Kaufmann, S., Gordon, S. & Medzhitov, R.) 71-94 (ASM Press, New York, 2004); Ross and Auger, *in*: *The macrophage* (eds. Burke, B. & Lewis, C.) (Oxford University Press, Oxford, 2002)).

[0005] The cognate receptor, which is the c-fms proto-oncogene (also known as M-CSFR, CSF-1R or CD115), is a 165-kD glycoprotein with an associated tyrosine kinase activity and belongs to the class III receptor tyrosine kinase family that includes PDGFR-α, PDGFR-β, VEGFR1, VEGFR2, VEGFR3, Flt3 and c-kit. Blume-Jensen and Hunter, 2001, *Nature* 411:355-365; Schlessinger and Ullrich, 1992, *Neuron* 9:383-391; Sherr *et al.*, 1985 *Cell* 41:665-676; van der Geer *et al.*, 1994, *Annu. Rev. Cell. Biol.* 10:251-337. The oncogenic form of c-fms, v-fms, which is carried by the McDonough strain of feline sarcoma virus is mutated to confer constitutively activated protein kinase activity (Sherr et al., 1985, *Cell* 41:665-676; Roussel and Sherr, 2003, Cell Cycle 2: 5-6). Expression of c-fms in normal cells is restricted to myelomonocytic cells (including monocytes, tissue macrophages, Kupffer cells, Langerhans cells, microglial cells and osteoclasts), hematopoietic precursors and trophoblasts. Arai *et al.,* 1999, *J. Exp. Med.* 190:1741-1754; Dai *et al.*, 2002, *Blood* 99:111-120; Pixley and Stanley, 2004, *Trends Cell Biol.* 14:628-638. Expression of c-fms has also been demonstrated in some tumor cells (Kirma *et al.*, 2007, *Cancer Res* 67:1918-1926). A variety of *in vitro* studies and analyses of mutant mice demonstrate that CSF-1 is a ligand for c-fms(see, e.g., Bourette and Rohrschneider, 2000, *Growth Factors* 17:155-166; Wiktor-Jedrzejczak *et al.*, 1990, *Proc. Natl. Acad. Sci. U.S.A.* 87:4828-4832; Yoshida *et al.*, 1990, *Nature* 345:442-444; van Wesenbeeck and van Hul, 2005, *Crit. Rev. Eukaryot. Gene Expr.* 15:133-162). Binding of CSF-1 to c-fms induces autophosphorylation of the receptor at particular sites that result in downstream activation of signaling pathways including PI3-K/AKT and Ras/Raf/MEK/MAPK and macrophage differentiation is mediated primarily through persistent MEK activity (Gosse *et al.*, 2005, *Cellular Signaling* 17:1352-1362). Very recent evidence indicates that interleukin-34 (IL-34) is also a ligand for c-fms (Lin, *et al*. 2008, *Science* 320:807-811).

SUMMARY

[0006] Antigen-binding proteins that bind c-fms, including human c-fms, are described herein. The human c-fms antigen-binding proteins were found to inhibit, interfere with, or modulate at least one of the biological responses related to c-fms, and, as such, are useful for ameliorating the effects of c-fms-related diseases or disorders. Binding of certain antigen-binding proteins to c-fms can, therefore, have one or more of the following activities: inhibiting, interfering with, or modulating c-fms–CSF-1 binding or signaling, inhibiting c-fms-IL-34 binding or signaling, reducing monocyte migration into tumors, and/or reducing the accumulation of tumor-associated macrophages (TAMs).

[0006a] In one aspect, the present disclosure refers to an antibody selected from the group consisting of an antibody comprising complementarity determining regions

(CDRs) CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, wherein said CDRs comprise the amino acid sequences as set forth below:

(a) CDRH1 comprises SEQ ID NO:147, CDRH2 comprises SEQ ID NO:163, CDRH3 comprises SEQ ID NO:186, CDRL1 comprises SEQ ID NO:193, CDRL2 comprises SEQ ID NO:214, and CDRL3 comprises SEQ ID NO:228,

(b) CDRH1 comprises SEQ ID NO:137, CDRH2 comprises SEQ ID NO:150, CDRH3 comprises SEQ ID NO:166, CDRL1 comprises SEQ ID NO:198, CDRL2 comprises SEQ ID NO:216, and CDRL3 comprises SEQ ID NO:233,

