of fresh M-CSF. Differentiated human macrophages were polarized by adding the following cytokines to the media for 24 hours at 37 C: 100ng/ml of IFNγ (M1 condition) and 25ng/ml of recombinant human IL-10 (M2 condition) for 24 hours at 37 C. On day 7, polarized macrophages were gently harvested non-enzymatically using a sterile cell scraper (Nunc) into FACS buffer (D-PBS containing 2 mM EDTA and 0.5% (w/v) bovine serum albumin (BSA) (Sigma)) followed by centrifugation at 400xg for 5 min at ~20°C.

[0901] Cells were counted and seeded onto 96-well plates at 100,000 cells per well. After 30 minutes to 1h at 37°C to allow the cells to attach, hMDMs were treated with 5µg/ml of the anti-human MARCO antibodies PI-3010.15, PI-3010.25 (PI-3025), PI-3030.41 (PI-3041), and PI-3010.48 (PI-3048) and their corresponding isotypes controls hIgG1 and hIgG4 (Ultra-leaf from Biolegend). After 3 hours of incubation with the antibodies, LPS (tested 0.1 and 1 µg/ml) was added to prime the inflammasome pathway for an additional 2.5 hours. ATP (5mM) was then added for 30 minutes to activate the inflammasome and induce cytokine secretion of IL-1 β that was measured by MSD. Tukey's multiple comparison test was used to calculate statistical significance of secreted IL-1β fold change over untreated (no LPS and no ATP) hIgG1. Tukey's multiple comparisons test (*P<0.05; ***P<0.0006, ****P<0.0001).

[0902] *E.coli Phagocytosis assay*

[0903] Human monocyte-derived macrophages (MDM) were generated by culturing CD14+ human monocytes in RPMI 1640 medium (Gibco) supplemented with 10% Fetal Bovine Serum (Gibco), 1% ß-mercaptoethanol (ThermoFisher), 1X non-essential amino acids (Gibco), 1x Sodium Pyruvate (Gibco), 1X GlutaMax (Gibco), 1x anti-anti (Gibco), 50 ng/ml of M-CSF (Peprotech) in 15cm plate. Medium was refreshed after 3 days. On day 6 of culture, 100 ng/ml of human IFN-g (Peprotech) + 50 ng/ml of LPS (Invivogen) or 25 ng/ml of IL-10 (Peprotech) were added to the culture. The following day, cells were harvested, and 200,000 cells were plated per well of 96-well flat bottom plate and incubated with a dose titration of PI-3101.15, PI-3010.25 or PI-3030.41 and isotype control antibody for 2 hours at 37°C and 5% CO2 to allow cells to adhere.

[0904] To measure phagocytosis, the Vybrant Phagocytosis Assay Kit (Molecular Probes) was used. After the 2-hour antibody incubation, media was removed, and cells were incubated with E. coli fluorescent BioParticles solution for 2 hours at 37°C and 5% CO2. The particles solution was removed and replaced by the trypan blue solution. After 1 min incubation at room temperature, the solution was removed, and fluorescence was measured using 480 nm for excitation and 520 nm emission wavelengths on the Tecan microplate plate reader.

[0905] Results

[0906] PI-3008 induced statistically significant IL-1β secretion by the inflammasome in both non-polarized macrophages (**FIG. 33A** and **33C**) and IL-10 polarized macrophages (**FIG. 33B** and **33D**). This effect was observed in two separate murine lineages, C57BL/6 mice (**FIG. 33A** and **33B**) and Balb/c mice (**FIG. 33C** and **33D**). Thus, PI-3008 enhances and increases inflammasome activation in mouse BMDMs.

[0907] A similar results was observed in human MDMs (**FIG. 34A** , **34B,** and **35**). Both PI-3010.25 (IgG1 format) and PI-3010.48 (IgG4 format) induced statistically significant IL-1β secretion in IL-10 polarized macrophages after incubation with 0.1 μg/ml LPS+ATP and 1 μg/ml LSP+ATP (**FIG. 34A**). In IFN-γ polarized hMDMs, PI-3025 induced IL-1β secretion after incubation with 0.1 μg/ml LPS+ATP, while PI-3010.48 induced IL-1β secretion after treatment with 1 μg/ml LPS+ATP (**FIG. 34B**). Bars for PI-3010.25 are shown second from the left in each grouping, bars for PI-3010.48 are shown on the right in each grouping.

[0908] In a separate assay, all of PI-3010.15, PI-3010.25, and PI-3030.41 induced IL-1β production when treated with LPS and ATP compared to the untreated condition (**FIG. 35**), indicating that anti-human MARCO antibodies induce inflammasome activation.

[0909] The percent induction of phagocytosis by PI-3010.15, PI-3101.25, and PI-3030.41 in the IL-10 hMDM donor cells is provided in **Table 26**.

Table 26

Antibody	Isotype	Phagocytosis
PI-3010.25	IgG1	90%
PI-3010.15	IgG1	88%
PI-3030.41	IgG1	50%

[0910] PI-3010.25 and PI-3010.15 showed more consistent phagocytosis induction across multiple donors when hDMMs were polarized with IL-10.

Example 10: In vivo monotherapy efficacy of anti-mouse MARCO antibodies in EMT6 model

[0911] Methods

[0912] EMT6 breast cancer tumor cells (1x10^6 cells per mouse) were implanted on Day 0, and dosing (10 mg/kg; Q5dx4; ip) was initiated when tumors reached an average volume of ~90 mm3. Animals were dosed intraperitoneally every 5 days, for total of four doses. Tumor volumes were monitored over time and presented as averages per group, individual tumor volumes at the end of study, or as %TGI.

[0913] Results

[0914] PI-3008 demonstrated anti-tumor activity as a single agent in the EMT6 model (FIG. 36). In some groups, up to a 20% complete response (CR) was achieved (responders).

Example 11: In vivo monotherapy efficacy of anti-mouse MARCO antibodies in E0771 model

[0915] Methods

[0916] *E0771 syngeneic mouse model*

[0917] The mouse studies were performed under the guidance of and approved by the Institutional Animal Care and Use Committee of Explora BioLabs, South San Francisco, CA.

[0918] Eight to ten-week old female C57/BL6 mice (Taconic) were implanted with subconfluent E0771 cells (ATCC) grown in log-phase. One million tumor cells resuspended in serum-free media with Matrigel were implanted orthotopically in the mammary fat pad of the mice under isoflurane anesthesia. When the majority of tumors were between 110-120 cubic millimeters (mm3), mice were randomized into the treatment groups (PI-3008-AB and PI-0002 mIgG2a isotype) before initiation of treatment.

[0919] *PD Study*

[0920] Mice randomized in 2 groups were dosed intraperitoneally with 10 mg/kg of PI-3008-AB or PI-0002-AB (isotype) based on group average body weight for each group. Tumor volume was calculated using the formula [length x (width)2]/2 after measuring two orthogonal diameters using digital calipers. At three different timepoints (2 days after 1 dose, 5 days after 1 dose, 24 hours after second dose Q5dx2), 15 mice per group were sacrificed and tumor, spleen and blood were collected. 9 animals were used for flow cytometry processing of tumors and spleen, and 6 mice were used for IHC evaluation of tumors and spleen. Tumor volumes were monitored over time and presented as averages per group, individual tumor volumes at the end of study, or as %TGI.

[0921] *Effector dead antibody efficacy*

[0922] The effector dead anti-MARCO antibody, PI-3021 (PI-3008 with an N297A mutation) was also assessed in the E0771 model. Mice were dosed as described in Example 4. Briefly, 10 mice per group, IP dosing initiated when tumors were ~100 mm^3. Dosing was 10mg/kg; Q5dx4. mIgG2a isotypes of both PI-3008 and the effector dead PI-3021 were used. An anti-PD-1 antibody was also used.

[0923] *PK/PD efficacy in E0771 syngeneic mouse model*

[0924] To determine PK-PD-efficacy relationships, the E0771 orthotopic breast cancer model was used since PI-3008 elicited monotherapy in this model. The study design included a PD

arm where tumors and spleens were collected 24 hr after the second dose, and a "PK" arm to determine PI-3008 serum levels. A schematic of the study timeline is shown in **FIG. 39A**.

[0925] C57BL/6 female mice were injected into mammary fat pad with syngeneic E0771 tumor cells (5x105 cells per mouse) on Day 0, and dosing with PI-3008 or isotype controls (10 mg/kg, N=10/group) was initiated when tumor volumes reached an average of ~100 mm3. Animals were dosed intraperitoneally every 5 days, for total of four doses. A subset of animals was sampled 24 hr after the second dose for the assessment of PD changes in tumors and spleens. Additional PD takedown were done at 2 days and 5 days after first dose. Tissues sampled were tumors, spleens, and blood via Luminex and flow cytometry.

[0926] The rest of the animals were monitored for anti-tumor efficacy and were sampled at end of study for drug exposure analysis. The endpoint PD assays included flow cytometry profiling on the tumors and spleens to determine changes in myeloid and lymphoid composition, measurement of cytokines/chemokines in tumor and spleen, and assessment of CD8 T cells, NK cells, MARCO cells, and CD19 B cells frequencies and tissue distribution by IHC (monoplex and multiplex).

[0927] *Flow cytometry assay*

[0928] Mouse tumor tissue was harvested and placed in ice cold RPMI-1640 (Invitrogen) media. Tumors were enzymatically dissociated using the Mouse Tumor Dissociation Kit (Miltenyi) according to the manufacturer's recommendation. Following dissociation, single cell suspensions were pelleted and tumor supernatant was collected, spun at high speed to remove insoluble material, enzymatically inactivated using Halt™ Protease Inhibitor Cocktail (Thermo Scientific) and promptly frozen at -80degC until downstream analysis was performed. Cell pellets were resuspended in stain media (DPBS/1% BSA/2 mM EDTA) and passed through a 100 uM filter to remove undissociated material. Single cell suspensions were counted on a ViCell XR (Beckman Coulter) and plated in 96-well V bottom plates for flow cytometric staining.

[0929] Cells were incubated with Zombie NIR (BioLegend), followed by FcgR block using a combination cocktail of TruStain FcX PLUS (Biolegend), Mouse Serum, Rat Serum, Hamster Serum (Jackson Immuno Research), all prepared in Fc Receptor Blocker (Innovex). Cell surface proteins were stained for 30 minutes on ice, followed by either a secondary stain step or fixation with 1% PFA overnight at 4°C. For staining intracellular proteins, cells were fixed and permeabilized with the FoxP3/Transcription Factor Staining Buffer Set (Thermo Fisher Scientific). Intracellular antibodies were prepared in permeabilization buffer with 2% rat serum and cells were incubated for at least 30 minutes at room temperature. Cells were

run on an Attune NXT (ThermoFisher). Flow cytometric analysis was performed using FlowJo (Beckton Dickinson).

[0930] The flow antibodies used for each panel are described in **Table 27** below and were prepared by adding the appropriate antibodies to the FACS buffer containing Ca2+/Mg2+ PBS and 2% FBS.

Table 27

Immune Population	Cell Surface Markers
Neutrophils	Ly6G+
Monocytes	Ly6G-/Ly6C+ and sub-gating on MHCII-, $MHCII^{int}$, $MHCII^{high}$
TAMs	CD11b+/F4/80+ and sub-gating on MHCII-, $MHCII^{int}$, $MHCII^{high}$
DCs	F4/80-/CD11c+/MHC-II+
CD4+ T cell	CD90.2+/CD8-/CD4
CD8+ T cell	CD90.2+/CD4-/CD8+
NK cell	CD90.2+/CD4-/CD8-/NK1.1+
Memory B cells	CD90.2- /CD45R+/CD19+
Plasma B cells	CD90.2- /CD45R+/$CD19^{Low}$/Blimp1+
Marginal Zone B cells	CD90.2- /CD45R+/CD21+/$CD35^{mid}$/CD23+
Follicular B cells	CD90.2- /CD45R+/CD21+/$CD35^{high}$
Spleen macrophages	CD11b+/F4/80+ and sub-gating on MHCII- and MHCII+
Red pulp macrophages	CD11b+/F4/80+/CD206+
Marginal zone macrophages	$CD11b^{int}$/F480+ And/or CD11 $CD11b^{int}$/F480+/TIM4+
Non marginal zone macrophages	All CD11b/F480+ populations for the exception of $CD11b^{int}$/F480+ marginal zone

[0931] *Receptor Occupancy (RO) assay*

[0932] For the tumor/spleen myeloid and blood flow cytometry antibody panels, the PI-3008 antibody conjugated with PE at BioLegend or the mIgG2a-PE from BioLegend were added to the staining cocktail at 10 µg/ml to assess receptor occupancy (RO) in the various myeloid cells in the tumors, spleen, and blood.

[0933] *In vivo serum concentrations*

[0934] Serum levels of anti-mouse MARCO mAbs were determined using a standard ligand-binding ELISA (LBA) format with coated recombinant extracellular domain (ECD) mouse MARCO His-tagged fusion construct protein. PI-3008 mAb levels in the serum of CT26 tumor-bearing mice were assessed for multiple studies and various timepoints. For the PD study, PI-3008 was measured 4h after the first IV dose and 4h after the second IV dose, 7 days apart.

[0935] *In vivo* antibody serum levels in the CT26 combination studies with anti-MARCO antibody and anti-PD-1 antibody were also assessed for comparison. PI-3008 and PD-1 were dosed IP at 10 mg/kg or 5 mg/kg at Q5d X4 in the CT26 efficacy study (Example 4). The serum samples for PI-3008 and PD-1 concentration determinations were collected before the third dose (pre dose) and 24 hr after the final dose (post dose).

[0936] *Mouse cytokine and chemokine secretion by Luminex*

[0937] Mouse plasma, spleen supernatants, or tumor supernatants were evaluated for cytokine levels using ProcartaPlex Multiplex Immunoassay from ThermoFisher Scientific (Cat# PPX-25-MX47WJ7). The kit uses color coded beads for measurement of multiple cytokines via Luminex xMAP technology. The beads are internally dyed with different proportions of red and infrared fluorophores that correspond to distinct spectral regions. For the experiment, 50 µl of magnetic capture beads are first added to the plate. Samples for analysis or kit standards were added at 25 µl per well volume and an equal amount of universal assay buffer was added to adjust the matrix. Following a two-hour incubation at room temperature, the beads are captured on a magnetic plate and were then washed followed by the addition of 25 µl /well of detection antibody. Following a one-hour incubation at room temperature, the beads were washed again and streptavidin phycoerythrin (SAPE) was added at 50 µl /well. After a final one-hour incubation, the beads were washed and 120 µl /well of read buffer was added. The plate was run on the Luminex 200 Instrument. Data was analyzed using Luminex Xponent software v4.3 and analytes levels in pg were normalized to the tumor or spleen weight. Cytokine/chemokine data was presented as fold changes of PI-3008 treated supernatants over the average of the isotype treated supernatants for each analyte.

[0938] *Detection of IgG/IgM in Mouse Tissue and Serum*

[0939] 25 µL/well of Diluent 100 (MSD, Catalog R50AA-4) was added to the pre-coated plate with capture antibodies (MSD, Catalog # K15183B-1 and K15203D-1). The plate was incubated at room temperature for 30 min with vigorous shaking. Standards (Mouse Isotyping Panel 1, MSD Catalog # K15183B-1) and samples were diluted in Diluent 100 (MSD, Catalog # R50AA-4) and added to the coated plate. The plate was incubated for 120 min with vigorous shaking at room temperature and washed. 25 µL of 1X detection antibody solution was added to each well, and the plate was incubated for 120 min with vigorous shaking at room temperature. The plate was washed and 2x Read Buffer (MSD, Catalog # R92TC-3) was added to the MSD plate. The plate was read on an MSD Sector Imager. The IgG/IgM assay range for the Mouse Isotyping Panel was 24 pg/mL to 100,000 pg/mL. The LLOQ was 97.7 pg/mL and the ULOQ was 100,000 pg/mL. The IgG levels in mouse tissue samples ranged from 0.8 µg/mL to 1 µg/mL. The IgM levels in Mouse Tissue samples ranged from 0.2 µg/mL to 1 µg/mL. The IgG levels in mouse serum samples ranged from 41 µg/mL to 56 µg/mL. The IgM levels in mouse serum samples ranged from 15 µg/mL to 24 µg/mL.

[0940] *Histology of mouse tissues and Antibody Staining in a monoplex DAB IHC assay*

[0941] Animals were euthanized as per the institutionally approved standard operating procedure (SOP) for CO2 asphyxiation followed by cervical dislocation. Animals were sprayed with 70% ethanol to ensure sterility and reduce airborne allergens. Tumors and spleens were then collected in 10% Neutral Buffered Formalin (VWR, 16004). Formalin was removed 24 hrs later and tumors and spleen were transferred to 70% ethanol.

[0942] All tumors and spleens were shipped to Cureline (Brisbane, CA). Cureline performed histology based on their institutional SOP and fully automated workflow. Larger tumors were cut in half and smaller tumor were left intact and were then processed, embedded in paraffin, and cut into 5 μm thin sections. Spleens were cut cross sectionally and were then processed, embedded in paraffin, and cut into 3 μm thin sections.

[0943] CD8a (Cell Signaling, 98941S) immunohistochemistry (IHC) was performed using a Bond Rx autostainer (Leica Biosystems) with Heat-Induced Epitope Retrieval (HIER) at pH 9.0 for 20 minutes. The CD8a primary antibody (98941S, Cell Signaling Technologies, diluted for use at 3.2 μg/ml) and Bond Polymer Refine Detection (Leica Biosystems) were used according to manufacturer's protocol. Both spleen and tumor tissues were stained.

[0944] Marco (Abcam, ab239369) IHC was performed using a Bond Rx autostainer (Leica Biosystems) with HIER at pH 6.0 for 20 minutes. The Marco primary antibody (ab239369, Abcam, diluted for use at 1.5 μg/ml) and Bond Polymer Refine Detection (Leica Biosystems) were used according to manufacturer's protocol. Both spleen and tumor tissues were stained.

[0945] NCR1 IHC was performed using a Bond Rx autostainer (Leica Biosystems) with HIER at pH 9.0 for 20 minutes. The NCR1 primary antibody (ab233558, Abcam, diluted for use at 1.25 μg/ml) and Bond Polymer Refine Detection (Leica Biosystems) were used according to manufacturer's protocol. Both spleen and tumor tissues were stained.

[0946] CD19 (Abcam, ab245235) IHC was performed using a Bond Rx autostainer (Leica Biosystems) with HIER at pH 9.0 for 20 minutes. The CD19 primary antibody (ab245235, Abcam, diluted for use at 0.91 μg/ml) and Bond Polymer Refine Detection (Leica Biosystems) were used according to manufacturer's protocol. Both spleen and tumor tissues were stained.

[0947] CD206 (MRC1; Invitrogen, PA5-114370) IHC was performed using a Bond Rx autostainer (Leica Biosystems) with HIER at pH 9.0 for 20 minutes. The CD206 primary antibody (PA5-114370, ThermoFisher Scientific, diluted for use at 0.5 μg/ml for spleen and 1 μg/ml for tumor) and Bond Polymer Refine Detection (Leica Biosystems) were used according to manufacturer's protocol. Both spleen and tumor tissues were stained.

[0948] After staining, sections were rinsed in dH2O and mounted with Xylene and Cytoseal XYL (ThermoFisher Scientific) mounting medium. Whole slide scanning (40x) was performed on an Aperio AT2 (Leica Biosystems) and all scans were deposited electronically on the Pionyr Pathcore webpage.

[0949] *CD8a, MARCO, NCR1, CD19 and CD206 Quantification*

[0950] The tissue sections were analyzed using the image analysis software HALO v3.3.2541.202 (Indica Labs). The images were imported into the HALO database, and brush annotation tool was used to identify the area for analysis (labelled layer 1). The entire spleen and tumor tissue areas were included, excluding any artifact staining, folds, necrotic regions, glass, or skin regions using the scissor annotation tool. IHC analysis was performed on each annotation layer for all markers separately (CD8a, MARCO, NCR1, CD19 and CD206) using the Indica Labs – Area Quantification v2.1.11 algorithm. The algorithm was set to detect the blue pixels from the hematoxylin stain, and brown pixels from the DAB IHC stain. The data was exported as an excel file and the % positive DAB staining over total annotated area was collected for each individual marker and was used to plot the data in prism.

[0951] *Multiplex immunofluorescent (IF) staining and image analysis*

[0952] FFPE sections from mouse spleens and tumors were stained using 5-plex IF panels. Spleens from 6 PI-3008 treated, and 6 isotype treated mice, and tumors from 4 PI-3008 treated, and 4 isotype treated mice were stained and analyzed. All IHC antibodies included in the multiplex mouse spleen panel and the mouse tumor (E0771) panel were first optimized by DAB IHC on FFPE mouse spleen and tumor sections (E0771 tumors). Optimal antibody concentrations and staining conditions were then considered when developing the multiplex panels. Antibodies used were: CD8a from Cell Signaling, 98941S; MARCO from Abcam, ab239369; CD19 from Abcam, ab245235, CD206 (MRC1) from Invitrogen; PA5-114370; NCRI from Abcam ab233558; and nuclei from Akoya, SKU FP1490.

[0953] Sections were subjected to 4 sequential rounds of staining with each primary antibody followed by a secondary HRP-conjugated polymer, and signal amplification using TSA-Opal fluorophores. A heat-induced epitope retrieval step was performed after each round of staining to remove the primary-secondary-HRP complexes. The slides were then counterstained with Spectral DAPI and mounted using anti-fade mounting medium.

[0954] Stained slides were imaged using the Vectra 3 imaging system (Akoya Biosciences). After a low magnification scan, regions of interest (ROI) were stamped by using the Phenochart viewer (Akoya Bioscience) and these stamps were subsequently scanned at a higher resolution (20x). Four stamps per spleen section were selected by choosing regions

where representative white pulp, red pulp and marginal zone areas were included. In the tumor sections, stamps were selected to cover the majority of the tumor area, purposely selecting edge regions and center regions to facilitate comparative analysis of these tumor areas. The acquired ROI image files were opened in InForm (Akoya Biosciences) and there spectrally unmixed followed by removal of auto fluorescent staining. Image analysis was performed in InForm by first manually segmenting the spleen tissue into red pulp, white pulp, and marginal zone. Glass regions were excluded from analysis. Tumor tissues were manually segmented to just include tumor and exclude skin, glass, and necrotic regions. Nuclei were identified and segmented using the DAPI counterstain, followed by training of the cell phenotyping algorithm for the identification of the cell types of interest. The data generated by InForm was then loaded into R studio and using the phenoptrReports package (Akoya Biosciences) from which data including cell counts, cell percentages, cell densities, and nearest neighbor analysis for the different tissue compartments was generated

[0955] Results

[0956] PI-3008-AB also demonstrated anti-tumor activity as single agent in the orthotopic E0771 model as compared to isotype control antibodies (**FIG. 37**). At the end of the study on day 33, mice dosed with PI-3008 showed a statistically significant reduction in tumor volume as compared to isotype controls (p=0.0037) (**FIG. 38A**). The percentage of tumor growth inhibition (TGI) is shown in **FIG. 38B** for isotype antibody and PI-3008.

[0957] In addition, both PI-3008 and effector dead PI-elicited similar single agent activity in the orthotopic E0771 Model (**FIG. 38C**). Individual panels show the tumor volume in individual mice after treatment with the indicated antibody or isotypes control. The upper right panel shows the tumor valiums in each mouse at Day 28. The lower right panel shows the antibody concentration in serum for PI-3008 and PI-3021.

[0958] *PK-PD-efficacy assay*

[0959] The *in vivo* PK-PD study in E0771 showed that PI-3008 elicited single agent activity compared to the isotype antibody after 4 doses of treatment. Significant differences in tumor size was observed starting at the second dose (**FIG. 39B**). Individual tumor volumes in the isotype control mice are provided in **FIG. 39C**. Individual tumor volumes in the PI-3008 mice on are provided in **FIG. 39D**. The final tumor volumes at Day 28 are provided in **FIG. 39E**. In addition, the serum levels of PI-3008 maintained robust exposure until the end of the study (**FIG. 39F**).

[0960] The serum concentrations of anti-PD-1 when combined with PI-3008 were also in the expected exposure range as seen in previous studies when dosed as single agent **(FIG. 40A**

and **40B**). **FIG. 40A** provides the PI-3008 concentrations in mono and combination experiments with PD-1 antibody, while **FIG. 40B** provides the PD-1 concentrations in combination experiments.

[0961] PI-3008 also activated intra-tumoral immunity in the E0771 model, as seen by an increase in CD8+ T cells and NK cells in the TME after administration of the antibody. **FIG. 41A** provides IHC images of CD8 T cells and NCR1 (NK cells) stained with DAB after administration of isotype control or PI-3008. **FIG. 41B** provides quantification of the cytotoxic CD8+ T cells and NK cells in the tumor area by HALO image analysis of the IHC staining. PI-3008 promoted changes in the TME indicative of improved anti-tumor response. The anti-MARCO antibody increased $MHCII^{High}$ Ly6C+ monocytes, DC infiltration, and NK1.1 NK cells in the TME by flow cytometry (**FIG. 41C**). Without wishing to be bound by theory, increases in these cells may increase intra-tumoral immune activation and improve antigen presentation in the TME.

[0962] Increases in CD8+ T cells and NK cells in the TME were also observed by multiplex IF. **FIG. 41D** provides quantification of CD206+, cells, MARCO+ cells, NCR1+ cells, and CD8a+ cells at the tumor edge, the cell density of the indicated cell at the tumor edge, the median distance to the nearest neighbor from CD206 and the indicated cell types, and the median distance to the nearest neighbor from MARCO and the indicated cell types in mice after treatment with isotype antibody or PI-3008. Data for isotype antibody is provided on the left of each data pair with circle icons, while data for PI-3008 is provided on the right of each data pair with diamond icons. This multiplex analysis showed that NK cells and CD8T cells are increased in the tumors after anti-MARCO treatment. The spatial mapping showed a closer distance of CD8+ T cells and NK cells with MARCO+ cells in the TME in the PI-3008 treated tumors compared to isotype.

[0963] Proinflammatory cytokines and chemokines induced by PI-3008 in the E0771 model tumor supernatants were also assessed (**FIG. 42A**). PI-3008 treatment induced cytokines and chemokines in the tumor supernatants in the E0771 model. The same cytokines were induced in the E0771 model as identified via RNAseq in the CT26 study. Cytokines associated with T-cell activation and NK cells activation were also observed at Day 1 post-dose 2 in the tumor supernatants (**FIG. 42B**).

