

ANTI-PERIOSTIN ANTIBODIES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application Serial Number 62/779,996, filed December 14, 2018, and U.S. Provisional Application Serial Number 62/899,075, filed September 11, 2019, all of which are hereby incorporated by reference in their entireties.

BACKGROUND

[0002] Periostin (POSTN) is a matricellular protein involved in many physiological processes including epithelial-mesenchymal transition (EMT), cell-matrix interactions and inflammation. POSTN is overexpressed in several pathological contexts, including inflammation, fibrotic diseases and cancer where it correlates with poor prognosis. In cancer, POSTN is typically expressed by stromal cells such as cancer associated fibroblasts (CAFs), however POSTN expression has also been reported in cancer initiating cells (CICs) and MDSCs. POSTN regulates extracellular remodeling by binding other matricellular proteins such as fibronectin and collagen and acts as an integrin receptor ligand to promote cell survival, migration/invasion, EMT, angiogenesis and recruitment of immune cells. POSTN is hypothesized to drive tumor growth and progression by acting on multiple aspects of cancer biology including suppressing anti-tumor immunity by promoting immune exclusion and increasing immunosuppression by tumor infiltrating myeloid cells.

SUMMARY

[0003] Described herein are antibodies that inhibit periostin functions, such as integrin mediated cell attachment. Such antibodies are useful for the treatment of cancer. The anti-periostin antibodies described herein decrease the collagen content of tumors, reduce infiltration of suppressive myeloid cell populations, such as granulocytic cells and tumor associated macrophages, while increasing macrophage polarization to an M1 phenotype, and increase the accumulation and anti-tumor properties of tumor infiltrating T cells.

[0004] In one aspect, described herein is a recombinant antibody or antigen binding fragment thereof that binds periostin, wherein the antibody or antigen binding fragment thereof comprises: a) an immunoglobulin heavy chain CDR1 (CDR-H1) comprising the amino acid sequence set forth in SEQ ID NO: 1 (GYTFTSYG); b) an immunoglobulin heavy chain CDR2 (CDR-H2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 2 (ISAYNGNT), 3 (ISAYSGNT), 4

(ISAYQGNT), 5 (ISAYTGNT), or 6 (ISAYDGNT); c) an immunoglobulin heavy chain CDR3 (CDR-H3) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 7 (DILVVPFDY), 8 (DVLVVPFDY), or 9 (DMLVVPFDY); d) an immunoglobulin light chain CDR1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 10 (SSDIGSNR); e) an immunoglobulin light chain CDR2 (CDR-L2) amino comprising the amino acid sequence set forth in SEQ ID NO: 11 (SND); and f) an immunoglobulin light chain CDR3 (CDR-L3) comprising the amino acid sequence set forth in SEQ ID NO: 12 (AAWDDSLSTYV). In some examples, the antibody or antigen binding fragment thereof comprises: an immunoglobulin heavy chain CDR1 (CDR-H1) comprising the amino acid sequence set forth in SEQ ID NO: 1 (GYTFTSYG); an immunoglobulin heavy chain CDR2 (CDR-H2) comprising the amino acid sequence set forth in SEQ ID NO: 2 (ISAYNGNT); an immunoglobulin heavy chain CDR3 (CDR-H3) comprising the amino acid sequence set forth in SEQ ID NO: 9 (DMLVVPFDY); an immunoglobulin light chain CDR1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 10 (SSDIGSNR); an immunoglobulin light chain CDR2 (CDR-L2) comprising the amino acid sequence set forth in SEQ ID NO: 11 (SND); and an immunoglobulin light chain CDR3 (CDR-L3) comprising the amino acid sequence set forth in SEQ ID NO: 12 (AAWDDSLSTYV). In another aspect, described herein is a recombinant antibody or antigen binding fragment thereof that binds periostin, wherein the antibody or antigen binding fragment thereof comprises any one, two, three, four, five, or six of: a) an immunoglobulin heavy chain CDR1 (CDR-H1) comprising the amino acid sequence set forth in SEQ ID NO: 1 (GYTFTSYG); b) an immunoglobulin heavy chain CDR2 (CDR-H2) comprising an amino acid sequence set forth in SEQ ID NO: 16 (ISAYXGNT); c) an immunoglobulin heavy chain CDR3 (CDR-H3) comprising an amino acid sequence set forth in SEQ ID NO: 17 (DXLVVPFDY); d) an immunoglobulin light chain CDR1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 10 (SSDIGSNR); e) an immunoglobulin light chain CDR2 (CDR-L2) amino comprising the amino acid sequence set forth in SEQ ID NO: 11 (SND); and f) an immunoglobulin light chain CDR3 (CDR-L3) comprising the amino acid sequence set forth in SEQ ID NO: 12 (AAWDDSLSTYV). In some examples, the recombinant antibody or antigen binding fragment thereof is human, chimeric, or humanized.

