SUMMARY

[0005a] In one aspect, provided herein is an isolated antibody or antigen binding fragment thereof that binds to human MARCO (SEQ ID NO: 384), comprising three heavy chain complementarity determining regions (CDRs) (CDR-H1, CDR-H2, and CDR-H3) and three light chain complementarity determining regions (CDRs) (CDR-L1, CDR-L2, and CDR-L3), wherein the CDR-H1, CDR-H2, and CDR-H3 are from a heavy chain variable domain (VH) comprising the amino acid sequence set forth in SEQ ID NO: 61, 21, 31, 41, 51, 91, 121, 474, 1, 11, 71, 81, 101, 111, 131, 434, or 444; and wherein the CDR-L1, CDR-L2, and CDR-L3 are from a light chain variable domain (VL) comprising the amino acid sequence set forth in SEQ ID NO: 66, 26, 36, 46, 56, 96, 126, 479, 6, 16, 76, 86, 106, 116, 136, 439, or 449.

[0005b] In another aspect, provided herein is a method of producing an antibody comprising expressing the antibody as described herein from a host cell and isolating the expressed antibody.

[0005c] In another aspect, provided herein is a pharmaceutical composition comprising the antibody as described herein and a pharmaceutically acceptable excipient.

[0005d] In another aspect, provided herein is a kit comprising the antibody as described herein and instructions for use.

[0005e] In another aspect, provided herein is the use of an antibody that competes for binding to human MARCO (SEQ ID NO: 384) in the manufacture of a medicament for treating cancer in a subject, wherein the medicament is to be administered to the subject with a reference antibody, wherein the reference antibody comprises three heavy chain complementarity determining regions (CDRs) (CDR-H1, CDR-H2, and CDR-H3) and three light chain complementarity determining regions (CDRs) (CDR-L1, CDR-L2, and CDR-L3), wherein the CDR-H1, CDR-H2, and CDR-H3 are from a heavy chain variable domain (VH) comprising the amino acid sequence set forth in SEQ ID NO: 61, 21, 31, 41, 51, 91, 121, 474, 1, 11, 71, 81, 101, 111, 131, 434, or 444; and wherein the CDR-L1, CDR-L2, and CDR-L3 are from a light chain variable domain (VL) comprising the amino acid sequence set forth in SEQ ID NO: 66, 26, 36, 46, 56, 96, 126, 479, 6, 16, 76, 86, 106, 116, 136, 439, and 449.

[0005f] In yet another example, provided herein is the use of an antibody that competes for binding to human MARCO (SEQ ID NO: 384) in the manufacture of a medicament for increasing an immune response in a subject, wherein the medicament is to be administered to the subject with a reference antibody, wherein the reference antibody comprises three heavy chain complementarity determining regions (CDRs) (CDR-H1, CDR-H2, and CDR-H3) and three light chain complementarity determining regions (CDRs) (CDR-L1, CDR-L2, and

CDR-L3), wherein the CDR-H1, CDR-H2, and CDR-H3 are from a heavy chain variable domain (VH) comprising the amino acid sequence set forth in SEQ ID NO: 61, 21, 31, 41, 51, 91, 121, 474, 1, 11, 71, 81, 101, 111, 131, 434, or 444; and wherein the CDR-L1, CDR-L2, and CDR-L3 are from a light chain variable domain (VL) comprising the amino acid sequence set forth in SEQ ID NO: 66, 26, 36, 46, 56, 96, 126, 479, 6, 16, 76, 86, 106, 116, 136, 439, and 449.

[0006] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the antibody or antigen binding fragment comprises a chimeric, human, humanized, or rat antibody or antigen binding fragment.

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

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

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

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

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

[0017] In some examples, 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 examples, the VL sequence comprises the VL sequence set forth in SEQ ID NO: 66.

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

[0020] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 65.

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

[0027] In some examples, 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 examples, the antibody comprises a light chain sequence as set forth in SEQ ID NO: 70.

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

[0030] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, CDR-L1 comprises the sequence ASAGISNDLA (SEQ ID NO: 432).

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

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

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

[0040] In some examples, 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 examples, the VL sequence comprises the VL sequence as set forth in SEQ ID NO: 459.

[0042] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 458.

[0047] In some examples, 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 examples, the antibody comprises a light chain sequence as set forth in SEQ ID NO: 463.

[0049] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, CDR-L1 comprises the sequence ASKSIGTFLA (SEQ ID NO: 433).

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

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

[0057] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 example, 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 examples, the VH sequence comprises a sequence as set forth in SEQ ID NO: 251 or 261.

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

[0068] In some examples, 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 examples, 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 examples, the antibody comprises a heavy chain sequence as set forth in SEQ ID NO: 255 or 265.