[0964] MARCO is highly expressed in the spleen, primarily on marginal zone macrophages, monocytes and dendritic cells (**FIG. 43**). The samples from mice treated with isotype antibody are provided on the left of each sample pair, the samples from mice treated with PI-3008 antibody are provided on the right of each sample pair. The data in **FIG. 43** is plotted

based on the delta gMFI between the PI-3008-PE and the mIgG2a-PE isotype antibody used in the flow cytometry analysis. In this assay, the MARCO flow antibody competes with the previously administered therapeutic PI-3008 for binding on the MARCO+ cells in the samples. Thus, receptor occupancy and competition were expected and observed in the samples from the PI-3008 treated mice, provided on the right side of the sample pairs, as evidenced by the low delta gMFI levels indicating low anti-MARCO binding in the flow assay (**FIG. 43**). No receptor occupancy and competition for MARCO staining in the flow cytometry assay was observed in the isotype treated mice samples, provided on the left side of the sample pairs, as evidence by high delta gMFI levels indicating high anti-MARCO binding in the flow assay (**FIG. 43**). Higher RO and lower gMFI in PI-3008 treated samples as compared to isotype treated samples for each myeloid target population confirmed the expression of MARCO on each specific population. The isotype treated group thus shows MARCO expression (using the PI-3008 flow antibody) to detect MARCO levels on the myeloid target population when no therapeutic antibody is present. MARCO expression was observed on dendritic cells, CD11bint F480+ macrophages, TM4+ marginal macrophages, Ly6C+ $MHCII^{High}$ monocytes, and Ly6C+ $MHCII^{mid}$ monocytes. MARCO expression was highest on the marginal zone macrophages, identified by CD11bintF480+ and TIM4+ marginal zone macrophages. MARCO was also expressed on the MHCII+ monocytes. Receptor occupancy was achieved in the PI-3008 antibody treated group (24 hours following 2^{nd} dose) in those myeloid populations.

[0965] In sum, **FIG. 43** shows that the delta gMFI in the isotype group showed expression of MARCO receptor in the spleen and the delta gMFI on the PI-3008 treated groups confirmed that PI-3008 was bound on the MARCO positive myeloid cells and thus could not be detected with the PI-3008 flow antibody. The samples from mice treated with isotype antibody are provided on the left of each sample pair, the samples from mice treated with PI-3008 antibody are provided on the right of each sample pair.

[0966] PI-3008 did not affect the myeloid populations in the spleen but potentially affected B-cells 24 hours after the second dose. As shown in **FIG. 44A, 44B,** and **44C**, PI-3008 treatment did not alter the MARCO+ myeloid or lymphoid cell populations in the spleen. However, PI-3008 treatment did result in a decrease of CD19+ B-cells and plasma B-cells in the spleen (**FIG. 44D**). The samples from mice treated with isotype antibody are provided on the left of each sample pair, the samples from mice treated with PI-3008 antibody are provided on the right of each sample pair.

[0967] PI-3008 treatment decreased IgM production and increased IgG production in the spleen and serum at Dose 2 (**FIG. 45**).

[0968] MARCO expression on the marginal zone macrophages decreased with PI-3008 treatment in spleen when measured by IHC (**FIG. 46**). MARCO+ cells in the spleen were assessed at the second dose and at the end of the study. PI-3008 mice showed a decreased number of MARCO+ marginal zone macrophages as compared to isotype antibody treated mice. Monoplex IHC was also used to determine changes in the spleen after PI-3008 treatment (**FIG. 47A-D**). An increase in CD8+ T cells and NK cells was observed in the total area after PI-3008 treatment (**FIG. 47A** and **47B**). The CD19+ cell population was variable and challenging to measure by IHC (**FIG. 47C**). A significant increase in CD206 (red pulp macrophages) was observed after PI-3008 treatment (**FIG. 47D**). The samples from mice treated with isotype antibody are provided on the left of each sample pair, the samples from mice treated with PI-3008 antibody are provided on the right of each sample pair.

[0969] The percentage positive cells per tissue compartment after treatment with isotype antibody and PI-3008 was determined via image analysis of multiplex IF (**FIG. 48A-D**). A decrease in MARCO in the red pulp after PI-3008 therapy and in total areas was observed (**FIG. 48A**). A small decrease in CD19 across all tissue compartments was observed in the total area after PI-3008 treatment (**FIG. 48B**). An increase in CD8a across all tissue compartments was observed after PI-3008 treatment (**FIG. 48C**). A small increase in CD206 in the red pulp was observed after PI-3008 treatment (**FIG. 48D**). The samples from mice treated with isotype antibody are provided on the left of each sample pair, the samples from mice treated with PI-3008 antibody are provided on the right of each sample pair.

[0970] *Day 2 and Day 5 PD sample analysis*

[0971] Digested supernatants and plasma from tumors, spleen and blood sampled at 2 days and 5 days post antibody treatment were analyzed via Luminex. Anti-MARCO treatment induced cytokines and chemokines in the tumor supernatants in the E0771 model at early timepoints (**FIG. 58** and **FIG. 59**). Samples from Day 2 are shown on the right, samples from Day 5 are shown on the left. Changes in cytokines and chemokines were observed at both timepoints, G-CSF, IL27, IL10, and TNFα increased at day 2, IL12p70, IL10, IL6, and IL4 increased at day 5. Chemokines involved in migration and chemotaxis were increased in the spleen at day 2 after the first antibody dose.

[0972] Anti-MARCO treatment also modulated IgG1 production in the mouse tumor (**Table 28**).

Table 28						
Day 2						
	IgA	IgG1	IgG2a	IgG2b	IgM	Total IgG
Isotype (μg/ml)	1.22	14.67	2.39	9.58	4.83	26.65
PI-3008 (μg/ml)	1.12	19.42	2.48	8.48	4.57	30.38
Day 5						
Isotype (μg/ml)	1.10	20.61	1.69	13.56	6.54	35.86
PI-3008 (μg/ml)	1.20	15.52	2.25	12.34	6.59	30.12

[0973] Anti-MARCO treatment decreased IgM production at day 2 and IgG1 decreased slightly at day 5 in the spleen (**Table 29**).

Table 29						
Day 2						
	IgA	IgG1	IgG2a	IgG2b	IgM	Total IgG
Isotype (μg/ml)	4.36	15.50	5.08	12.73	43.58	33.31
PI-3008 (μg/ml)	3.65	14.02	3.18	10.69	28.13	27.88
Day 5						
Isotype (μg/ml)	1.90	14.58	1.46	7.74	18.37	23.77
PI-3008 (μg/ml)	2.43	10.99	2.01	9.63	17.22	22.62

[0974] Anti-MARCO treatment decreased IgG1 and IgG2b in the plasma after PI-3008 treatment (**Table 30**).

Table 30						
Day 5						
	IgA	IgG1	IgG2a	IgG2b	IgM	Total IgG
Isotype (μg/ml)	21	16	13	45	6	74
PI-3008 (μg/ml)	18	6	13	37	6	56

[0975] First, tumor myeloid cells were assessed at Days 2 and 5 after one does of MARCO antibody treatment. Anti-MARCO affected the total number of TAMs (decreased, **FIG. 60**) and monocytes (increased, **FIG. 61**) in tumors at D2 and D5. Anti-MARCO also reprogramed TAMs from immunosuppressive MHCII- to pro-inflammatory MHCII+ at day 2 (**FIG. 60**) and monocytes from immunosuppressive MHCII- to proinflammatory MHCII+ at D2 (**FIG. 61**).

[0976] Anti-MARCO increased CD11c+ MHCII+ DCs at D2 and D5, and slightly decreased Ly6G+ neutrophils at D2 and D5 (**FIG. 62**). In summary, in the tumor myeloid cells, anti-MARCO antibody increased pro-inflammatory monocytes and DCs, and decreased tumor associated neutrophils (TANs) and TAMs. In addition, 2 days after first dose, anti-MARCO

reprogrammed MHCII- TAMs to MHCII+ TAMs, and MHCII- monocytes to MHCII+ monocytes.

[0977] Next, tumor lymphoid cells were assessed at Days 2 and 5 after one dose of MARCO antibody treatment. Anti-MARCO increased CD8+ T cells and CD4+ T at day 2 and 5 in the tumors (**FIG. 63**). Anti-MARCO also increased NK1.1 NK cells at day 5 in the tumors (**FIG. 63**).

[0978] Next, spleen lymphoid cells were assessed at Days 2 and 5 after 1 dose of MARCO antibody treatment. Anti-MARCO decreased CD19+ B cells at both days and did not change Plasma B Cells (**FIG. 64** and data not shown). Anti-MARCO increased follicular B cells and decreased marginal zone B cells at day 5 in the spleen (**FIG. 64**). Anti-MARCO affected B-cell populations in the spleen by decreasing CD19+ B-cells, decreasing marginal zone B-cells, and increasing follicular B cells at day 5 (**FIG. 64**). Anti-MARCO increased splenic CD8+ and CD4+ T cells at both days (**FIG. 65** and data not shown). Anti-MARCO did not change NK1.1 NK cells at day 2, but increased them at day 5 (**FIG. 65** and data not shown). Anti-MARCO also increased splenic DCs, and did not alter neutrophil levels in the spleen (**FIG. 65**).

[0979] Spleen myeloid cells were also assessed at Day 5 after one dose of MARCO antibody treatment. Anti-MARCO decreased MHCII- monocytes and increased MHCII+ monocytes (high and intermediate) at day 5 by subtyping Ly6C+ monocytes into various MHCII level cells (**FIG. 66**). Anti-MARCO increased the number of total macrophages in the spleen at D2 and D5, including red pulp macrophages (**FIG. 67** and data not shown). Anti-MARCO also increased the number of Marginal Zone Macrophages (MZMs) at D5, MHCII+ DCs, and increased the non-marginal zone macrophages at D5 (**FIG. 67** and **68**).

[0980] Blood was also profiled by flow cytometry at Day 5. A slight decrease in $Ly6C^{high}$monocytes and DCs at day 5 and an increase in T-cells was observed. No change in B-cells was observed. (**FIG. 69**).

[0981] MARCO expression and Receptor Occupancy in mouse spleens, E0771 tumors, and blood (**FIG. 70**) at Day 5 was also assessed. As shown in **FIG. 70**, MARCO was expressed at high levels in the spleen, in particular on the marginal zone (MZ) macrophages gated by $CD11b^{int}$ F480+ and TIM4+ Macs. MARCO was not expressed on the non-Marginal zone macrophages (non-MZ), as evidenced by the MARCO flow cytometry staining of the mIgG2a isotype samples, in which the flow cytometry MARCO antibody did not compete with prior MARCO antibody for binding to cells. MARCO was expressed on MHCII+ monocytes ($MHCII^{high}$ and $MHCII^{inter}$) and on DCs. MARCO was also expressed on CD206+

red pulp macrophages outside the marginal zone and on MHCII+ Macs. Receptor Occupancy of the therapeutic MARCO antibody was achieved in the positive MARCO expressing cells of **FIG. 70** listed above, as evidenced by the lack of MARCO flow cytometry staining of the MARCO samples, in which the flow cytometry MARCO antibody was out competed for binding to cells by the prior therapeutic MARCO antibody.

[0982] In the E0771 tumors, MARCO was expressed at low levels inside the tumors. Receptor Occupancy could not be accurately measured at day 2 but was achieved in $MHCII^{high}$ and intermediate monocytes; MHCII+ DCs; and both MHCII+ TAMs and MHCII- TAMs at day 5 (**FIG. 70**). No MARCO expression was observed on blood immune cells (**FIG. 70**).

[0983] In sum, PI-3008 induced motility and/or phagocytosis changes in the tumor, as evidenced by altered gene expression in cytoskeletal, actin and muscle, migration, and cell-adhesion and migration related pathways. PI-3008 also induced immune activation as evidenced by NK cell activation, T cell activation, and myeloid cell differentiation. In the lymph nodes, PI-3008 altered gene expression in pathways associated with cell signaling, cell-adhesion, cytoskeletal, and motility genes. In the spleen, PI-3008 altered gene expression in pathways associated with cell signaling, cell-adhesion, cytoskeletal, chemotaxis, and motility genes as well as B cell activation. Without wishing to be bound by theory, taken together, this data indicates that anti-MARCO antibodies activate intra-tumor immunity at least by mediating repolarization of MARCO+ myeloid M2-like TAMs to M1-like TAMs, and repolarization of mMDSCs to pro-inflammatory monocytes. This repolarization leads to production of cytokines, chemokines, and activation receptors, which in turn leads to activation of T and NK cells. The repolarization of myeloid M2-like TAMs and mMDSCs and activation of T and NK cells then leads to tumor destruction mediated by NK cells, CD8 cells, and M1-like macrophages. Further, without wishing to be bound by theory, potential binding of the anti-MARCO antibody to medullary cord macrophages (MCMs) may induce changes in adhesion and motility in the lymph node, and potential binding of the anti-MARCO antibody to marginal zone macrophages (MZMs) in the spleen may lead to changes in adhesion and motility, leading to potential B cell activation.

Example 12: Pharmacodynamic assay in CT26 in vivo model

[0984] Methods

[0985] A PD study was conducted in CT26 tumor bearing mice. Eight to ten-week old female BALB/c mice (Taconic) were implanted with subconfluent CT26.WT cells (ATCC, banked

at Pionyr) grown in log-phase. One million tumor cells resuspended in serum-free media were implanted subcutaneously on the right ventral flank of the mice under isoflurane anesthesia. For the pilot CT26 PD study, mice with tumor volumes of 150-200 mm3, were dosed once intravenously with 10mg/kg of PI-3008-AB or PI-0002-AB (isotype) and tumors and spleens were collected 4 days after treatment inn 10% formalin for IHC staining with anti-mouse MARCO, anti-CD8, and anti-granzyme B . HALO image analysis software (Indica Labs) was used to quantify the percentage of CD8+ T cells and Granzyme B+ cells over the whole tumor area. Spleens were stained with a non-PI-3008 competing anti-mouse MARCO IHC compatible antibody.

[0986] Results

[0987] The anti-MARCO antibody PI-3008 induced an increase in CD8+ T-cells and the cytotoxic marker granzyme B in tumors as compared to isotype control treated tumors (**FIG. 49**). Data is presented as mean percentage values from 3 mice within each treatment group of ± standard error of the mean (SEM).

[0988] In the spleen, changes in MARCO levels on the marginal zone macrophages were observed with noticeable gaps in the marginal zone area (**FIG. 50**). Control spleens showed several layers of MARCO+ stained cells in the marginal zone. Layers continue around most of the periarteriolar lymphoid sheath (PALS) and B cell follicle caps. Spleens from PI-3008 treated mice showed much less MARCO+ staining that include fewer cells and layers. There were also gaps in the coverage of the PALS and B cell caps. Thus, there was a decrease in MARCO-positive cells in the splenic marginal zone of animals treated with PI-3008. Without wishing to be bound by theory, these data suggest that anti-MARCO induces proinflammatory actuation within the TME and leads to changes in adhesion and motility as seen in the spleen.

Example 13: Immunohistochemistry MARCO assay

[0989] To identify a suitable anti-human MARCO IHC antibody to profile MARCO expression in human FFPE tissues, 15 commercial and internal antibodies were screened. The primary screening comprised staining FFPE embedded MARCO over-expressing (CL3010), endogenous (L1236), and negative control (HEK-293T cells and Jurkat cells that do not express MARCO) cell pellets. Antibodies that passed the primary screen were included in the secondary screen, in which lung cancer and colon cancer FFPE sections, identified as having high RNA expression by in situ hybridization (ISH), were stained using different IHC staining conditions (different antibody concentrations, incubation times, and antigen

retrieval). Two potential human MARCO specific off the shelf IHC antibodies from R&D, RDM5 (clone # 858428.11, catalog CUST0l7MABP) and RDM9 (clone # 858423.11, catalog CUST0l7MABP), were identified. RDM5 was slightly superior to RDM9 and thus was selected for further optimization of IHC assay conditions on additional control tissues. RDM5 demonstrated specific, strong, and sensitive labeling of MARCO-positive cells when used at 2.5 µg/mL with a high pH antigen retrieval (ER2), on an automated Leica platform (**FIG. 51A**). The staining was validated on normal and tumor tissue microarrays (TMAs) and MARCO specificity was confirmed by a certified-board pathologist. In addition, MARCO expression in normal tissues was restricted to the tissue resident macrophages in the lung, liver, and spleen, confirming the previous RNA data.

[0990] Next, further profiling of MARCO expression was explored on 20 tissue microarrays (TMA) from 17 different tumor indications and contained duplicate cores per subject with different diagnoses (Pathology, Grade, and TNM stage). The TMA at Reveal Biosciences was made by acquiring tissues that were fixed in 10% neutral buffer formalin for 24 hours and processed using identical SOPs. Sections were picked onto Superfrost Plus or Startfrost Adhesive slides and all TMAs were cut fresh in 4um serial sections upon ordering and stored at 4degC prior to IHC staining.

[0991] After whole slide scanning of each TMA at 40x using the Aperio AT2 Scanner, quantification of the MARCO+ cells in the tumor intervening stroma were assessed by a board-certified pathologist using the following scoring system: 0 = <1% positive cells, 0.5 = 1-10% positive cells, 1 = 10-25% positive cells, 1.5 = 25-50% positive cells, 2 = approximately 50% positive cells, 2.5 = 50-75% positive cells, 3 = approximately 75% positive cells, and 3.5 = >75% positive cells over stroma. Lost or folded cores with more than half of the area distorted were removed from the analysis and not scored. The staining for each patient was considered positive if MARCO+ cells were expressed at 1% or above 1% over stroma. Each dot represents one case, and the median for each indication is depicted as a line

[0992] The percentage of positive cases, with a cutoff at 1% MARCO+ cells in the stroma, was highest in colon cancer (92%), followed by lung cancer (87%), endometrial cancer (78%), mesothelioma (64%), ovarian cancer (61%), lymphoma (60%), thyroid cancer (60%), TNBC (53%), breast cancer (51%), head and neck cancer (45%), stomach cancer (44%), pancreatic cancer (43%), liver cancer (39%), and kidney cancer (33%) (**FIG. 51B**). The median MARCO IHC scores were highest with a score of 1 in colon, lung, thyroid, and mesothelioma, followed by a median score of 0.75 in lymphoma and endometrial cancer for

all tumor grades (data not shown). When focusing only on the advanced grade III tumors, the median MARCO IHC scores increased from 0.5 to 1 in breast cancer and from 0 to 0.5 in kidney cancer, indicating that increased MARCO expression is correlated to higher tumor grade in these tumor indications (**FIG. 51C**). Moreover, the MARCO IHC score in normal tissues was highest in normal liver, lung, spleen, colon, ovary and nerve tissue, corroborating previously described MARCO RNA expression data. Thus, based on MARCO IHC scoring using the RDM5 antibody, colon cancer, lung cancer, mesothelioma, lymphoma, thyroid cancer, endometrial cancer, and ovarian cancer have the highest IHC scores and number of MARCO positive cases.

Example 14: Cell line development for MARCO antibody production

[0993] Two independent transfections were performed per double gene vector, with three static 96-shallow well plates per transfection. A transfer to suspension culture in 96-deep well plates occurs, then four transfection pools are generated from top cultures. All cultures maintained viabilities of ≥ 97% throughout 6 days of culture.

[0994] Evaluation of the transfection pool product quality was performed following partial purification (i.e., MabSelect™ SuRe™ affinity chromatography and sample neutralization to pH 7). Lonza performed product quality evaluation by gel permeation high performance liquid chromatography (GP-HPLC), sodium dodecyl sulfate (SDS) electrophoresis (reduced and non-reduced) and imaged capillary isoelectric focusing (iCIEF). Aggregation data for PI-3030.41 was significantly elevated compared to the other candidates. The results of the transfection pool analysis are shown in **Tables 31** through **36** below.

[0995] Table 31: Transfection Pool Concentration Data

Transfection Pool	Partially Purified Concentration (mg/mL)	Partially Purified Volume (µL)	Total Quantity (mg)
3010.15 (1)	0.818	650	0.53
3010.15 (2)	0.959	645	0.62
3010.15 (3)	1.372	650	0.89
3010.15 (4)	1.150	750	0.86
3010.25 (1)	1.248	740	0.92
3010.25 (2)	0.936	655	0.61
3010.25 (3)	1.243	590	0.73
3010.25 (4)	1.271	605	0.77
3030.41 (1)	0.972	650	0.63
3030.41 (2)	1.073	655	0.70
3030.41 (3)	1.025	655	0.67
3030.41 (4)	0.871	650	0.57

[0996] Table 32: Transfection Pool Aggregation by GP-HPLC Data

Transfection Pool	Fragments (%)	Monomer (%)		Aggregates (%)	
3010.15 (1)	< 0.10	89.98	90.0 – 92.1	10.02	7.9 – 10.0
3010.15 (2)	< 0.10	91.52		8.48	
3010.15 (3)	< 0.10	92.06		7.94	
3010.15 (4)	< 0.10	91.63		8.37	
3010.25 (1)	< 0.10	95.15	90.2 – 95.2	4.85	4.9 – 9.8
3010.25 (2)	< 0.10	90.20		9.80	
3010.25 (3)	< 0.10	94.47		5.53	
3010.25 (4)	< 0.10	92.49		7.51	
3030.41 (1)	< 0.10	80.83	80.3 – 82.5	19.17	17.5 – 19.7
3030.41 (2)	< 0.10	81.69		18.31	
3030.41 (3)	< 0.10	82.46		17.54	
3030.41 (4)	< 0.10	80.33		19.67	

[0997] Table 33: Transfection Pool SDS Electrophoresis (Reduced) Data

Transfection Pool	LC Size (kDa)		LC Purity (%)		HC Size (kDa)		HC Purity (%)		LC + HC Purity (%)	
3010.15 (1)	27.36	27.3 – 27.6	42.11	41.8 – 43.3	62.47	62.2 – 62.8	57.66	56.4 – 58.0	99.77	99.8
3010.15 (2)	27.27		43.33		62.24		56.42		99.75	
3010.15 (3)	27.61		41.77		62.82		58.02		99.80	
3010.15 (4)*	27.52		36.73		62.61		57.55		94.27	
3010.25 (1)*	27.02	26.5 – 27.0	26.93	39.8 – 41.5	63.01	61.5 – 63.0	32.45	58.1 – 59.9	59.38	99.6 – 99.7
3010.25 (2)	26.70		41.47		62.09		58.13		99.60	
3010.25 (3)	26.48		40.72		61.48		58.95		99.67	
3010.25 (4)	26.59		39.77		61.55		59.89		99.65	
3030.41 (1)	26.51	26.5 – 26.8	43.32	42.5 – 43.5	61.65	61.7 – 62.2	56.47	56.0 – 57.3	99.79	98.7 – 99.8
3030.41 (2)	26.48		43.53		61.78		56.27		99.80	
3030.41 (3)	26.72		42.71		62.24		56.01		98.72	
3030.41 (4)	26.75		42.49		62.21		57.30		99.79	

[0998] * Difference in value may be due to not fully reduced samples (supported by reduced electropherogram and sample non-reduced data). Small amount of higher molecular weight species for 3010.15 (4) and significant amount of higher molecular weight species for 3010.25 (1). These values were excluded in the purity ranges for per candidate.

[0999] Table 34: Transfection Pool SDS Electrophoresis (Non-Reduced) Data

Transfection Pool	IgG Size (kDa)		IgG Purity (%)	
3010.15 (1)	170.16	167.8 – 170.2	96.04	95.8 – 97.0
3010.15 (2)	169.62		95.83	
3010.15 (3)	167.81		96.67	
3010.15 (4)	168.09		96.99	

3010.25 (1)	168.83	167.7 – 169.2	96.72	95.7 – 96.7
3010.25 (2)	168.47		96.53	
3010.25 (3)	169.19		96.43	
3010.25 (4)	167.72		95.70	
3030.41 (1)	165.78	165.0 – 167.5	96.04	95.2 – 96.0
3030.41 (2)	164.99		95.59	
3030.41 (3)	167.45		95.90	
3030.41 (4)	166.61		95.24	

[1000] Table 35: Transfection Pool iCIEF Isoform Data

Transfection Pool	Peak Area (%) *									
	Acidic Variant Peaks				Main Peak		Basic Variant Peaks			
	Isoform 5		Isoform 4		Isoform 3		Isoform 2		Isoform 1	
3010.15 (1)	5.7	< LOQ – 6	18.4	17 – 20	67.7	67 – 71	6.8	6 – 7	< LOQ	< LOQ
3010.15 (2)	5.3		17.3		69.2		6.9		< LOQ	
3010.15 (3)	5.1		20.1		67.4		6.4		< LOQ	
3010.15 (4)	< LOQ		19.2		70.6		5.8		< LOQ	
3010.25 (1)	< LOQ	< LOQ	15.9	15 – 16	72.8	72 – 73	6.6	7	< LOQ	< LOQ
3010.25 (2)	< LOQ		15.9		72.3		6.8		< LOQ	
3010.25 (3)	< LOQ		15.4		72.9		6.7		< LOQ	
3010.25 (4)	< LOQ		16.2		71.9		6.7		< LOQ	
3030.41 (1)	5.4	5 – 7	19.4	19 – 21	69.5	68 – 70	< LOQ	< LOQ – 5	< LOQ	< LOQ
3030.41 (2)	7.0		20.0		67.8		< LOQ		< LOQ	
3030.41 (3)	5.8		20.5		68.9		< LOQ		< LOQ	
3030.41 (4)	6.5		20.2		67.6		5.0		< LOQ	

[1001] * LOQ is 4.9%.

[1002] 3010.15: calculated pI: 9.1; Isoform 5: pI 8.87 to 8.89; Isoform 4: pI 8.96; Isoform 3: pI 9.04 to 9.05; Isoform 2: pI 9.15 to 9.16; Isoform 1: pI 9.24 to 9.25.

[1003] 3010.25: calculated pI: 8.8; Isoform 5: pI 8.30 to 8.31; Isoform 4: pI 8.46 to 8.47; Isoform 3: pI 8.61 to 8.62; Isoform 2: pI 8.75; Isoform 1: pI 8.90.

[1004] 3030.41: calculated pI: 9.1; Isoform 5: pI 8.80 to 8.82; Isoform 4: pI 8.89; Isoform 3: pI 8.99 to 9.00; Isoform 2: pI 9.10 to 9.11; Isoform 1: pI 9.20.

[1005] Table 36: Transfection Pool iCIEF Summarized Data

Transfection Pool	Peak Area (%)					
	Acidic Variant Peaks		Main Peak		Basic Variant Peaks	
3010.15 (1)	24.1	23 – 25	67.7	67 – 71	8.2	7 – 8
3010.15 (2)	22.6		69.2		8.2	
3010.15 (3)	25.2		67.4		7.5	
3010.15 (4)	22.6		70.6		6.8	
3010.25 (1)	19.8	20 – 21	72.8	72 – 73	7.4	7 – 8

3010.25 (2)	20.0		72.3		7.7	
3010.25 (3)	19.6		72.9		7.4	
3010.25 (4)	20.6		71.9		7.5	
3030.41 (1)	24.8	25 – 27	69.5	68 – 70	5.7	5 – 6
3030.41 (2)	27.0		67.8		5.2	
3030.41 (3)	26.3		68.9		4.8	
3030.41 (4)	26.7		67.6		5.7	

[1006] Transfection pools for the 3 antibodies were tested for binding by ELISA and flow cytometry on MARCO transfectant cells. The binding of the pool material was compared to reference antibodies produced by transient transfection in CHO-S cells. Antibodies produced by the stable transfection method demonstrated comparable binding to the reference antibodies made via transient transfection (**FIG. 53**).

Example 15: Soluble MARCO Assay

[1007] Materials and methods

[1008] A streptavidin MSD Plate (MSD, Catalog # L15SA-1) was coated with biotinylated anti-MARCO antibody (PI-3041-AB, Pionyr) at 2 µg/mL. The plate was incubated at room temperature for 60 min and then washed.