In some examples, the recombinant antibody or antigen binding fragment thereof is an IgG antibody. In certain examples, the recombinant antibody or antigen binding fragment thereof comprises one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof. In certain examples, the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise one or more mutations or sets of mutations selected from: N434A, N434H, T307A/E380A/N434A, M252Y/S254T/T256E, 433K/434F/436H, T250Q, T250F, M428L, M428F, T250Q/M428L, N434S, V308W, V308Y, V308F, M252Y/M428L, D259I/V308F, M428L/V308F, Q311V/N434S, T307Q/N434A, E258F/V427T, S228P, L235E, S228P/L235E/R409K, S228P/L235E, K370Q, K370E, deletion of G446, deletion of K447, and combinations thereof of IgG4 according to the EU numbering system. In certain examples, the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise S228P, F234A, and L235A mutations of IgG4 according to the EU numbering system. In some examples, the recombinant antibody or antigen binding fragment thereof is a Fab, F(ab)₂, a single-domain antibody, or a single chain variable fragment (scFv). In some examples, the antibody or antigen binding fragment thereof comprises an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region: wherein the

immunoglobulin heavy chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 13; and wherein the immunoglobulin light chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 14, wherein the amino acid at amino acid residue number 55 of SEQ ID NO: 13 is asparagine, serine, glutamine, threonine, or aspartic acid, and wherein the amino acid at amino acid residue number 100 of SEQ ID NO: 13 is methionine, isoleucine, or valine. In another aspect, described herein is a recombinant antibody or antigen binding fragment thereof that binds periostin, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region: a) wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 13; and b) wherein the immunoglobulin light chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 14; wherein amino acid residue number 55 of SEQ ID NO 13: is asparagine, serine, glutamine, threonine, or aspartic acid, or wherein amino acid number 100 of SEQ ID NO: 13 is methionine, isoleucine, or valine. In another aspect, described herein is a recombinant antibody or antigen binding fragment thereof that binds periostin, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region: a) wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 13; and b) wherein the immunoglobulin light chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 14. In another aspect, described herein is a recombinant antibody or antigen binding fragment thereof that binds periostin, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region: a) wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence identical to that set forth in SEQ ID NO: 13; and b) wherein the immunoglobulin light chain variable region comprises an amino acid sequence identical to that set forth in SEQ ID NO: 14.

In some examples, the recombinant antibody or antigen binding fragment thereof requires at least one of the following residues: N276, R284, E288, L287, V295, or K302 of SEQ ID NO: 15 for specific binding to periostin. In some examples, the recombinant antibody or antigen binding fragment thereof requires at least two, three, four or five of the following residues: N276, R284, E288, L287, V295, or K302 of SEQ ID NO: 15 for specific binding to periostin. In some examples, the recombinant antibody or antigen binding fragment thereof requires at least all of the following residues: N276, R284, E288, L287, V295, or K302 of SEQ ID NO: 15 for specific binding to periostin. In another aspect, also described herein is a pharmaceutical composition comprising the recombinant antibody or antigen binding fragment thereof described above and a pharmaceutically acceptable excipient, carrier, or diluent. In some examples, the pharmaceutical composition is formulated for intravenous administration. In some examples, the pharmaceutical composition is formulated for subcutaneous administration. In some examples, the pharmaceutical composition is formulated for intratumoral administration. In another aspect, also described herein is the recombinant antibody or antigen binding fragment thereof described above or the pharmaceutical composition described above for use in decreasing collagen content in a tumor. The recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition is for use in treating cancer. In another aspect, described herein is the use of the recombinant antibody or antigen binding fragment thereof described above or the pharmaceutical composition described above in the manufacture of a medicament for treating cancer. In another aspect, described herein is the recombinant antibody or antigen binding fragment thereof described above or the pharmaceutical composition described above for use in treating a cancer. In some examples, the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer. Also described herein is a method of decreasing collagen content in a tumor in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition.

Also described herein is a method of increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. In another aspect, also described herein is the recombinant antibody or antigen binding fragment thereof described above or the pharmaceutical composition described above for use in increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor. Also described herein is a method of reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. In another aspect, also described herein is the recombinant antibody or antigen binding fragment thereof described above or the pharmaceutical composition described above for use in reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in a tumor.