(d) CDRH1 comprises SEQ ID NO:147, CDRH2 comprises SEQ ID NO:163, CDRH3 comprises SEQ ID NO:186, CDRL1 comprises SEQ ID NO:195, CDRL2 comprises SEQ ID NO:214, and CDRL3 comprises SEQ ID NO:228,

(e) CDRH1 comprises SEQ ID NO:137, CDRH2 comprises SEQ ID NO:152, CDRH3 comprises SEQ ID NO:170, CDRL1 comprises SEQ ID NO:198, CDRL2 comprises SEQ ID NO:216, and CDRL3 comprises SEQ ID NO:233,

(f) CDRH1 comprises SEQ ID NO:147, CDRH2 comprises SEQ ID NO:163, CDRH3 comprises SEQ ID NO:186, CDRL1 comprises SEQ ID NO:194, CDRL2 comprises SEQ ID NO:214, and CDRL3 comprises SEQ ID NO:228,

(g) CDRH1 comprises SEQ ID NO:141, CDRH2 comprises SEQ ID NO:156, CDRH3 comprises SEQ ID NO:172, CDRL1 comprises SEQ ID NO:209, CDRL2 comprises SEQ ID NO:223, and CDRL3 comprises SEQ ID NO:245,

(i) CDRH1 comprises SEQ ID NO:140, CDRH2 comprises SEQ ID NO:155, CDRH3 comprises SEQ ID NO:169, CDRL1 comprises SEQ ID NO:202, CDRL2 comprises SEQ ID NO:218, and CDRL3 comprises SEQ ID NO:236,

(j) CDRH1 comprises SEQ ID NO:140, CDRH2 comprises SEQ ID NO:155, CDRH3 comprises SEQ ID NO:169, CDRL1 comprises SEQ ID NO:201, CDRL2 comprises SEQ ID NO:218, and CDRL3 comprises SEQ ID NO:236,

(k)CDRH1 comprises SEQ ID NO:143, CDRH2 comprises SEQ ID NO:158, CDRH3 comprises SEQ ID NO:190, CDRL1 comprises SEQ ID NO:199, CDRL2 comprises SEQ ID NO:219, and CDRL3 comprises SEQ ID NO:237,

(L) CDRH1 comprises SEQ ID NO:137, CDRH2 comprises SEQ ID NO:151, CDRH3 comprises SEQ ID NO:167, CDRL1 comprises SEQ ID NO:199, CDRL2 comprises SEQ ID NO:217, and CDRL3 comprises SEQ ID NO:233,

(m) CDRH1 comprises SEQ ID NO:137, CDRH2 comprises SEQ ID NO:150, CDRH3 comprises SEQ ID NO:173, CDRL1 comprises SEQ ID NO:198, CDRL2 comprises SEQ ID NO:216, and CDRL3 comprises SEQ ID NO:233,
(n) CDRH1 comprises SEQ ID NO:142, CDRH2 comprises SEQ ID NO:157, CDRH3 comprises SEQ ID NO:187, CDRL1 comprises SEQ ID NO:206, CDRL2 comprises SEQ ID NO:221, and CDRL3 comprises SEQ ID NO:242,
(o) CDRH1 comprises SEQ ID NO:143, CDRH2 comprises SEQ ID NO:158, CDRH3 comprises SEQ ID NO:177, CDRL1 comprises SEQ ID NO:200, CDRL2 comprises SEQ ID NO:216, and CDRL3 comprises SEQ ID NO:235, or
(p) CDRH1 comprises SEQ ID NO:142, CDRH2 comprises SEQ ID NO:157, CDRH3 comprises SEQ ID NO:176, CDRL1 comprises SEQ ID NO:207, CDRL2 comprises SEQ ID NO:224, and CDRL3 comprises SEQ ID NO:243; and
wherein said antibody binds to human c-fms with a KD of less than 10-8M, measured as described herein.

[0006b] In another aspect, the present disclosure refers to a nucleic acid encoding the antibody as described herein, optionally wherein said nucleic acid is operably linked to a control sequence. In yet another aspect, the present disclosure refers to a vector comprising the nucleic acid as described herein. In yet another aspect, the present disclosure refers to a host cell comprising the vector as described herein and/or the nucleic acid as described herein. In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising at least one antibody as described herein, and a pharmaceutically acceptable excipient.

