IMMUNOMODULATORY ANTIBODIES AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to and benefit from U.S. Provisional Application Nos. 62/876,580, filed July 19, 2019, 62/876,579, filed July 19, 2019, and 62/878,265, filed July 24, 2019, the entire contents of each of which are herein incorporated by reference.

SUMMARY OF THE DISCLOSURE

[0001a] In one aspect, the present disclosure refers to an antibody or a recombinant antibody comprising a heavy chain variable region (VH) having at least 80% identity to amino acid sequence SEQ ID NO: 8 and a light chain variable region (VL) having at least 80% identity to amino acid sequence SEQ ID NO: 7.

[0001b] In another aspect, the present disclosure refers to a pharmaceutical composition, comprising an antibody or a recombinant antibody as described herein and a pharmaceutically acceptable excipient.

[0001c] In another aspect, the present disclosure refers to a use of an antibody or a recombinant antibody as described herein, for the manufacture of a medicament for treating cancer in a human subject.

[0001d] In yet another aspect, the present disclosure refers to the antibody or the recombinant antibody as described herein or the pharmaceutical composition as described herein for use in therapy.

[0002] Provided herein are antibodies, including antigen-binding fragments and other antigen-binding polypeptides, that are useful in the treatment of cancer and other disorders. In some examples~~embodiments~~ the antibodies specifically bind to M2 and M2-like immune-suppressive macrophages but not to M1 and M1-like anti-tumor macrophages. The disclosed antibodies bind to M2 and M2-like tumor-associated macrophages and modulate the physical and functional characteristics of tumor-associated M2 and M2-like macrophages to relieve immunosuppression of the tumor microenvironment and increase cytotoxic T-cell activation and proliferation, which promotes tumor cell killing. The antibody molecules of the present disclosure specifically bind to human CD163 expressed on the surface of M2 and M2-like macrophages.

[0003] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a heavy chain variable region (VH) having at least 80% identity to amino acid sequence SEQ ID NO: 8.

[0004] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a heavy chain variable region (VH) having at least 90% identity to amino acid sequence SEQ ID NO: 8.

[0005] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a heavy chain variable region (VH) having at least 95% identity to amino acid sequence SEQ ID NO: 8.

[0006] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a heavy chain variable region (VH) having at least 99% identity to amino acid sequence SEQ ID NO: 8.

[0007] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a heavy chain variable region (VH) having at least 100% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a light chain variable region (VL) having at least 80% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a light chain variable region (VL) having at least 90% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a light chain

variable region (VL) having at least 95% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a light chain variable region (VL) having at least 99% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a light chain variable region (VL) having at least 100% identity to amino acid sequence SEQ ID NO: 7.

[0008] Disclosed herein, in certain examples~~embodiments~~, are a light chain variable region (VL) having at least 80% identity to amino acid sequence SEQ ID NO: 7.

[0009] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a light chain variable region (VL) having at least 90% identity to amino acid sequence SEQ ID NO: 7.

[0010] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a light chain variable region (VL) having at least 95% identity to amino acid sequence SEQ ID NO: 7

[0011] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a light chain variable region (VL) having at least 99% identity to amino acid sequence SEQ ID NO: 7.

[0012] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a light chain variable region (VL) having at least 100% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a heavy chain variable region (VH) having at least 80% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a heavy chain variable region (VH) having at least 90% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a heavy chain variable region (VH) having at least 95% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a heavy chain variable region (VH) having at least 99% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a heavy chain variable region (VH) having at least 100% identity to amino acid sequence SEQ ID NO: 8.

[0013] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a heavy chain variable region (V_H) having at least 80% identity to amino acid sequence SEQ ID NO: 8 and a light chain variable region (V_L) having at least 80% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the light chain variable region (V_L) having at least 85% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the

light chain variable region (V_L) having at least 90% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the light chain variable region (V_L) having at least 95% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the light chain variable region (V_L) having at least 99% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the light chain variable region (V_L) having at least 100% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain variable region (V_H) having at least 85% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain variable region (V_H) having at least 90% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain variable region (V_H) having at least 95% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain variable region (V_H) having at least 99% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain variable region (V_H) having at least 100% identity to amino acid sequence SEQ ID NO: 8.

[0014] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody comprising a heavy chain sequence comprising a complementarity determining region (CDR) H1 having at least 80% identity to amino acid sequence SEQ ID NO: 4, a CDR H2 having at least 80% identity to amino acid sequence SEQ ID NO: 5, and a CDR H3 having at least 80% identity to amino acid sequence SEQ ID NO: 6, and a light chain sequence comprising a CDR L1 having at least 80% identity to amino acid sequence SEQ ID NO: 1, a CDR L2 having at least 80% identity to amino acid sequence SEQ ID NO: 2, and a CDR L3 having at least 80% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the light chain sequence comprising the CDR L1 having at least 85% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 having at least 85% identity to amino acid sequence SEQ ID NO: 2, and the CDR L3 having at least 85% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the light chain sequence comprising the CDR L1 having at least 90% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 having at least 90% identity to amino acid sequence SEQ ID NO: 2, and the CDR L3 having at least 90% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises light chain sequence comprising the CDR L1 having at least 95% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 having at least