Also described herein is a method of increasing the frequency of CD4⁺ and/or CD8⁺ T cells in a tumor of an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. In another aspect, also described herein is the recombinant antibody or antigen binding fragment thereof described above or the pharmaceutical composition described above for use in increasing the frequency of CD4⁺ and/or CD8⁺ T cells in a tumor. In another aspect, also described herein is the recombinant antibody or antigen binding fragment thereof described above or the pharmaceutical composition described above for use in increasing the frequency of CD8⁺ T cells in a tumor. Also described herein is a method of increasing the function of CD8⁺ T cells in a tumor, measured by interferon gamma expression and/or release by CD8⁺ T cells in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. In another aspect, also described herein is the recombinant antibody or antigen binding fragment thereof described above or the pharmaceutical composition described above for use in increasing CD8⁺ T cell function as measured by interferon gamma expression and/or release by CD8⁺ T cells. Also described herein is a method of treating cancer in an individual comprising administering to the individual a therapeutically effective amount of the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. In some examples, the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer. In another aspect, also described herein is a method of making a composition for decreasing collagen content in a tumor comprising admixing the recombinant antibody or antigen binding fragment thereof described above and a pharmaceutically acceptable excipient, carrier, or diluent. In another aspect, also described herein is a method of making a composition for increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor comprising admixing the recombinant antibody or antigen binding fragment thereof described above and a pharmaceutically acceptable excipient, carrier, or diluent.

In another aspect, also described herein is a method of making a composition for reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof described above and a pharmaceutically acceptable excipient, carrier, or diluent. In another aspect, also described herein is a method of making a composition for increasing the frequency of CD4⁺ and/or CD8⁺ T cells in a tumor of an individual comprising admixing the recombinant antibody or antigen binding fragment thereof described above and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making a composition for increasing the function of CD8⁺ T cells in a tumor, measured by interferon gamma expression and/or release by CD8⁺ T cells in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. In another aspect, described herein is a method of making a composition for increasing interferon gamma expression and/or release by CD8⁺ T cells in a tumor in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof described above and a pharmaceutically acceptable excipient, carrier, or diluent. In another aspect, described herein is a method of making a composition for treating cancer comprising admixing the recombinant antibody or antigen binding fragment thereof described above and a pharmaceutically acceptable excipient, carrier, or diluent. In some examples, the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer.

[0005] Also described herein is a recombinant antibody or antigen binding fragment thereof that binds periostin, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region: wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 13; and wherein the immunoglobulin light chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 14, wherein amino acid residue number 55 of SEQ ID NO 13: is asparagine, serine, glutamine, threonine, or aspartic acid, and wherein amino acid residue number 100 of SEQ ID NO: 13 is methionine, isoleucine, or valine. In some examples, the recombinant antibody or antigen binding fragment thereof is a human antibody. In some examples, the recombinant antibody or antigen binding fragment thereof is an IgG antibody. In certain examples, the recombinant antibody or antigen binding fragment thereof comprises one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof. In certain examples, the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise one or more mutations or sets of mutations selected from: N434A, N434H, T307A/E380A/N434A, M252Y/S254T/T256E, 433K/434F/436H, T250Q, T250F, M428L, M428F, T250Q/M428L, N434S, V308W, V308Y, V308F, M252Y/M428L, D259I/V308F, M428L/V308F, Q311V/N434S, T307Q/N434A, E258F/V427T, S228P, L235E, S228P/L235E/R409K, S228P/L235E, K370Q, K370E, deletion of G446, deletion of K447, and combinations thereof of IgG4 according to the EU numbering system. In certain examples, the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise S228P, F234A, and L235A mutations of IgG4 according to the EU numbering system. In some examples, the recombinant antibody or antigen binding fragment thereof is a Fab, F(ab)2, a single-domain antibody, or a single chain variable fragment (scFv). Also described herein is a pharmaceutical composition comprising the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. In some examples, the pharmaceutical composition is formulated for intravenous administration. In some examples, the pharmaceutical composition is formulated for subcutaneous administration. In some examples, the pharmaceutical composition is formulated for intratumoral administration. Also described herein is the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition for use in decreasing collagen content in a tumor. In some examples, the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition is for use in treating cancer. In some examples, the cancer comprises glioblastoma, pancreatic

cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer. Also described herein is a method of decreasing collagen content in a tumor in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of increasing the frequency of CD4⁺ and/or CD8⁺ T cells in a tumor of an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of increasing the function of CD8⁺ T cells in a tumor, as measured by interferon gamma expression and/or release by CD8⁺ T cells in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of treating cancer in an individual comprising administering to the individual a therapeutically effective amount of the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. In some examples, the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer. Also described herein is a method of making composition for decreasing collagen content in a tumor comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making composition for increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making a composition for reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making a composition for increasing the frequency of CD4⁺ and/or CD8⁺ T cells in a tumor in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof

and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making a composition for increasing the function of CD8⁺ T cells in a tumor, as measured by interferon gamma expression and/or release by CD8⁺ T cells in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making composition for treating cancer comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. In some examples, the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer.