[0006c] In another aspect, the present disclosure refers to use of the antibody as described herein in the manufacture of a medicament for treating or preventing a condition associated with c-fms in a patient, wherein the condition is selected from cancer, bone disease, and inflammatory disease. In yet another aspect, the present disclosure refers to an *in vitro* method of preparing the antibody as described herein, comprising the step of preparing said antibody from a host cell that secretes said antibody.

[0007] One example includes expression systems, including cell lines, for the production of c-fms receptor antigen binding proteins and methods for diagnosing and treating diseases related to human c-fms.

[0008] Some of the isolated antigen-binding proteins that are described comprise (A) one or more heavy chain complementary determining regions (CDRHs) selected from the group consisting of: (i) a CDRH1 selected from the group consisting of SEQ ID NOs:**136-147**; (ii) a CDRH2 selected from the group consisting of SEQ ID NOs:**148-164**; (iii) a CDRH3 selected from the group consisting of SEQ ID NOs:**165-190**; and (iv) a CDRH of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions that collectively total no more than four amino acids; (B) one or more light chain

complementary determining regions (CDRLs) selected from the group consisting of: (i) a CDRL1 selected from the group consisting of SEQ ID NOs:**191-210**; (ii) a CDRL2 selected from the group consisting of SEQ ID NOs:**211-224**; (iii) a CDRL3 selected from the group consisting of SEQ ID NOs:**225-246**; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions that collectively total no more than four amino acids; or (C) one or more heavy chain CDRHs of (A) and one or more light chain CDRLs of (B).

[0009] In one example, the isolated antigen-binding protein may comprise at least one or two CDRH of the above-mentioned (A) and at least one or two CDRL of the above-mentioned (B). In yet another example, the isolated antigen-binding protein includes a CDRH1, a CDRH2, a CDRH3, a CDRL1, a CDRL2 and a CDRL3.

[0010] In certain antigen binding proteins, the CDRH of the above-mentioned (A) is further selected from the group consisting of: (i) a CDRH1 selected from the group consisting of SEQ ID NOs:**136-147**; (ii) a CDRH2 selected from the group consisting of SEQ ID NOs:**148-164**; (iii) a CDRH3 selected from the group consisting of SEQ ID NOs:**165-190**; and (iv) a CDRH of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than two amino acids; the CDRL of the above-mentioned (B) is selected from the group consisting of: (i) a CDRL1 selected from the group consisting of SEQ ID NOs:**191-210**; (ii) a CDRL2 selected from the group consisting of SEQ ID NOs:**211-224**; (iii) a CDRL3 amino acid sequence selected from the group consisting of SEQ ID NOs:**225-246**; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than two amino acids; or (C) one or more heavy chain CDRHs of (A) and one or more light chain CDRLs of (B).

[0011] In yet another example, the isolated antigen-binding protein may comprise (A) a CDRH selected from the group consisting of (i) a CDRH1 selected from the group consisting of SEQ ID NOs:**136-147**; (ii) a CDRH2 selected from the group consisting of SEQ ID NOs:**148-164**; and (iii) a CDRH3 selected from the group consisting of SEQ ID NOs:**165-190**; (B) a CDRL selected from the group consisting of (i) a CDRL1 selected from the group consisting of SEQ ID NOs:**191-210**; (ii) a CDRL2 selected from the group consisting of SEQ ID NOs:**211-224**; and (iii) a CDRL3 selected from the group consisting of SEQ ID NOs:**225-246**; or (C) one or more heavy chain CDRHs of (A) and one or more light chain CDRLs of (B). In one example, the isolated antigen-binding protein may include (A) a CDRH1 of SEQ ID NOs:**136-147**, a CDRH2 of SEQ ID NOs:**148-164,** and a CDRH3 of SEQ ID NOs:**165-190**, and (B) a CDRL1 of SEQ ID NOs:**191-210**, a CDRL2 of SEQ ID NOs:**211-224**, and a CDRL3 of SEQ ID NOs:**225-246**. In another example, the variable heavy chain (V_H) has at least 90% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NOs:**70-101**, and/or the variable light chain (V_L) has at least 90% sequence identity with an amino acid sequence

selected from the group consisting of SEQ ID NOs:**102-135**. In a further example, the V_H is selected from the group consisting of SEQ ID NOs:**70-101**, and/or the V_L is selected from the group consisting of SEQ ID NOs:**102-135**.