95% identity to amino acid sequence SEQ ID NO: 2, and the CDR L3 having at least 95% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the light chain sequence comprising the CDR L1 having at least 99% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 having at least 99% identity to amino acid sequence SEQ ID NO: 2, and the CDR L3 having at least 99% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the light chain sequence comprising the CDR L1 having at least 100% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 having at least 100% identity to amino acid sequence SEQ ID NO: 2, and the CDR L3 having at least 100% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain sequence comprising a the CDR H1 having at least 85% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 having at least 85% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 having at least 85% identity to amino acid sequence SEQ ID NO: 6. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain sequence comprising a the CDR H1 having at least 90% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 having at least 90% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 having at least 90% identity to amino acid sequence SEQ ID NO: 6. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain sequence comprising a the CDR H1 having at least 95% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 having at least 95% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 having at least 95% identity to amino acid sequence SEQ ID NO: 6. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises the heavy chain sequence comprising a the CDR H1 having at least 99% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 having at least 99% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 having at least 99% identity to amino acid sequence SEQ ID NO: 6. In some ~~embodiments~~examples, the antibody or the recombinant antibody comprises the heavy chain sequence comprising a the CDR H1 having at least 100% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 having at least 100% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 having at least 100% identity to amino acid sequence SEQ ID NO: 6.

[0015] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a heavy chain sequence comprising at least one complementarity determining region (CDR) H1 having at least 80% identity to amino acid sequence SEQ ID NO: 4, a CDR H2 having at least 80% identity to amino acid sequence SEQ ID NO: 5, and a CDR H3 having at least 80% identity to amino acid sequence SEQ ID NO: 6.

[0016] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a heavy chain sequence comprising at least one complementarity determining region (CDR) H1 having at least 90% identity to amino acid sequence SEQ ID NO: 4, a CDR H2 having at least 90% identity to amino acid sequence SEQ ID NO: 5, and a CDR H3 having at least 90% identity to amino acid sequence SEQ ID NO: 6.

[0017] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a heavy chain sequence comprising at least one complementarity determining region (CDR) H1 having at least 95% identity to amino acid sequence SEQ ID NO: 4, a CDR H2 having at least 95% identity to amino acid sequence SEQ ID NO: 5, and a CDR H3 having at least 95% identity to amino acid sequence SEQ ID NO: 6.

[0018] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a heavy chain sequence comprising at least one complementarity determining region (CDR) H1 having at least 99% identity to amino acid sequence SEQ ID NO: 4, a CDR H2 having at least 99% identity to amino acid sequence SEQ ID NO: 5, and a CDR H3 having at least 99% identity to amino acid sequence SEQ ID NO: 6.

[0019] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a heavy chain sequence comprising at least one complementarity determining region (CDR) H1 having at least 100% identity to amino acid sequence SEQ ID NO: 4, a CDR H2 having at least 100% identity to amino acid sequence SEQ ID NO: 5, and a CDR H3 having at least 100% identity to amino acid sequence SEQ ID NO: 6.

[0020] In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a light chain sequence comprising at least one complementarity determining region (CDR) L1 having at least 80% identity to amino acid sequence SEQ ID NO: 1, a CDR L2 having at least 80% identity to amino acid sequence SEQ ID NO: 2, and a CDR L3 having at least 80% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the CDR L1 has at least 90% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 has at least 90% identity to amino acid sequence SEQ ID NO: 2, and the CDR L3 has at least 90% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the CDR L1 has at least 95% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 has at least 95% identity to amino acid sequence SEQ ID NO: 2, and the CDR L3 has at least 95% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the CDR L1 has at least 99% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 has at least 99% identity to amino acid sequence SEQ ID NO: 2, and the CDR L3 has at least 99% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the CDR L1 has at least 100% identity to amino acid sequence SEQ ID NO: 1, the CDR L2 has at least 100% identity to amino acid

sequence SEQ ID NO: 2, and the CDR L3 has at least 100% identity to amino acid sequence SEQ ID NO: 3. In some examples~~embodiments~~, the light chain variable region (VL) has at least 80% identity to amino acid sequence SEQ ID NO: 7.

[0021] In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a light chain variable region (VL) having at least 80% identity to amino acid sequence SEQ ID NO: 7. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises a heavy chain variable region (VH) having at least 80% identity to amino acid sequence SEQ ID NO: 8.

[0022] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a light chain sequence comprising a complementarity determining region (CDR) CDR L1 having at least 80% identity to amino acid sequence SEQ ID NO: 1, a CDR L2 having at least 80% identity to amino acid sequence SEQ ID NO: 2, and a CDR L3 having at least 80% identity to amino acid sequence SEQ ID NO: 3.

[0023] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a light chain sequence comprising a complementarity determining region (CDR) CDR L1 having at least 90% identity to amino acid sequence SEQ ID NO: 1, a CDR L2 having at least 90% identity to amino acid sequence SEQ ID NO: 2, and a CDR L3 having at least 90% identity to amino acid sequence SEQ ID NO: 3.

[0024] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a light chain sequence comprising a complementarity determining region (CDR) CDR L1 having at least 95% identity to amino acid sequence SEQ ID NO: 1, a CDR L2 having at least 95% identity to amino acid sequence SEQ ID NO: 2, and a CDR L3 having at least 95% identity to amino acid sequence SEQ ID NO: 3.

[0025] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a light chain sequence comprising a complementarity determining region (CDR) CDR L1 having at least 99% identity to amino acid sequence SEQ ID NO: 1, a CDR L2 having at least 99% identity to amino acid sequence SEQ ID NO: 2, and a CDR L3 having at least 99% identity to amino acid sequence SEQ ID NO: 3.