Also described herein is a recombinant antibody or antigen binding fragment thereof that binds periostin, wherein when bound to periostin, the recombinant antibody or antigen binding fragment thereof binds to the Fasciclin 2 (FAS2) domain of periostin. In another aspect, also described herein is a recombinant antibody or antigen binding fragment thereof that binds to the Fasciclin 2 (FAS2) domain of periostin. In some examples, the recombinant antibody or antigen binding fragment thereof binds to any residue between and including amino acid residues 276 to 302 of periostin (SEQ ID NO: 15). In some examples, when bound to periostin, the recombinant antibody or antigen binding fragment thereof binds to at least one of the following residues: N276, R284, E288, L287, V295, or K302 of periostin (SEQ ID NO: 15). In some examples, when bound to periostin, the recombinant antibody or antigen binding fragment thereof binds to two, three, four, or five of the following residues: N276, R284, E288, L287, V295, or K302 of periostin (SEQ ID NO: 15). In some examples, when bound to periostin, the recombinant antibody or antigen binding fragment thereof binds to all of the following residues: N276, R284, E288, L287, V295, or K302 of periostin (SEQ ID NO: 15).

In some examples, the antibody or antigen binding fragment thereof comprises an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region: wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 13; and wherein the immunoglobulin light chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 14, wherein amino acid residue number 55 of SEQ ID NO: 13 is asparagine, serine, glutamine, threonine, or aspartic acid, and wherein amino acid residue number 100 of SEQ ID NO: 13 is methionine, isoleucine, or valine. In some examples, the antibody or antigen binding fragment thereof comprises: an immunoglobulin heavy chain CDR1 (CDR-H1) comprising the amino acid sequence set forth in SEQ ID NO: 1 (GYTFTSYG); an immunoglobulin heavy chain CDR2 (CDR-H2) comprising an amino acid

sequence set forth in any one of SEQ ID Nos: 2 (ISAYNGNT), 3 (ISAYSGNT), 4 (ISAYQGNT), 5 (ISAYTGNT), or 6 (ISAYDGNT); an immunoglobulin heavy chain CDR3 (CDR-H3) comprising an amino acid sequence set forth in any one of SEQ ID Nos: 7 (DILVVPFDY), 8 (DVLVVPFDY), or 9 (DMLVVPFDY); an immunoglobulin light chain CDR1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 10 (SSDIGSNR); an immunoglobulin light chain CDR2 (CDR-L2) amino comprising the amino acid sequence set forth in SEQ ID NO: 11 (SND); and an immunoglobulin light chain CDR3 (CDR-L3) comprising the amino acid sequence set forth in SEQ ID NO: 12 (AAWDDSLSTYV). In some examples, the antibody has an IC₅₀ of less than about 50 nanomolar in a cell adhesion assay performed with human lung fibroblast cells and/or mouse fibroblast cells. Also described herein is a pharmaceutical composition comprising the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. In some examples, the pharmaceutical composition is formulated for intravenous administration. In some examples, the pharmaceutical composition is formulated for subcutaneous administration. In some examples, the pharmaceutical composition is formulated for intratumoral administration. Also described herein is the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition for use in decreasing collagen content in a tumor. In some examples, the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition is for use in treating cancer. In some examples, the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer. Also described herein is a method of decreasing collagen content in a tumor in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of increasing the frequency of CD4⁺ and/or CD8⁺ T cells in a tumor in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of increasing the function of CD8⁺ T cells in a tumor, as measured by interferon gamma expression and/or release by CD8⁺ T

cells in an individual comprising administering to the individual the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. Also described herein is a method of treating cancer in an individual comprising administering to the individual a therapeutically effective amount of the recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition. In some examples, the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer. Also described herein is a method of making composition for decreasing collagen content in a tumor comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making composition for increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making a composition for reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making a composition for increasing the frequency of CD4⁺ and/or CD8⁺ T cells in a tumor of an individual comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making a composition for increasing the function of CD8⁺ T cells in a tumor, as measured by interferon gamma expression and/or release by CD8⁺ T cells in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. Also described herein is a method of making composition for treating cancer comprising admixing the recombinant antibody or antigen binding fragment thereof and a pharmaceutically acceptable excipient, carrier, or diluent. In some examples, the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer.

[0006] Also described herein is a nucleic acid encoding any one of the recombinant antibodies or antigen binding fragments thereof described above. In another aspect, also described herein is a nucleic acid encoding the recombinant antibody or antigen binding fragment thereof described above.