[1009] Protein standards (RG-3000A, Atum) and serum samples (BioVT) were diluted in buffer (PBS/0.5%BSA/0.05%Tween + Ca2+/Mg2+) and added to the coated plate in D43 diluent (MSD, Catalog # R50AG-2) with 2mM Ca2+. The plate was incubated for 90 min at room temperature and washed. 1 µg/mL of the detection antibody, anti-MARCO (PI-3071-AB, Pionyr) was added, and the plate incubated for 60 min at room temperature. The plate was washed and 1x Read Buffer [MSD, Catalog # R92TC-1) was added to the MSD plate. The plate was read on an MSD Sector Imager.

[1010] Results

[1011] The sMARCO assay range was 0.1 ng/mL to 100 ng/mL. The LLOQ was 0.1 ng/mL and the ULOQ was 100 ng/mL. The sMARCO calibration curve for RG-3000A is shown in **FIG. 55A** and **Table 37**.

Table 37

Nominal Conc. ng/ml	Detected Mean Conc. (ng/ml)	% Recovery Mean
100	102.2	102.2
25.0	23.5	94.0
6.25	7.09	113.4
1.56	1.76	113.0
0.39	0.32	83.1
0.10	0.10	100.0

[1012] The sMARCO levels in normal human serum samples ranged from 9 ng/mL to 13 ng/mL. The sMARCO levels in cancer serum samples ranged from 6 ng/mL to 22 ng/mL. The sMARCO levels are shown in **FIG. 55B**.

[1013] An immunoassay to detect sMARCO from serum samples (human, cynomolgus monkey and mouse) was successfully developed. The sMARCO assay was qualified for its specificity, sensitivity, dilution linearity and selectivity and accurately determined sMARCO levels in patient serum samples obtained from commercial sources. sMARCO levels were observed to be higher in patients diagnosed with breast, colorectal, mesothelioma, cervical, small lymphocytic lymphoma, and non-Hodgkin lymphoma (**FIG. 55B**).

Example 16: In vivo B-cell deficient mouse study

[1014] Methods

[1015] Balb/c mice with J B-cell mutation were obtained from Taconic. The mouse experiment was set up as described in **Example 4**. Briefly, IP dosing was initiated when CT26 tumors reached a median of ~100 mm^3. Mice were dosed with 10 mg/kg PI-3008 or 5 mg/kg PD-1 antibody at Q5dx4. WT mice were used as a control.

[1016] Results

[1017] The absence of B-cells dampened the combination efficacy of PI-3008 with anti-PD1 in CT26 tumors (**FIG. 56**). PI-3008 antibody in combination with PD-1 antibody resulted in greater tumor reduction in WT mice (top row) as compared to the combination treatment in the B-cell knock out mice (middle row). The bottom graph provides tumor volumes in individual mice in each condition.

Example 17: PI-3010.15 induces NF-kB signaling pathway

[1018] Materials and methods

[1019] THP1-Blue™ NF-κB cells were obtained from Invivogen and cultured in RPMI 1640 medium (Gibco) supplemented with 10% Fetal Bovine Serum (Gibco), 25mM HEPES (Gibco), 1x GlutaMax (Gibco), 100ug/ml Normacin (Gibco), 10 ug/mL Blasticidin (ThermoFisher). Approximately 50,000 cells were transduced with lentivirus containing the full-length MARCO construct (CL#3010) at MOI 10 in 500 ul media containing 8 ug/mL polybrene per well of 24-well plate. After overnight incubation at 37°C with 5% CO_2, cells were washed in PBS and plated in 6-well plate in complete growth media. After 2-3 days, media was replaced with growth media containing 0.3 ug/ml puromycin (Invitrogen) for stable cell selection, and pooled cells were cultured and expanded

[1020] For the reporter assay, 300,000 cells were plated per well of 96-well U-bottom plate and co-incubated with a dose titration of PI-3010.15 or isotype antibody control and 10e6/ml of HKLM (Invivogen) or 10ng/ml of FALSTup (Invivogen) agonist and incubated for 4 hours or overnight at 37°C with 5% CO_2. After incubation, 20 ul of supernatant was transferred to a new 96-well plate and incubated with 180 ul/well of QuantiBlue Solution (Invivogen) for 30-60 minutes at 37°C with 5% CO_2. Alkaline Phosphatase activity was calculated by measuring the optical density (OD) at 650nm using the Tecan microplate reader.

[1021] The THP-1 MARCO overexpressing cells were also used to validate the biomarker signature of pro-inflammatory genes activated after PI-3010.15 treatment. 1x10^6 cells in 1ml of media were plated per well in a 24 well plate. PI-3010.15 and PI-0003 (corresponding hIgG1 isotype) were added to the cells at 1 μg/ml, 5 μg/ml, and 10 μg/ml for 4 hours and 24 hours. Cells were lysed with RLT buffer and RNA extracted for qPCR testing using the human primers to measure TNFα, IL-6, IL-1β, IL-10, CCL24, CXCL8, IL-1α, IL-18, and CCL20 expression.

[1022] Results

[1023] PI-3010.15 induced the NF-kB signaling pathway after 4hrs with the addition of HKLM, FSL-1, and FLA-ST UP after 24 hrs. PI-3010.15 also induced the NF-κB pathway in non-treated cells after 24 hrs (**FIG. 57**).

[1024] The THP-1 OVX cells were also used as a surrogate for primary hMDMs cells to test pro-inflammatory cytokine activation by MARCO antibody PI-3010.15. Cells were incubated with PI-3010.15 or isotype antibody at 1 μg/ml, 5 μg/ml, or 10 μg/ml (TNFα only) for 4 hrs or 24 hrs. Cells were collected and assessed for TNFα, IL-6, IL-1β, CXCL8, CCL20, CCL24, and IL-18 gene expression via qRT-PCR. PI-3010.15 induced TNFα gene expression after 4h and 24h at all antibody concentrations tested (**FIG. 71**). PI-3010.15 also induced expression of pro-inflammatory cytokines IL-6, IL1β, and CXCL8 at 4 hrs and 24 hrs (**FIG. 71**). The 5 μg/ml dosage of PI-3010.15 also induced pro-inflammatory cytokines such as CCL20, CCL24, and IL18 at 24 hrs (**FIG. 71**).

Example 18: Phospho array assay in hMDMs

[1025] Methods

[1026] A phospho array assay was performed using the Full Moon Biosystems Phospho Explorer Antibody Array on primary human monocyte derived macrophages (hMDMs) polarized with IL10 (2 donors).

[1027] Two frozen human peripheral blood CD14+ monocytes isolated from peripheral blood mononuclear cells using negative immunomagnetic selection (StemCell Technologies) were thawed and cultured in RPMI 1640 medium supplemented with 10% (v/v) heat-inactivated FBS (HyClone), 1 mM sodium pyruvate, non-essential amino-acids, 2 mM L-glutamine, 55 uM 2-mercaptoethanol and antimycotic antibiotic (all from Gibco). Monocytes were differentiated into macrophages by culturing in complete RPMI 1640 medium in the presence of 50 ng/ml human macrophage colony-stimulating factor (M-CSF) (PeproTech) at a density of 500,000 cells per well in 24 well plates. At day 3 of differentiation, media was replenished with the addition of fresh M-CSF. Differentiated human macrophages were polarized on day 6 by adding 25 ng/ml of recombinant human IL-10 (M2 condition) for 24 hours at 37°C. On day 7, the media was aspirated and cells washed gently. 500 µl of incubation medium (1xRPMI with 0.5% BSA) was added to the wells with 5 µg/ml of PI-3010.15 or hIgG1 isotype control (PI-0003). Treatment was terminated after 5 minutes and 15 minutes by washing with ice cold PBS and lysing cells with 300 µl of mPer and 1:100 HALT proteases and phosphatase inhibitors. Approximately 300 µg of protein lysate was sent to Full Moon Biosystems to perform the Phospho Explorer Antibody Array. Full Moon Biosystems used their standard protocol to label, couple, and detect the Average Signal Intensity of Replicate Spots, for each pair of site-specific antibody and phospho site-specific antibody, and determine the Signal Ratio of the paired antibodies. Fold changes between control and control samples were calculated using the following formula: Treatment Sample / Control Sample (hIgG1 treated or untreated).

[1028] Phospho hits were considered significant when the fold change was less than 0.6 or greater than 1.8 for both PI-3010.15/isotype and PI-3010.15/untreated ratio analysis. In addition, few hits were included if the isotype by itself had a substantial effect over the untreated due to Fc mediated signaling changes in the hMDMs (less than 0.75 fold decrease or greater than 1.5 fold increase compared to untreated). For those hits, a ratio of PI-3010.15/untreated was considered significant when below 0.75 fold decrease and above 1.5 fold increase if the ratio of PI-3010.15/isotype fell in the significant range (<0.6 and above 1.8 fold).

[1029] Results

[1030] Table 38 shows significant phosphorylation in PI-3010.15 vs. Isotype treated cells and PI-3010.15 vs. untreated (UT) cells at 5 minutes.

Table 38
UP (>1.8 FC)

Gene	3015 vs. Isotype (5 minutes)	3015 vs. UT (5 minutes)
Cyclin B1 (Phospho-Ser147)	5.084445769	2.561147785
IRS-1 (Phospho-Ser794)	4.447939568	2.871815775
PDGFR alpha (Phospho-Tyr849)	3.247023728	2.0112109
Elk1 (Phospho-Ser389)	2.650795969	1.93843226
HSP27 (Phospho-Ser78)	2.618765237	2.781365032
CDK1/CDC2 (Phospho-Tyr15)	2.495918288	2.915628441
CDK5 (Phospho-Tyr15)	2.495088042	3.772464066
IL-2RA/CD25 (Phospho-Ser268)	2.385317047	2.26149298
Raf1 (Phospho-Ser259)	2.345569464	2.986531327
GluR1 (Phospho-Ser863)	2.218294441	2.416141632
LYN (Phospho-Tyr507)- Src pathway	2.16499766	1.97114872
Ezrin (Phospho-Thr566)	2.148744088	2.992168753
Lamin A/C (Phospho-Ser392)	2.141294348	2.948772441
BAD (Phospho-Ser91/128)	2.011033931	2.461349555
Tau (Phospho-Ser396)	1.955441551	1.918036855
MAP3K8/COT (Phospho-Thr290)	1.943373784	1.967650786
HDAC5 (Phospho-Ser259)	1.922487843	2.088809947
PAK3 (Phospho-Ser154)	1.910328132	2.017578127
mTOR (Phospho-Thr2446)	1.8	2.42
DOWN (<0.6 FC)		
14-3-3 beta/zeta (Phospho-Ser186/184)	0.528463565	0.574004751
Synapsin (Phospho-Ser9)	0.468698508	0.444984245
PKC delta (Phospho-Ser645)	0.452312753	0.359573251
14-3-3 zeta (Phospho-Ser58)	0.446714092	0.3453927
Abl1 (Phospho-Thr754/735)	0.399803417	0.334055031
AKT1 (Phospho-Ser246)	0.38984194	0.479793736
Smad1 (Phospho-Ser187)	0.380264132	0.442638779

[1031] **Table 39** provides additional hits for the 5 minute samples that fell outside the first filtering bucket.

Table 39

Gene	3015 vs. Isotype	3015 vs. Untreated	Iso vs. Untreated
ATF2 (Phospho-Ser62/44)	2.13	1.59	0.75
Claudin 3 (Phospho-Tyr219)	0.22	0.68	3.04
Connexin 43 (Phospho-Ser367)	0.29	0.67	2.32
LCK (Phospho-Tyr192)	0.30	0.63	2.06
Src (Phospho-Tyr529)	0.32	0.78	2.45
IKK-beta (Phospho-Tyr188)	0.42	0.77	1.84
PLD1 (Phospho-Ser561)	0.42	0.78	1.86

[1032] **Table 40** provides additional hits for the 5 minute samples where the isotype decreased the signal (below <0.6 fold over untreated) and PI-3010.15 rescued the effect with a biological significance. The fold increase over PI-3010.15/untreated could be >0.9.

Table 40			
Gene	**3015 vs. Isotype**	**3015 vs. Untreated**	**Iso vs. Untreated**
CaMK1-alpha (Phospho-Thr177)	4.58	1.13	0.25
p27Kip1 (Phospho-Thr187)	3.35	0.95	0.28
Cortactin (Phospho-Tyr421)	3.00	1.29	0.43
Keratin 18 (Phospho-Ser52)	2.36	0.96	0.41
FAK (Phospho-Tyr397)	2.19	0.88	0.40
IkB-beta (Phospho-Thr19)	2.13	1.10	0.52
PLC beta3 (Phospho-Ser1105)	2.11	1.10	0.52

[1033] **Table 41** shows the significant phosphorylation in PI-3010.15 vs. Isotype treated cells and PI-3010.15 vs. untreated (UT) cells at 15 minutes.

Table 41		
UP (>1.8 FC)		
Gene	**Gene**	**Gene**
SYK (Phospho-Tyr525)	3.763491432	2.629401334
Dok-1 (Phospho-Tyr398)	3.086467586	2.609649844
IKK-alpha/beta (Phospho-Ser180/181)	2.959202923	1.934873037
HSP90B (Phospho-Ser226)	2.870020923	3.546965968
GluR1 (Phospho-Ser863)	2.609270653	2.21995696
Synaptotagmin (Phospho-Ser309)	2.600941915	2.136658796
SHP-2 (Phospho-Tyr580)	2.597416517	2.242046774
Filamin A (Phospho-Ser2152)	2.335627516	1.996061335
CaMK4 (Phospho-Thr196/200)	2.279954736	1.893568987
Synuclein alpha (Phospho-Tyr133)	2.131004882	1.874499543
HDAC5 (Phospho-Ser498)	2.110924432	2.744099757
P70S6K (Phospho-Ser424)	2.076974184	1.870856295
4E-BP1 (Phospho-Ser65)	2.06037659	2.827767866
Calmodulin (Phospho-Thr79/Ser81)	2.046380319	2.662693319
MKK4/SEK1 (Phospho-Thr261)	2.035499973	3.040392853
IL-2RA/CD25 (Phospho-Ser268)	1.973584034	2.080305927
Synaptotagmin (Phospho-Thr202)	1.930362488	1.991073071
Rb (Phospho-Ser780)	1.874035219	1.974833058
Tyrosine Hydroxylase (Phospho-Ser40)	1.852127179	1.934979677
DOWN (>0.6 FC)		
PLCG2 (Phospho-Tyr1217)	0.591517857	0.563418522
Kv1.3/KCNA3 (Phospho-Tyr135)	0.57141834	0.586825891
DARPP-32 (Phospho-Thr34)	0.55741993	0.41127774
Claudin 7 (Phospho-Tyr210)	0.556173961	0.597139861
Rel (Phospho-Ser503)	0.554992754	0.509612791
Ezrin (Phospho-Tyr478)	0.535586574	0.508394478
LKB1 (Phospho-Ser428)	0.531130409	0.520111023
AurA (Phospho-Ser342)	0.527800917	0.49832997
p130Cas (Phospho-Tyr165)	0.519493014	0.521059511
Cortactin (Phospho-Tyr421)	0.474466269	0.464638242
Dok-1 (Phospho-Tyr362)	0.456406193	0.482008648
Keratin 18 (Phospho-Ser33)	0.417597114	0.288197731

CaMK2-beta/gamma/delta (Phospho-Thr287)	0.410587574	0.537483464
ETK (Phospho-Tyr40)	0.409259434	0.437316317
NFkB-p65 (Phospho-Thr435)	0.400460795	0.344387917
p27Kip1 (Phospho-Ser10)	0.383076583	0.540101088
NFkB-p100/p52 (Phospho-Ser869)	0.37145326	0.532229421
VEGFR2 (Phospho-Tyr1175)	0.368651283	0.39699714
PKC delta (Phospho-Ser645)	0.3449432	0.538228023
Estrogen Receptor-alpha (Phospho-Ser118)	0.322713977	0.305382748
HSL (Phospho-Ser554)	0.31391716	0.411180773
CD3Z (Phospho-Tyr142)	0.309319341	0.377863121
PAK3 (Phospho-Ser154)	0.288315803	0.472978229
Raf1 (Phospho-Ser296)	0.241201384	0.310819568
CDK1/CDC2 (Phospho-Thr14)	0.232456135	0.311120574

[1034] **Table 42** provides additional hits that fell outside the first filtering bucket for the 15 minute samples.

Table 42

Gene	3015 vs. Isotype	3015 vs. Untreated	Iso vs. Untreated
PKC epsilon (Phospho-Ser729)	0.34	0.75	2.19
EGFR (Phospho-Tyr1110)	0.41	0.71	1.71
ASK1 (Phospho-Ser966)	0.42	0.67	1.58
c-Jun (Phospho-Ser63)	0.43	0.76	1.78
TOP2A/DNA topoisomerase II (Phospho-Ser1106)	0.45	0.77	1.72
STAT6 (Phospho-Thr645)	0.48	0.74	1.53

[1035] Based on the phospho array screen, the pathways downregulated after 5 minutes were: Cell adhesion: Claudin 3, Connexin 43, Syapsin; 14-3-3 beta and zeta: adaptor that modulates multiple inflammatory pathways; PI3K master regulator pathway: AKT1; PKC delta (upstream of Src); TGFb signaling: Smad1; c-Abl signaling (modulates STAT signaling); and Src pathway: LCK, Src (cytoskeletal rearrangement, phagocytosis and survival).

[1036] The pathways upregulated after 5 minutes were: Cell cycle: Cyclin B1, CDK1/CDC2, CDK5, PAK3; IRS-1: insulin receptor activated by Insulin and IL-4, upstream of AKT; PDGFR: platelet derived factor receptor activates Ras/ERK to regulate angiogenesis, proliferation, migration genes; ELK1: transcription factor downstream of ERK/PDGFR and Rac/JNK during inflammasome; Raf1: activated by LPS or mCSF and upstream of ERK1/2 activation for proliferation and activation; LYN: activated by LDL on CD36 and BCR, and phosphorylates AKTand SYK among others (metabolic reprogramming); IL-2RA/CD25: activates JAK/STAT, PI3K and Ras signaling; Lamin A/C, Ezrin, PAK3 (group 1 PAK downstream effectors of Ras-related Rho GTPase Cdc42 and Rac, and AKT), cytoskeletal rearrangement; MAPK38 (TPL2): (MAP3 K) activated downstream of TNFαR, IL1R, TLR, CD40, IL17R. TPL2 regulates the MEK1/2 and ERK1/2 pathways to regulate a cascade of

inflammatory responses; BAD: Survival, downstream of AKT; and Chromatin modification: HDAC5.

[1037] The pathways upregulated after 15 minutes were: Regulation: Calmodulin, GLUR1, HSP90; Induction of Enzymatic activity: SYK, GLUR1, SHP-2, MKK4, CAMK4; Molecular Association: DOK1, GLUR1, SHP-2, HSP90; Cell motility and cytoskeletal Reorganization: Filamin A, IKKa/b, SHP-2; Activation of transcription: IKKa/b, CAMK4, MKK4; IL2 Receptor activation; mTOR and Translation modification: P70S6K, 4E-BP1; and Calcium signaling, endocytosis, exocytosis, Synapses, microtubules: Synaptogamin, CAMK4, Synuclein alpha.

[1038] The pathways downregulated after 15 minutes were: Regulation (survival): Raf1, VEGFR2, PKC delta, EGFR, STAT6; Molecular Association: DOK1, GLUR1, SHP-2, HSP90; Cell motility and cytoskeletal reorganization: Claudin 7, Cortactin, PKC delta, p130Cas, Ezrin, PAK3; NfkB pathway regulation: NFkb p100, Rel, Nfkb-p65; Cell Cycle progression: CDK1, p27Kip1, AurA, PKC, CAMK2; Calcium signaling: PKC, CaMK2; TCR signaling: CD3z is downstream of LCK signaling and upstream of ZAP70.

[1039] While the invention has been particularly shown and described with reference to a preferred embodiment and various alternate embodiments, it will be understood by persons skilled in the relevant art that various changes in form and details can be made therein without departing from the spirit and scope of the invention.

[1040] All references, issued patents and patent applications cited within the body of the instant specification are hereby incorporated by reference in their entirety, for all purposes.

Sequence listing

SEQ ID NO	Name	Sequence
1	HX-3031 Heavy Chain Variable	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNSLLKSRL SISRDTSKSQVFLKMNSLQTEDTATYYCARDLSDYYSSYTSFDYWGQGVMVTVST
2	HX-3031 CDR-H1	GFSLTSYHVS
3	HX-3031 CDR-H2	AIWTGGSIA
4	HX-3031 CDR-H3	DLSDYYSSYTSFDY
5	HX-3031 Heavy chain	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNSLLKSRL SISRDTSKSQVFLKMNSLQTEDTATYYCARDLSDYYSSYTSFDYWGQGVMVTVSTAETTAPSVYPLA PGTALKSNSMVTLGCLVKGYFPEPVTVTWNSGALSSGVHTFPAVLQSGLYTLTSSVTVPSSTWSSQA VTCNVAHPASSTKVDKKIVPRECNPCGCTGSEVSSVFIFPPKTKDVLTITLTPKVTCVVVDISQNDP EVRFSWFIDDVEVHTAQTHAPEKQSNSTLRSVSELPIVHRDWLNGKTFKCKVNSGAFPAPIEKSISK PEGTPRGPQVYTMAPPKEEMTQSQVSITCMVKGFYPPDIYTEWKMNGQPQENYKNTPPTMDTDGSYF LYSKLNVKKETWQQGNTFTCSVLHEGLHNHHTEKSLSHSP*
6	HX-3031 Light Chain Variable	DIQMTQSPASLSTSLGETVSIECLASEGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRYSLKISGMQPEDEADYFCQQSYKYPLTFGSGTKLEIK
7	HX-3031 CDR-L1	LASEGISNDLA
8	HX-3031 CDR-L2	AASRLQD
9	HX-3031 CDR-L3	QQSYKYPLT
10	HX-3031 Light chain	DIQMTQSPASLSTSLGETVSIECLASEGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRYSLKISGMQPEDEADYFCQQSYKYPLTFGSGTKLEIKRADAAPTVSIFPPSTEQLATGGASVVC LMNNFYPRDISVKWKIDGTERRDGVLDSVTDQDSKDSTYSMSSTLSLTKADYESHNLYTCEVVHKTS SSPVVKSFNRNEC*
11	PI-3010-AB Heavy Chain Variable	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNSLLKSRL SISRDTSKSQVFLKMNSLQTEDTATYYCARDLSDYYSSYTSFDYWGQGVMVTVST
12	PI-3010-AB CDR-H1	GFSLTSYHVS
13	PI-3010-AB CDR-H2	AIWTGGSIA
14	PI-3010-AB CDR-H3	DLSDYYSSYTSFDY
15	PI-3010-AB Heavy chain	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNSLLKSRL SISRDTSKSQVFLKMNSLQTEDTATYYCARDLSDYYSSYTSFDYWGQGVMVTVSTASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
16	PI-3010-AB Light Chain Variable	DIQMTQSPASLSTSLGETVSIECLASEGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRYSLKISGMQPEDEADYFCQQSYKYPLTFGSGTKLEIK
17	PI-3010-AB CDR-L1	LASEGISNDLA
18	PI-3010-AB CDR-L2	AASRLQD
19	PI-3010-AB CDR-L3	QQSYKYPLT
20	PI-3010-AB	DIQMTQSPASLSTSLGETVSIECLASEGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS

	Light chain	GTRYSLKISGMQPEDEADYFCQQSYKYPLTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
21	PI-3011-AB Heavy Chain Variable	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWIRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISVDTSKNQFSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
22	PI-3011-AB CDR-H1	GFSLTSYHVS
23	PI-3011-AB CDR-H2	AIWTGGSIA
24	PI-3011-AB CDR-H3	DLSDYYSSYTSFDY
25	PI-3011-AB Heavy chain	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWIRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISVDTSKNQFSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
26	PI-3011-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIK
27	PI-3011-AB CDR-L1	RASEGISNDLA
28	PI-3011-AB CDR-L2	AASRLQD
29	PI-3011-AB CDR-L3	QQSYKYPLT
30	PI-3011-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
31	PI-3012-AB Heavy Chain Variable	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
32	PI-3012-AB CDR-H1	GFSLTSYHVS
33	PI-3012-AB CDR-H2	AIWTGGSIA
34	PI-3012-AB CDR-H3	DLSDYYSSYTSFDY
35	PI-3012-AB Heavy chain	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
36	PI-3012-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIK
37	PI-3012-AB CDR-L1	RASEGISNDLA
38	PI-3012-AB CDR-L2	AASRLQD
39	PI-3012-AB CDR-L3	QQSYKYPLT
40	PI-3012-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL

		SSPVTKSFNRGEC*
41	PI-3013-AB Heavy Chain Variable	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
42	PI-3013-AB CDR-H1	GFSLTSYHVS
43	PI-3013-AB CDR-H2	AIWTGGSIA
44	PI-3013-AB CDR-H3	DLSDYYSSYTSFDY
45	PI-3013-AB Heavy chain	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
46	PI-3013-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSMQPEDFATYYCQQSYKYPLTFGQGTKLEIK
47	PI-3013-AB CDR-L1	RASEGISNDLA
48	PI-3013-AB CDR-L2	AASRLQD
49	PI-3013-AB CDR-L3	QQSYKYPLT
50	PI-3013-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSMQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
51	PI-3014-AB Heavy Chain Variable	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNPSLKSRL TISRDTSKNQVSLKMSSLTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
52	PI-3014-AB CDR-H1	GFSLTSYHVS
53	PI-3014-AB CDR-H2	AIWTGGSIA
54	PI-3014-AB CDR-H3	DLSDYYSSYTSFDY
55	PI-3014-AB Heavy chain	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNPSLKSRL TISRDTSKNQVSLKMSSLTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
56	PI-3014-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIK
57	PI-3014-AB CDR-L1	RASEGISNDLA
58	PI-3014-AB CDR-L2	AASRLQD
59	PI-3014-AB CDR-L3	QQSYKYPLT
60	PI-3014-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
61	PI-3015-AB	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNPSLKSRL

	Heavy Chain Variable	TISRDTSKNQVSLKMSSLTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
62	PI-3015-AB CDR-H1	GFSLTSYHVS
63	PI-3015-AB CDR-H2	AIWTGGSIA
64	PI-3015-AB CDR-H3	DLSDYYSSYTSFDY
65	PI-3015-AB Heavy chain	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNPSLKSRL TISRDTSKNQVSLKMSSLTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
66	PI-3015-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSMQPEDFATYYCQQSYKYPLTFGQGTKLEIK
67	PI-3015-AB CDR-L1	RASEGISNDLA
68	PI-3015-AB CDR-L2	AASRLQD
69	PI-3015-AB CDR-L3	QQSYKYPLT
70	PI-3015-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSMQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
71	PI-3020-AB Heavy Chain Variable	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNSLLKSRL SISRDTSKSQVFLKMNSLQTEDTATYYCARDLSDYYSSYTSFDYWGQGVMVTVST
72	PI-3020-AB CDR-H1	GFSLTSYHVS
73	PI-3020-AB CDR-H2	AIWTGGSIA
74	PI-3020-AB CDR-H3	DLSDYYSSYTSFDY
75	PI-3020-AB Heavy chain	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNSLLKSRL SISRDTSKSQVFLKMNSLQTEDTATYYCARDLSDYYSSYTSFDYWGQGVMVTVSTASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTK TYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*
76	PI-3020-AB Light Chain Variable	DIQMTQSPASLSTSLGETVSIECLASEGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRYSLKISGMQPEDEADYFCQQSYKYPLTFGSGTKLEIK
77	PI-3020-AB CDR-L1	LASEGISNDLA
78	PI-3020-AB CDR-L2	AASRLQD
79	PI-3020-AB CDR-L3	QQSYKYPLT
80	PI-3020-AB Light chain	DIQMTQSPASLSTSLGETVSIECLASEGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRYSLKISGMQPEDEADYFCQQSYKYPLTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
81	PI-3022-AB Heavy Chain Variable	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS

82	PI-3022-AB CDR-H1	GFSLTSYHVS
83	PI-3022-AB CDR-H2	AIWTGGSIA
84	PI-3022-AB CDR-H3	DLSDYYSSYTSFDY
85	PI-3022-AB Heavy chain	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
86	PI-3022-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIK
87	PI-3022-AB CDR-L1	RASEGISNDLA
88	PI-3022-AB CDR-L2	AASRLQD
89	PI-3022-AB CDR-L3	QQSYKYPLT
90	PI-3022-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
91	PI-3023-AB Heavy Chain Variable	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
92	PI-3023-AB CDR-H1	GFSLTSYHVS
93	PI-3023-AB CDR-H2	AIWTGGSIA
94	PI-3023-AB CDR-H3	DLSDYYSSYTSFDY
95	PI-3023-AB Heavy chain	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
96	PI-3023-AB Light Chain Variable	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSLQPEDFATYFCQQSYKYPLTFGQGTKLEIK
97	PI-3023-AB CDR-L1	RASEGISNDLA
98	PI-3023-AB CDR-L2	AASRLQD
99	PI-3023-AB CDR-L3	QQSYKYPLT
100	PI-3023-AB Light chain	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSLQPEDFATYFCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
101	PI-3024-AB Heavy Chain Variable	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
102	PI-3024-AB CDR-H1	GFSLTSYHVS

103	PI-3024-AB CDR-H2	AIWTGGSIA
104	PI-3024-AB CDR-H3	DLSDYYSSYTSFDY
105	PI-3024-AB Heavy chain	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
106	PI-3024-AB Light Chain Variable	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDEATYFCQQSYKYPLTFGQGTKLEIK
107	PI-3024-AB CDR-L1	RASEGISNDLA
108	PI-3024-AB CDR-L2	AASRLQD
109	PI-3024-AB CDR-L3	QQSYKYPLT
110	PI-3024-AB Light chain	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDEATYFCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
111	PI-3025-AB Heavy Chain Variable	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
112	PI-3025-AB CDR-H1	GFSLTSYHVS
113	PI-3025-AB CDR-H2	AIWTGGSIA
114	PI-3025-AB CDR-H3	DLSDYYSSYTSFDY
115	PI-3025-AB Heavy chain	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
116	PI-3025-AB Light Chain Variable	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDEATYFCQQSYKYPLTFGQGTKLEIK
117	PI-3025-AB CDR-L1	RASEGISNDLA
118	PI-3025-AB CDR-L2	AASRLQD
119	PI-3025-AB CDR-L3	QQSYKYPLT
120	PI-3025-AB Light chain	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDEATYFCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
121	PI-3026-AB Heavy Chain Variable	VQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRVT ISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
122	PI-3026-AB CDR-H1	GFSLTSYHVS
123	PI-3026-AB CDR-H2	AIWTGGSIA

124	PI-3026-AB CDR-H3	DLSDYYSSYTSFDY
125	PI-3026-AB Heavy chain	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
126	PI-3026-AB Light Chain Variable	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSLQPEDFATYFCQQSYKYPLTFGQGTKLEIK
127	PI-3026-AB CDR-L1	RASEGISNDLA
128	PI-3026-AB CDR-L2	AASRLQD
129	PI-3026-AB CDR-L3	QQSYKYPLT
130	PI-3026-AB Light chain	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSLQPEDFATYFCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
131	PI-3027-AB Heavy Chain Variable	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
132	PI-3027-AB CDR-H1	GFSLTSYHVS
133	PI-3027-AB CDR-H2	AIWTGGSIA
134	PI-3027-AB CDR-H3	DLSDYYSSYTSFDY
135	PI-3027-AB Heavy chain	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
136	PI-3027-AB Light Chain Variable	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDEATYFCQQSYKYPLTFGQGTKLEIK
137	PI-3027-AB CDR-L1	RASEGISNDLA
138	PI-3027-AB CDR-L2	AASRLQD
139	PI-3027-AB CDR-L3	QQSYKYPLT
140	PI-3027-AB Light chain	DIQMTQSPSSLSTSVGDRVTITCRASEGISNDLAWYQQKPGKSPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDEATYFCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
141	HX-3061 Heavy Chain Variable	EVQLVESGGGLVQPGSSLKLSCVASKFTFSNYGMNWIRQAPKKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLEMNSLRSEDTAMYYCAKSLTGGSDYFDSWGQGVMVTVSS
142	HX-3061 CDR-H1	KFTFSNYGMN
143	HX-3061 CDR-H2	LIYYNSNNKY
144	HX-3061 CDR-H3	SLTGGSDYFDS

145	HX-3061 Heavy chain	EVQLVESGGGLVQPGSSLKLSCVASKFTFSNYGMNWIRQAPKKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLEMNSLRSEDTAMYYCAKSLTGGSDYFDSWGQGVMVTVSSAETTAPSVYPLAPG TALKSNSMVTLGCLVKGYFPEPVTVTWNSGALSSGVHTFPAVLQSGLYTLTSSVTVPSSTWPSQTVT CNVAHPASSTKVDKKIVPRNCGGDCKPCICTGSEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISQD DPEVHFSWFVDDVEVHTAQTRPPEEQFNSTFRSVSELPILHQDWLNGRTFRCKVTSAAFPSPIEKTI SKPEGRTQVPHVYTMSPTKEEMTQNEVSITCMVKGFYPPDIYVEWQMNGQPQENYKNTPPTMDTDGS YFLYSKLNVKKEKWQQGNTFTCSVLHEGLHNHHTEKSLSHSP*
146	HX-3061 Light Chain Variable	DVQMTQSPSYLAASPGESVSISCKASKSIGTFLAWYQEKPEKTNKLLIYSGSTLQSGTPSRFSGSGS GTDFTLTIRNLEPEDFAVYYCQQHDEYPFTFGSGTKLEIK
147	HX-3061 CDR-L1	KASKSIGTFLA
148	HX-3061 CDR-L2	SGSTLQS
149	HX-3061 CDR-L3	QQHDEYPFT
150	HX-3061 Light chain	DVQMTQSPSYLAASPGESVSISCKASKSIGTFLAWYQEKPEKTNKLLIYSGSTLQSGTPSRFSGSGS GTDFTLTIRNLEPEDFAVYYCQQHDEYPFTFGSGTKLEIKRADAAPTVSIFPPSTEQLATGGASVVC LMNNFYPRDISVKWKIDGTERRDGVLDSVTDQDSKDSTYSMSSTLSLTKADYESHNLYTCEVVHKTS SSPVVKSFNRNEC*
151	PI-3016-AB Heavy Chain Variable	EVQLVESGGGLVQPGGSLRLSCAASKFTFSNYGMNWVRQAPGKGLEWVSLIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSS
152	PI-3016-AB CDR-H1	KFTFSNYGMN
153	PI-3016-AB CDR-H2	LIYYNSNNKY
154	PI-3016-AB CDR-H3	SLTGGSDYFDS
155	PI-3016-AB Heavy chain	EVQLVESGGGLVQPGGSLRLSCAASKFTFSNYGMNWVRQAPGKGLEWVSLIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
156	PI-3016-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIK
157	PI-3016-AB CDR-L1	RASKSIGTFLA
158	PI-3016-AB CDR-L2	SGSTLQS
159	PI-3016-AB CDR-L3	QQHDEYPFT
160	PI-3016-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
161	PI-3017-AB Heavy Chain Variable	EVQLVESGGGLVQPGGSLRLSCAASKFTFSNYGMNWIRQAPGKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSS
162	PI-3017-AB CDR-H1	KFTFSNYGMN
163	PI-3017-AB CDR-H2	LIYYNSNNKY
164	PI-3017-AB CDR-H3	SLTGGSDYFDS
165	PI-3017-AB Heavy chain	EVQLVESGGGLVQPGGSLRLSCAASKFTFSNYGMNWIRQAPGKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSSASTKGPSVFPLAPS

		SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
166	PI-3017-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIK
167	PI-3017-AB CDR-L1	RASKSIGTFLA
168	PI-3017-AB CDR-L2	SGSTLQS
169	PI-3017-AB CDR-L3	QQHDEYPFT
170	PI-3017-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
171	PI-3018-AB Heavy Chain Variable	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMNWIRQAPGKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSS
172	PI-3018-AB CDR-H1	KFTFSNYGMN
173	PI-3018-AB CDR-H2	LIYYNSNNKY
174	PI-3018-AB CDR-H3	SLTGGSDYFDS
175	PI-3018-AB Heavy chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMNWIRQAPGKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
176	PI-3018-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIK
177	PI-3018-AB CDR-L1	RASKSIGTFLA
178	PI-3018-AB CDR-L2	SGSTLQS
179	PI-3018-AB CDR-L3	QQHDEYPFT
180	PI-3018-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
181	PI-3019-AB Heavy Chain Variable	EVQLVESGGGLVQPGSSLKLSCVASKFTFSNYGMNWIRQAPKKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLEMNSLRSEDTAMYYCAKSLTGGSDYFDSWGQGVMVTVSS
182	PI-3019-AB CDR-H1	KFTFSNYGMN
183	PI-3019-AB CDR-H2	LIYYNSNNKY
184	PI-3019-AB CDR-H3	SLTGGSDYFDS
185	PI-3019-AB Heavy chain	EVQLVESGGGLVQPGSSLKLSCVASKFTFSNYGMNWIRQAPKKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLEMNSLRSEDTAMYYCAKSLTGGSDYFDSWGQGVMVTVSSAKTTAPSVYPLAPV CGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVD

		VSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPI ERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD SDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK*
186	PI-3019-AB Light Chain Variable	DVQMTQSPSYLAASPGESVSISCKASKSIGTFLAWYQEKPEKTNKLLIYSGSTLQSGTPSRFSGSGS GTDFTLTIRNLEPEDFAVYYCQQHDEYPFTFGSGTKLEIK
187	PI-3019-AB CDR-L1	KASKSIGTFLA
188	PI-3019-AB CDR-L2	SGSTLQS
189	PI-3019-AB CDR-L3	QQHDEYPFT
190	PI-3019-AB Light chain	DVQMTQSPSYLAASPGESVSISCKASKSIGTFLAWYQEKPEKTNKLLIYSGSTLQSGTPSRFSGSGS GTDFTLTIRNLEPEDFAVYYCQQHDEYPFTFGSGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVC FLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTS TSPIVKSFNRNEC*
191	PI-3028-AB Heavy Chain Variable	EVQLVESGGGLVQPGSSLKLSCVASKFTFSNYGMNWIRQAPKKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLEMNSLRSEDTAMYYCAKSLTGGSDYFDSWGQGVMVTVSS
192	PI-3028-AB CDR-H1	KFTFSNYGMN
193	PI-3028-AB CDR-H2	LIYYNSNNKY
194	PI-3028-AB CDR-H3	SLTGGSDYFDS
195	PI-3028-AB Heavy chain	EVQLVESGGGLVQPGSSLKLSCVASKFTFSNYGMNWIRQAPKKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLEMNSLRSEDTAMYYCAKSLTGGSDYFDSWGQGVMVTVSSAKTTAPSVYPLAPV CGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVD VSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPI ERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD SDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK*
196	PI-3028-AB Light Chain Variable	DVQMTQSPSYLAASPGESVSISCKASKSIGTFLAWYQEKPEKTNKLLIYSGSTLQSGTPSRFSGSGS GTDFTLTIRNLEPEDFAVYYCQQHDEYPFTFGSGTKLEIK
197	PI-3028-AB CDR-L1	KASKSIGTFLA
198	PI-3028-AB CDR-L2	SGSTLQS
199	PI-3028-AB CDR-L3	QQHDEYPFT
200	PI-3028-AB Light chain	DVQMTQSPSYLAASPGESVSISCKASKSIGTFLAWYQEKPEKTNKLLIYSGSTLQSGTPSRFSGSGS GTDFTLTIRNLEPEDFAVYYCQQHDEYPFTFGSGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVC FLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTS TSPIVKSFNRNEC*
201	PI-3029-AB Heavy Chain Variable	EVQLVESGGGLVQPGSSLKLSCVASKFTFSNYGMNWIRQAPKKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLEMNSLRSEDTAMYYCAKSLTGGSDYFDSWGQGVMVTVSS
202	PI-3029-AB CDR-H1	KFTFSNYGMN
203	PI-3029-AB CDR-H2	LIYYNSNNKY
204	PI-3029-AB CDR-H3	SLTGGSDYFDS
205	PI-3029-AB Heavy chain	EVQLVESGGGLVQPGSSLKLSCVASKFTFSNYGMNWIRQAPKKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLEMNSLRSEDTAMYYCAKSLTGGSDYFDSWGQGVMVTVSSAKTTAPSVYPLAPV CGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSIT CNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVD VSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPI ERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD

		SDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK*
206	PI-3029-AB Light Chain Variable	DVQMTQSPSYLAASPGESVSISCKASKSIGTFLAWYQEKPEKTNKLLIYSGSTLQSGTPSRFSGSGS GTDFTLTIRNLEPEDFAVYYCQQHDEYPFTFGSGTKLEIK
207	PI-3029-AB CDR-L1	KASKSIGTFLA
208	PI-3029-AB CDR-L2	SGSTLQS
209	PI-3029-AB CDR-L3	QQHDEYPFT
210	PI-3029-AB Light chain	DVQMTQSPSYLAASPGESVSISCKASKSIGTFLAWYQEKPEKTNKLLIYSGSTLQSGTPSRFSGSGS GTDFTLTIRNLEPEDFAVYYCQQHDEYPFTFGSGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVC FLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTS TSPIVKSFNRNEC*
211	PI-3032-AB Heavy Chain Variable	EVQLVESGGGLVQPGGSLRLSCAASKFTFSNYGMNWIRQAPGKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSS
212	PI-3032-AB CDR-H1	KFTFSNYGMN
213	PI-3032-AB CDR-H2	LIYYNSNNKY
214	PI-3032-AB CDR-H3	SLTGGSDYFDS
215	PI-3032-AB Heavy chain	EVQLVESGGGLVQPGGSLRLSCAASKFTFSNYGMNWIRQAPGKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
216	PI-3032-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYSGSTLESGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIK
217	PI-3032-AB CDR-L1	KASKSIGTFLA
218	PI-3032-AB CDR-L2	SGSTLQS
219	PI-3032-AB CDR-L3	QQHDEYPFT
220	PI-3032-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYSGSTLESGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
221	PI-3033-AB Heavy Chain Variable	EVQLVESGGGLVQPGGSLRLSCAASKFTFSNYGMNWIRQAPGKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSS
222	PI-3033-AB CDR-H1	KFTFSNYGMN
223	PI-3033-AB CDR-H2	LIYYNSNNKY
224	PI-3033-AB CDR-H3	SLTGGSDYFDS
225	PI-3033-AB Heavy chain	EVQLVESGGGLVQPGGSLRLSCAASKFTFSNYGMNWIRQAPGKGLEWIALIYYNSNNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSLTGGSDYFDSWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
226	PI-3033-AB	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGS

	Light Chain Variable	GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIK
227	PI-3033-AB CDR-L1	KASKSIGTFLA
228	PI-3033-AB CDR-L2	SGSTLQS
229	PI-3033-AB CDR-L3	QQHDEYPFT
230	PI-3033-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASKSIGTFLAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQHDEYPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
231	HX-3011 Heavy Chain Variable	QIQLVQSGPELKKPGESVKISCKASGYTFTDYAVNWVKQAPGNGLKWMGWINTQTGKPTYADDFKQR FVFSLETSASTSFLQINNLNIEDTATYFCTRDSYYYSSSLDYWGQGVMVTVSS
232	HX-3011 CDR-H1	GYTFTDYAVN
233	HX-3011 CDR-H2	WINTQTGKPT
234	HX-3011 CDR-H3	DSYYYSSSLDY
235	HX-3011 Heavy chain	QIQLVQSGPELKKPGESVKISCKASGYTFTDYAVNWVKQAPGNGLKWMGWINTQTGKPTYADDFKQR FVFSLETSASTSFLQINNLNIEDTATYFCTRDSYYYSSSLDYWGQGVMVTVSSAETTAPSVYPLAPG TALKSNSMVTLGCLVKGYFPEPVTVTWNSGALSSGVHTFPAVLQSGLYTLTSSVTVPSSTWSSQAVT CNVAHPASSTKVDKKIVPRECNPCGCTGSEVSSVFIFPPKTKDVLTITLTPKVTCVVVDISQNDPEV RFSWFIDDVEVHTAQTHAPEKQSNSTLRSVSELPIVHRDWLNGKTFKCKVNSGAFPAPIEKSISKPE GTPRGPQVYTMAPPKEEMTQSQVSITCMVKGFYPPDIYTEWKMNGQPQENYKNTPPTMDTDGSYFLY SKLNVKKETWQQGNTFTCSVLHEGLHNHHTEKSLSHSP*
236	HX-3011 Light Chain Variable	DIQMTQSPASLSASLGETVSIECLASAGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRFSLKISDMQPEDEADYFCQQSYKYPWTFGGGTKLELK
237	HX-3011 CDR-L1	LASAGISNDLA
238	HX-3011 CDR-L2	AASRLQD
239	HX-3011 CDR-L3	QQSYKYPWT
240	HX-3011 Light chain	DIQMTQSPASLSASLGETVSIECLASAGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRFSLKISDMQPEDEADYFCQQSYKYPWTFGGGTKLELKRADAAPTVSIFPPSTEQLATGGASVVC LMNNFYPRDISVKWKIDGTERRDGVLDSVTDQDSKDSTYSMSSTLSLTKADYESHNLYTCEVVHKTS SSPVVKSFNRNEC*
241	PI-3030-AB Heavy Chain Variable	QIQLVQSGPELKKPGESVKISCKASGYTFTDYAVNWVKQAPGNGLKWMGWINTQTGKPTYADDFKQR FVFSLETSASTSFLQINNLNIEDTATYFCTRDSYYYSSSLDYWGQGVMVTVSS
242	PI-3030-AB CDR-H1	GYTFTDYAVN
243	PI-3030-AB CDR-H2	WINTQTGKPT
244	PI-3030-AB CDR-H3	DSYYYSSSLDY
245	PI-3030-AB Heavy chain	QIQLVQSGPELKKPGESVKISCKASGYTFTDYAVNWVKQAPGNGLKWMGWINTQTGKPTYADDFKQR FVFSLETSASTSFLQINNLNIEDTATYFCTRDSYYYSSSLDYWGQGVMVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
246	PI-3030-AB Light Chain Variable	DIQMTQSPASLSASLGETVSIECLASAGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRFSLKISDMQPEDEADYFCQQSYKYPWTFGGGTKLELK

247	PI-3030-AB CDR-L1	LASAGISNDLA
248	PI-3030-AB CDR-L2	AASRLQD
249	PI-3030-AB CDR-L3	QQSYKYPWT
250	PI-3030-AB Light chain	DIQMTQSPASLSASLGETVSIECLASAGISNDLAWYQQKSGKSPQLLIYAASRLQDGVPSRFSGSGS GTRFSLKISDMQPEDEADYFCQQSYKYPWTFGGGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
251	HX-3043 Heavy Chain Variable	QVNLLQSRAALVKPGASVKLSCKASGYTFTDYYLHWVKQSHAKSLEWIGYINPNNAYTSYNEKFKSK ATLTVDKSTNTAYMELSRLTSADSATYYCARDTTDYYNLHFAYWGQGTLVTVSS
252	HX-3043 CDR-H1	GYTFTDYYLH
253	HX-3043 CDR-H2	YINPNNAYTS
254	HX-3043 CDR-H3	DTTDYYNLHFAY
255	HX-3043 Heavy chain	QVNLLQSRAALVKPGASVKLSCKASGYTFTDYYLHWVKQSHAKSLEWIGYINPNNAYTSYNEKFKSK ATLTVDKSTNTAYMELSRLTSADSATYYCARDTTDYYNLHFAYWGQGTLVTVSSAETTAPSVYPLAP GTALKSNSMVTLGCLVKGYFPEPVTVTWNSGALSSGVHTFPAVLQSGLYTLTSSVTVPSSTWSSQAV TCNVAHPASSTKVDKKIVPRECNPCGCTGSEVSSVFIFPPKTKDVLTITLTPKVTCVVVDISQNDPE VRFSWFIDDVEVHTAQTHAPEKQSNSTLRSVSELPIVHRDWLNGKTFKCKVNSGAFPAPIEKSISKP EGTPRGPQVYTMAPPKEEMTQSQVSITCMVKGFYPPDIYTEWKMNGQPQENYKNTPPTMDTDGSYFL YSKLNVKKETWQQGNTFTCSVLHEGLHNHHTEKSLSHSP*
256	HX-3043 Light Chain Variable	DIQMTQSPASLSASLGETVSIECLTSEGISNDLAWYQQKSGKSPQLLIYDASRLEDGVPSRFSGSGS GTRYSLKISGMQTEDEADYFCQQSYKYPLTFGSGTKLEIK
257	HX-3043 CDR-L1	LTSEGISNDLA
258	HX-3043 CDR-L2	DASRLED
259	HX-3043 CDR-L3	QQSYKYPLT
260	HX-3043 Light chain	DIQMTQSPASLSASLGETVSIECLTSEGISNDLAWYQQKSGKSPQLLIYDASRLEDGVPSRFSGSGS GTRYSLKISGMQTEDEADYFCQQSYKYPLTFGSGTKLEIKRADAAPTVSIFPPSTEQLATGGASVVC LMNNFYPRDISVKWKIDGTERRDGVLDSVTDQDSKDSTYSMSSTLSLTKADYESHNLYTCEVVHKTS SSPVVKSFNRNEC*
261	PI-3031-AB Heavy Chain Variable	QVNLLQSRAALVKPGASVKLSCKASGYTFTDYYLHWVKQSHAKSLEWIGYINPNNAYTSYNEKFKSK ATLTVDKSTNTAYMELSRLTSADSATYYCARDTTDYYNLHFAYWGQGTLVTVSS
262	PI-3031-AB CDR-H1	GYTFTDYYLH
263	PI-3031-AB CDR-H2	YINPNNAYTS
264	PI-3031-AB CDR-H3	DTTDYYNLHFAY
265	PI-3031-AB Heavy chain	QVNLLQSRAALVKPGASVKLSCKASGYTFTDYYLHWVKQSHAKSLEWIGYINPNNAYTSYNEKFKSK ATLTVDKSTNTAYMELSRLTSADSATYYCARDTTDYYNLHFAYWGQGTLVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
266	PI-3031-AB Light Chain Variable	DIQMTQSPASLSASLGETVSIECLTSEGISNDLAWYQQKSGKSPQLLIYDASRLEDGVPSRFSGSGS GTRYSLKISGMQTEDEADYFCQQSYKYPLTFGSGTKLEIK
267	PI-3031-AB CDR-L1	LTSEGISNDLA

268	PI-3031-AB CDR-L2	DASRLED
269	PI-3031-AB CDR-L3	QQSYKYPLT
270	PI-3031-AB Light chain	DIQMTQSPASLSASLGETVSIECLTSEGISNDLAWYQQKSGKSPQLLIYDASRLEDGVPSRFSGSGS GTRYSLKISGMQTEDEADYFCQQSYKYPLTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
271	PI-3006-AB Heavy Chain Variable	EVQLVESGGGLVKPGASLKLSCVASGFTFSDYWMNWVRQTPGKTMEWIGDIKDDGSYTNYTPSLKNR FTISRDNAKSTLYLQMNNVRSEDTGTYYCTSGGVFDYWGQGVMVTVSS
272	PI-3006-AB CDR-H1	GFTFSDYW
273	PI-3006-AB CDR-H2	IKDDGSYT
274	PI-3006-AB CDR-H3	TSGGVFDY
275	PI-3006-AB Heavy chain	EVQLVESGGGLVKPGASLKLSCVASGFTFSDYWMNWVRQTPGKTMEWIGDIKDDGSYTNYTPSLKNR FTISRDNAKSTLYLQMNNVRSEDTGTYYCTSGGVFDYWGQGVMVTVSSAKTTAPSVYPLAPVCGDTT GSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTIS KPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSY FMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK*
276	PI-3006-AB Light Chain Variable	EIVLTQSPTTMAASPGEMVTITCRASSSVNYMHWFQQKSGTSPKPWIYDTSKLASGVPDRFSGSGSG TSYSLTISSMEAEDAASYYCLQRSTFPPTFGAGTKLELK
277	PI-3006-AB CDR-L1	SSVNY
278	PI-3006-AB CDR-L2	DTS
279	PI-3006-AB CDR-L3	LQRSTFPPT
280	PI-3006-AB Light chain	EIVLTQSPTTMAASPGEMVTITCRASSSVNYMHWFQQKSGTSPKPWIYDTSKLASGVPDRFSGSGSG TSYSLTISSMEAEDAASYYCLQRSTFPPTFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCF LNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTST SPIVKSFNRNEC*
281	PI-3007-AB Heavy Chain Variable	QVRLVQSGTALVRPGASVRMSCTASGYSFTDYWVSWVKQSHGQSLEWIGEIYPNSGTTNFNEKFEGK ATLTVDKSTSTAYMELSRLTSEDSAIYYCTGEGTFDYWGQGVMVTVSS
282	PI-3007-AB CDR-H1	GYSFTDYW
283	PI-3007-AB CDR-H2	IYPNSGTT
284	PI-3007-AB CDR-H3	TGEGTFDY
285	PI-3007-AB Heavy chain	QVRLVQSGTALVRPGASVRMSCTASGYSFTDYWVSWVKQSHGQSLEWIGEIYPNSGTTNFNEKFEGK ATLTVDKSTSTAYMELSRLTSEDSAIYYCTGEGTFDYWGQGVMVTVSSAKTTAPSVYPLAPVCGDTT GSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTIS KPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSY FMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK*
286	PI-3007-AB Light Chain Variable	EIVLTQSPTTMAASPGEKVTITCRPSSSLSNMHWFQQKSGTSPKPWIYDTSKLASGVPDRFSGSGSG TSYSLTISSMEAEDAATYYCLQRSSYPPTFGAGTKLELK
287	PI-3007-AB CDR-L1	SSLSN
288	PI-3007-AB CDR-L2	DTS