[0026] Disclosed herein, in certain examples~~embodiments~~, are an antibody or a recombinant antibody, comprising a light chain sequence comprising a complementarity determining region (CDR) CDR L1 having at least 100% identity to amino acid sequence SEQ ID NO: 1, a CDR L2 having at least 100% identity to amino acid sequence SEQ ID NO: 2, and a CDR L3 having at least 100% identity to amino acid sequence SEQ ID NO: 3.

[0027] In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a heavy chain sequence comprising at least one complementarity determining region (CDR) H1 having at

least 80% identity to amino acid sequence SEQ ID NO: 4, a CDR H2 having at least 80% identity to amino acid sequence SEQ ID NO: 5, and a CDR H3 having at least 80% identity to amino acid sequence SEQ ID NO: 6. In some examples~~embodiments~~, the CDR H1 has at least 90% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 has at least 90% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 has at least 90% identity to amino acid sequence SEQ ID NO: 6. In some examples~~embodiments~~, the CDR H1 has at least 95% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 has at least 95% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 has at least 95% identity to amino acid sequence SEQ ID NO: 6. In some examples~~embodiments~~, the CDR H1 has at least 99% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 has at least 99% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 has at least 99% identity to amino acid sequence SEQ ID NO: 6. In some examples~~embodiments~~, the CDR H1 has at least 100% identity to amino acid sequence SEQ ID NO: 4, the CDR H2 has at least 100% identity to amino acid sequence SEQ ID NO: 5, and the CDR H3 has at least 100% identity to amino acid sequence SEQ ID NO: 6. In some examples~~embodiments~~, the heavy chain variable region (VH) has at least 80% identity to amino acid sequence SEQ ID NO: 8.

[0028] In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a heavy chain variable region (VH) having at least 80% identity to amino acid sequence SEQ ID NO: 8. In some examples~~embodiments~~, the light chain variable region (VL) having at least 80% identity to amino acid sequence SEQ ID NO: 7.

[0029] In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a human heavy chain constant region or a human light chain constant region. In some examples~~embodiments~~, the human heavy chain constant region is IgG1 or IgG4 or a fragment thereof. In some examples~~embodiments~~, the heavy chain has at least 80% identity to the amino acid sequence of SEQ ID NO: 10. In some examples~~embodiments~~, the light chain has at least 80% identity to the amino acid sequence of SEQ ID NO: 9. In some examples~~embodiments~~, wherein the heavy chain has at least 80% identity to the amino acid sequence of SEQ ID NO: 12. In some examples~~embodiments~~, the heavy chain has at least 80% identity to the amino acid sequence of SEQ ID NO: 11. In some examples~~embodiments~~, heavy chain has at least 80% identity to the amino acid sequence of SEQ ID NO: 13. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises a human a human variable framework region and a murine constant region. In some examples~~embodiments~~, the antibody or the recombinant antibody further comprises a murine heavy chain constant region or a murine light chain constant region. In some examples~~embodiments~~, the antibody or the murine heavy chain constant region is IgG2A. In some examples~~embodiments~~, the heavy chain has at least 80% identity to the amino acid sequence of SEQ ID NO: 15. In some examples~~embodiments~~, the heavy chain has at least 80% identity to the amino acid sequence of

SEQ ID NO: 16. In some examples~~embodiments~~, the light chain has at least 80% identity to the amino acid sequence of SEQ ID NO: 14. In some examples~~embodiments~~, the antibody or the recombinant antibody is an antibody fragment comprising a single heavy chain, a single light chain, Fab, Fab', F(ab)', F(ab')2, Fd, scFv, a variable heavy domain, a variable light domain, a variable NAR domain, bi-specific scFv, a bi-specific Fab2, a tri-specific Fab3 a single chain binding polypeptide, a dAb fragment, or a diabody.

[0030] In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to a CD163 protein expressed on an immunosuppressive human myeloid cell, wherein binding of the antibody or the recombinant antibody to the myeloid cell promotes an immune cell function as measured by one or both of the following parameters: (i) activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (ii) proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof. In some examples~~embodiments~~, wherein activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof is measured as an increased level of IFN-γ, TNF-α, or perforin, or any combination thereof. In some examples~~embodiments~~, the immunosuppressive human myeloid cell is a macrophage or a myeloid-derived suppressor cell. In some examples~~embodiments~~, the immune cell function is in a tumor microenvironment. In some examples~~embodiments~~, the immune cell function is in vivo. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to a CD163 protein expressed on a human macrophage, wherein binding of the antibody to the macrophage increases an immunostimulatory activity in a tumor microenvironment. In some examples~~embodiments~~, the tumor microenvironment is *in vivo*. In some examples~~embodiments~~, binding of the antibody or the recombinant antibody to the macrophage reduces an immunosuppression activity of the macrophage. In some examples~~embodiments~~, binding of the antibody or the recombinant antibody to the macrophage reduces a tumor promoting activity of the macrophage. In some examples~~embodiments~~, the macrophage is a tumor-associated macrophage. In some examples~~embodiments~~, the antibody or recombinant antibody alters expression of at least one marker on the macrophage. In some examples~~embodiments~~, the CD163 protein is a glycoform of CD163. In some examples~~embodiments~~, the CD163 protein is a 150 kDa glycoform of CD163. In some examples~~embodiments~~, the antibody does not specifically bind to a 130 kDa glycoform of CD163 expressed by the human macrophage.