[0007] In another aspect, also described herein is a cell line comprising the nucleic acid described above. In some examples, the cell line is a Chinese Hamster Ovary cell line. Also described herein is a method of producing the recombinant antibody or antigen binding fragment thereof comprising

incubating the cell line in a cell culture medium under conditions sufficient to allow expression and secretion of any one of the recombinant antibodies or antigen binding fragments thereof. In another aspect, also described herein is a method of producing the recombinant antibody or antigen binding fragment thereof described above comprising incubating the cell line described above in a cell culture medium under conditions sufficient to allow expression and secretion of the recombinant antibody or antigen binding fragment thereof described above.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] The novel features described herein are set forth with particularity in the appended claims. A better understanding of the features and advantages of the features described herein will be obtained by reference to the following detailed description that sets forth illustrative examples, in which the principles of the features described herein are utilized, and the accompanying drawings of which:

[0009] **FIG. 1** illustrates inhibition of periostin (POSTN) mediated cell attachment by 78 sequence unique IgGs tested at a single concentration of 500nM.

[0010] **FIG. 2** illustrates tumor growth in the mouse MB49 bladder cancer model following treatment with NB0828 or vehicle control.

[0011] **FIG. 3** illustrates the impact of NB0828 treatment on accumulation of intratumoral myeloid cells. MB49 tumor-bearing mice were treated with NB0828 or vehicle as described in **FIG. 2**. Data is presented as percent of total CD45+ immune infiltrate.

[0012] **FIG. 4** illustrates changes in total tumor collagen content following treatment with NB0828. MB49 tumor-bearing mice were treated as described in **FIG. 2**, and total tumor collagen content of endpoint MB49 tumors was assessed as described in the methods.

[0013] **FIG. 5** illustrates tumor growth in the mouse CT26 colon cancer model following treatment with NB0828 or vehicle control.

[0014] **FIG. 6** illustrates reduced intratumoral accumulation of granulocytic cells/TAMs (Tumor associated macrophages) and macrophage skewing towards an M1 phenotype in NB0828 treated CT26 tumor-bearing mice.

[0015] **FIG. 7** illustrates increased accumulation of CD8+ and CD4+ tumor infiltrating lymphocytes (TILs) and enhanced CD8+ TIL function in NB0828 treated CT26 tumor-bearing mice.

[0016] **FIG. 8** illustrates tumor growth in the mouse MC38 colon cancer model following treatment with NB0828 or vehicle control.

[0017] **FIGS. 9A-9D** illustrate that in the MC38 colon cancer model NB0828 decreases the overall amount of tumor associated macrophages (**9A**), while increasing the frequency of pro-inflammatory type I macrophages (**9B**), and CD8⁺ T cells (**9C**), and that NB0828 tumor efficacy is dependent on CD8⁺ T cells (**9D**).

[0018] **FIG. 10** illustrates a schematic for generating transforming growth factor beta-induced protein (BIGH3)/Periostin chimeras for epitope mapping studies.

CLAIMS

WHAT IS CLAIMED IS:

1. A recombinant antibody or antigen binding fragment thereof that binds periostin, wherein the antibody or antigen binding fragment thereof comprises:
 - a) an immunoglobulin heavy chain CDR1 (CDR-H1) comprising the amino acid sequence set forth in SEQ ID NO: 1 (GYTFTSYG);
 - b) an immunoglobulin heavy chain CDR2 (CDR-H2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 2 (ISAYNGNT), 3 (ISAYSGNT), 4 (ISAYQGNT), 5 (ISAYTGNT), or 6 (ISAYDGNT);
 - c) an immunoglobulin heavy chain CDR3 (CDR-H3) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 7 (DILVVPFDY), 8 (DVLVVPFDY), or 9 (DMLVVPFDY);
 - d) an immunoglobulin light chain CDR1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 10 (SSDIGSNR);
 - e) an immunoglobulin light chain CDR2 (CDR-L2) comprising the amino acid sequence set forth in SEQ ID NO: 11 (SND); and
 - f) an immunoglobulin light chain CDR3 (CDR-L3) comprising the amino acid sequence set forth in SEQ ID NO: 12 (AAWDDSLSTYV).
2. A recombinant antibody or antigen binding fragment thereof that binds periostin, wherein the antibody or antigen binding fragment thereof comprises any one, two, three, four, five, or six of:
 - a) an immunoglobulin heavy chain CDR1 (CDR-H1) comprising the amino acid sequence set forth in SEQ ID NO: 1 (GYTFTSYG);
 - b) an immunoglobulin heavy chain CDR2 (CDR-H2) comprising an amino acid sequence set forth in SEQ ID NO: 16 (ISAYXGNT);
 - c) an immunoglobulin heavy chain CDR3 (CDR-H3) comprising an amino acid sequence set forth in SEQ ID NO: 17 (DXLVVPFDY);
 - d) an immunoglobulin light chain CDR1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 10 (SSDIGSNR);
 - e) an immunoglobulin light chain CDR2 (CDR-L2) comprising the amino acid sequence set forth in SEQ ID NO: 11 (SND); and
 - f) an immunoglobulin light chain CDR3 (CDR-L3) comprising the amino acid sequence set forth in SEQ ID NO: 12 (AAWDDSLSTYV);

wherein X is any amino acid residue.