[0012] In another example, an isolated antigen binding protein is provided that specifically binds to an epitope containing the c-fms subdomains Ig-like1-1 and Ig-like 1-2 of human c-fms.

[0013] In yet another example, an isolated antigen binding protein is provided that binds c-fms that comprises: (A) one or more heavy chain CDRs (CDRHs) selected from the group consisting of (i) a CDRH1 with at least 80% sequence identity to SEQ ID NOs:**136-147**; (ii) a CDRH2 with at least 80% sequence identity to SEQ ID NOs:**148-164**; and (iii) a CDRH3 with at least 80% sequence identity to SEQ ID NOs:**165-190**; (B) one or more light chain CDRs (CDRLs) selected from the group consisting of: (i) a CDRL1 with at least 80% sequence identity to SEQ ID NOs:**191-210**; (ii) a CDRL2 with at least 80% sequence identity to SEQ ID NOs:**211-224**; and (iii) a CDRL3 with at least 80% sequence identity to SEQ ID NOs:**225-246**; or (C) one or more heavy chain CDRHs of (A) and one or more light chain CDRLs of (B). In one example, the isolated antigen-binding protein includes (A) one or more CDRHs selected from the group consisting of: (i) a CDRH1 with at least 90% sequence identity to SEQ ID NOs:**136-147**; (ii) a CDRH2 with at least 90% sequence identity to SEQ ID NOs:**148-164**; and (iii) a CDRH3 with at least 90% sequence identity to SEQ ID NOs:**165-190**; (B) one or more CDRLs selected from the group consisting of: (i) a CDRL1 with at least 90% sequence identity to SEQ ID NOs:**191-210**; (ii) a CDRL2 with at least 90% sequence identity to SEQ ID NOs:**211-224**; and (iii) a CDRL3 with at least 90% sequence identity to SEQ ID NOs:**225-246**; or (C) one or more heavy chain CDRHs of (A) and one or more light chain CDRLs of (B).

[0014] Another example is an isolated antigen-binding protein that binds c-fms, the antigen-binding protein including one or a combination of CDRs having the consensus sequences described below. Groups A, B, and C refer to sequences derived from phylogenetically related clones. In one example, the CDRs from the various groups may be mixed and matched. In another example, the antigen binding protein comprises two or more CDRHs from one and the same group A, B, or C. In again another example, the antigen binding protein comprises two or more CDRLs from the same group A, B, or C. In again another example, the antigen binding protein comprises at least two or three CDRHs, and/or at least two or three CDRLs from the same group A, B, or C. The consensus sequences for the different groups are as follows:

[0015] Group A: (a) a CDRH1 of the generic formula $GYTX_1TSYGIS$ (SEQ ID NO:**307**), wherein X_1 is selected from the group consisting of F and L; (b) a CDRH2 of the generic formula $WISAYNGNX_1NYAQKX_2QG$ (SEQ ID NO:**308**), wherein X_1 is selected from the group consisting of T and P, and X_2 is selected from the group consisting of L and F; (c) a CDRH3 of the generic formula

$X_1X_2X_3X_4X_4X_5FGEX_6X_7X_8X_9FDY$ (SEQ ID NO:**309**), wherein X_1 is selected from the group consisting of E and D, X_2 is selected from the group consisting of S and Q, X_3 is selected from the group consisting of G and no amino acid, X_4 is selected from the group consisting of L and no amino acid, X_5 is selected from the group consisting of W and G, X_6 is selected from the group consisting of V and L, X_7 is selected from the group consisting of E and no amino acid, X_8 is selected from the group consisting of G and no amino acid, and X_9 is selected from the group consisting of F and L; (d) a CDRL1 of the generic formula $KSSX_1GVLX_2SSX_3NKNX_4LA$ (SEQ ID NO:**310**), wherein X_1 is selected from the group consisting of Q and S, X_2 is selected from the group consisting of D and Y, X_3 is selected from the group consisting of N and D, and X_4 is selected from the group consisting of F and Y; (e) a CDRL2 of the generic formula $WASX_1RES$ (SEQ ID NO:**311**), wherein X_1 is selected from the group consisting of N and T; and (f) a CDRL3 of the generic formula $QQYYX_1X_2PX_3T$ (SEQ ID NO:**312**), wherein X_1 is selected from the group consisting of S and T, X_2 is selected from the group consisting of D and T, and X_3 is selected from the group consisting of F and P.