[0031] In some examples~~embodiments~~, the antibody or the recombinant antibody has a constant domain that enables binding to an Fc receptor. In some examples~~embodiments~~, the Fc receptor is expressed on the macrophage. In some examples~~embodiments~~, the antibody or the recombinant antibody has an antibody fragment comprising a single heavy chain, a single light chain, Fab, Fab', F(ab)', F(ab')2, Fd, scFv, a variable heavy domain, a variable light domain, a variable NAR domain, bi-specific scFv, a bi-specific Fab2, a tri-specific Fab3 a single chain binding polypeptide, a dAb fragment, or a diabody.

In some examples~~embodiments~~, at least one marker on the human macrophage is CD16, CD64, TLR2, or Siglec-15. In some examples~~embodiments~~, the human macrophage is an M2 macrophage or a M2-like macrophage. In some examples~~embodiments~~, the human macrophage is an M2a, M2b, M2c, or M2d macrophage. In some examples~~embodiments~~, the CD163 protein is a component of a cell surface complex comprising at least one other protein expressed by the macrophage. In some examples~~embodiments~~, the at least one other protein is a galectin-1 protein, a LILRB2 protein, a casein kinase II protein, or any combination thereof. In some examples~~embodiments~~, upon binding with the CD163 protein, the antibody or the antibody is internalized by the human macrophage. In some examples~~embodiments~~, binding to the CD163 protein is not cytotoxic to the macrophage. In some examples~~embodiments~~, binding to the CD163 protein promotes $CD4^+$ T cell activation, $CD4^+$ T cell proliferation, or both $CD4^+$ T cell activation and proliferation. In some examples~~embodiments~~, binding to the CD163 protein promotes expression of CD69, ICOS, OX40, PD1, LAG3, CTLA4, or any combination thereof by $CD4^+$ T cells. In some examples~~embodiments~~, binding to the CD163 protein promotes $CD8^+$ T cell activation, $CD8^+$ T cell proliferation, or both $CD8^+$ T cell activation and proliferation. In some examples~~embodiments~~, binding to the CD163 protein promotes expression of ICOS, OX40, PD1, LAG3, CTLA4, or any combination thereof by $CD8^+$ T cells. In some examples~~embodiments~~, binding to the CD163 protein reduces immunosuppression in a tumor microenvironment. In some examples~~embodiments~~, binding to the CD163 protein promotes tumor cell killing in a tumor microenvironment. In some examples~~embodiments~~, binding to the CD163 protein promotes cytotoxic lymphocyte-mediated killing of cancer cells. In some examples~~embodiments~~, binding to the CD163 protein promotes NK cell-mediated tumor cell killing. In some examples~~embodiments~~, binding to the CD163 protein promotes expression of IL-2 by T cells. In some examples~~embodiments~~, binding to the CD163 protein increases $CD4^+$ T cells, $CD196^-$ T cells, $CXCR3^+$ T cells, $CCR4^-$ T cells, or any combination thereof.

[0032] In some examples~~embodiments~~, binding to CD163 reduces immunosuppression in a tumor microenvironment caused by a macrophage. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to a CD163 protein expressed on a human macrophage, wherein binding results in at least one of the following effects: (a) reduced expression of at least one marker by the macrophage, wherein the at least one marker is CD16, CD64, TLR2, or Siglec-15; (b) internalization of the antibody by the macrophage; (c) activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; (d) proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (e) promotion of tumor cell killing in a tumor microenvironment. In some examples~~embodiments~~, the binding results in: two or more of (a) through (e); three or more of (a) through (e); four or more of (a) through (e); or all of (a) through (e). In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to a $CD163^+$ immunosuppressive myeloid

cell in a tumor microenvironment, wherein the binding reduces suppression of cytotoxic T cell-mediated killing of tumor cells in the tumor microenvironment. In some examples~~embodiments~~, the antibody or the recombinant antibody according specifically binds to a CD163 protein expressed on a human tumor-associated macrophage and reduces expression of CD16, CD64, TLR2, Siglec-15, or a combination thereof by the macrophage, for use in a method of treating cancer. In some examples~~embodiments~~, binding of the antibody or the recombinant antibody to the macrophage modulates an immune function of a cell in a tumor microenvironment. In some examples~~embodiments~~, binding of the antibody or the recombinant antibody to the macrophage promotes an anti-tumor immune function.

[0033] In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to a CD163 epitope comprising amino acid sequence of SEQ ID NO: 18. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to a CD163 epitope comprising amino acid sequence of SEQ ID NO: 19. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to a CD163 epitope comprising amino acid sequence of SEQ ID NO: 20. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to a CD163 epitope comprising each of amino acid sequence SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 20. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to CD163 with a K_D from 1nM to 100nM. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to CD163 with a K_D from 1nM to 50nM. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to CD163 with a K_D from 1nM to 10nM. In some examples~~embodiments~~, the antibody or the CD163 is human CD163. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to M2c macrophages with a K_D from 1nM to 100nM. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to M2c macrophages with a K_D from 1nM to 50nM. In some examples~~embodiments~~, the antibody or the recombinant antibody specifically binds to M2c macrophages with a K_D from 1nM to 10nM. In some examples~~embodiments~~, the M2c macrophages are human M2c macrophages.

[0034] Disclosed herein, in certain examples~~embodiments~~, are a composition comprising an antibody or a recombinant antibody and an excipient.