3. The recombinant antibody or antigen binding fragment thereof of claim 1 or 2, wherein the recombinant antibody or antigen binding fragment thereof comprises:
 - a) an immunoglobulin heavy chain CDR1 (CDR-H1) comprising the amino acid sequence set forth in SEQ ID NO: 1 (GYTFTSYG);
 - b) an immunoglobulin heavy chain CDR2 (CDR-H2) comprising the amino acid sequence set forth in SEQ ID NO: 2 (ISAYNGNT);
 - c) an immunoglobulin heavy chain CDR3 (CDR-H3) comprising the amino acid sequence set forth in SEQ ID NO: 9 (DMLVVPFDY);
 - d) an immunoglobulin light chain CDR1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 10 (SSDIGSNR);
 - e) an immunoglobulin light chain CDR2 (CDR-L2) comprising the amino acid sequence set forth in SEQ ID NO: 11 (SND); and
 - f) an immunoglobulin light chain CDR3 (CDR-L3) comprising the amino acid sequence set forth in SEQ ID NO: 12 (AAWDDSLSTYV).
4. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 3, wherein the recombinant antibody or antigen binding fragment thereof is human, chimeric, or humanized.
5. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 4, wherein the recombinant antibody or antigen binding fragment thereof is an IgG antibody.
6. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 5, wherein the recombinant antibody or antigen binding fragment thereof comprises one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof.
7. The recombinant antibody or antigen binding fragment thereof of claim 6, wherein the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise one or more mutations or sets of mutations selected from: N434A, N434H, T307A/E380A/N434A, M252Y/S254T/T256E, 433K/434F/436H, T250Q, T250F, M428L, M428F, T250Q/M428L, N434S, V308W, V308Y, V308F, M252Y/M428L, D259I/V308F, M428L/V308F, Q311V/N434S, T307Q/N434A, E258F/V427T, S228P, L235E, S228P/L235E/R409K, S228P/L235E, K370Q, K370E, deletion of G446, deletion of K447, and combinations thereof of IgG4 according to the EU numbering system.

8. The recombinant antibody or antigen binding fragment thereof of claim 6, wherein the more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise: S228P, F234A, and L235A mutations of IgG4 according to the EU numbering system.
9. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 5, wherein the recombinant antibody or antigen binding fragment thereof is a Fab, F(ab)₂, a single-domain antibody, or a single chain variable fragment (scFv).
10. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 9, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region:
 - a) wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 13; and
 - b) wherein the immunoglobulin light chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 14;wherein amino acid residue number 55 of SEQ ID NO: 13 is asparagine, serine, glutamine, threonine, or aspartic acid, or wherein amino acid residue number 100 of SEQ ID NO: 13 is methionine, isoleucine, or valine.
11. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 10, wherein the recombinant antibody or antigen binding fragment thereof when bound to periostin contacts one of the following amino acid residues: N276, R284, E288, L287, V295, and K302 of SEQ ID NO: 15.
12. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 11, wherein the recombinant antibody or antigen binding fragment thereof when bound to periostin contacts two, three, four, or five of the following amino acid residues: N276, R284, E288, L287, V295, and K302 of SEQ ID NO: 15.
13. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 12, wherein the recombinant antibody or antigen binding fragment thereof when bound to periostin contacts all of the following amino acid residues: N276, R284, E288, L287, V295, and K302 of SEQ ID NO: 15.
14. A recombinant antibody or antigen binding fragment thereof that binds periostin, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region:

- a) wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 13; and
 - b) wherein the immunoglobulin light chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 14;
- wherein amino acid residue number 55 of SEQ ID NO 13: is asparagine, serine, glutamine, threonine, or aspartic acid, or wherein amino acid number 100 of SEQ ID NO: 13 is methionine, isoleucine, or valine.
15. A recombinant antibody or antigen binding fragment thereof that binds periostin, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region:
- a) wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 13; and
 - b) wherein the immunoglobulin light chain variable region comprises an amino acid sequence which is at least about 90%, 95%, 97%, 99%, or which is 100% identical to that set forth in SEQ ID NO: 14.
16. A recombinant antibody or antigen binding fragment thereof that binds periostin, comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region:
- a) wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence identical to that set forth in SEQ ID NO: 13; and
 - b) wherein the immunoglobulin light chain variable region comprises an amino acid sequence identical to that set forth in SEQ ID NO: 14.
17. The recombinant antibody or antigen binding fragment thereof of any one of claims 14 to 16, wherein the recombinant antibody or antigen binding fragment thereof is human, humanized, or chimeric.
18. The recombinant antibody or antigen binding fragment thereof of any one of claims 14 to 17, wherein the recombinant antibody or antigen binding fragment thereof is an IgG antibody.
19. The recombinant antibody or antigen binding fragment thereof of any one of claims 14 to 18, wherein the recombinant antibody or antigen binding fragment thereof comprises one

or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof.