289	PI-3007-AB CDR-L3	LQRSSYPPT
290	PI-3007-AB Light chain	EIVLTQSPTTMAASPGEKVTITCRPSSSLSNMHWFQQKSGTSPKPWIYDTSKLASGVPDRFSGSGSG TSYSLTISSMEAEDAATYYCLQRSSYPPTFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCF LNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTST SPIVKSFNRNEC*
291	PI-3008-AB Heavy Chain Variable	EVQLVESGGGLVKPGASLKLSCVASGFTFSDDWMNWVRQTPGKAMEWIGDIKYDGSYTNYVPSLKNR LTISRDNAKNTLYLQMTNVRSEDTATYYCTSGGVFDYWGQGVMVTVSS
292	PI-3008-AB CDR-H1	GFTFSDDW
293	PI-3008-AB CDR-H2	IKYDGSYT
294	PI-3008-AB CDR-H3	TSGGVFDY
295	PI-3008-AB Heavy chain	EVQLVESGGGLVKPGASLKLSCVASGFTFSDDWMNWVRQTPGKAMEWIGDIKYDGSYTNYVPSLKNR LTISRDNAKNTLYLQMTNVRSEDTATYYCTSGGVFDYWGQGVMVTVSSAKTTAPSVYPLAPVCGDTT GSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH PASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDD PDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTIS KPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSY FMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK*
296	PI-3008-AB Light Chain Variable	EIVLSQSPTTMAASPGEKVTITCRASSSVSYMHWFQQKSGTSPKPWIYDTSKLASGVPDRFSGSGSG TSYSLTISSMEAEDAATYYCLQRSGYPPTFGAGTKLEVK
297	PI-3008-AB CDR-L1	SSVSY
298	PI-3008-AB CDR-L2	DTS
299	PI-3008-AB CDR-L3	LQRSGYPPT
300	PI-3008-AB Light chain	EIVLSQSPTTMAASPGEKVTITCRASSSVSYMHWFQQKSGTSPKPWIYDTSKLASGVPDRFSGSGSG TSYSLTISSMEAEDAATYYCLQRSGYPPTFGAGTKLEVKRADAAPTVSIFPPSSEQLTSGGASVVCF LNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTST SPIVKSFNRNEC*
301	PI-3009-AB Heavy Chain Variable	EVQLVESGGGLVQPGRSLKFSCSASGFTFSAYSMAWVRQAPKTGLEWVATIIYDGSSTYYRDSVKGR FTISRDNAKNTLYLQMDSLRSEDTATYYCARLGYSGHYFDYWGQGVMVTVSS
302	PI-3009-AB CDR-H1	GFTFSAYS
303	PI-3009-AB CDR-H2	IIYDGSST
304	PI-3009-AB CDR-H3	ARLGYSGHYFDY
305	PI-3009-AB Heavy chain	EVQLVESGGGLVQPGRSLKFSCSASGFTFSAYSMAWVRQAPKTGLEWVATIIYDGSSTYYRDSVKGR FTISRDNAKNTLYLQMDSLRSEDTATYYCARLGYSGHYFDYWGQGVMVTVSSAKTTAPSVYPLAPVC GDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITC NVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIE RTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDS DGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK*
306	PI-3009-AB Light Chain Variable	DTVLTQSPALAVSLGQRVTISCQASESVSSSLHSYLHWYQQKPGQQPKLLIYRASNLESGVPARFSG SGSGTDFTLNIDPVEADDIATYFCQQSWNDPRTFGGGTKLELK
307	PI-3009-AB CDR-L1	ESVSSSLHSY
308	PI-3009-AB CDR-L2	RAS
309	PI-3009-AB CDR-L3	QQSWNDPRT

310	PI-3009-AB Light chain	DTVLTQSPALAVSLGQRVTISCQASESVSSSLHSYLHWYQQKPGQQPKLLIYRASNLESGVPARFSG SGSGTDFTLNIDPVEADDIATYFCQQSWNDPRTFGGGTKLELKRADAAPTVSIFPPSSEQLTSGGAS VVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATH KTSTSPIVKSFNRNEC*
311	PI-3036-AB Heavy Chain Variable	VQLVQSGAEVKKPGASVKVSCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYCARDSYYYSSSLDYWGQGTLVTVSS
312	PI-3036-AB CDR-H1	GYTFTDYAVN
313	PI-3036-AB CDR-H2	WINTQTGKPT
314	PI-3036-AB CDR-H3	DSYYYSSSLDY
315	PI-3036-AB Heavy chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR VTMTRDTSTSTVYMELSSLRSEDTAVYYCARDSYYYSSSLDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
316	PI-3036-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQSYKYPWTFGQGTKLEIK
317	PI-3036-AB CDR-L1	RASAGISNDLA
318	PI-3036-AB CDR-L2	AASRLQD
319	PI-3036-AB CDR-L3	QQSYKYPWT
320	PI-3036-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQSYKYPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
321	PI-3037-AB Heavy Chain Variable	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR VTMTLDTSTSTAYMELSSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSS
322	PI-3037-AB CDR-H1	GYTFTDYAVN
323	PI-3037-AB CDR-H2	WINTQTGKPT
324	PI-3037-AB CDR-H3	DSYYYSSSLDY
325	PI-3037-AB Heavy chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR VTMTLDTSTSTAYMELSSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
326	PI-3037-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIK
327	PI-3037-AB CDR-L1	RASAGISNDLA
328	PI-3037-AB CDR-L2	AASRLQD
329	PI-3037-AB CDR-L3	QQSYKYPWT
330	PI-3037-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC

		LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
331	PI-3038-AB Heavy Chain Variable	QVQLVQSGAEVKKPGASVKISCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR FTFTLDTSTSTAYLEISSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSS
332	PI-3038-AB CDR-H1	GYTFTDYAVN
333	PI-3038-AB CDR-H2	WINTQTGKPT
334	PI-3038-AB CDR-H3	DSYYYSSSLDY
335	PI-3038-AB Heavy chain	QVQLVQSGAEVKKPGASVKISCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR FTFTLDTSTSTAYLEISSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
336	PI-3038-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIK
337	PI-3038-AB CDR-L1	RASAGISNDLA
338	PI-3038-AB CDR-L2	AASRLQD
339	PI-3038-AB CDR-L3	QQSYKYPWT
340	PI-3038-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
341	PI-3039-AB Heavy Chain Variable	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR VTMTLDTSTSTSYMELSSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSS
342	PI-3039-AB CDR-H1	GYTFTDYAVN
343	PI-3039-AB CDR-H2	WINTQTGKPT
344	PI-3039-AB CDR-H3	DSYYYSSSLDY
345	PI-3039-AB Heavy chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR VTMTLDTSTSTSYMELSSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
346	PI-3039-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIK
347	PI-3039-AB CDR-L1	RASAGISNDLA
348	PI-3039-AB CDR-L2	AASRLQD
349	PI-3039-AB CDR-L3	QQSYKYPWT
350	PI-3039-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL

		SSPVTKSFNRGEC*
351	PI-3040-AB Heavy Chain Variable	QVQLVQSGAEVKKPGASVKISCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR FTFTLDTSTSTSYLEISSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSS
352	PI-3040-AB CDR-H1	GYTFTDYAVN
353	PI-3040-AB CDR-H2	WINTQTGKPT
354	PI-3040-AB CDR-H3	DSYYYSSSLDY
355	PI-3040-AB Heavy chain	QVQLVQSGAEVKKPGASVKISCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR FTFTLDTSTSTSYLEISSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
356	PI-3040-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIK
357	PI-3040-AB CDR-L1	RASAGISNDLA
358	PI-3040-AB CDR-L2	AASRLQD
359	PI-3040-AB CDR-L3	QQSYKYPWT
360	PI-3040-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC*
361	PI-HX-3092 Heavy Chain Variable	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYTLSWVRQPPGKGLEWIGAIWGGDNTDYNSALKSRL SITWDTSKSQVLLKMNSLQTEDTAIYFCTRELGGSFDYWGQGVMVTVSS
362	PI-HX-3092 CDR-H1	GFSLTSYTLS
363	PI-HX-3092 CDR-H2	AIWGGDNTD
364	PI-HX-3092 CDR-H3	ELGGSFDY
365	PI-HX-3092 Heavy chain	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYTLSWVRQPPGKGLEWIGAIWGGDNTDYNSALKSRL SITWDTSKSQVLLKMNSLQTEDTAIYFCTRELGGSFDYWGQGVMVTVSSAETTAPSVYPLAPGTALK SNSMVTLGCLVKGYFPEPVTVTWNSGALSSGVHTFPAVLQSGLYTLTSSVTVPSSTWSSQAVTCNVA HPASSTKVDKKIVPRECNPCGCTGSEVSSVFIFPPKTKDVLTITLTPKVTCVVVDISQNDPEVRFSW FIDDVEVHTAQTHAPEKQSNSTLRSVSELPIVHRDWLNGKTFKCKVNSGAFPAPIEKSISKPEGTPR GPQVYTMAPPKEEMTQSQVSITCMVKGFYPPDIYTEWKMNGQPQENYKNTPPTMDTDGSYFLYSKLN VKKETWQQGNTFTCSVLHEGLHNHHTEKSLSHSP*
366	PI-HX-3092 Light Chain Variable	DIQMTQSPPVLSASVGDRVTLSCKTSQNINKKLDWYQQKHGEAPKLLIYYTNNLQTGIPSRFSGSGS GTDFTLTISTLQPEDVATYYCYQYDSGFTFGAGTKLELK
367	PI-HX-3092 CDR-L1	KTSQNINKKLD
368	PI-HX-3092 CDR-L2	YTNNLQT
369	PI-HX-3092 CDR-L3	YQYDSGFT
370	PI-HX-3092 Light chain	DIQMTQSPPVLSASVGDRVTLSCKTSQNINKKLDWYQQKHGEAPKLLIYYTNNLQTGIPSRFSGSGS GTDFTLTISTLQPEDVATYYCYQYDSGFTFGAGTKLELKRADAAPTVSIFPPSTEQLATGGASVVCL MNNFYPRDISVKWKIDGTERRDGVLDSVTDQDSKDSTYSMSSTLSLTKADYESHNLYTCEVVHKTSS SPVVKSFNRNEC
371	PI-3035-AB	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYTLSWVRQPPGKGLEWIGAIWGGDNTDYNSALKSRL

	Heavy Chain Variable	SISRDTSKSQVLLKMNSLQTEDTAIYFCTRELGGSFDYWGQGVMVTVSS
372	PI-3035-AB CDR-H1	GFSLTSYTLS
373	PI-3035-AB CDR-H2	AIWGGDNTD
374	PI-3035-AB CDR-H3	ELGGSFDY
375	PI-3035-AB Heavy chain	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTSYTLSWVRQPPGKGLEWIGAIWGGDNTDYNSALKSRL SISRDTSKSQVLLKMNSLQTEDTAIYFCTRELGGSFDYWGQGVMVTVSSAKTTAPSVYPLAPVCGDT TGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVA HPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSED DPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTI SKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGS YFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK*
376	PI-3035-AB Light Chain Variable	DIQMTQSPPVLSASVGDRVTLSCKTSQNINKKLDWYQQKHGEAPKLLIYYTNNLQTGIPSRFSGSGS GTDFTLTISTLQPEDVATYYCYQYDSGFTFGAGTKLELK
377	PI-3035-AB CDR-L1	KTSQNINKKLD
378	PI-3035-AB CDR-L2	YTNNLQT
379	PI-3035-AB CDR-L3	YQYDSGFT
380	PI-3035-AB Light chain	DIQMTQSPPVLSASVGDRVTLSCKTSQNINKKLDWYQQKHGEAPKLLIYYTNNLQTGIPSRFSGSGS GTDFTLTISTLQPEDVATYYCYQYDSGFTFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCF LNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTST SPIVKSFNRNEC
381	HX-3011 CDR-L1 Consensus sequence	XASAGISNDLA
382	HX-3061 CDR-L1 Consensus sequence	XASKSIGTFLA
383	HX-3031 CDR-L1 Consensus sequence	XASEGISNDLA
384	Human MARCO protein UNIPROT Q9UEW3	MRNKKILKEDELLSETQQAAFHQIAMEPFEINVPKPKRRNGVNFSLAVVVIYLILLTAGA GLLVVQVLNLQARLRVLEMYFLNDTLAAEDSPSFSLLQSAHPGEHLAQGASRLQVLQAQL TWVRVSHEHLLQRVDNFTQNPGMFRIKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAK GAMGRDGATGPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPK GETGTKGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGDQ GQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTGLQGQQ GRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGVKGEKGERGEN SVSVRIVGSSNRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGYSKGRALYKVGAGTGQ IWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV
385	PI-3010-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTAAGGAATCCGGACCGGGACTCGTGCAGCCGTCACAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATG GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACTCGCTGCTGAAGTCGCGCTTGTCCATTTCGA GAGATACCTCCAAGTCCCAAGTGTTTCTGAAGATGAACTCCCTGCAAACTGAAGATACTGCCACTTA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT GTAATGGTCACTGTGTCGACTGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA

		GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
386	PI-3010-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCGCCTCGCTTTCAACCTCCCTGGGAGAAACCGTGTCCATCGAATG CCTGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGTCCGGAAAGTCACCTCAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGGACGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTCGGTACTCGCTGAAGATTTCCGGGATGCAGCCTGAGGACGAAGCGGACTACTTCTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCTCCGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
387	PI-3011-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGATCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTGACTATTTCGG TGGATACCTCCAAGAACCAATTCAGCCTGAAGTTGTCCTCCGTGACTGCCGCCGATACTGCCGTATA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
388	PI-3011-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAGCCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGGCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGTCCGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTTCACCCTGACCATTTCCAGCCTGCAGCCTGAGGACTTCGCGACCTACTACTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
389	PI-3012-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTAACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCCCTGAAGCTGTCGTCCGTGACTGCCGCCGATACTGCCGTGTA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC

		GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
390	PI-3012-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAGCCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGGCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGTCCGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCCTGCAGCCTGAGGACTTCGCGACCTACTACTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
391	PI-3013-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTAACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCCCTGAAGCTGTCGTCCGTGACTGCCGCCGATACTGCCGTGTA CTACTGTGCCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
392	PI-3013-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAGCCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGGCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGTCCGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCATGCAGCCTGAGGACTTCGCGACCTACTACTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
393	PI-3014-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATG

		GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCTTGACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCGCTGAAGATGTCCTCCCTGACTGCCGCCGATACTGCCGTATA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
394	PI-3014-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAGCCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGGCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGTCCGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCCTGCAGCCTGAGGACTTCGCGACCTACTACTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
395	PI-3015-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATG GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCTTGACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCGCTGAAGATGTCCTCCCTGACTGCCGCCGATACTGCCGTATA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
396	PI-3015-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAGCCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGGCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGTCCGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCATGCAGCCTGAGGACTTCGCGACCTACTACTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG

		ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
397	PI-3022-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTAACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCCCTGAAGCTGTCGTCCGTGACTGCCGCCGATACTGCCGTGTA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
398	PI-3022-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAGCCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGGCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGGACGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCCTGCAGCCTGAGGACTTCGCGACCTACTACTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
399	PI-3023-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTAACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCCCTGAAGCTGTCGTCCGTGACTGCCGCCGATACTGCCGTGTA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
400	PI-3023-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAACCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGTCGCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGTCCGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG

		GGACTGACTACACCCTGACCATTTCCAGCCTGCAGCCTGAGGACTTCGCGACCTACTTCTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
401	PI-3024-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTAACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCCCTGAAGCTGTCGTCCGTGACTGCCGCCGATACTGCCGTGTA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
402	PI-3024-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAACCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGTCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGGACGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCCTGCAGCCTGAGGACGAAGCGACCTACTTCTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
403	PI-3025-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCAGAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTAACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCCCTGAAGCTGTCGTCCGTGACTGCCGCCGATACTGCCGTGTA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG

		GGTAAATAG
404	PI-3025-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAGCCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGGCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGGACGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCCTGCAGCCTGAGGACTTCGCGACCTACTACTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
405	PI-3026-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCAGAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTAACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCCCTGAAGCTGTCGTCCGTGACTGCCGCCGATACTGCCGTGTA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
406	PI-3026-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAACCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGTCGCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGTCCGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCCTGCAGCCTGAGGACTTCGCGACCTACTTCTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
407	PI-3027-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCAGAAGTGCAAC TTCAAGAATCCGGACCGGGACTCGTGAAGCCGTCAGAAACTCTTTCGCTTACCTGTACCGTGTCCGG ATTTTCCCTGACTTCCTACCATGTGTCCTGGGTCAGACAGCCTCCTGGAAAGGGACTGGAATGGATC GGTGCCATTTGGACTGGGGGATCCATTGCGTATAACCCGTCCCTGAAGTCGCGCGTAACTATTTCGA GAGATACCTCCAAGAACCAAGTGTCCCTGAAGCTGTCGTCCGTGACTGCCGCCGATACTGCCGTGTA CTACTGTGCCCGCGATCTGTCCGACTATTACTCGAGTTACACCTCGTTCGATTACTGGGGACAGGGT ACTCTGGTCACTGTGTCGTCGGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGA

		AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCG GGTAAATAG
408	PI-3027-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCCTCATCGCTTTCAACCTCCGTGGGAGACAGAGTGACCATCACTTG CCGGGCTTCCGAAGGGATTTCCAACGATCTGGCCTGGTACCAGCAGAAGCCCGGAAAGTCCCCTAAG CTCCTGATCTACGCGGCCAGCCGGCTGCAGGACGGCGTGCCTTCCCGCTTTTCCGGTTCGGGATCAG GGACTGACTACACCCTGACCATTTCCAGCCTGCAGCCTGAGGACGAAGCGACCTACTTCTGCCAACA ATCCTACAAGTACCCGCTGACCTTCGGCCAAGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
409	PI-3030-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAATCCAGC TCGTGCAGTCCGGGCCAGAGCTGAAAAAGCCCGGAGAATCCGTCAAGATTAGCTGCAAGGCCTCCGG CTACACCTTCACCGACTACGCAGTGAACTGGGTCAAGCAGGCCCCGGGAAATGGTCTGAAGTGGATG GGCTGGATTAACACGCAGACCGGGAAGCCTACCTACGCCGACGACTTCAAGCAACGGTTCGTGTTCT CGCTTGAAACTAGCGCCTCGACCTCGTTCCTGCAAATCAACAACCTGAACATCGAGGACACCGCCAC CTACTTCTGCACAAGAGACTCCTACTATTACTCATCCTCCCTCGATTACTGGGGACAGGGCGTGATG GTCACTGTGTCCAGCGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCA CCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC GTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCA CACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAA CCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACG AAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC GCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGG CTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCT GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCT CCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCGGGTAAA TAG
410	PI-3030-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATCCAAATGACTCAGTCCCCTGCATCCCTGAGCGCGAGCCTGGGGGAGACTGTGTCCATTGAATG CCTCGCCTCCGCCGGAATTTCTAACGACCTGGCCTGGTACCAGCAGAAGTCCGGAAAGTCGCCCCAG CTGCTGATCTACGCCGCTTCGAGGCTTCAGGATGGTGTCCCGTCACGGTTTAGCGGATCAGGATCCG GCACCAGATTCTCCCTGAAAATCAGCGACATGCAGCCAGAGGACGAAGCCGACTACTTCTGCCAACA ATCGTACAAGTATCCCTGGACCTTCGGCGGGGGCACCAAGCTCGAACTGAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
411	PI-3036-AB HC cDNA	ATGGACTGGACCTGGAGATTTTTATTCGTCGTCGCTGCCGCCACCGGAGTGCAATCACAAGTACAAC TGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCCGGCGCCTCCGTGAAAGTGTCGTGCAAAGCCTCGGG TTACACATTCACTGACTACGCAGTGAACTGGGTCAGACAGGCACCGGGCCAGGGACTCGAGTGGATG GGCTGGATCAACACTCAGACTGGGAAGCCCACCTATGCTCAGAAGTTCCAGGGAAGGGTCACCATGA CCCGCGACACCAGCACCTCCACCGTGTACATGGAATTGAGCAGCCTGCGGTCCGAAGATACAGCCGT GTACTATTGTGCGAGGGACTCCTACTACTACTCATCCTCGCTCGACTACTGGGGCCAGGGTACCCTC GTGACCGTTAGCTCGGCCTCTACTAAGGGTCCGTCCGTGTTCCCGTTGGCCCCGAGCTCGAAGTCCA CCTCCGGGGGAACCGCTGCGCTTGGATGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACGGTGTC CTGGAACTCCGGGGCCCTGACCTCGGGAGTGCACACTTTCCCTGCGGTGCTGCAGAGCTCAGGACTG TACAGCCTCAGCTCCGTCGTGACCGTGCCTTCGTCCTCGCTGGGCACCCAGACCTACATCTGCAACG TGAACCACAAGCCGAGCAACACCAAGGTCGACAAGAAAGTCGAGCCGAAGTCATGCGACAAGACTCA

		CACTTGCCCGCCGTGCCCCGCGCCTGAGCTTCTTGGCGGGCCCTCCGTGTTCCTGTTTCCGCCAAAG CCCAAGGATACTCTGATGATTTCGCGGACTCCTGAAGTGACCTGTGTGGTCGTCGATGTGTCCCATG AGGACCCCGAGGTCAAGTTCAATTGGTACGTGGACGGCGTGGAGGTCCACAATGCCAAGACGAAGCC GCGGGAAGAACAGTACAACTCCACTTATCGCGTGGTGTCCGTGCTCACCGTGCTGCATCAGGACTGG CTGAACGGAAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCCCTGCCTGCCCCAATTGAAAAGACCA TCTCAAAAGCGAAGGGCCAGCCGCGCGAACCACAAGTGTACACCCTGCCTCCTTCCCGGGATGAACT GACCAAGAACCAAGTGTCCCTGACTTGCCTCGTGAAGGGTTTCTACCCGTCCGACATCGCCGTGGAA TGGGAGAGCAACGGACAGCCCGAGAACAATTACAAGACTACCCCACCCGTGCTCGATTCGGACGGCA GCTTCTTCCTGTACTCCAAGCTGACCGTGGATAAGTCCCGCTGGCAACAGGGAAACGTGTTCAGTTG TTCCGTGATGCACGAAGCCCTGCACAACCACTACACCCAGAAGTCACTGTCCCTGTCTCCGGGAAAA TAA
412	PI-3036-AB LC cDNA	ATGGATATGAGAGTGCCTGCACAACTTCTTGGATTACTGCTGCTTTGGTTGTCGGGAGCCAGATGCG ATATCCAGATGACCCAGTCCCCGTCGAGCCTGTCAGCTTCCGTGGGCGACCGGGTCACCATTACTTG TCGCGCCTCGGCCGGTATTAGCAATGACTTGGCCTGGTACCAGCAGAAGCCTGGGAAGGCCCCCAAG CTCCTCATCTACGCGGCTTCCCGCCTGCAAGACGGCGTGCCGTCAAGGTTCAGCGGTTCGGGCTCCG GAACTGACTTCACCCTCACTATCTCGTCCCTGCAACCCGAAGATTTCGCAACCTACTACTGCCAGCA GTCCTATAAGTACCCCTGGACTTTCGGACAAGGCACCAAGCTCGAGATCAAGCGGACCGTGGCCGCC CCGAGCGTGTTTATCTTCCCGCCATCTGACGAACAGCTGAAGTCCGGGACAGCGTCCGTGGTCTGCC TGCTCAACAACTTCTACCCCCGCGAGGCCAAAGTGCAGTGGAAAGTCGATAACGCGCTGCAGTCCGG AAACAGCCAGGAAAGCGTGACTGAGCAAGACTCCAAGGACTCCACCTACTCCCTGTCATCCACCCTG ACGCTGTCCAAGGCCGACTACGAAAAGCACAAGGTCTACGCCTGCGAAGTGACCCATCAGGGCCTGT CAAGCCCTGTGACCAAGTCGTTCAACCGGGGAGAGTGTTAA
413	PI-3038-AB HC cDNA	ATGGACTGGACCTGGAGATTTTTATTCGTCGTCGCTGCCGCCACCGGAGTGCAATCACAAGTACAAC TGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCCGGCGCCTCCGTGAAAGTGTCGTGCAAAGCCTCGGG TTACACATTCACTGACTACGCAGTGAACTGGGTCAGACAGGCACCGGGCCAGGGACTCGAGTGGATG GGCTGGATCAACACTCAGACTGGGAAGCCCACCTATGCTCAGAAGTTCCAGGGAAGGGTCACCATGA CCCTGGACACCAGCACCTCCACCGCATACATGGAATTGAGCAGCCTGCGGTCCGAAGATACAGCCGT GTACTATTGTACTAGGGACTCCTACTACTACTCATCCTCGCTCGACTACTGGGGCCAGGGTACCCTC GTGACCGTTAGCTCGGCCTCTACTAAGGGTCCGTCCGTGTTCCCGTTGGCCCCGAGCTCGAAGTCCA CCTCCGGGGGAACCGCTGCGCTTGGATGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACGGTGTC CTGGAACTCCGGGGCCCTGACCTCGGGAGTGCACACTTTCCCTGCGGTGCTGCAGAGCTCAGGACTG TACAGCCTCAGCTCCGTCGTGACCGTGCCTTCGTCCTCGCTGGGCACCCAGACCTACATCTGCAACG TGAACCACAAGCCGAGCAACACCAAGGTCGACAAGAAAGTCGAGCCGAAGTCATGCGACAAGACTCA CACTTGCCCGCCGTGCCCCGCGCCTGAGCTTCTTGGCGGGCCCTCCGTGTTCCTGTTTCCGCCAAAG CCCAAGGATACTCTGATGATTTCGCGGACTCCTGAAGTGACCTGTGTGGTCGTCGATGTGTCCCATG AGGACCCCGAGGTCAAGTTCAATTGGTACGTGGACGGCGTGGAGGTCCACAATGCCAAGACGAAGCC GCGGGAAGAACAGTACAACTCCACTTATCGCGTGGTGTCCGTGCTCACCGTGCTGCATCAGGACTGG CTGAACGGAAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCCCTGCCTGCCCCAATTGAAAAGACCA TCTCAAAAGCGAAGGGCCAGCCGCGCGAACCACAAGTGTACACCCTGCCTCCTTCCCGGGATGAACT GACCAAGAACCAAGTGTCCCTGACTTGCCTCGTGAAGGGTTTCTACCCGTCCGACATCGCCGTGGAA TGGGAGAGCAACGGACAGCCCGAGAACAATTACAAGACTACCCCACCCGTGCTCGATTCGGACGGCA GCTTCTTCCTGTACTCCAAGCTGACCGTGGATAAGTCCCGCTGGCAACAGGGAAACGTGTTCAGTTG TTCCGTGATGCACGAAGCCCTGCACAACCACTACACCCAGAAGTCACTGTCCCTGTCTCCGGGAAAA TAA
414	PI-3038-AB LC cDNA	ATGGATATGAGAGTGCCTGCACAACTTCTTGGATTACTGCTGCTTTGGTTGTCGGGAGCCAGATGCG ATATCCAGATGACCCAGTCCCCGTCGAGCCTGTCAGCTTCCGTGGGCGACCGGGTCACCATTACTTG TCGCGCCTCGGCCGGTATTAGCAATGACTTGGCCTGGTACCAGCAGAAGCCTGGGAAGGCCCCCAAG CTCCTCATCTACGCGGCTTCCCGCCTGCAAGACGGCGTGCCGTCAAGGTTCAGCGGTTCGGGCTCCG GAACTGACTTCACCCTCACTATCTCGTCCCTGCAACCCGAAGATTTCGCAACCTACTACTGCCAGCA GTCCTATAAGTACCCCTGGACTTTCGGACAAGGCACCAAGCTCGAGATCAAGCGGACCGTGGCCGCC CCGAGCGTGTTTATCTTCCCGCCATCTGACGAACAGCTGAAGTCCGGGACAGCGTCCGTGGTCTGCC TGCTCAACAACTTCTACCCCCGCGAGGCCAAAGTGCAGTGGAAAGTCGATAACGCGCTGCAGTCCGG AAACAGCCAGGAAAGCGTGACTGAGCAAGACTCCAAGGACTCCACCTACTCCCTGTCATCCACCCTG ACGCTGTCCAAGGCCGACTACGAAAAGCACAAGGTCTACGCCTGCGAAGTGACCCATCAGGGCCTGT CAAGCCCTGTGACCAAGTCGTTCAACCGGGGAGAGTGTTAA
415	PI-3039-AB HC cDNA	ATGGACTGGACCTGGAGATTTTTATTCGTCGTCGCTGCCGCCACCGGAGTGCAATCACAAGTACAAC TGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCCGGCGCCTCCGTGAAAATCTCGTGCAAAGCCTCGGG TTACACATTCACTGACTACGCAGTGAACTGGGTCAGACAGGCACCGGGCCAGGGACTCGAGTGGATG GGCTGGATCAACACTCAGACTGGGAAGCCCACCTATGCTCAGAAGTTCCAGGGAAGGTTCACCTTTA CCTTGGACACCAGCACCTCCACCGCGTACTTGGAAATTAGCAGCCTGCGGTCCGAAGATACAGCCGT GTACTATTGTACTAGGGACTCCTACTACTACTCATCCTCGCTCGACTACTGGGGCCAGGGTACCCTC