[0016] Group B: (a) a CDRH1 having the generic formula $GFTX_1X_2X_3AWMS$ (SEQ ID NO:**313**), wherein X_1 is selected from the group consisting of F and V, X_2 is selected from the group consisting of S and N, and X_3 is selected from the group consisting of N and T; (b) a CDRH2 having the generic formula $RIKX_1KTDGX_2TX_3DX_4AAPVKG$ (SEQ ID NO:**314**), wherein X_1 is selected from the group consisting of S and T, X_2 is selected from the group consisting of G and W, X_3 is selected from the group consisting of T and A, and X_4 is selected from the group consisting of Y and N; (c) a CDRH3 having the generic formula $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}YYGX_{14}DV$ (SEQ ID NO:**315**), wherein X_1 is selected from the group consisting of E, D and G, X_2 is selected from the group consisting of Y, L and no amino acid, X_3 is selected from the group consisting of Y, R, G and no amino acid, X_4 is selected from the group consisting of H, G, S and no amino acid, X_5 is selected from the group consisting of I, A, L and no amino acid, X_6 is selected from the group consisting of L, V, T, P and no amino acid, X_7 is selected from the group consisting of T, V, Y, G, W and no amino acid, X_8 is selected from the group consisting of G, V, S and T, X_9 is selected from the group consisting of S, T, D, N and G, X_{10} is selected from the group consisting of G, F, P, and Y, X_{11} is selected from the group consisting of G, Y and N, X_{12} is selected from the group consisting of V and Y, X_{13} is selected from the group consisting of W, S and Y, and X_{14} is selected from the group consisting of M, T and V; (d) a CDRL1 having the generic formula $QASQDIX_1NYLN$ (SEQ ID NO:**316**), wherein X_1 is selected from the group consisting of S and N; (e) a CDRL2 having the generic formula DX_1SNLEX_2 (SEQ ID NO:**317**), wherein X_1 is selected from the group consisting of A and T, and X_2 is selected from the group consisting of T and P; and (f) a CDRL3 having the generic formula $QQYDX_1LX_2T$ (SEQ ID NO:**318**), wherein X_1 is selected from the group consisting of N and D, and X_2 is selected from the group consisting of L and I.

[0017] Group C: (a) a CDRH1 having the generic formula GFTFX$_1$SYGMH (SEQ ID NO:**319**), wherein X$_1$ is selected from the group consisting of S and I; (b) a CDRH2 having the generic formula VIWYDGSNX$_1$YYADSVKG (SEQ ID NO:**320**), wherein X$_1$ is selected from the group consisting of E and K; (c) a CDRH3 having the generic formula SSX$_1$X$_2$X$_3$YX$_4$MDV (SEQ ID NO:**321**), wherein X$_1$ is selected from the group consisting of G, S and W, X$_2$ is selected from the group consisting of N, D and S, X$_3$ is selected from the group consisting of Y and F, and X$_4$ is selected from the group consisting of D and G; (d) a CDRL1 having the generic formula QASX$_1$DIX$_2$NX$_3$LN (SEQ ID NO:**322**), wherein X$_1$ is selected from the group consisting of Q and H, X$_2$ is selected from the group consisting of S and N, and X$_3$ is selected from the group consisting of F and Y; (e) a CDRL2 having the generic formula DASNLEX$_1$ (SEQ ID NO:**323**), wherein X$_1$ is selected from the group consisting of T and I; and (f) a CDRL3 having the generic formula QX$_1$YDX$_2$X$_3$PX$_4$T (SEQ ID NO:**324**), wherein X$_1$ is selected from the group consisting of Q and R, X$_2$ is selected from the group consisting of N and D, X$_3$ is selected from the group consisting of L and F, and X$_4$ is selected from the group consisting of F, L and I.