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

[0072] In some examples, 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 examples, 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 example, 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 examples, the VH sequence comprises a sequence as set forth in SEQ ID NO: 361 or 371.

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

[0077] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the antibody is an scFv.

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

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

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

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

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

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

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

[0090] In some examples, 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 examples, the human Fc region comprises a wild-type, human IgG1 Fc region.

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

[0093] In some examples, 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 examples, the Fc region binds an Fcγ Receptor selected from the group consisting of: FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb.

[0095] In some examples, 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 examples, binding of the antibody to human MARCO is divalent cation dependent.

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

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

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

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

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

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

[0103] In some examples, 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 examples, the antibody has receptor-ligand blocking activity.

[0105] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, upon administration to a subject the antibody induces an increased anti-tumor memory response as compared to an isotype control antibody.

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

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

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

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

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

[0121] In some examples, 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 examples, the antibody is for use as a medicament.

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

[0124] In some examples, 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 example, 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 example, provided herein are vectors or set of vectors comprising the polynucleotide or set of polynucleotides.

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

[0128] In another example, 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 example, provided herein are pharmaceutical compositions comprising the isolated antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient.

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

[0131] In another example, 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 examples, 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 examples, the composition comprises the isolated antibody or the pharmaceutical composition.

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

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

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

[0137] In some examples, 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 examples, 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 examples, 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 examples, upon cell contact the antibody induces In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the antibody induces an increased memory immune response.

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

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

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

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

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

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

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

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

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

[0157] In some examples, 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 examples, the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

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

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

[0161] In another example, 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 examples, 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 examples, the composition comprises the antibody disclosed herein or the pharmaceutical composition thereof.

[0164] In another example, 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 examples, the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

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

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

[0168] In another example, 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 examples, 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 examples, the composition comprises the antibody disclosed herein or the pharmaceutical composition thereof.

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

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

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

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

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

[0176] In some examples, 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 examples, the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

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

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

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

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

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

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

[0184] In some examples, 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 examples, 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 examples, 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 examples, upon cell contact the antibody induces In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the cell is a MARCO+ cell.

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

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

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

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

[0199] In another example, 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 example, 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 examples, 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 examples, the myeloid cell is a MARCO+ cell.

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

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

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

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

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

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

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

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

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

[0212] In some examples, 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 examples, the cancer is colon cancer, breast cancer, basal-like breast cancer, ovarian cancer, or gastric cancer.

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

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

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

[0217] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

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

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

[0230] In some examples, 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 examples, 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.

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 (SEQ ID NOS 141, 511, 151, 161, and 171, respectively, in order of appearance). **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 (SEQ ID NOS 146, 512, and 156, respectively, in order of appearance).

[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 (SEQ ID NOS 6, 512, 26, 36, 46, 86, 96, and 106, respectively, in order of appearance).

[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. FIG. 21 discloses SEQ ID NOS 513-521, 513-514, 522-527, and 503, respectively, in order of appearance.

[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. FIG. 22 discloses SEQ ID NOS 513-514, 524, 526-527, 513, 520, and 514, respectively, in order of appearance.

[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

QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGR ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS (SEQ ID NO: 484)

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

[0658] HHHHHHHHKGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQ GPQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGD KGDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGK PGVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQ KGTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEK GQKGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGYSKGRA LYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV (SEQ ID NO: 485)

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

[0660] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV KGEKGERGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLG YSRGRALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS (SEQ ID NO: 486)

[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 (SEQ ID NO: 487)

[0670] GSP2-mk: ACATTGATGTCTTTGGGGTAGAAG (SEQ ID NO: 488)

[0671] GSP1- mHC: AGCTGGGAAGGTGTGCACAC (SEQ ID NO: 489)

[0672] GSP2-mHC: GGGATCCAGAGTTCCAGGTC (SEQ ID NO: 490)

[0673] GSP1-rk: GT GAG GAT GAT GTC TTA TGA ACA (SEQ ID NO: 491)

[0674] GSP2-rk: GCCATCAATCTTCCACTTGACAC (SEQ ID NO: 492)

[0675] GSP1-rHC: GAG ATG STT TTC TCG ATG GG (SEQ ID NO: 493)

[0676] GSP2-rHC: GS GGG AAG ATG AAG ACA GAT G (SEQ ID NO: 494)

[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

[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*
(SEQ ID NO: 495)

[0781] hVar1 (RG3034)

[0782] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYY**NNE**WGTICDDEWQNSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV*
(SEQ ID NO: 496)

[0783] hVar2 (RG3035)