[0035] Disclosed herein, in certain examples~~embodiments~~, are a pharmaceutical composition, comprising an antibody or a recombinant antibody of any one of the previous examples~~embodiments~~ and a pharmaceutically acceptable carrier.

[0036] Disclosed herein, in certain examples~~embodiments~~, are a use of an antibody or a recombinant antibody of any one of the previous examples ~~embodiments~~ for the manufacture of a medicament for treating cancer in a human subject.

[0037] Disclosed herein, in certain examples~~embodiments~~, are a use of an antibody or a recombinant antibody of any one of the previous examples~~embodiments~~ for the manufacture of a medicament that reduces immunosuppression by a tumor-associated macrophage in a human subject having a cancer.

[0038] Disclosed herein, in certain examples~~embodiments~~, are a use of an antibody or a recombinant antibody of any one of the previous examples~~embodiments~~ for the manufacture of a medicament that promotes T cell-mediated tumor cell killing in a human subject having a cancer.

[0039] Disclosed herein, in certain examples~~embodiments~~, are a method of promoting an immune cell function, the method comprising: administering an antibody or a recombinant antibody of any one of the previous examples~~embodiments~~ to an individual in need thereof, and promoting an immune cell function as measured by one or both of the following parameters: (i) activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (ii) proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof. In some examples~~embodiments~~, the activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof is measured as an increased level of IFN-γ, TNF-α, or perforin, or any combination thereof. In some examples~~embodiments~~, the immunosuppressive human myeloid cell is a macrophage. In some examples~~embodiments~~, the immunosuppressive human myeloid cell is a myeloid-derived suppressor cell. In some examples~~embodiments~~, the antibody or the recombinant antibody is an antibody or a recombinant antibody of any one of the previous examples~~embodiments~~.

[0040] Disclosed herein, in certain examples~~embodiments~~, are a method of treating cancer in an individual in need thereof, the method comprising administering to the individual a therapeutically effective amount of an antibody or a recombinant antibody of any one of the previous examples~~embodiments~~, thereby treating the cancer in the individual.

[0041] Disclosed herein, in certain examples~~embodiments~~, are a method of treating cancer in an individual in need thereof, the method comprising administering to the individual a therapeutically effective amount of an antibody or a recombinant antibody of any one of the previous examples~~embodiments~~, whereby immunosuppression by a tumor-associated macrophage in the individual is reduced.

[0042] Disclosed herein, in certain examples~~embodiments~~, are a method of treating cancer in an individual in need thereof, the method comprising administering to the individual a therapeutically effective amount of an antibody or a recombinant antibody of any one of the previous examples~~embodiments~~, whereby T cell-mediated tumor cell killing in the individual is increased.

[0043] Disclosed herein, in certain examples~~embodiments~~, are a method of reducing a tumor-promoting activity of a tumor-associated macrophage in an individual in need thereof, the method comprising administering to the individual an amount of a pharmaceutical composition of any one of the previous examples~~embodiments~~ that is effective to modulate a $CD4^+$ T cell activation, $CD4^+$ T cell

proliferation, $CD8^+$ T cell activation, $CD8^+$ T cell proliferation, or any combination thereof in the tumor microenvironment.

[0044] Disclosed herein, in certain examplesembodiments, are a method of promoting lymphocyte-mediated tumor cell killing in an individual in need thereof, the method comprising administering to the individual an effective amount of an antibody or a recombinant antibody of any one of the previous examplesembodiments or a pharmaceutical composition of any one of the previous examplesembodiments.

[0045] In some examplesembodiments, the method further comprises promoting tumor cell killing in the tumor microenvironment. In some examplesembodiments, the cancer is a lung cancer or sarcoma. In some examplesembodiments, the lung cancer is a lung carcinoma or lung adenocarcinoma. In some examplesembodiments, the method further comprises administering to the individual an additional anticancer therapeutic or anticancer therapy. In some examplesembodiments, the additional anticancer therapy is surgical therapy, chemotherapy, radiation therapy, cryotherapy, hormonal therapy, immunotherapy, and cytokine therapy, and combinations thereof. In some examplesembodiments, the additional anticancer therapy is an immunotherapy. In some examplesembodiments, the immunotherapy is a composition comprising a checkpoint inhibitor.

[0046] Disclosed herein, in certain examplesembodiments, are a method of modulating an activity of a tumor-associated macrophage in a tumor microenvironment, the method comprising contacting the tumor-associated macrophage with an antibody or a recombinant antibody that binds to a CD163-expressing human macrophage and comprises at least one of the following effects: (a) the binding of the antibody reduces expression of at least one marker on the macrophage, wherein the at least one marker is CD16, CD64, TLR2, or Siglec-15; (b) upon binding of the antibody with the CD163 protein, the antibody is internalized by the human macrophage; (c) the binding of the antibody is not cytotoxic to the macrophage; (d) the binding of the antibody or the recombinant antibody produces IFN-γ, TNF-α, perforin, or any combination thereof by a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; (e) the binding of the antibody or the recombinant antibody promotes an activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; (f) the binding of the antibody or the recombinant antibody promotes a proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (g) the binding of the antibody or the recombinant antibody promotes tumor cell killing in the tumor microenvironment. In some examplesembodiments, the binding results in: two or more of (a) through (g); three or more of (a) through (g); four or more of (a) through (g); five or more of (a) through (g); six or more of (a) through (g); or all of (a) through (f).