[0018] In yet another example, the isolated antigen binding protein described hereinabove comprises a first amino acid sequence comprising at least one CDRH and a second amino acid sequence comprising at least one CDRL. In one example, the first and the second amino acid sequences are covalently bonded to each other. In a further example, the first amino acid sequence of the isolated antigen-binding protein includes the CDRH3 of SEQ ID NOs:**165-190**, CDRH2 of SEQ ID NOs:**148-164**, and CDRH1 of SEQ ID NOs:**136-147**, and the second amino acid sequence of the isolated antigen binding protein comprises the CDRL3 of SEQ ID NOs:**225-246**, CDRL2 of SEQ ID NOs:**211-224**, and CDRL1 of SEQ ID NOs:**191-210**.

[0019] In one example, the isolated antigen-binding proteins provided herein can be a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof. In another example, the antibody fragment of the isolated antigen-binding proteins can be an Fab fragment, an Fab' fragment, an F(ab')$_2$ fragment, an Fv fragment, a diabody, or a single chain antibody molecule. In a further example, the isolated antigen binding protein is a human antibody and can be of the IgG1-, IgG2-, IgG3-, or IgG4-type.

[0020] In yet another example, the isolated antigen-binding protein can compete for binding to the extracellular portion of human c-fms with an antigen binding protein of one of the isolated antigen-binding proteins provided. In one example, the isolated antigen binding protein can reduce monocyte chemotaxis, inhibit monocyte migration into tumors, inhibit accumulation of tumor associated macrophage in a tumor or inhibit accumulation of macrophages in a disease tissue when administered to a patient.

[0021] In a further example, also provided are isolated nucleic acid molecules that encode the antigen-binding proteins that bind to c-fms. In some instances, the isolated nucleic acid molecules are operably-linked to a control sequence.

[0022] In another example, also provided are expression vectors and host cells transformed or transfected with the expression vectors that comprise the aforementioned isolated nucleic acid molecules that encode antigen-binding proteins that can bind to c-fms.

[0023] In another example, also provided are methods of preparing the antigen-binding proteins that includes the step of preparing the antigen binding protein from a host cell that secretes the antigen-binding protein.

[0024] In yet another example, a pharmaceutical composition is provided comprising at least one of the aforementioned antigen-binding proteins provided and a pharmaceutically acceptable excipient. In one example, the pharmaceutical composition may comprise an additional active agent that is selected from the group consisting of a radioisotope, radionuclide, a toxin, or a therapeutic and a chemotherapeutic group.

[0025] Example s of the disclosure further provide a method for treating or preventing a condition associated with c-fms in a patient, comprising administering to a patient an effective amount of at least one isolated antigen-binding protein. In one example, the condition is cancer that is selected from the group consisting of breast cancer, prostate cancer, colorectal cancer, endometrial adenocarcinoma, leukemia, lymphoma, melanoma, esophageal squamous cell cancer, gastric cancer, astrocytic cancer, endometrial cancer, cervical cancer, bladder cancer, renal cancer, bladder cancer, lung cancer, and ovarian cancer.

[0026] In another example, the disclosure provides a method of inhibiting binding of CSF-1 to the extracellular portion of c-fms in a patient comprising administering an effective amount of at least one antigen-binding protein provided herein.

[0027] In yet another example, also provided is a method of inhibiting autophosphorylation of human c-fms in a patient comprising administering an effective amount of at least one antigen binding protein provided herein.

[0028] Further provided, as yet another example, is a method of reducing monocyte chemotaxis in a patient comprising administering an effective amount of at least one antigen binding protein.

[0029] In one example, also provided is a method of inhibiting monocyte migration into tumors in a patient comprising administering an effective amount of at least one antigen binding protein.

[0030] In another example, also provided is a method of inhibiting accumulation of tumor associated macrophage in a tumor in a patient comprising administering an effective amount of at least one antigen binding protein.

[0031] These and other examples will be described in greater detail herein. Each of the aspects provided can encompass various examples provided herein. It is therefore anticipated that each of the embodiments involving one element or combinations of elements can be included in each example described. Other features, objects, and advantages of the disclosed are apparent in the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] FIGURE 1A shows a sequence comparison of the heavy chain variable regions provided herein. FIGURE 1B shows a sequence comparison of the light chain variable regions provided herein. The CDR and framework regions are indicated.