[0784] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDD**D**W**D**N**N**DAIVFCRMLGYS
RGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV*
(SEQ ID NO: 497)

[0785] hVar3 (RG3036)

[0786] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD

QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEW**D**NSDAIVFCRMLGYS
KGRAL**SS**VGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV*
(SEQ ID NO: 498)

[0787] hVar4 (RG3037)

[0788] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNVQCRGTE**NS**LW**D**C**S**KNSWGHHDCSHEEDAGVECSV*
(SEQ ID NO: 499)

[0789] hVar5 (RG3038)

[0790] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWG**N**H**N**C**V**H**N**EDAGVECSV
* (SEQ ID NO: 500)

[0791] hVar6 (RG3039)

[0792] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG
LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV
KGEKGERGENSVSVRIVGSSNRGRAEVYYSGTWGTICDD**D**W**D**NSDAIVFCRMLGYS
KGRALYKVGAGTGQIWLDNV**N**CRGTESTLWSC**S**KNSWGHHDCSHEEDAGVECSV*
(SEQ ID NO: 501)

[0793] hVar7 (RG3040)

[0794] HHHHHHKGEQGAPGLQGHKGAMGMPGAPGPPGPPAEKGAKGAMGRDGAT
GPSGPQGPPGVKGEAGLQGPQGAPGKQGATGTPGPQGEKGSKGDGGLIGPKGETGT
KGEKGDLGLPGSKGDRGMKGDAGVMGPPGAQGSKGDFGRPGPPGLAGFPGAKGD
QGQPGLQGVPGPPGAVGHPGAKGEPGSAGSPGRAGLPGSPGSPGATGLKGSKGDTG

LQGQQGRKGESGVPGPAGVKGEQGSPGLAGPKGAPGQAGQKGDQGVKGSSGEQGV KGEKGERGE**SFQR**VRIVG**GT**NRGRAEVYYSGTWGTICDDEWQNSDAIVFCRMLGY SKGRALYKVGAGTGQIWLDNVQCRGTESTLWSCTKNSWGHHDCSHEEDAGVECSV * (SEQ ID NO: 502)

[0795] mMARCO (RG3016)

[0796] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGR ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS (SEQ ID NO: 484)

[0797] mVar1 (RG3026)

[0798] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG QKGESFQRVRIMGGTNRGRAEVYY**SGT**WGTICDDDWDNNDATVFCRMLGYSRGR ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS* (SEQ ID NO: 504)

[0799] mVar2 (RG3027)

[0800] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDD**E**W**Q**N**S**DATVFCRMLGYS**K**GR ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS* (SEQ ID NO: 505)

[0801] mVar3 (RG3028)

[0802] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK

GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP
GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG

QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDW**Q**NNDATVFCRMLGYSRGR AL**YK**YGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS* (SEQ ID NO: 506)

[0803] mVar4 (RG3029)

[0804] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGR ALSSYGGGSGNIWLDNVNCRGTE**ST**LW**S**C**T**KNSWGNHNCVHNEDAGVECS* (SEQ ID NO: 507)

[0805] mVar5 (RG3030)

[0806] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGR ALSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWG**H**H**D**C**S**H**E**EDAGVECS* (SEQ ID NO: 508)

[0807] mVar6 (RG3031)

[0808] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG QKGESFQRVRIMGGTNRGRAEVYYNNEWGTICDD**E**W**Q**NNDATVFCRMLGYSRGR ALSSYGGGSGNIWLDNV**Q**CRGTENSLWDC**T**KNSWGNHNCVHNEDAGVECS* (SEQ ID NO: 509)

[0809] mVar7 (RG3032)

[0810] HHHHHHHHGERGSPGPKGAPGAPGIPGLPGPAAEKGEKGAAGRDGTPGVQG PQGPPGSKGEAGLQGLTGAPGKQGATGAPGPRGEKGSKGDIGLTGPKGEHGTKGDK GDLGLPGNKGDMGMKGDTGPMGSPGAQGGKGDAGKPGLPGLAGSPGVKGDQGKP

GVQGVPGPQGAPGLSGAKGEPGRTGLPGPAGPPGIAGNPGIAGVKGSKGDTGIQGQK
GTKGESGVPGLVGRKGDTGSPGLAGPKGEPGRVGQKGDPGMKGSSGQQGQKGEKG
QKGE**NSVS**VRIMG**SS**NRGRAEVYYNNEWGTICDDDWDNNDATVFCRMLGYSRGRA
LSSYGGGSGNIWLDNVNCRGTENSLWDCSKNSWGNHNCVHNEDAGVECS* (SEQ
ID NO: 510)

	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
528	CDR-L2	AASRLQS