20. The recombinant antibody or antigen binding fragment thereof of claim 19, wherein the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise one or more mutations or sets of mutations selected from: N434A, N434H, T307A/E380A/N434A, M252Y/S254T/T256E, 433K/434F/436H, T250Q, T250F, M428L, M428F, T250Q/M428L, N434S, V308W, V308Y, V308F, M252Y/M428L, D259I/V308F, M428L/V308F, Q311V/N434S, T307Q/N434A, E258F/V427T, S228P, L235E, S228P/L235E/R409K, S228P/L235E, K370Q, K370E, deletion of G446, deletion of K447, and combinations thereof of IgG4 according to the EU numbering system.
21. The recombinant antibody or antigen binding fragment thereof of claim 19, wherein the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise: S228P, F234A, and L235A mutations of IgG4 according to the EU numbering system.
22. The recombinant antibody or antigen binding fragment thereof of any one of claims 14 to 16, wherein the recombinant antibody or antigen binding fragment thereof is a Fab, F(ab)₂, a single-domain antibody, or a single chain variable fragment (scFv).
23. A recombinant antibody or antigen binding fragment thereof that binds to the Fasciclin 2 (FAS2) domain of periostin.
24. The recombinant antibody or antigen binding fragment thereof of claim 23, wherein the recombinant antibody or antigen binding fragment thereof when bound to periostin contacts an amino acid residue selected from amino acid 276 to 302 of SEQ ID NO: 15.
25. The recombinant antibody or antigen binding fragment thereof of claims 23 or 24, wherein the recombinant antibody or antigen binding fragment thereof when bound to periostin contacts one of the following amino acid residues: N276, R284, E288, L287, V295, or K302 and SEQ ID NO: 15.
26. The recombinant antibody or antigen binding fragment thereof of any one of claims 23 to 25, wherein the recombinant antibody or antigen binding fragment thereof when bound to periostin contacts two, three, four, or five of the following amino acid residues: N276, R284, E288, L287, V295, and K302 of SEQ ID NO: 15.
27. The recombinant antibody or antigen binding fragment thereof of any one of claims 23 to 26, wherein the recombinant antibody or antigen binding fragment thereof when bound to

periostin contacts all of the following amino acid residues: N276, R284, E288, L287, V295, or K302 and SEQ ID NO: 15.

28. The recombinant antibody or antigen binding fragment thereof of any one of claims 23 to 27, wherein the antibody or antigen binding fragment thereof comprises:
- a) an immunoglobulin heavy chain CDR1 (CDR-H1) comprising the amino acid sequence set forth in SEQ ID NO: 1 (GYTFTSYG);
 - b) an immunoglobulin heavy chain CDR2 (CDR-H2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 2 (ISAYNGNT), 3 (ISAYSGNT), 4 (ISAYQGNT), 5 (ISAYTGNT), or 6 (ISAYDGNT);
 - c) an immunoglobulin heavy chain CDR3 (CDR-H3) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 7 (DILVVPFDY), 8 (DVLVVPFDY), or 9 (DMLVVPFDY);
 - d) an immunoglobulin light chain CDR1 (CDR-L1) comprising the amino acid sequence set forth in SEQ ID NO: 10 (SSDIGSNR);
 - e) an immunoglobulin light chain CDR2 (CDR-L2) comprising the amino acid sequence set forth in SEQ ID NO: 11 (SND); and
 - f) an immunoglobulin light chain CDR3 (CDR-L3) comprising the amino acid sequence set forth in SEQ ID NO: 12 (AAWDDSLSTYV).
29. The recombinant antibody or antigen binding fragment thereof of any one of claims 23 to 28, wherein the recombinant antibody or antigen binding fragment thereof is chimeric, humanized, or human.
30. The recombinant antibody or antigen binding fragment thereof of any one of claims 23 to 29, wherein the recombinant antibody or antigen binding fragment thereof is an IgG antibody.
31. The recombinant antibody or antigen binding fragment thereof of any one of claims 23 to 30, wherein the recombinant antibody or antigen binding fragment thereof comprises one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof.
32. The recombinant antibody or antigen binding fragment thereof of claim 31, wherein the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise one or more mutations or sets of mutations is selected from: N434A, N434H, T307A/E380A/N434A, M252Y/S254T/T256E, 433K/434F/436H, T250Q, T250F, M428L, M428F, T250Q/M428L, N434S, V308W, V308Y, V308F, M252Y/M428L, D259I/V308F,