		GTGACCGTTAGCTCGGCCTCTACTAAGGGTCCGTCCGTGTTCCCGTTGGCCCCGAGCTCGAAGTCCA CCTCCGGGGGAACCGCTGCGCTTGGATGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACGGTGTC CTGGAACTCCGGGGCCCTGACCTCGGGAGTGCACACTTTCCCTGCGGTGCTGCAGAGCTCAGGACTG TACAGCCTCAGCTCCGTCGTGACCGTGCCTTCGTCCTCGCTGGGCACCCAGACCTACATCTGCAACG TGAACCACAAGCCGAGCAACACCAAGGTCGACAAGAAAGTCGAGCCGAAGTCATGCGACAAGACTCA CACTTGCCCGCCGTGCCCCGCGCCTGAGCTTCTTGGCGGGCCCTCCGTGTTCCTGTTTCCGCCAAAG CCCAAGGATACTCTGATGATTTCGCGGACTCCTGAAGTGACCTGTGTGGTCGTCGATGTGTCCCATG AGGACCCCGAGGTCAAGTTCAATTGGTACGTGGACGGCGTGGAGGTCCACAATGCCAAGACGAAGCC GCGGGAAGAACAGTACAACTCCACTTATCGCGTGGTGTCCGTGCTCACCGTGCTGCATCAGGACTGG CTGAACGGAAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCCCTGCCTGCCCCAATTGAAAAGACCA TCTCAAAAGCGAAGGGCCAGCCGCGCGAACCACAAGTGTACACCCTGCCTCCTTCCCGGGATGAACT GACCAAGAACCAAGTGTCCCTGACTTGCCTCGTGAAGGGTTTCTACCCGTCCGACATCGCCGTGGAA TGGGAGAGCAACGGACAGCCCGAGAACAATTACAAGACTACCCCACCCGTGCTCGATTCGGACGGCA GCTTCTTCCTGTACTCCAAGCTGACCGTGGATAAGTCCCGCTGGCAACAGGGAAACGTGTTCAGTTG TTCCGTGATGCACGAAGCCCTGCACAACCACTACACCCAGAAGTCACTGTCCCTGTCTCCGGGAAAA TAA
416	PI-3039-AB LC cDNA	ATGGATATGAGAGTGCCTGCACAACTTCTTGGATTACTGCTGCTTTGGTTGTCGGGAGCCAGATGCG ATATCCAGATGACCCAGTCCCCGTCGAGCCTGTCAGCTTCCGTGGGCGACCGGGTCACCATTACTTG TCGCGCCTCGGCCGGTATTAGCAATGACTTGGCCTGGTACCAGCAGAAGCCTGGGAAGGCCCCCAAG CTCCTCATCTACGCGGCTTCCCGCCTGCAAGACGGCGTGCCGTCAAGGTTCAGCGGTTCGGGCTCCG GAACTGACTTCACCCTCACTATCTCGTCCCTGCAACCCGAAGATTTCGCAACCTACTACTGCCAGCA GTCCTATAAGTACCCCTGGACTTTCGGACAAGGCACCAAGCTCGAGATCAAGCGGACCGTGGCCGCC CCGAGCGTGTTTATCTTCCCGCCATCTGACGAACAGCTGAAGTCCGGGACAGCGTCCGTGGTCTGCC TGCTCAACAACTTCTACCCCCGCGAGGCCAAAGTGCAGTGGAAAGTCGATAACGCGCTGCAGTCCGG AAACAGCCAGGAAAGCGTGACTGAGCAAGACTCCAAGGACTCCACCTACTCCCTGTCATCCACCCTG ACGCTGTCCAAGGCCGACTACGAAAAGCACAAGGTCTACGCCTGCGAAGTGACCCATCAGGGCCTGT CAAGCCCTGTGACCAAGTCGTTCAACCGGGGAGAGTGTTAA
417	PI-3040-AB HC cDNA	ATGGACTGGACCTGGAGATTTTTATTCGTCGTCGCTGCCGCCACCGGAGTGCAATCACAAGTACAAC TGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCCGGCGCCTCCGTGAAAGTGTCGTGCAAAGCCTCGGG TTACACATTCACTGACTACGCAGTGAACTGGGTCAGACAGGCACCGGGCCAGGGACTCGAGTGGATG GGCTGGATCAACACTCAGACTGGGAAGCCCACCTATGCTCAGAAGTTCCAGGGAAGGGTCACCATGA CCTTGGACACCAGCACCTCCACCTCCTACATGGAATTGAGCAGCCTGCGGTCCGAAGATACAGCCGT GTACTATTGTACTAGGGACTCCTACTACTACTCATCCTCGCTCGACTACTGGGGCCAGGGTACCCTC GTGACCGTTAGCTCGGCCTCTACTAAGGGTCCGTCCGTGTTCCCGTTGGCCCCGAGCTCGAAGTCCA CCTCCGGGGGAACCGCTGCGCTTGGATGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACGGTGTC CTGGAACTCCGGGGCCCTGACCTCGGGAGTGCACACTTTCCCTGCGGTGCTGCAGAGCTCAGGACTG TACAGCCTCAGCTCCGTCGTGACCGTGCCTTCGTCCTCGCTGGGCACCCAGACCTACATCTGCAACG TGAACCACAAGCCGAGCAACACCAAGGTCGACAAGAAAGTCGAGCCGAAGTCATGCGACAAGACTCA CACTTGCCCGCCGTGCCCCGCGCCTGAGCTTCTTGGCGGGCCCTCCGTGTTCCTGTTTCCGCCAAAG CCCAAGGATACTCTGATGATTTCGCGGACTCCTGAAGTGACCTGTGTGGTCGTCGATGTGTCCCATG AGGACCCCGAGGTCAAGTTCAATTGGTACGTGGACGGCGTGGAGGTCCACAATGCCAAGACGAAGCC GCGGGAAGAACAGTACAACTCCACTTATCGCGTGGTGTCCGTGCTCACCGTGCTGCATCAGGACTGG CTGAACGGAAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCCCTGCCTGCCCCAATTGAAAAGACCA TCTCAAAAGCGAAGGGCCAGCCGCGCGAACCACAAGTGTACACCCTGCCTCCTTCCCGGGATGAACT GACCAAGAACCAAGTGTCCCTGACTTGCCTCGTGAAGGGTTTCTACCCGTCCGACATCGCCGTGGAA TGGGAGAGCAACGGACAGCCCGAGAACAATTACAAGACTACCCCACCCGTGCTCGATTCGGACGGCA GCTTCTTCCTGTACTCCAAGCTGACCGTGGATAAGTCCCGCTGGCAACAGGGAAACGTGTTCAGTTG TTCCGTGATGCACGAAGCCCTGCACAACCACTACACCCAGAAGTCACTGTCCCTGTCTCCGGGAAAA TAA
418	PI-3040-AB LC cDNA	ATGGATATGAGAGTGCCTGCACAACTTCTTGGATTACTGCTGCTTTGGTTGTCGGGAGCCAGATGCG ATATCCAGATGACCCAGTCCCCGTCGAGCCTGTCAGCTTCCGTGGGCGACCGGGTCACCATTACTTG TCGCGCCTCGGCCGGTATTAGCAATGACTTGGCCTGGTACCAGCAGAAGCCTGGGAAGGCCCCCAAG CTCCTCATCTACGCGGCTTCCCGCCTGCAAGACGGCGTGCCGTCAAGGTTCAGCGGTTCGGGCTCCG GAACTGACTTCACCCTCACTATCTCGTCCCTGCAACCCGAAGATTTCGCAACCTACTACTGCCAGCA GTCCTATAAGTACCCCTGGACTTTCGGACAAGGCACCAAGCTCGAGATCAAGCGGACCGTGGCCGCC CCGAGCGTGTTTATCTTCCCGCCATCTGACGAACAGCTGAAGTCCGGGACAGCGTCCGTGGTCTGCC TGCTCAACAACTTCTACCCCCGCGAGGCCAAAGTGCAGTGGAAAGTCGATAACGCGCTGCAGTCCGG AAACAGCCAGGAAAGCGTGACTGAGCAAGACTCCAAGGACTCCACCTACTCCCTGTCATCCACCCTG ACGCTGTCCAAGGCCGACTACGAAAAGCACAAGGTCTACGCCTGCGAAGTGACCCATCAGGGCCTGT CAAGCCCTGTGACCAAGTCGTTCAACCGGGGAGAGTGTTAA
419	PI-3041-AB	ATGGACTGGACCTGGAGATTTTTATTCGTCGTCGCTGCCGCCACCGGAGTGCAATCACAAGTACAAC

	HC cDNA	TGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCCGGCGCCTCCGTGAAAATCTCGTGCAAAGCCTCGGG TTACACATTCACTGACTACGCAGTGAACTGGGTCAGACAGGCACCGGGCCAGGGACTCGAGTGGATG GGCTGGATCAACACTCAGACTGGGAAGCCCACCTATGCTCAGAAGTTCCAGGGAAGGTTTACCTTCA CCCTCGACACCAGCACCTCCACCTCCTACTTGGAAATTAGCAGCCTGCGGTCCGAAGATACAGCCGT GTACTATTGTACTAGGGACTCCTACTACTACTCATCCTCGCTCGACTACTGGGGCCAGGGTACCCTC GTGACCGTTAGCTCGGCCTCTACTAAGGGTCCGTCCGTGTTCCCGTTGGCCCCGAGCTCGAAGTCCA CCTCCGGGGGGAACCGCTGCGCTTGGATGCCTGGTCAAGGACTACTTCCCCGAGCCCGTGACGGTGTC CTGGAACTCCGGGGCCCTGACCTCGGGAGTGCACACTTTCCCTGCGGTGCTGCAGAGCTCAGGACTG TACAGCCTCAGCTCCGTCGTGACCGTGCCTTCGTCCTCGCTGGGCACCCAGACCTACATCTGCAACG TGAACCACAAGCCGAGCAACACCAAGGTCGACAAGAAAGTCGAGCCGAAGTCATGCGACAAGACTCA CACTTGCCCGCCGTGCCCCGCGCCTGAGCTTCTTGGCGGGCCCTCCGTGTTCCTGTTTCCGCCAAAG CCCAAGGATACTCTGATGATTTCGCGGACTCCTGAAGTGACCTGTGTGGTCGTCGATGTGTCCCATG AGGACCCCGAGGTCAAGTTCAATTGGTACGTGGACGGCGTGGAGGTCCACAATGCCAAGACGAAGCC GCGGGAAGAACAGTACAACTCCACTTATCGCGTGGTGTCCGTGCTCACCGTGCTGCATCAGGACTGG CTGAACGGAAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCCCTGCCTGCCCCAATTGAAAAGACCA TCTCAAAAGCGAAGGGCCAGCCGCGCGAACCACAAGTGTACACCCTGCCTCCTTCCCGGGATGAACT GACCAAGAACCAAGTGTCCCTGACTTGCCTCGTGAAGGGTTTCTACCCGTCCGACATCGCCGTGGAA TGGGAGAGCAACGGACAGCCCGAGAACAATTACAAGACTACCCCACCCGTGCTCGATTCGGACGGCA GCTTCTTCCTGTACTCCAAGCTGACCGTGGATAAGTCCCGCTGGCAACAGGGAAACGTGTTCAGTTG TTCCGTGATGCACGAAGCCCTGCACAACCACTACACCCAGAAGTCACTGTCCCTGTCTCCGGGAAAA TAA
420	PI-3041-AB LC cDNA	ATGGATATGAGAGTGCCTGCACAACTTCTTGGATTACTGCTGCTTTGGTTGTCGGGAGCCAGATGCG ATATCCAGATGACCCAGTCCCCGTCGAGCCTGTCAGCTTCCGTGGGCGACCGGGTCACCATTACTTG TCGCGCCTCGGCCGGTATTAGCAATGACTTGGCCTGGTACCAGCAGAAGCCTGGGAAGGCCCCCAAG CTCCTCATCTACGCGGCTTCCCGCCTGCAAGACGGCGTGCCGTCAAGGTTCAGCGGTTCGGGCTCCG GAACTGACTTCACCCTCACTATCTCGTCCCTGCAACCCGAAGATTTCGCAACCTACTACTGCCAGCA GTCCTATAAGTACCCCTGGACTTTCGGACAAGGCACCAAGCTCGAGATCAAGCGGACCGTGGCCGCC CCGAGCGTGTTTATCTTCCCGCCATCTGACGAACAGCTGAAGTCCGGGACAGCGTCCGTGGTCTGCC TGCTCAACAACTTCTACCCCCGCGAGGCCAAAGTGCAGTGGAAAGTCGATAACGCGCTGCAGTCCGG AAACAGCCAGGAAAGCGTGACTGAGCAAGACTCCAAGGACTCCACCTACTCCCTGTCATCCACCCTG ACGCTGTCCAAGGCCGACTACGAAAAGCACAAGGTCTACGCCTGCGAAGTGACCCATCAGGGCCTGT CAAGCCCTGTGACCAAGTCGTTCAACCGGGGAGAGTGTTAA
421	PI-3028-AB HC cDNA	ATGGATTGGACTTGGAGATTTTTGTTTGTGGTGGCGGCGGCCACTGGAGTGCAATCCGAAGTGCAAT TGGTGGAATCGGGTGGTGGACTTGTGCAGCCTGGATCGTCACTTAAGCTGTCCTGTGTGGCCTCGAA GTTTACCTTCTCCAACTATGGGATGAACTGGATTAGACAAGCCCCGAAGAAGGGACTGGAATGGATT GCGCTGATCTATTACAACTCGAACAACAAGTACTACGCTGATTCCGTGAAGGGTCGCTTCACTATTT CCCGCGACAACTCGAAGAACACTCTGTACCTTGAGATGAACTCCCTGCGCTCGGAAGATACTGCCAT GTACTACTGTGCCAAGTCGCTGACTGGCGGATCCGATTACTTCGATTCCTGGGGACAAGGAGTGATG GTCACTGTATCCAGTGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCA CCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC GTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCA CACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAA CCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACG AAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC GCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGG CTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCT GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCT CCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCGGGTAAA TAG
422	PI-3028-AB LC cDNA	ATGGACATGCGCGTGCCTGCGCAATTGCTGGGGCTGCTTCTCCTGTGGCTTTCGGGAGCCCGCTGCG ACGTGCAGATGACCCAGTCCCCTTCCTACCTGGCTGCGTCACCGGGAGAATCAGTGTCCATCAGCTG CAAGGCCTCCAAGTCCATTGGTACCTTCCTGGCCTGGTACCAAGAGAAGCCTGAAAAGACCAACAAG CTCCTGATCTACTCGGGATCAACCCTGCAATCCGGCACTCCGTCGCGGTTCTCCGGATCCGGGTCCG GCACCGACTTTACTCTGACCATTCGGAACCTGGAACCCGAAGATTTCGCCGTGTACTACTGTCAGCA GCACGACGAATACCCGTTTACTTTCGGCTCCGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC

		TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
423	PI-3029-AB HC cDNA	ATGGATTGGACTTGGAGATTTTTGTTTGTGGTGGCGGCGGCCACTGGAGTGCAATCCGAAGTGCAAT TGGTGGAATCGGGTGGTGGACTTGTGCAGCCTGGATCGTCACTTAAGCTGTCCTGTGTGGCCTCGAA GTTTACCTTCTCCAACTATGGGATGAACTGGATTAGACAAGCCCCGAAGAAGGGACTGGAATGGATT GCGCTGATCTATTACAACTCGAACAACAAGTACTACGCTGATTCCGTGAAGGGTCGCTTCACTATTT CCCGCGACAACTCGAAGAACACTCTGTACCTTGAGATGAACTCCCTGCGCTCGGAAGATACTGCCAT GTACTACTGTGCCAAGTCGCTGACTGGCGGATCCGATTACTTCGATTCCTGGGGACAAGGAGTGATG GTCACTGTATCCAGTGCCAGCACAAAGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCA CCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC GTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACG TAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCC ATCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCCAAAACCCAAGGAC ACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCG AGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGA GCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGC AAGGAGTACAAGTGCAAGGTCAGCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAG CCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAA CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC TCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGAT GCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATAG
424	PI-3029-AB LC cDNA	ATGGACATGCGCGTGCCTGCGCAATTGCTGGGGCTGCTTCTCCTGTGGCTTTCGGGAGCCCGCTGCG ACGTGCAGATGACCCAGTCCCCTTCCTACCTGGCTGCGTCACCGGGAGAATCAGTGTCCATCAGCTG CAAGGCCTCCAAGTCCATTGGTACCTTCCTGGCCTGGTACCAAGAGAAGCCTGAAAAGACCAACAAG CTCCTGATCTACTCGGGATCAACCCTGCAATCCGGCACTCCGTCGCGGTTCTCCGGATCCGGGTCCG GCACCGACTTTACTCTGACCATTCGGAACCTGGAACCCGAAGATTTCGCCGTGTACTACTGTCAGCA GCACGACGAATACCCGTTTACTTTCGGCTCCGGCACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
425	PI-3031-AB HC cDNA	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCACAAGTCAACC TTCTGCAATCCCGGGCAGCACTCGTGAAGCCCGGTGCTTCAGTGAAGCTGAGCTGCAAGGCCTCCGG GTACACCTTCACCGACTACTATCTGCATTGGGTCAAGCAGTCCCACGCCAAGAGCCTGGAGTGGATT GGCTACATCAACCCGAACAACGCCTACACCTCGTACAATGAGAAGTTCAAGTCCAAAGCGACCCTGA CCGTGGATAAGTCCACTAACACCGCCTACATGGAACTGTCCAGACTCACGTCCGCCGACTCGGCCAC CTATTACTGTGCCCGGGACACCACAGACTACTACAACCTCCACTTCGCCTACTGGGGCCAGGGAACT CTGGTCACCGTGTCGAGCGCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGA GCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGT GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGA CTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCA ACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAAC TCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCA AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCC ACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA GCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCAGCAACAAAGCCCTCCCAGCCCCCATCGAGAAAA CCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGA GCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG GAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACG GCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCCCTCTCCCTGTCTCCGGGT AAATAG
426	PI-3031-AB LC cDNA	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGTG ACATTCAAATGACCCAGTCCCCTGCATCACTGAGCGCCTCACTGGGGGAAACTGTCAGCATTGAGTG CCTGACCTCCGAGGGAATCTCGAACGACCTGGCCTGGTATCAGCAGAAGTCCGGAAAGTCGCCGCAG

		CTGCTTATCTACGACGCCAGCAGACTCGAGGACGGCGTGCCCTCCCGCTTTTCCGGCTCTGGTTCCG GCACTCGGTACAGCCTGAAGATCTCCGGAATGCAGACCGAAGATGAAGCTGACTACTTCTGCCAACA ATCGTACAAATACCCACTGACCTTCGGTTCCGGGACCAAGCTCGAAATCAAGCGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCC TGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA
427	HC signal peptide sequence	ATGGATTGGACTTGGCGCTTCTTGTTTGTGGTGGCGGCGGCTACTGGAGTGCAGTCA
428	HC signal peptide sequence	MDWTWRFLFVVAAATGVQS
429	LC signal peptide sequence	MDMRVPAQLLGLLLLWLSGARC
430	LC signal peptide sequence	ATGGATATGCGGGTGCCGGCCCAGCTTCTGGGCCTGTTGCTGCTCTGGCTCTCCGGAGCGCGCTGT
431	CDR L1	ASEGISNDLA
432	CDR L1	ASAGISNDLA
433	CDR L1	ASKSIGTFLA
434	PI-3025-AB2 Heavy Chain Variable	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
435	PI-3025-AB2 CDR-H1	GFSLTSYHVS
436	PI-3025-AB2 CDR-H2	AIWTGGSIA
437	PI-3025-AB2 CDR-H3	DLSDYYSSYTSFDY
438	PI-3025-AB2 Heavy chain	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
439	PI-3025-AB2 Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIK
440	PI-3025-AB2 CDR-L1	RASEGISNDLA
441	PI-3025-AB2 CDR-L2	AASRLQD
442	PI-3025-AB2 CDR-L3	QQSYKYPLT
443	PI-3025-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
444	PI-3048-AB Heavy Chain Variable	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
445	PI-3048-AB CDR-H1	GFSLTSYHVS
446	PI-3048-AB CDR-H2	AIWTGGSIA

447	PI-3048-AB CDR-H3	DLSDYYSSYTSFDY
448	PI-3048-AB Heavy chain	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWIGAIWTGGSIAYNPSLKSRV TISRDTSKNQVSLKLSSVTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTK TYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLGK
449	PI-3048-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIK
450	PI-3048-AB CDR-L1	RASEGISNDLA
451	PI-3048-AB CDR-L2	AASRLQD
452	PI-3048-AB CDR-L3	QQSYKYPLT
453	PI-3048-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDYTLTISSLQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
454	PI-3041-AB Heavy Chain Variable	QVQLVQSGAEVKKPGASVKISCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR FTFTLDTSTSTSYLEISSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSS
455	PI-3041-AB CDR-H1	GYTFTDYAVN
456	PI-3041-AB CDR-H2	WINTQTGKPT
457	PI-3041-AB CDR-H3	DSYYYSSSLDY
458	PI-3041-AB Heavy chain	QVQLVQSGAEVKKPGASVKISCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR FTFTLDTSTSTSYLEISSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
459	PI-3041-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIK
460	PI-3041-AB CDR-L1	RASAGISNDLA
461	PI-3041-AB CDR-L2	AASRLQD
462	PI-3041-AB CDR-L3	QQSYKYPWT
463	PI-3041-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
464	PI-3047-AB Heavy Chain Variable	EVQLVQSGAEVKKPGASVKISCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR FTFTLDTSTSTSYLEISSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSS
465	PI-3047-AB CDR-H1	GYTFTDYAVN
466	PI-3047-AB CDR-H2	WINTQTGKPT
467	PI-3047-AB	DSYYYSSSLDY

	CDR-H3	
468	PI-3047-AB Heavy chain	EVQLVQSGAEVKKPGASVKISCKASGYTFTDYAVNWVRQAPGQGLEWMGWINTQTGKPTYAQKFQGR FTFTLDTSTSTSYLEISSLRSEDTAVYYCTRDSYYYSSSLDYWGQGTLVTVSSASTKGPSVFPLAPC SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTY TCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKT ISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
469	PI-3047-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIK
470	PI-3047-AB CDR-L1	RASAGISNDLA
471	PI-3047-AB CDR-L2	AASRLQD
472	PI-3047-AB CDR-L3	QQSYKYPWT
473	PI-3047-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASAGISNDLAWYQQKPGKAPKLLIYAASRLQDGVPSRFSGSGS GTDFTLTISSMQPEDFATYYCQQSYKYPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
474	PI-3046-AB Heavy Chain Variable	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNPSLKSRL TISRDTSKNQVSLKMSSLTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSS
475	PI-3046-AB CDR-H1	GFSLTSYHVS
476	PI-3046-AB CDR-H2	AIWTGGSIA
477	PI-3046-AB CDR-H3	DLSDYYSSYTSFDY
478	PI-3046-AB Heavy chain	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSYHVSWVRQPPGKGLEWMGAIWTGGSIAYNPSLKSRL TISRDTSKNQVSLKMSSLTAADTAVYYCARDLSDYYSSYTSFDYWGQGTLVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTK TYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
479	PI-3046-AB Light Chain Variable	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSMQPEDFATYYCQQSYKYPLTFGQGTKLEIK
480	PI-3046-AB CDR-L1	RASEGISNDLA
481	PI-3046-AB CDR-L2	AASRLQD
482	PI-3046-AB CDR-L3	QQSYKYPLT
483	PI-3046-AB Light chain	DIQMTQSPSSLSASVGDRVTITCRASEGISNDLAWYQQKPGKAPKLLIYAASRLQSGVPSRFSGSGS GTDYTLTISSMQPEDFATYYCQQSYKYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC

CLAIMS

1. An isolated antibody or antigen binding fragment thereof that binds to a Scavenger Receptor Cysteine-Rich (SRCR) domain (residues 424-519 of SEQ ID NO: 384) of human Macrophage Receptor with Collagenous Structure (MARCO) (SEQ ID NO: 384).

2. The isolated antibody of claim 1, wherein the antibody comprises a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2),

b. CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3),

c. CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4),

d. CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L),

e. CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and

f. CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

3. The isolated antibody of claim 1 or 2, wherein the antibody or antigen binding fragment thereof binds to at least one of the following residues: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of MARCO (SEQ ID NO: 384).

4. The isolated antibody of claims 1-3, wherein the antibody or antigen binding fragment comprises a chimeric, human, humanized, or rat antibody or antigen binding fragment.

5. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2),

b. CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3),

c. CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4),

d. CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L) ,

e. CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and

f. CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

6. The isolated antibody of claim 5, wherein: CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431).

7. The isolated antibody of claim 5, wherein: CDR-L1 comprises the sequence RASEGISNDLA (SEQ ID NO: 27).

8. The isolated antibody of claim 5, wherein: CDR-L1 comprises the sequence LASEGISNDLA (SEQ ID NO: 7).

9. The isolated antibody of any one of claims 5-7, wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 61.

10. The isolated antibody of any one of claims 5-7, wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 111.

11. The isolated antibody of any one of claims 5-8, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474.

12. The isolated antibody of any one of claims 5-11, wherein the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

13. The isolated antibody of any one of claims 5-11, wherein the VL sequence comprises the VL sequence set forth in SEQ ID NO: 116.