[0047] In some examplesembodiments, the method occurs in a tumor microenvironment. In some examplesembodiments, the method occurs *in vivo*. In some examplesembodiments, binding of the antibody or the

recombinant antibody to the macrophage modulates an immune function of a cell in a tumor microenvironment. In some examples~~embodiments~~, binding of the antibody or the recombinant antibody to the macrophage promotes an anti-tumor immune function. In some examples~~embodiments~~, the antibody or the recombinant antibody comprises a constant domain and the constant domain binds to an Fc receptor. In some examples~~embodiments~~, the Fc receptor is expressed on the macrophage. In some examples~~embodiments~~, the method further comprises internalizing the antibody or the recombinant antibody by the human macrophage upon binding with the CD163 protein. In some examples~~embodiments~~, binding to the CD163 protein is not cytotoxic to the human macrophage. In some examples~~embodiments~~, the method further comprises promoting expression of CD69, ICOS, OX40, PD1, LAG3, CTLA4, or any combination thereof by $CD4^+$ T cells. In some examples~~embodiments~~, the method further comprises promoting expression of ICOS, OX40, PD1, LAG3, CTLA4, or any combination thereof by $CD8^+$ T cells. In some examples~~embodiments~~, the method comprises reducing immunosuppression in a tumor microenvironment. In some examples~~embodiments~~, the method comprises promoting cytotoxic lymphocyte-mediated killing of cancer cells. In some examples~~embodiments~~, the method comprises promoting NK cell-mediated tumor cell killing. In some examples~~embodiments~~, the method comprises promoting expression of IL-2 by T cells. In some examples~~embodiments~~, the method comprises increasing $CD4^+$ T cells, $CD196^-$ T cells, $CXCR3^+$ T cells, $CCR4^-$ T cells, or any combination thereof.

[0048] Disclosed herein, in certain examples~~embodiments~~, is an antibody that specifically binds to a CD163 protein expressed on a immunosuppressive human myeloid cell, wherein binding of the antibody to the myeloid cell promotes an immune cell function as measured by one or both of the following parameters: (i) activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (ii) proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof. In some examples~~embodiments~~, the immunosuppressive human myeloid cell is a macrophage or a myeloid-derived suppressor cell. In some examples~~embodiments~~, the activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof is measured as increased production of IFN-γ, TNF-α, perforin, or any combination thereof.

[0049] Disclosed herein, in certain examples~~embodiments~~, is an antibody that specifically binds to a CD163 protein expressed on a human macrophage, wherein binding of the antibody to the macrophage promotes an immune cell function as measured by one or both of the following parameters: (i) activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (ii) proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof. In some examples~~embodiments~~, the immune cell function is in a tumor microenvironment. In some examples~~embodiments~~, the immune cell function is *in vivo*. In some examples~~embodiments~~, the activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or

any combination thereof is measured as increased production of IFN-γ, TNF-α, perforin, or any combination thereof.

[0050] Disclosed herein, in certain examplesembodiments, is an antibody that specifically binds to a CD163 protein expressed on a human macrophage, wherein binding of the antibody to the macrophage increases an immunostimulatory activity in a tumor microenvironment. In some examplesembodiments, the tumor microenvironment is *in vivo*. In some examplesembodiments, binding of the antibody to the macrophage reduces an immunosuppression activity of the macrophage. In some examplesembodiments, binding of the antibody to the macrophage reduces a tumor promoting activity of the macrophage. In some examplesembodiments, the macrophage is a tumor-associated macrophage. In some examplesembodiments, the antibody alters expression of at least one marker on the macrophage. In some examplesembodiments, the CD163 protein is a glycoform of CD163. In some examplesembodiments, the CD163 protein is a 150 kDa glycoform of CD163. In some examplesembodiments, the antibody does not specifically bind to a 130 kDa glycoform of CD163 expressed by the human macrophage. In some examplesembodiments, the antibody has a constant domain that enables binding to an Fc receptor. In some examplesembodiments, the Fc receptor is expressed on the macrophage. In some examplesembodiments, an antibody fragment comprises a single heavy chain, a single light chain, Fab, Fab', F(ab)', $F(ab')_2$, Fd, scFv, a variable heavy domain, a variable light domain, a variable NAR domain, bi-specific scFv, a bi-specific Fab_2, a tri-specific Fab_3 a single chain binding polypeptide, a dAb fragment, or a diabody. In some examplesembodiments, at least one marker on the human macrophage is CD16, CD64, TLR2, or Siglec-15. In some examplesembodiments, the human macrophage is an M2 macrophage or a M2-like macrophage. In some examplesembodiments, the human macrophage is an M2a, M2b, M2c, or M2d macrophage. In some examplesembodiments, the CD163 protein is a component of a cell surface complex comprising at least one other protein expressed by the macrophage. In some examplesembodiments, the at least one other protein is a galectin-1 protein, a LILRB2 protein, a casein kinase II protein, or any combination thereof. In some examplesembodiments, upon binding with the CD163 protein, the antibody is internalized by the human macrophage. In some examplesembodiments, binding to the CD163 protein is not cytotoxic to the macrophage. In some examplesembodiments, binding to the CD163 protein promotes $CD4^+$ T cell activation, $CD4^+$ T cell proliferation, or both $CD4^+$ T cell activation and proliferation. In some examplesembodiments, binding to the CD163 protein promotes expression of CD69, ICOS, OX40, PD1, LAG3, CTLA4, or any combination thereof by $CD4^+$ T cells. In some examplesembodiments, binding to the CD163 protein promotes $CD8^+$ T cell activation, $CD8^+$ T cell proliferation, or both $CD8^+$ T cell activation and proliferation. In some examplesembodiments, binding to the CD163 protein promotes expression of ICOS, OX40, PD1, LAG3, CTLA4, or any combination thereof by $CD8^+$ T cells. In some examplesembodiments, binding to the CD163 protein reduces immunosuppression in a tumor microenvironment. In some