[0033] FIGURE 2 shows the lineage analysis for 29 anti-c-fms hybridomas. Amino acid sequences corresponding to either the variable heavy (V_H) or variable light (V_L) domain of all cloned hybridomas were aligned and compared to one another to resolve antibody diversity. Dendrograms representing these comparative alignments are shown wherein horizontal branch length corresponds to the relative number of substitutions (differences) between any two sequences or sequence clades (groups of closely related sequences). Sequences grouped together for determination of consensus sequences are indicated.

[0034] FIGURE 3 demonstrates the inhibition of AML-5 proliferation by the various hybridoma anti-c-fms supernatants. FIGURE 3A shows AML-5 Bioassary with hybridoma anti-c-fms supernatans. FIGURE 3B shows AML-5 bioassay with purified recombinant anti-c-fms antibodies. AML-5 cells were incubated with 10 ng/ml CSF-1 in the presence of decreasing concentrations of antibody. After 72 hours, cell proliferation was measured using Alamar Blue.

Claims

1. An antibody selected from the group consisting of an antibody comprising complementarity determining regions (CDRs) CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, wherein said CDRs comprise the amino acid sequences as set forth below:

(a) CDRH1 comprises SEQ ID NO:147, CDRH2 comprises SEQ ID NO:163, CDRH3 comprises SEQ ID NO:186,
CDRL1 comprises SEQ ID NO:193, CDRL2 comprises SEQ ID NO:214, and CDRL3 comprises SEQ ID NO:228,
(b) CDRH1 comprises SEQ ID NO:137, CDRH2 comprises SEQ ID NO:150, CDRH3 comprises SEQ ID NO:166,
CDRL1 comprises SEQ ID NO:198, CDRL2 comprises SEQ ID NO:216, and CDRL3 comprises SEQ ID NO:233,
(d) CDRH1 comprises SEQ ID NO:147, CDRH2 comprises SEQ ID NO:163, CDRH3 comprises SEQ ID NO:186,
CDRL1 comprises SEQ ID NO:195, CDRL2 comprises SEQ ID NO:214, and CDRL3 comprises SEQ ID NO:228,
(e) CDRH1 comprises SEQ ID NO:137, CDRH2 comprises SEQ ID NO:152, CDRH3 comprises SEQ ID NO:170,
CDRL1 comprises SEQ ID NO:198, CDRL2 comprises SEQ ID NO:216, and CDRL3 comprises SEQ ID NO:233,
(f) CDRH1 comprises SEQ ID NO:147, CDRH2 comprises SEQ ID NO:163, CDRH3 comprises SEQ ID NO:186,
CDRL1 comprises SEQ ID NO:194, CDRL2 comprises SEQ ID NO:214, and CDRL3 comprises SEQ ID NO:228,
(g) CDRH1 comprises SEQ ID NO:141, CDRH2 comprises SEQ ID NO:156, CDRH3 comprises SEQ ID NO:172,
CDRL1 comprises SEQ ID NO:209, CDRL2 comprises SEQ ID NO:223, and CDRL3 comprises SEQ ID NO:245,
(i) CDRH1 comprises SEQ ID NO:140, CDRH2 comprises SEQ ID NO:155, CDRH3 comprises SEQ ID NO:169,
CDRL1 comprises SEQ ID NO:202, CDRL2 comprises SEQ ID NO:218, and CDRL3 comprises SEQ ID NO:236,
(j) CDRH1 comprises SEQ ID NO:140, CDRH2 comprises SEQ ID NO:155, CDRH3 comprises SEQ ID NO:169,
CDRL1 comprises SEQ ID NO:201, CDRL2 comprises SEQ ID NO:218, and CDRL3 comprises SEQ ID NO:236,
(k)CDRH1 comprises SEQ ID NO:143, CDRH2 comprises SEQ ID NO:158, CDRH3 comprises SEQ ID NO:190,
CDRL1 comprises SEQ ID NO:199, CDRL2 comprises SEQ ID NO:219, and CDRL3 comprises SEQ ID NO:237,
(L) CDRH1 comprises SEQ ID NO:137, CDRH2 comprises SEQ ID NO:151, CDRH3 comprises SEQ ID NO:167,
CDRL1 comprises SEQ ID NO:199, CDRL2 comprises SEQ ID NO:217, and CDRL3 comprises SEQ ID NO:233,
(m) CDRH1 comprises SEQ ID NO:137, CDRH2 comprises SEQ ID NO:150, CDRH3 comprises SEQ ID NO:173,
CDRL1 comprises SEQ ID NO:198, CDRL2 comprises SEQ ID NO:216, and CDRL3 comprises SEQ ID NO:233,
(n) CDRH1 comprises SEQ ID NO:142, CDRH2 comprises SEQ ID NO:157, CDRH3 comprises SEQ ID NO:187,
CDRL1 comprises SEQ ID NO:206, CDRL2 comprises SEQ ID NO:221, and CDRL3 comprises SEQ ID NO:242,
(o) CDRH1 comprises SEQ ID NO:143, CDRH2 comprises SEQ ID NO:158, CDRH3 comprises SEQ ID NO:177,
CDRL1 comprises SEQ ID NO:200, CDRL2 comprises SEQ ID NO:216, and CDRL3 comprises SEQ ID NO:235,
or
(p) CDRH1 comprises SEQ ID NO:142, CDRH2 comprises SEQ ID NO:157, CDRH3 comprises SEQ ID NO:176,
CDRL1 comprises SEQ ID NO:207, CDRL2 comprises SEQ ID NO:224, and CDRL3 comprises SEQ ID NO:243;
and