14. The isolated antibody of any one of claims 5-11, wherein the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

15. The isolated antibody of any one of claims 5-14, wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 61; and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

16. The isolated antibody of any one of claims 5-14, wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 111; and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 116.

17. The isolated antibody of any one of claims 5-14, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474 and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

18. The isolated antibody of any one of claims 5-14, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474 and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

19. The isolated antibody of any one of claims 5-18, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 65.

20. The isolated antibody of any one of claims 5-18, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 115.

21. The isolated antibody of any one of claims 5-20, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478.

22. The isolated antibody of any one of claims 5-21, wherein the antibody comprises a light chain sequence as set forth in SEQ ID NO: 70.

23. The isolated antibody of any one of claims 5-21, wherein the antibody comprises a light chain sequence as set forth in SEQ ID NO: 120.

24. The isolated antibody of any of claims 5-23, wherein the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

25. The isolated antibody of any one of claims 5-24, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 65; and a light chain sequence as set forth in SEQ ID NO: 70.

26. The isolated antibody of any one of claims 5-24, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 115; and a light chain sequence as set forth in SEQ ID NO: 120.

27. The isolated antibody of any one of claims 5-24, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478; and a light chain sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

28. The isolated antibody of any one of claims 5-24, wherein the antibody comprises a heavy chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478; and/or a light chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

29. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GYTFTDYAVN (SEQ ID NO: 232),

b. CDR-H2 comprises the sequence WINTQTGKPT (SEQ ID NO: 233),

c. CDR-H3 comprises the sequence DSYYYSSSLDY (SEQ ID NO: 234),

d. CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432) or XASAGISNDLA (SEQ ID NO: 381), wherein X is arginine (R) or leucine (L),

e. CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 238), and

f. CDR-L3 comprises the sequence QQSYKYPWT (SEQ ID NO: 239).

30. The isolated antibody of claim 29, wherein: CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432).

31. The isolated antibody of claim 29, wherein: CDR-L1 comprises the sequence RASAGISNDLA (SEQ ID NO: 317).

32. The isolated antibody of claim 29, wherein: CDR-L1 comprises the sequence LASAGISNDLA (SEQ ID NO: 237).

33. The isolated antibody of any one of claims 29-32, wherein the VH sequence comprises the VH sequence as set forth in SEQ ID NO: 454.

34. The isolated antibody of any one of claims 29-32, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464.

35. The isolated antibody of any one of claims 29-34, wherein the VL sequence comprises the VL sequence as set forth in SEQ ID NO: 459.

36. The isolated antibody of any one of claims 29-34, wherein the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

37. The isolated antibody of any one of claims 29-36, wherein the VH sequence comprises the VH sequence as set forth in SEQ ID NO: 454; and the VL sequence comprises the VL sequence as set forth in SEQ ID NO: 459.

38. The isolated antibody of any one of claims 29-36, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464, and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

39. The isolated antibody of any one of claims 29-36, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464; and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

40. The isolated antibody of any one of claims 29-38 wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 458.

41. The isolated antibody of any one of claims 29-38, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468.

42. The isolated antibody of any one of claims 29-41 wherein the antibody comprises a light chain sequence as set forth in SEQ ID NO: 463.

43. The isolated antibody of any one of claims 29-41, wherein the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

44. The isolated antibody of any one of claims 29-43, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 458; and a light chain sequence as set forth in SEQ ID NO: 463.

45. The isolated antibody of any one of claims 29-43, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468; and a light chain sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

46. The isolated antibody of any one of claims 29-43, wherein the antibody comprises a heavy chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468; and/or a light chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

47. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence KFTFSNYGMN (SEQ ID NO: 142),

b. CDR-H2 comprises the sequence LIYYNSNNKY (SEQ ID NO: 143),

c. CDR-H3 comprises the sequence SLTGGSDYFDS (SEQ ID NO: 144),

d. CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433) or XASKSIGTFLA (SEQ ID NO: 382), wherein X is arginine (R) or lysine (K),

e. CDR-L2 comprises the sequence SGSTLQS (SEQ ID NO: 148), and

f. CDR-L3 comprises the sequence QQHDEYPFT (SEQ ID NO: 149).

48. The isolated antibody of claim 47, wherein: CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433).

49. The isolated antibody of claim 47, wherein: CDR-L1 comprises the sequence KASKSIGTFLA (SEQ ID NO: 147).

50. The isolated antibody of claim 47, wherein: CDR-L1 comprises the sequence RASKSIGTFLA (SEQ ID NO: 157).

51. The isolated antibody of any one of claims 47-50, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221.

52. The isolated antibody of any one of claims 47-51, wherein the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

53. The isolated antibody of any one of claims 47-52, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221 and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

54. The isolated antibody of any one of claims 47-52, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221 and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

55. The isolated antibody of any one of claims 47-54, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225.

56. The isolated antibody of any one of claims 47-55, wherein the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

57. The isolated antibody of any one of claims 47-56, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225 and a light chain sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

58. The isolated antibody of any one of claims 47-54, wherein the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225 and/or a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

59. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising ~~a~~ a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GYTFTDYYLH (SEQ ID NO: 252),

b. CDR-H2 comprises the sequence YINPNNAYTS (SEQ ID NO: 253),

c. CDR-H3 comprises the sequence DTTDYYNLHFAY (SEQ ID NO: 254),

d. CDR-L1 comprises the sequence LTSEGISNDLA (SEQ ID NO: 257),

e. CDR-L2 comprises the sequence DASRLED (SEQ ID NO: 258), and

f. CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 259).

60. The isolated antibody of claim 59, wherein the VH sequence comprises a sequence as set forth in SEQ ID NO: 251 or 261.

61. The isolated antibody of claim 59 or 60, wherein the VL sequence comprises a sequence as set forth in SEQ ID NO: 256 or 266.

62. The isolated antibody of any one of claims 59-61, wherein the VH sequence comprises a sequence as set forth in SEQ ID NO: 251 or 261, and the VL sequence comprises a sequence s set forth in SEQ ID NO: 256 or 266.

63. The isolated antibody of any one of claims 59-61, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence as set forth in

SEQ ID NO: 251 or 261, and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence set forth in SEQ ID NO: 256 or 266.

64. The isolated antibody of any one of claims 59-62, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 255 or 265.

65. The isolated antibody of any one of claims 59-64, wherein the antibody comprises a light chain sequence as set forth in SEQ ID NO: 260 or 270.

66. The isolated antibody of any one of claims 59-65, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 255 or 265; and a light chain sequence as set forth in SEQ ID NO: 260 or 270.

67. The isolated antibody of any one of claims 59-65, wherein the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 255 or 265; and a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 260 or 270.

68. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising ~~a~~ a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GFSLTSYTLS (SEQ ID NO: 362),

b. CDR-H2 comprises the sequence AIWGGDNTD (SEQ ID NO: 363),

c. CDR-H3 comprises the sequence ELGGSFDY (SEQ ID NO: 364),

d. CDR-L1 comprises the sequence KTSQNINKKLD (SEQ ID NO: 367),

e. CDR-L2 comprises the sequence YTNNLQT (SEQ ID NO: 368), and

f. CDR-L3 comprises the sequence YQYDSGFT (SEQ ID NO: 369).

69. The isolated antibody of claim 68, wherein the VH sequence comprises a sequence as set forth in SEQ ID NO: 361 or 371.

70. The isolated antibody of claim 68 or 69, wherein the VL sequence comprises a sequence as set forth in SEQ ID NO: 366 or 376.

71. The isolated antibody of any one of claims 68-70, wherein the VH sequence comprises a sequence as set forth in SEQ ID NO: 361 or 371, and the VL sequence comprises a sequence s set forth in SEQ ID NO: 366 or 376.

72. The isolated antibody of any one of claims 68-70, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence as set forth in SEQ ID NO: 361 or 371, and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence set forth in SEQ ID NO: 366 or 376.

73. The isolated antibody of any one of claims 68-72, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 365 or 375; and a light chain sequence as set forth in SEQ ID NO: 370 or 380.

74. The isolated antibody of any one of claims 68-72, wherein the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 365 or 375; and a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 370 or 380.

75. The isolated antibody of any of the above claims, wherein the antibody is a monoclonal antibody, a neutral antibody, an antagonistic antibody, an agonist antibody, a polyclonal antibody, an afucosylated antibody, a human antibody, a humanized antibody, a chimeric antibody, a full-length antibody, and an scFv.

76. The isolated antibody of any of the above claims, wherein the antibody is an scFv.

77. The isolated antibody of any of the above claims, wherein the antibody is a monoclonal antibody.

78. The isolated antibody of any of the above claims wherein the antibody is a humanized antibody.

79. The isolated antibody of any of the above claims wherein the antibody is a human antibody.

80. The isolated antibody of any of the above claims, wherein the antibody comprises an Fc region.

81. The isolated antibody of any of the above claims, wherein the Fc region comprises a human Fc region.

82. The isolated antibody of any of the above claims, wherein the antibody comprises an active human Fc region.

83. The isolated antibody of any of the above claims, wherein the antibody comprises a heavy chain human constant region of a class selected from IgG, IgA, IgD, IgE, and IgM.

84. The isolated antibody of any of the above claims, wherein the antibody comprises a human heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4.

85. The isolated antibody of claim 84, wherein the human Fc region comprises a wild-type, human IgG1 Fc region.

86. The isolated antibody of claim 84, wherein the human Fc region comprises a wild-type, human IgG4 Fc region.

87. The isolated antibody of any one of claims 80-86, wherein the Fc region comprises one or more amino acid substitutions, wherein the one or more substitutions result in increased antibody half-life, increased ADCC activity, increased ADCP activity, increased CDC activity, decreased ADCC activity, decreased ADCP activity, or decreased CDC activity compared with an Fc region without the one or more substitutions.

88. The isolated antibody of any one of claims 80-84, wherein the Fc region binds an Fcγ Receptor selected from the group consisting of: FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb.

89. The isolated antibody of any of the above claims, wherein the antibody binds to human MARCO with a K_D of less than or equal to about 0.5, 1, 2, 3, 4, 5, 6, or $7x10^{-9}$ M, as measured by surface plasmon resonance (SPR) assay.

90. The isolated antibody of any of the above claims, wherein binding of the antibody to human MARCO is divalent cation dependent.

91. The isolated antibody of any one of claim 1-89, wherein binding of the antibody to human MARCO is divalent cation independent.

92. The isolated antibody of claim 90 or 91, wherein the divalent cation comprises $Ca2^+$ or $Mg2^+$.

93. The isolated antibody of any of the above claims, wherein the antibody binds an extracellular domain of human MARCO.

94. The isolated antibody of any of the above claims, wherein the antibody binds to soluble MARCO.

95. The isolated antibody of any of the above claims, wherein the antibody binds the SRCR domain of human MARCO, cynomolgus MARCO, or human and cynomolgus MARCO.

96. The isolated antibody of claim 95, wherein the antibody binds the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

97. The isolated antibody of claim 96, wherein the antibody or antigen binding fragment thereof binds to at least one of: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of MARCO (SEQ ID NO: 384).

98. The isolated antibody of any of the above claims, wherein the antibody has receptor-ligand blocking activity.

99. The isolated antibody of any of the above claims, wherein the antibody induces increased expression of at least one cytokine or chemokine upon contact with a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

100. The isolated antibody of claim 99, wherein the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

101. The isolated antibody of any of the above claims, wherein upon cell contact the antibody induces increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

102. The isolated antibody of any of the above claims, wherein upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

103. The isolated antibody of any of the above claims, wherein upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src

signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

104. The isolated antibody of any of the above claims, wherein upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

105. The isolated antibody of any of the above claims, wherein upon cell contact the antibody induces repolarization of myeloid M2-like TAMS to M1-like tumor associated macrophages (TAMs), and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

106. The isolated antibody of any of the above claims, wherein upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, $MHCII^{high}$ monocytes, or $MHCII^{mid}$ monocytes as compared to an isotype control antibody.

107. The isolated antibody of any of the above claims, wherein upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

108. The isolated antibody of any of the above claims, wherein upon cell contact the antibody decreases TAMs, tumor associated neutrophils (TANs), plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

109. The isolated antibody of any of the above claims, wherein upon administration to a subject the antibody induces an increased anti-tumor memory response as compared to an isotype control antibody.

110. The isolated antibody of any of the above claims, wherein a cell is a MARCO+ cell.

111. The isolated antibody of any of the above claims, wherein the cell is a human MARCO+ cell.

112. The isolated antibody of claim 110 or 111, wherein the MARCO + cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

113. The isolated antibody of claim 112, wherein the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

114. The isolated antibody of any of the above claims, wherein the antibody binds to MARCO on the cell surface of a MARCO+ cell.

115. The isolated antibody of any one of the above claims, wherein the antibody:

a. competes for binding to human MARCO with humanized PI-HX-3011, PI-HX-3031, PI-HX-3043, PI-HX-3061, PI-HX-3092 antibody;

b. binds to human MARCO;

c. binds to cynomolgus MARCO;

d. binds to human and cynomolgus MARCO;

e. binds to the SRCR domain of human MARCO;

f. binds to the SRCR domain of cynomolgus MARCO;

g. binds to the SRCR domain of human and cynomolgus MARCO;

h. binds to human or cynomolgus MARCO in a divalent cation dependent manner;

i. binds to human or cynomolgus MARCO in a divalent cation independent manner;

j. stimulates MARCO signaling upon binding to a MARCO+ cell;

k. induces one or more immune signaling pathways upon binding to a MARCO+ cell;

l. induces cytokine or chemokine secretion upon binding to a MARCO+ cell, optionally wherein the cytokine or chemokine is IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin;

m. induces increased NK cell activation, B cell regulation, T cell proliferation, T cell activation, or T cell differentiation upon binding to a MARCO+ cell;

n. induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via

NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response;

o. decreases a cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway;

p. induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis;

q. induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes;

r. modulates B cells in the spleen upon binding to a MARCO+ cell;

s. increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, $MHCII^{high}$ monocytes, and/or $MHCII^{mid}$ monocytes in the spleen and/or tumor;

t. increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen and/or tumor;

u. decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages in the spleen and/or tumor;

v. induces changes in cell adhesion, cytoskeletal, chemotaxis and cell migration upon binding to a MARCO+ cell;

w. induces cell signaling pathways comprising adhesion, migration, chemotaxis cell cycle, T cell receptor, phagocytosis, autophagy, and wnt pathways upon binding to a MARCO+ cell;

x. disables MARCO+ myeloid cells; or

y. is capable of any combination of a.- x.

116. The isolated antibody of any of the above claims for use as a medicament.

117. The isolated antibody of any of the above claims for use in the treatment of a cancer or infection.

118. The isolated antibody of any of the above claims for use in the treatment of a cancer, wherein the cancer is selected from a solid tumor and a liquid tumor.

119. An isolated polynucleotide or set of polynucleotides encoding the antibody of any of the above claims, a VH thereof, a VL thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof; optionally the isolated polynucleotide or set of polynucleotides is cDNA.

120. A vector or set of vectors comprising the polynucleotide or set of polynucleotides of claim 119.

121. A host cell comprising the polynucleotide or set of polynucleotides of claim 119 or the vector or set of vectors of claim 120.

122. A method of producing an antibody comprising expressing the antibody or antigen binding fragment thereof with the host cell of claim 121 and isolating the expressed antibody.

123. A pharmaceutical composition comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 118 and a pharmaceutically acceptable excipient.

124. A kit comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 118 or a pharmaceutical composition of claim 123 and instructions for use.

125. A method of increasing an immune response in a subject comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof.

126. The method of claim 125, wherein the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

127. The method of claim 125 or 126, wherein the composition comprises the isolated antibody of any one of claims 11 to 118 or the pharmaceutical composition of claim 123.

128. The method of claim 127, wherein the antibody has receptor-ligand blocking activity.

129. The method of any one of claims 125-128, wherein the increased immune response is an adaptive immune response.

130. The method of any one of claims 125-128, wherein the increased immune response is an innate immune response.

131. The method of any one of claims 125-130, wherein the increased immune response comprises increased expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

132. The method of claim 131, wherein the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

133. The method of any one of claims 125-129, wherein the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

134. The method of any one of claims 125-133, wherein upon cell contact the antibody induces In some embodiments, upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

135. The method of any one of claims 125-134, wherein upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

136. The method of any one of claims 125-135, wherein upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

137. The method of any one of claims 125-136, wherein upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

138. The method of any one of claims 125-137, wherein upon cell contact the antibody increases increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+

macrophages, $MHCII^{high}$ monocytes, or $MHCII^{mid}$ monocytes as compared to an isotype control antibody.

139. The method of any one of claims 125-138, wherein upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

140. The method of any one of claims 125-139, wherein upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

141. The method of any one of claims 125-140, wherein the antibody induces an increased memory immune response.

142. The method of any one of claims 125-141, wherein the cell is a MARCO+ cell.

143. The method of any one of claims 125-142, wherein the cell is a human MARCO+ cell.

144. The method of claim 142 or 143, wherein the MARCO+ cells is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

145. The method of claim 144, wherein the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

146. The method of any one of claims 125-145, wherein the antibody binds to MARCO on the cell surface of a MARCO + cell.

147. The method of any one of claims 125-146, wherein the subject is human.

148. The method of any one of claims 125-147, wherein the subject has cancer.

149. The method of claim 148, wherein the cancer is a solid cancer.

150. The method of claim 148 or 149, wherein the cancer is a liquid cancer.

151. The method of claim any one of claims 148-150, wherein the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small

lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

152. The method of claim 151, wherein the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

153. The method of any one of claims 148-152, wherein MARCO is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

154. The method of any one of claims 148-153, wherein IL-10 is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

155. A method of treating cancer in a subject, comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof.

156. The method of claim 155, wherein the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

157. The method of claim 155 or 156, wherein the composition comprises the antibody of any one of claims 1 to 118 or the pharmaceutical composition of claim 123.

158. A method of treating cancer in a subject, comprising administering to the subject a composition comprising the anti-human MARCO antibody or antigen binding fragment thereof of any one of claims 1 to 118 or the pharmaceutical composition of claim 123.

159. The method of any one of claims 155-158, wherein the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

160. The method of claim 159, wherein the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.

161. The method of claim 160, wherein the immunotherapy comprises an anti-PD1 antibody.

162. A method of treating cancer in a subject, comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof and an immunotherapy.

163. The method of claim 162, wherein the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

164. The method of claim 162 or 163, wherein the composition comprises the antibody of any one of claims 1 to 118 or the pharmaceutical composition of claim 123.

165. The method of any one of claims 162-164, wherein the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.

166. The method of claim 165, wherein the immunotherapy comprises an anti-PD1 antibody.

167. The method of any one of claims 155-190 ,wherein the subject is human.

168. The method of any one of claims 155-167, wherein the cancer is a solid cancer.

169. The method of any one of claims 155-168, wherein the cancer is a liquid cancer.

170. The method of claim any one of claims 155-169, wherein the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

171. The method of claim 170, wherein the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

172. The method of any one of claims 155-171, wherein MARCO is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

173. The method of any one of claims 155-172, wherein IL-10 is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

174. The method of any one of claims 155-173, wherein the antibody induces an increased anti-tumor memory response as compared to an isotype control antibody.

175. The method of claim any one of claims 155-174, wherein the administration increases an immune response in the subject as compared to an isotype control antibody.

176. The method of claim 175, wherein the increased immune response is an adaptive immune response.

177. The method of claim 175, wherein the increased immune response is an innate immune response.

178. The method of any one of claims 175-177, wherein the increased immune response comprises expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

179. The method of claim 178, wherein the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

180. The method of any one of claims 175-179, wherein the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

181. The method of any one of claims 175-180, wherein upon cell contact the antibody induces In some embodiments, upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

182. The method of any one of claims 175-181, wherein upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

183. The method of any one of claims 175-182, wherein upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

184. The method of any one of claims 175-183, wherein upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

185. The method of any one of claims 175-184, wherein upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, $MHCII^{high}$ monocytes, or $MHCII^{mid}$ monocytes as compared to an isotype control antibody.

186. The method of any one of claims 175-185, wherein upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

187. The method of any one of claims 175-186, wherein upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

188. The method of any one of claims 155-187, wherein the cell is a MARCO+ cell.

189. The method of claim 188, wherein the cell is a human MARCO+ cell.

190. The method of claim 188 or 189, wherein the MARCO+ cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

191. The method of claim 190, wherein the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

192. The method of any one of claims 155-191, wherein the antibody binds to MARCO on the cell surface of a MARCO + cell.

193. A method of disabling myeloid cells that express MARCO on the cell surface, comprising contacting the myeloid cells with an anti-human MARCO antibody or antigen binding fragment thereof.

194. A method of disabling myeloid cells that express MARCO on the cell surface, comprising contacting the myeloid cells with the antibody of any one of claims 1 to 118 or the pharmaceutical composition of claim 123.

195. The method of claim 193 or 194, wherein the antibody disables the myeloid cells by at least one of ADCC activity, CDC activity, or ADCP activity, optionally wherein the antibody disables the myeloid cells by ADCC activity, optionally wherein the antibody disables the myeloid cells by CDC activity, and optionally wherein the antibody disables the myeloid cells by ADCP activity.

196. The method of any one of claims 193-195, wherein the myeloid cell is a MARCO+ cell.

197. The method of claim 196, wherein the myeloid cell is a human MARCO+ cell.

198. The method of any one of claims 193-197, wherein the myeloid cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

199. The method of claim 198, wherein the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

200. The method of any one of claims 193-199, wherein the myeloid cells are intratumoral or splenic myeloid cells.

201. The method of claim 200, wherein the contacting is *in vitro* or *in vivo*.

202. The method of claim 201, wherein the contacting occurs *in vivo* in a subject, optionally wherein the subject has cancer.

203. The method of claim 202, wherein the subject is a human.

204. The method of claim 202, wherein the cancer is a solid cancer.

205. The method of claim 202, wherein the cancer is a liquid cancer.

206. The method of claim any one of claims 202-205, wherein the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

207. The method of claim 206, wherein the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

208. The method of any one of claims 194-207, wherein the contacting increases an immune response in the subject as compared to an isotype control antibody.

209. The method of claim 208, wherein the increased immune response is an adaptive immune response.

210. The method of claim 208, wherein the increased immune response is an innate immune response.

211. The method of any one of claims 208-210, wherein the increased immune response comprises expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

212. The method of claim 211, wherein the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

213. The method of any one of claims 208-212, wherein the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

214. The method of any one of claims 208-213, wherein upon cell contact the antibody IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

215. The method of any one of claims 208-214, wherein upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia pathway, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

216. The method of any one of claims 208-215, wherein upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or and IL-18 secretion and/or phagocytosis.

217. The method of any one of claims 208-216, wherein upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes.

218. The method of any one of claims 208-217, wherein upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, $MHCII^{high}$ monocytes, or $MHCII^{mid}$ monocytes as compared to an isotype control antibody.

219. The method of any one of claims 208-218, wherein upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

220. The method of any one of claims 208-219, wherein upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

221. The method of any one of claims 194-220, wherein the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

222. The method of claim 221, wherein the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.The method of claim 222, wherein the immunotherapy comprises an anti-PD1 antibody.

223. A method of determining an expression level of MARCO protein in a sample from a subject comprising contacting the sample with an anti-MARCO antibody and performing an immunohistochemistry assay or a soluble MARCO assay.

224. The method of claim 223, wherein the assay is an immunohistochemistry assay and the antibody comprises RDM5, RDM9, PI-3010.15, PI-3010.25, or PI-3030.41.

CLAIMS

1. An isolated antibody or antigen binding fragment thereof that binds to a Scavenger Receptor Cysteine-Rich (SRCR) domain (residues 424-519 of SEQ ID NO: 384) of human Macrophage Receptor with Collagenous Structure (MARCO) (SEQ ID NO: 384).

2. The isolated antibody of claim 1, wherein the antibody comprises a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2),

b. CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3),

c. CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4),

d. CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L),

e. CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and

f. CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

3. The isolated antibody of claim 1 or 2, wherein the antibody or antigen binding fragment thereof binds to at least one of the following residues: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of MARCO (SEQ ID NO: 384).

4. The isolated antibody of claims 1-3, wherein the antibody or antigen binding fragment comprises a chimeric, human, humanized, or rat antibody or antigen binding fragment.

5. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GFSLTSYHVS (SEQ ID NO: 2),

b. CDR-H2 comprises the sequence AIWTGGSIA (SEQ ID NO: 3),

c. CDR-H3 comprises the sequence DLSDYYSSYTSFDY (SEQ ID NO: 4),

d. CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431) or XASEGISNDLA (SEQ ID NO: 383), wherein X is arginine (R) or leucine (L) ,

e. CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 8), and

f. CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 9).

6. The isolated antibody of claim 5, wherein: CDR-L1 comprises the sequence ASEGISNDLA (SEQ ID NO: 431).

7. The isolated antibody of claim 5, wherein: CDR-L1 comprises the sequence RASEGISNDLA (SEQ ID NO: 27).

8. The isolated antibody of claim 5, wherein: CDR-L1 comprises the sequence LASEGISNDLA (SEQ ID NO: 7).

9. The isolated antibody of any one of claims 5-7, wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 61.

10. The isolated antibody of any one of claims 5-7, wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 111.

11. The isolated antibody of any one of claims 5-8, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474.

12. The isolated antibody of any one of claims 5-11, wherein the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

13. The isolated antibody of any one of claims 5-11, wherein the VL sequence comprises the VL sequence set forth in SEQ ID NO: 116.

14. The isolated antibody of any one of claims 5-11, wherein the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

15. The isolated antibody of any one of claims 5-14, wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 61; and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

16. The isolated antibody of any one of claims 5-14, wherein the VH sequence comprises the VH sequence set forth in SEQ ID NO: 111; and the VL sequence comprises the VL sequence set forth in SEQ ID NO: 116.

17. The isolated antibody of any one of claims 5-14, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474 and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

18. The isolated antibody of any one of claims 5-14, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 434, 444, and 474 and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 6, 16, 26, 36, 46, 57, 66, 76, 86, 96 , 106, 116, 126, 136, 439, 449, and 479.

19. The isolated antibody of any one of claims 5-18, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 65.

20. The isolated antibody of any one of claims 5-18, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 115.

21. The isolated antibody of any one of claims 5-20, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478.

22. The isolated antibody of any one of claims 5-21, wherein the antibody comprises a light chain sequence as set forth in SEQ ID NO: 70.

23. The isolated antibody of any one of claims 5-21, wherein the antibody comprises a light chain sequence as set forth in SEQ ID NO: 120.

24. The isolated antibody of any of claims 5-23, wherein the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

25. The isolated antibody of any one of claims 5-24, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 65; and a light chain sequence as set forth in SEQ ID NO: 70.

26. The isolated antibody of any one of claims 5-24, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 115; and a light chain sequence as set forth in SEQ ID NO: 120.