examplesembodiments, binding to the CD163 protein promotes tumor cell killing in a tumor microenvironment. In some examplesembodiments, binding to the CD163 protein promotes cytotoxic lymphocyte-mediated killing of cancer cells. In some examplesembodiments, binding to the CD163 protein promotes NK cell-mediated tumor cell killing. In some examplesembodiments, binding to the CD163 protein promotes expression of IL-2 by T cells. In some examplesembodiments, binding to the CD163 protein increases $CD4^+$ T cells, CD196- T cells, $CXCR3^+$ T cells, $CCR4^-$ T cells, or any combination thereof. In some examplesembodiments, binding to CD163 reduces immunosuppression in a tumor microenvironment caused by a macrophage.

[0051] Disclosed herein, in certain examplesembodiments, is an antibody that specifically binds to a CD163 protein expressed on a human macrophage, wherein binding results in at least one of the following effects: (a) reduced expression of at least one marker by the macrophage, wherein the at least one marker is CD16, CD64, TLR2, or Siglec-15; (b) internalization of the antibody by the macrophage; (c) activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; (d) proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (e) promotion of tumor cell killing in a tumor microenvironment. In some examplesembodiments, the binding results in: two or more of (a) through (e); three or more of (a) through (e); four or more of (a) through (e); or all of (a) through (e). In some examplesembodiments, the activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof is measured as increased production of IFN-γ, TNF-α, perforin, or any combination thereof.

[0052] Disclosed herein, in certain examplesembodiments, is an antibody that specifically binds to a $CD163^+$ immunosuppressive myeloid cell in a tumor microenvironment, wherein the binding reduces suppression of cytotoxic T cell-mediated killing of tumor cells in the tumor microenvironment.

[0053] Disclosed herein, in certain examplesembodiments, is an antibody that specifically binds to a CD163 protein expressed on a human tumor-associated macrophage and reduces expression of CD16, CD64, TLR2, Siglec-15, or a combination thereof by the macrophage, for use in a method of treating cancer. In some examplesembodiments, binding of the antibody to the macrophage modulates an immune function of a cell in a tumor microenvironment. In some examplesembodiments, binding of the antibody to the macrophage promotes an anti-tumor immune function.

[0054] In some examplesembodiments, a composition comprises an antibody according to any exampleembodiment as disclosed herein, and an excipient.

[0055] In some examplesembodiments, a pharmaceutical composition comprises an antibody according to any exampleembodiment as disclosed herein and a pharmaceutically acceptable carrier.

[0056] In some examplesembodiments, a use of an antibody as disclosed herein is for the manufacture of a medicament for treating cancer in a human subject.

[0057] In some examples~~embodiments~~, a use of an antibody as disclosed herein is for the manufacture of a medicament that reduces immunosuppression by a tumor-associated macrophage in a human subject having a cancer.

[0058] In some examples~~embodiments~~, a use of an antibody as disclosed herein is for the manufacture of a medicament that promotes T cell-mediated tumor cell killing in a human subject having a cancer.

[0059] Disclosed herein, in certain examples~~embodiments~~, is a method of promoting an immune cell function, the method comprising: specifically binding an antibody to a CD163 protein expressed on an immunosuppressive human myeloid cell; and promoting an immune cell function as measured by one or both of the following parameters: (i) activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (ii) proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof. In some examples~~embodiments~~, the immunosuppressive human myeloid cell is a macrophage. In some examples~~embodiments~~, the immunosuppressive human myeloid cell is a myeloid-derived suppressor cell. In some examples~~embodiments~~, the antibody is any example~~embodiment~~ as disclosed herein.

[0060] Disclosed herein, in certain examples~~embodiments~~, is a method of treating cancer in an individual in need thereof, the method comprising administering to the individual a therapeutically effective amount of an antibody of any one the examples~~embodiments~~ disclosed herein, thereby treating the cancer in the individual.

[0061] Disclosed herein, in certain examples~~embodiments~~, is a method of treating cancer in an individual in need thereof, the method comprising administering to the individual a therapeutically effective amount of an antibody of any one of the examples~~embodiments~~ disclosed herein, whereby immunosuppression by a tumor-associated macrophage in the individual is reduced.

[0062] Disclosed herein, in certain examples~~embodiments~~, is a method of treating cancer in an individual in need thereof, the method comprising administering to the individual a therapeutically effective amount of an antibody of any one of the examples~~embodiments~~ disclosed herein, whereby T cell-mediated tumor cell killing in the individual is increased. In some examples~~embodiments~~, the cancer is a lung cancer or sarcoma. In some examples~~embodiments~~, the lung cancer is a lung carcinoma or lung adenocarcinoma.