M428L/V308F, Q311V/N434S, T307Q/N434A, E258F/V427T, S228P, L235E, S228P/L235E/R409K, S228P/L235E, K370Q, K370E, deletion of G446, deletion of K447, and combinations thereof of IgG4 according to the EU numbering system.

33. The recombinant antibody or antigen binding fragment thereof of claim 31, wherein the one or more mutations to reduce one or more effector functions of the recombinant antibody or antigen binding fragment thereof comprise S228P, F234A, and L235A mutations of IgG4 according to the EU numbering system.
34. The recombinant antibody or antigen binding fragment thereof of any one of claims 23 to 30, wherein the recombinant antibody or antigen binding fragment thereof is a Fab, F(ab)₂, a single-domain antibody, or a single chain variable fragment (scFv).
35. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 34, wherein the antibody has an IC₅₀ of less than about 50 nanomolar in a cell adhesion assay performed with human lung fibroblast cells and/or mouse fibroblast cells.
36. A nucleic acid encoding the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35.
37. A cell line comprising the nucleic acid of claim 36.
38. The cell line of claim 37, wherein the cell line is a Chinese Hamster Ovary cell line.
39. A pharmaceutical composition comprising the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 and a pharmaceutically acceptable excipient, carrier, or diluent.
40. The pharmaceutical composition of claim 39, formulated for intravenous administration.
41. The pharmaceutical composition of claim 39, formulated for subcutaneous administration.
42. The pharmaceutical composition of claim 39, formulated for intratumoral administration.
43. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 or the pharmaceutical composition of any one of claims 39 to 42 for use in decreasing collagen content in a tumor.
44. Use of the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 or the pharmaceutical composition of any one of claims 39 to 42 in the manufacture of a medicament for treating cancer.
45. The use of claim 44, wherein the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer.

46. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 or the pharmaceutical composition of any one of claims 39 to 42 for use in treating a cancer.
47. The recombinant antibody or antigen binding fragment thereof or the pharmaceutical composition for use of claim 46, wherein the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer.
48. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 or the pharmaceutical composition of any one of claims 39 to 42 for use in increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor.
49. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 or the pharmaceutical composition of any one of claims 39 to 42 for use in reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in a tumor.
50. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 or the pharmaceutical composition of any one of claims 39 to 42 for use in increasing the frequency of CD4⁺ and/or CD8⁺ T cells in a tumor.
51. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 or the pharmaceutical composition of any one of claims 39 to 42 for use in increasing the frequency of CD8⁺ T cells in a tumor.
52. The recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 or the pharmaceutical composition of any one of claims 39 to 42 for use in increasing CD8⁺ T cell function as measured by interferon gamma expression and/or release by CD8⁺ T cells.
53. A method of making a composition for decreasing collagen content in a tumor comprising admixing the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 and a pharmaceutically acceptable excipient, carrier, or diluent.
54. A method of making a composition for increasing M1 macrophage phenotype and/or reducing M2 macrophage phenotype in a tumor comprising admixing the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 and a pharmaceutically acceptable excipient, carrier, or diluent.
55. A method of making a composition for reducing accumulation of suppressive granulocytic myeloid cells and/or tumor associated macrophages in an individual

- comprising admixing the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 and a pharmaceutically acceptable excipient, carrier, or diluent.
56. A method of making a composition for increasing the frequency of CD4+ and/or CD8+ T cells in a tumor of an individual comprising admixing the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 and a pharmaceutically acceptable excipient, carrier, or diluent.
57. A method of making a composition for increasing interferon gamma expression and/or release by CD8+ T cells in a tumor in an individual comprising admixing the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 and a pharmaceutically acceptable excipient, carrier, or diluent.
58. A method of making a composition for treating a cancer comprising admixing the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 and a pharmaceutically acceptable excipient, carrier, or diluent.
59. The method of claim 58, wherein the cancer comprises glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, skin cancer, stomach cancer, mesothelioma, liver cancer, endometrial cancer, colon cancer, cervical cancer, prostate cancer, or lung cancer.
60. A method of producing the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35 comprising incubating the cell line of claims 37 or 38 in a cell culture medium under conditions sufficient to allow expression and secretion of the recombinant antibody or antigen binding fragment thereof of any one of claims 1 to 35.