27. The isolated antibody of any one of claims 5-24, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478; and a light chain sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

28. The isolated antibody of any one of claims 5-24, wherein the antibody comprises a heavy chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 5, 15, 125, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 145, 438, 448, and 478; and/or a light chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 10, 20, 30, 40, 50, 6, 70, 80, 90, 100, 110, 120, 130, 140, 443, 453, and 483.

29. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GYTFTDYAVN (SEQ ID NO: 232),

b. CDR-H2 comprises the sequence WINTQTGKPT (SEQ ID NO: 233),

c. CDR-H3 comprises the sequence DSYYYSSSLDY (SEQ ID NO: 234),

d. CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432) or XASAGISNDLA (SEQ ID NO: 381), wherein X is arginine (R) or leucine (L),

e. CDR-L2 comprises the sequence AASRLQD (SEQ ID NO: 238), and

f. CDR-L3 comprises the sequence QQSYKYPWT (SEQ ID NO: 239).

30. The isolated antibody of claim 29, wherein: CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432).

31. The isolated antibody of claim 29, wherein: CDR-L1 comprises the sequence RASAGISNDLA (SEQ ID NO: 317).

32. The isolated antibody of claim 29, wherein: CDR-L1 comprises the sequence LASAGISNDLA (SEQ ID NO: 237).

33. The isolated antibody of any one of claims 29-32, wherein the VH sequence comprises the VH sequence as set forth in SEQ ID NO: 454.

34. The isolated antibody of any one of claims 29-32, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464.

35. The isolated antibody of any one of claims 29-34, wherein the VL sequence comprises the VL sequence as set forth in SEQ ID NO: 459.

36. The isolated antibody of any one of claims 29-34, wherein the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

37. The isolated antibody of any one of claims 29-36, wherein the VH sequence comprises the VH sequence as set forth in SEQ ID NO: 454; and the VL sequence comprises the VL sequence as set forth in SEQ ID NO: 459.

38. The isolated antibody of any one of claims 29-36, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464, and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

39. The isolated antibody of any one of claims 29-36, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 241, 311, 321, 331, 341, 351, 454, and 464; and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 246, 316, 326, 336, 346, 356, 459, and 469.

40. The isolated antibody of any one of claims 29-38 wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 458.

41. The isolated antibody of any one of claims 29-38, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468.

42. The isolated antibody of any one of claims 29-41 wherein the antibody comprises a light chain sequence as set forth in SEQ ID NO: 463.

43. The isolated antibody of any one of claims 29-41, wherein the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

44. The isolated antibody of any one of claims 29-43, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 458; and a light chain sequence as set forth in SEQ ID NO: 463.

45. The isolated antibody of any one of claims 29-43, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468; and a light chain sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

46. The isolated antibody of any one of claims 29-43, wherein the antibody comprises a heavy chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 245, 315, 325, 335, 345 355, 458, and 468; and/or a light chain sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 250, 320, 330, 340, 350, 360, 463, and 473.

47. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence KFTFSNYGMN (SEQ ID NO: 142),

b. CDR-H2 comprises the sequence LIYYNSNNKY (SEQ ID NO: 143),

c. CDR-H3 comprises the sequence SLTGGSDYFDS (SEQ ID NO: 144),

d. CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433) or XASKSIGTFLA (SEQ ID NO: 382), wherein X is arginine (R) or lysine (K),

e. CDR-L2 comprises the sequence SGSTLQS (SEQ ID NO: 148), and

f. CDR-L3 comprises the sequence QQHDEYPFT (SEQ ID NO: 149).

48. The isolated antibody of claim 47, wherein: CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433).

49. The isolated antibody of claim 47, wherein: CDR-L1 comprises the sequence KASKSIGTFLA (SEQ ID NO: 147).

50. The isolated antibody of claim 47, wherein: CDR-L1 comprises the sequence RASKSIGTFLA (SEQ ID NO: 157).

51. The isolated antibody of any one of claims 47-50, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221.

52. The isolated antibody of any one of claims 47-51, wherein the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

53. The isolated antibody of any one of claims 47-52, wherein the VH sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221 and the VL sequence comprises a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

54. The isolated antibody of any one of claims 47-52, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 141, 151, 161, 171, 181, 191, 201, 211, and 221 and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 146, 156, 166, 176, 186, 196, 206, 216, and 226.

55. The isolated antibody of any one of claims 47-54, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225.

56. The isolated antibody of any one of claims 47-55, wherein the antibody comprises a light chain sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

57. The isolated antibody of any one of claims 47-56, wherein the antibody comprises a heavy chain sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225 and a light chain sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

58. The isolated antibody of any one of claims 47-54, wherein the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 145, 155, 165, 175, 185, 195, 205, 215, and 225 and/or a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence selected from the sequences set forth in SEQ ID NO: 150, 160, 170, 180, 190, 200, 210, 220, and 230.

59. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising ~~a~~ a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GYTFTDYYLH (SEQ ID NO: 252),

b. CDR-H2 comprises the sequence YINPNNAYTS (SEQ ID NO: 253),

c. CDR-H3 comprises the sequence DTTDYYNLHFAY (SEQ ID NO: 254),

d. CDR-L1 comprises the sequence LTSEGISNDLA (SEQ ID NO: 257),

e. CDR-L2 comprises the sequence DASRLED (SEQ ID NO: 258), and

f. CDR-L3 comprises the sequence QQSYKYPLT (SEQ ID NO: 259).

60. The isolated antibody of claim 59, wherein the VH sequence comprises a sequence as set forth in SEQ ID NO: 251 or 261.

61. The isolated antibody of claim 59 or 60, wherein the VL sequence comprises a sequence as set forth in SEQ ID NO: 256 or 266.

62. The isolated antibody of any one of claims 59-61, wherein the VH sequence comprises a sequence as set forth in SEQ ID NO: 251 or 261, and the VL sequence comprises a sequence s set forth in SEQ ID NO: 256 or 266.

63. The isolated antibody of any one of claims 59-61, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence as set forth in

SEQ ID NO: 251 or 261, and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence set forth in SEQ ID NO: 256 or 266.

64. The isolated antibody of any one of claims 59-62, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 255 or 265.

65. The isolated antibody of any one of claims 59-64, wherein the antibody comprises a light chain sequence as set forth in SEQ ID NO: 260 or 270.

66. The isolated antibody of any one of claims 59-65, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 255 or 265; and a light chain sequence as set forth in SEQ ID NO: 260 or 270.

67. The isolated antibody of any one of claims 59-65, wherein the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 255 or 265; and a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 260 or 270.

68. An isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising ~~a~~ a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

a. CDR-H1 comprises the sequence GFSLTSYTLS (SEQ ID NO: 362),

b. CDR-H2 comprises the sequence AIWGGDNTD (SEQ ID NO: 363),

c. CDR-H3 comprises the sequence ELGGSFDY (SEQ ID NO: 364),

d. CDR-L1 comprises the sequence KTSQNINKKLD (SEQ ID NO: 367),

e. CDR-L2 comprises the sequence YTNNLQT (SEQ ID NO: 368), and

f. CDR-L3 comprises the sequence YQYDSGFT (SEQ ID NO: 369).

69. The isolated antibody of claim 68, wherein the VH sequence comprises a sequence as set forth in SEQ ID NO: 361 or 371.

70. The isolated antibody of claim 68 or 69, wherein the VL sequence comprises a sequence as set forth in SEQ ID NO: 366 or 376.

71. The isolated antibody of any one of claims 68-70, wherein the VH sequence comprises a sequence as set forth in SEQ ID NO: 361 or 371, and the VL sequence comprises a sequence s set forth in SEQ ID NO: 366 or 376.

72. The isolated antibody of any one of claims 68-70, wherein the VH sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence as set forth in SEQ ID NO: 361 or 371, and/or the VL sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98, or 99% identity to a sequence set forth in SEQ ID NO: 366 or 376.

73. The isolated antibody of any one of claims 68-72, wherein the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 365 or 375; and a light chain sequence as set forth in SEQ ID NO: 370 or 380.

74. The isolated antibody of any one of claims 68-72, wherein the antibody comprises a heavy chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 365 or 375; and a light chain sequence comprises a sequence with at least 90%, 92%, 95%, 97%, 98%, or 99% identity to a sequence as set forth in SEQ ID NO: 370 or 380.

75. The isolated antibody of any of the above claims, wherein the antibody is a monoclonal antibody, a neutral antibody, an antagonistic antibody, an agonist antibody, a polyclonal antibody, an afucosylated antibody, a human antibody, a humanized antibody, a chimeric antibody, a full-length antibody, and an scFv.

76. The isolated antibody of any of the above claims, wherein the antibody is an scFv.

77. The isolated antibody of any of the above claims, wherein the antibody is a monoclonal antibody.

78. The isolated antibody of any of the above claims wherein the antibody is a humanized antibody.

79. The isolated antibody of any of the above claims wherein the antibody is a human antibody.

80. The isolated antibody of any of the above claims, wherein the antibody comprises an Fc region.

81. The isolated antibody of any of the above claims, wherein the Fc region comprises a human Fc region.

82. The isolated antibody of any of the above claims, wherein the antibody comprises an active human Fc region.

83. The isolated antibody of any of the above claims, wherein the antibody comprises a heavy chain human constant region of a class selected from IgG, IgA, IgD, IgE, and IgM.

84. The isolated antibody of any of the above claims, wherein the antibody comprises a human heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4.

85. The isolated antibody of claim 84, wherein the human Fc region comprises a wild-type, human IgG1 Fc region.

86. The isolated antibody of claim 84, wherein the human Fc region comprises a wild-type, human IgG4 Fc region.

87. The isolated antibody of any one of claims 80-86, wherein the Fc region comprises one or more amino acid substitutions, wherein the one or more substitutions result in increased antibody half-life, increased ADCC activity, increased ADCP activity, increased CDC activity, decreased ADCC activity, decreased ADCP activity, or decreased CDC activity compared with an Fc region without the one or more substitutions.

88. The isolated antibody of any one of claims 80-84, wherein the Fc region binds an Fcγ Receptor selected from the group consisting of: FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb.

89. The isolated antibody of any of the above claims, wherein the antibody binds to human MARCO with a K_D of less than or equal to about 0.5, 1, 2, 3, 4, 5, 6, or $7x10^{-9}$ M, as measured by surface plasmon resonance (SPR) assay.

90. The isolated antibody of any of the above claims, wherein binding of the antibody to human MARCO is divalent cation dependent.

91. The isolated antibody of any one of claim 1-89, wherein binding of the antibody to human MARCO is divalent cation independent.

92. The isolated antibody of claim 90 or 91, wherein the divalent cation comprises $Ca2^+$ or $Mg2^+$.

93. The isolated antibody of any of the above claims, wherein the antibody binds an extracellular domain of human MARCO.

94. The isolated antibody of any of the above claims, wherein the antibody binds to soluble MARCO.

95. The isolated antibody of any of the above claims, wherein the antibody binds the SRCR domain of human MARCO, cynomolgus MARCO, or human and cynomolgus MARCO.

96. The isolated antibody of claim 95, wherein the antibody binds the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

97. The isolated antibody of claim 96, wherein the antibody or antigen binding fragment thereof binds to at least one of: Q452, Y472, K473, E450, Q487, T499, H505, D507, S509, or E511 of MARCO (SEQ ID NO: 384).

98. The isolated antibody of any of the above claims, wherein the antibody has receptor-ligand blocking activity.

99. The isolated antibody of any of the above claims, wherein the antibody induces increased expression of at least one cytokine or chemokine upon contact with a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

100. The isolated antibody of claim 99, wherein the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

101. The isolated antibody of any of the above claims, wherein upon cell contact the antibody induces increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

102. The isolated antibody of any of the above claims, wherein upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

103. The isolated antibody of any of the above claims, wherein upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src

signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

104. The isolated antibody of any of the above claims, wherein upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

105. The isolated antibody of any of the above claims, wherein upon cell contact the antibody induces repolarization of myeloid M2-like TAMS to M1-like tumor associated macrophages (TAMs), and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

106. The isolated antibody of any of the above claims, wherein upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, $MHCII^{high}$ monocytes, or $MHCII^{mid}$ monocytes as compared to an isotype control antibody.

107. The isolated antibody of any of the above claims, wherein upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

108. The isolated antibody of any of the above claims, wherein upon cell contact the antibody decreases TAMs, tumor associated neutrophils (TANs), plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

109. The isolated antibody of any of the above claims, wherein upon administration to a subject the antibody induces an increased anti-tumor memory response as compared to an isotype control antibody.

110. The isolated antibody of any of the above claims, wherein a cell is a MARCO+ cell.

111. The isolated antibody of any of the above claims, wherein the cell is a human MARCO+ cell.

112. The isolated antibody of claim 110 or 111, wherein the MARCO + cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

113. The isolated antibody of claim 112, wherein the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

114. The isolated antibody of any of the above claims, wherein the antibody binds to MARCO on the cell surface of a MARCO+ cell.

115. The isolated antibody of any one of the above claims, wherein the antibody:

a. competes for binding to human MARCO with humanized PI-HX-3011, PI-HX-3031, PI-HX-3043, PI-HX-3061, PI-HX-3092 antibody;

b. binds to human MARCO;

c. binds to cynomolgus MARCO;

d. binds to human and cynomolgus MARCO;

e. binds to the SRCR domain of human MARCO;

f. binds to the SRCR domain of cynomolgus MARCO;

g. binds to the SRCR domain of human and cynomolgus MARCO;

h. binds to human or cynomolgus MARCO in a divalent cation dependent manner;

i. binds to human or cynomolgus MARCO in a divalent cation independent manner;

j. stimulates MARCO signaling upon binding to a MARCO+ cell;

k. induces one or more immune signaling pathways upon binding to a MARCO+ cell;

l. induces cytokine or chemokine secretion upon binding to a MARCO+ cell, optionally wherein the cytokine or chemokine is IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin;

m. induces increased NK cell activation, B cell regulation, T cell proliferation, T cell activation, or T cell differentiation upon binding to a MARCO+ cell;

n. induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via

NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response;

o. decreases a cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway;

p. induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis;

q. induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes;

r. modulates B cells in the spleen upon binding to a MARCO+ cell;

s. increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, $MHCII^{high}$ monocytes, and/or $MHCII^{mid}$ monocytes in the spleen and/or tumor;

t. increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen and/or tumor;

u. decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages in the spleen and/or tumor;

v. induces changes in cell adhesion, cytoskeletal, chemotaxis and cell migration upon binding to a MARCO+ cell;

w. induces cell signaling pathways comprising adhesion, migration, chemotaxis cell cycle, T cell receptor, phagocytosis, autophagy, and wnt pathways upon binding to a MARCO+ cell;

x. disables MARCO+ myeloid cells; or

y. is capable of any combination of a.- x.

116. The isolated antibody of any of the above claims for use as a medicament.

117. The isolated antibody of any of the above claims for use in the treatment of a cancer or infection.

118. The isolated antibody of any of the above claims for use in the treatment of a cancer, wherein the cancer is selected from a solid tumor and a liquid tumor.

119. An isolated polynucleotide or set of polynucleotides encoding the antibody of any of the above claims, a VH thereof, a VL thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof; optionally the isolated polynucleotide or set of polynucleotides is cDNA.

120. A vector or set of vectors comprising the polynucleotide or set of polynucleotides of claim 119.

121. A host cell comprising the polynucleotide or set of polynucleotides of claim 119 or the vector or set of vectors of claim 120.

122. A method of producing an antibody comprising expressing the antibody or antigen binding fragment thereof with the host cell of claim 121 and isolating the expressed antibody.

123. A pharmaceutical composition comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 118 and a pharmaceutically acceptable excipient.

124. A kit comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1 to 118 or a pharmaceutical composition of claim 123 and instructions for use.

125. A method of increasing an immune response in a subject comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof.

126. The method of claim 125, wherein the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

127. The method of claim 125 or 126, wherein the composition comprises the isolated antibody of any one of claims 11 to 118 or the pharmaceutical composition of claim 123.

128. The method of claim 127, wherein the antibody has receptor-ligand blocking activity.

129. The method of any one of claims 125-128, wherein the increased immune response is an adaptive immune response.

130. The method of any one of claims 125-128, wherein the increased immune response is an innate immune response.

131. The method of any one of claims 125-130, wherein the increased immune response comprises increased expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

132. The method of claim 131, wherein the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

133. The method of any one of claims 125-129, wherein the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

134. The method of any one of claims 125-133, wherein upon cell contact the antibody induces In some embodiments, upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

135. The method of any one of claims 125-134, wherein upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

136. The method of any one of claims 125-135, wherein upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

137. The method of any one of claims 125-136, wherein upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

138. The method of any one of claims 125-137, wherein upon cell contact the antibody increases increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+

macrophages, $MHCII^{high}$ monocytes, or $MHCII^{mid}$ monocytes as compared to an isotype control antibody.

139. The method of any one of claims 125-138, wherein upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

140. The method of any one of claims 125-139, wherein upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

141. The method of any one of claims 125-140, wherein the antibody induces an increased memory immune response.

142. The method of any one of claims 125-141, wherein the cell is a MARCO+ cell.

143. The method of any one of claims 125-142, wherein the cell is a human MARCO+ cell.

144. The method of claim 142 or 143, wherein the MARCO+ cells is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

145. The method of claim 144, wherein the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

146. The method of any one of claims 125-145, wherein the antibody binds to MARCO on the cell surface of a MARCO + cell.

147. The method of any one of claims 125-146, wherein the subject is human.

148. The method of any one of claims 125-147, wherein the subject has cancer.

149. The method of claim 148, wherein the cancer is a solid cancer.

150. The method of claim 148 or 149, wherein the cancer is a liquid cancer.

151. The method of claim any one of claims 148-150, wherein the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small

lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

152. The method of claim 151, wherein the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

153. The method of any one of claims 148-152, wherein MARCO is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

154. The method of any one of claims 148-153, wherein IL-10 is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

155. A method of treating cancer in a subject, comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof.

156. The method of claim 155, wherein the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

157. The method of claim 155 or 156, wherein the composition comprises the antibody of any one of claims 1 to 118 or the pharmaceutical composition of claim 123.

158. A method of treating cancer in a subject, comprising administering to the subject a composition comprising the anti-human MARCO antibody or antigen binding fragment thereof of any one of claims 1 to 118 or the pharmaceutical composition of claim 123.

159. The method of any one of claims 155-158, wherein the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

160. The method of claim 159, wherein the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.

161. The method of claim 160, wherein the immunotherapy comprises an anti-PD1 antibody.

162. A method of treating cancer in a subject, comprising administering to the subject a composition comprising an anti-human MARCO antibody or antigen binding fragment thereof and an immunotherapy.

163. The method of claim 162, wherein the composition comprises an antibody that binds to the SRCR domain (residues 424-519 of SEQ ID NO: 384) of human MARCO.

164. The method of claim 162 or 163, wherein the composition comprises the antibody of any one of claims 1 to 118 or the pharmaceutical composition of claim 123.

165. The method of any one of claims 162-164, wherein the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.

166. The method of claim 165, wherein the immunotherapy comprises an anti-PD1 antibody.

167. The method of any one of claims 155-190 ,wherein the subject is human.

168. The method of any one of claims 155-167, wherein the cancer is a solid cancer.

169. The method of any one of claims 155-168, wherein the cancer is a liquid cancer.

170. The method of claim any one of claims 155-169, wherein the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

171. The method of claim 170, wherein the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

172. The method of any one of claims 155-171, wherein MARCO is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

173. The method of any one of claims 155-172, wherein IL-10 is expressed at a higher level on a tumor immune cell as compared to a non-tumor immune cell.

174. The method of any one of claims 155-173, wherein the antibody induces an increased anti-tumor memory response as compared to an isotype control antibody.

175. The method of claim any one of claims 155-174, wherein the administration increases an immune response in the subject as compared to an isotype control antibody.

176. The method of claim 175, wherein the increased immune response is an adaptive immune response.

177. The method of claim 175, wherein the increased immune response is an innate immune response.

178. The method of any one of claims 175-177, wherein the increased immune response comprises expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

179. The method of claim 178, wherein the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

180. The method of any one of claims 175-179, wherein the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

181. The method of any one of claims 175-180, wherein upon cell contact the antibody induces In some embodiments, upon cell contact the antibody induces IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

182. The method of any one of claims 175-181, wherein upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

183. The method of any one of claims 175-182, wherein upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or IL-18 secretion and/or phagocytosis as compared to an isotype control antibody.

184. The method of any one of claims 175-183, wherein upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes as compared to an isotype control antibody.

185. The method of any one of claims 175-184, wherein upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, $MHCII^{high}$ monocytes, or $MHCII^{mid}$ monocytes as compared to an isotype control antibody.

186. The method of any one of claims 175-185, wherein upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

187. The method of any one of claims 175-186, wherein upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

188. The method of any one of claims 155-187, wherein the cell is a MARCO+ cell.

189. The method of claim 188, wherein the cell is a human MARCO+ cell.

190. The method of claim 188 or 189, wherein the MARCO+ cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

191. The method of claim 190, wherein the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

192. The method of any one of claims 155-191, wherein the antibody binds to MARCO on the cell surface of a MARCO + cell.

193. A method of disabling myeloid cells that express MARCO on the cell surface, comprising contacting the myeloid cells with an anti-human MARCO antibody or antigen binding fragment thereof.

194. A method of disabling myeloid cells that express MARCO on the cell surface, comprising contacting the myeloid cells with the antibody of any one of claims 1 to 118 or the pharmaceutical composition of claim 123.

195. The method of claim 193 or 194, wherein the antibody disables the myeloid cells by at least one of ADCC activity, CDC activity, or ADCP activity, optionally wherein the antibody disables the myeloid cells by ADCC activity, optionally wherein the antibody disables the myeloid cells by CDC activity, and optionally wherein the antibody disables the myeloid cells by ADCP activity.

196. The method of any one of claims 193-195, wherein the myeloid cell is a MARCO+ cell.

197. The method of claim 196, wherein the myeloid cell is a human MARCO+ cell.

198. The method of any one of claims 193-197, wherein the myeloid cell is a monocyte, a monocytic Myeloid Derived Suppressor Cell (mMDSC), or a macrophage.

199. The method of claim 198, wherein the macrophage is a tumor associated macrophage (TAM) or a monocyte-derived macrophage (MDM).

200. The method of any one of claims 193-199, wherein the myeloid cells are intratumoral or splenic myeloid cells.

201. The method of claim 200, wherein the contacting is *in vitro* or *in vivo*.

202. The method of claim 201, wherein the contacting occurs *in vivo* in a subject, optionally wherein the subject has cancer.

203. The method of claim 202, wherein the subject is a human.

204. The method of claim 202, wherein the cancer is a solid cancer.

205. The method of claim 202, wherein the cancer is a liquid cancer.

206. The method of claim any one of claims 202-205, wherein the cancer is selected from the group consisting of: lung cancer, lung adeno carcinoma, lung squamous cell carcinoma, lung small cell carcinoma, kidney cancer, liver cancer, renal cell carcinoma, cervical cancer, ovarian cancer, colorectal cancer, colon cancer, neuroblastoma, breast cancer, triple negative breast cancer, basal-like breast cancer, gastric cancer, stomach cancer, bladder cancer, prostate cancer, skin cancer, lymphoma, Diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma, non-Hodgkin lymphoma, mesothelioma, pancreatic cancer, thyroid cancer, endometrial cancer, head and neck cancer, or head and neck squamous carcinoma (HNSC) cancer.

207. The method of claim 206, wherein the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

208. The method of any one of claims 194-207, wherein the contacting increases an immune response in the subject as compared to an isotype control antibody.

209. The method of claim 208, wherein the increased immune response is an adaptive immune response.

210. The method of claim 208, wherein the increased immune response is an innate immune response.

211. The method of any one of claims 208-210, wherein the increased immune response comprises expression of at least one cytokine or chemokine by a cell as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

212. The method of claim 211, wherein the at least one cytokine or chemokine comprises at least one of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL7R, IL-12, IL12-p70, IL-15, IL-18, IL-27, IP-10, IFN-γ, TNFα, MIP1-α, MIP1-β, MIP-2, CSF2, CSF3, G-CSF, M-CSF, CCL3, CCL4, CCL5, CCL20, CCL24, CXCL1, CXCL3, CXCL8, CXCL9, CXCL10, CXCL12, gro-alpha, MCP-1, MCP-3, LIF, or eotaxin.

213. The method of any one of claims 208-212, wherein the increased immune response comprises increased NK cell activation, B cell regulation T cell proliferation, T cell activation, or T cell differentiation as compared to an isotype control antibody, optionally as measured by a nucleic acid or protein assay.

214. The method of any one of claims 208-213, wherein upon cell contact the antibody IL-2-STAT5 signaling, NF-kB signaling, TLR signaling, adhesion and motility signaling, cytoskeletal rearrangement signaling, TNFα signaling via NF-kB, IL-6-JAK-STAT3 signaling, SYK signaling, MAPK signaling, TPL2 signaling, calcium signaling, an IFNγ response, or an IFNα response as compared to an isotype control antibody.

215. The method of any one of claims 208-214, wherein upon cell contact the antibody decreases cell cycle pathway, cell survival, cell adhesion, Myc target pathway, E2F targets pathway, hypoxia pathway, mTOR signaling pathway, PI3K-AKT signaling pathway, Src signaling pathway, PKC signaling pathway, epithelial to mesenchymal transition signaling pathway, oxidative phosphorylation, or MAPK signaling pathway as compared to an isotype control antibody.

216. The method of any one of claims 208-215, wherein upon cell contact the antibody induces inflammasome activation as determined by IL-1β and/or and IL-18 secretion and/or phagocytosis.

217. The method of any one of claims 208-216, wherein upon cell contact the antibody induces repolarization of myeloid M2-like TAMs to M1-like TAMS, and/or repolarization of mMDSCs to pro-inflammatory monocytes.

218. The method of any one of claims 208-217, wherein upon cell contact the antibody increases CD8+ T cells, CD4+ T cells, NK cells, dendritic cells, MHCII+ macrophages, $MHCII^{high}$ monocytes, or $MHCII^{mid}$ monocytes as compared to an isotype control antibody.

219. The method of any one of claims 208-218, wherein upon cell contact the antibody increases macrophages, marginal zone macrophages, follicular B cells, and/or red pulp macrophages in the spleen as compared to an isotype control antibody.

220. The method of any one of claims 208-219, wherein upon cell contact the antibody decreases TAMs, tumor associated neutrophils, plasma B cells, marginal zone B cells, CD19+ B cells, MHCII- monocytes, and/or MHCII- macrophages as compared to an isotype control antibody.

221. The method of any one of claims 194-220, wherein the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

222. The method of claim 221, wherein the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; and an anti-PD1 antibody.The method of claim 222, wherein the immunotherapy comprises an anti-PD1 antibody.

223. A method of determining an expression level of MARCO protein in a sample from a subject comprising contacting the sample with an anti-MARCO antibody and performing an immunohistochemistry assay or a soluble MARCO assay.

224. The method of claim 223, wherein the assay is an immunohistochemistry assay and the antibody comprises RDM5, RDM9, PI-3010.15, PI-3010.25, or PI-3030.41.