[0063] Disclosed herein, in certain examples~~embodiments~~, is a method of reducing a tumor promoting activity of a tumor-associated macrophage in an individual in need thereof, the method comprising administering to the individual an amount of a pharmaceutical composition according to claim 43 that is effective to modulate a $CD4^+$ T cell activation, $CD4^+$ T cell proliferation, $CD8^+$ T cell activation, $CD8^+$ T cell proliferation, or any combination thereof in the tumor microenvironment. In some examples~~embodiments~~, the method further comprises promoting tumor cell killing in the tumor microenvironment.

[0064] Disclosed herein, in certain examples~~embodiments~~, is a method of promoting lymphocyte-mediated tumor cell killing in an individual in need thereof, the method comprising administering to the individual an effective amount of a pharmaceutical composition of any one of the examples~~embodiments~~ disclosed herein.

[0065] Disclosed herein, in certain examples~~embodiments~~, is a method of modulating an activity of a tumor-associated macrophage in a tumor microenvironment, the method comprising contacting the tumor-associated macrophage with an antibody that binds to a CD163-expressing human macrophage and comprises at least one of the following effects: (a) the binding of the antibody reduces expression of at least one marker on the macrophage, wherein the at least one marker is CD16, CD64, TLR2, or Siglec-15; (b) upon binding of the antibody with the CD163 protein, the antibody is internalized by the human macrophage; (c) the binding of the antibody is not cytotoxic to the macrophage; (d) the binding of the antibody promotes an activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; (e) the binding of the antibody promotes a proliferation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof; and (f) the binding of the antibody promotes tumor cell killing in the tumor microenvironment. In some examples~~embodiments~~, the binding results in: two or more of (a) through (f); three or more of (a) through (f); four or more of (a) through (f); five or more of (a) through (f); or all of (a) through (f). In some examples~~embodiments~~, the activation of a $CD4^+$ T cell, $CD8^+$ T cell, NK cell, or any combination thereof is measured as increased production of IFN-γ, TNF-α, perforin, or any combination thereof. In some examples~~embodiments~~, the method occurs in a tumor microenvironment. In some examples~~embodiments~~, the method occurs *in vivo*. In some examples~~embodiments~~, binding of the antibody to the macrophage modulates an immune function of a cell in a tumor microenvironment. In some examples~~embodiments~~, binding of the antibody to the macrophage promotes an anti-tumor immune function. In some examples~~embodiments~~, the antibody comprises a constant domain and the constant domain binds to an Fc receptor. In some examples~~embodiments~~, the Fc receptor is expressed on the macrophage. In some examples~~embodiments~~, the method further comprises internalizing the antibody by the human macrophage upon binding with the CD163 protein. In some examples~~embodiments~~, binding to the CD163 protein is not cytotoxic to the human macrophage. In some examples~~embodiments~~, the method further comprises promoting expression of CD69, ICOS, OX40, PD1, LAG3, CTLA4, or any combination thereof by $CD4^+$ T cells. In some examples~~embodiments~~, the method further comprises promoting expression of ICOS, OX40, PD1, LAG3, CTLA4, or any combination thereof by $CD8^+$ T cells. In some examples~~embodiments~~, the method comprises reducing immunosuppression in a tumor microenvironment. In some examples~~embodiments~~, the method comprises promoting cytotoxic lymphocyte-mediated killing of cancer cells. In some examples~~embodiments~~, the method comprises promoting NK cell-mediated tumor cell killing. In some examples~~embodiments~~, the method comprises promoting expression of

IL-2 by T cells. In some examples~~embodiments~~, the method comprises increasing $CD4^+$ T cells, $CD196^-$ T cells, $CXCR3^+$ T cells, $CCR4^-$ T cells, or any combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0066] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0067] FIG. 1 shows the AB101 antibody binding to human MDSC populations.

[0068] FIG. 2 shows AB101 binds to $CD163^{Hi}$ cells.

[0069] FIG. 3 shows AB101 binding to human M2c, M1, and M0 as compared to isotype controls.

[0070] FIG. 4 shows AB101 binding to human peripheral blood T cells, B cells, NKT cells, neutrophils, monocytes, and dendritic cells, in which the isotype control is shown in gray and the AB101 binding is shown in black.

[0071] FIG. 5 shows no binding of AB101 to a panel of human primary cells, including small airway epithelial cells (SAEC), renal proximal tubule epithelial cells (RPTEC), lung microvascular endothelial cells (HMVEC), umbilical vein endothelial cells (HUVEC), aortic smooth muscle cells (AOSMC), and keratinocytes.

[0072] FIG. 6A shows the top 20 targets for AB102 based on mass spectrometry analysis of a sample after immunoprecipitation.

[0073] FIG. 6B shows the top cell surface targets for AB102 based on mass spectrometry analysis of a sample after immunoprecipitation.

[0074] FIG. 6C shows the top cell surface targets for AB102 compared to ISO (isotype negative control) based on mass spectrometry analysis of AB102 and ISO samples after immunoprecipitation.

[0075] FIG. 7 shows AB102 coimmunoprecipitates a distinct higher molecular weight glycoform of CD163.

[0076] FIG. 8 shows AB101, AB102, and the control CD163 antibody bind to huCD163, while the isotype control showed no appreciable binding

[0077] FIG. 9 shows neither AB101 nor the control anti-huCD163 antibody bound to the recombinant murine CD163 compared to a commercially available anti-muCD163 antibody, which did bind to murine CD163.

[0078] FIG. 10 shows pretreatment of M2c macrophages with polyclonal anti-CD163 antibody blocked binding of the AB101 antibody compared to treatment with goat control polyclonal antibody, which did not block binding of AB101.