wherein said antibody binds to human c-fms with a K_D of less than 10^{-8}M, measured as described herein.

2. The antibody according to claim 1, wherein the antibody comprises a variable heavy chain (VH) and a variable light chain (VL), wherein VH and VL comprise the amino acid sequences set forth below:

(a) VH comprises SEQ ID NO:77 and VL comprises SEQ ID NO:109;
(b) VH comprises SEQ ID NO:77 and VL comprises SEQ ID NO:110;
(c) VH comprises SEQ ID NO:78 and VL comprises SEQ ID NO:133;
(e) VH comprises SEQ ID NO:80 and VL comprises SEQ ID NO:112;
(f) VH comprises SEQ ID NO:84 and VL comprises SEQ ID NO:115;
(g) VH comprises SEQ ID NO:85 and VL comprises SEQ ID NO:116;
(h) VH comprises SEQ ID NO:86 and VL comprises SEQ ID NO:117;
(j) VH comprises SEQ ID NO:70 and VL comprises SEQ ID NO:102;
(k) VH comprises SEQ ID NO:70 and VL comprises SEQ ID NO:103;
(I) VH comprises SEQ ID NO:73 and VL comprises SEQ ID NO:105;
(m) VH comprises SEQ ID NO:74 and VL comprises SEQ ID NO:106;
(n) VH comprises SEQ ID NO:89 and VL comprises SEQ ID NO:121;
(o) VH comprises SEQ ID NO:93 and VL comprises SEQ ID NO:123;
(p) VH comprises SEQ ID NO:94 and VL comprises SEQ ID NO:124;
(q) VH comprises SEQ ID NO:97 and VL comprises SEQ ID NO:127; or
(r) VH comprises SEQ ID NO:98 and VL comprises SEQ ID NO:128.

3. The antibody according to claim 1 or claim 2, wherein the binding between said antibody and a mutant human c-

fms is less than 50% of the binding between said antibody and human c-fms having the amino acid sequence set forth in SEQ ID NO:1, and wherein said mutant human c-fms has an amino acid sequence selected from:

(a) the amino acid sequence set forth in SEQ ID NO:1 wherein at least one mutation selected from K102E, R144E, R146E, D174R, and A226R is present,
(b) the amino acid sequence set forth in SEQ ID NO:1 wherein at least one mutation selected from E29R, Q 121R, T152R, and K185E is present,
(c) the amino acid sequence set forth in SEQ ID NO:1 wherein at least one mutation selected from E29R, Q121R, S172R, G274R, and Y276R is present, or
(d) the amino acid sequence set forth in SEQ ID NO:1 wherein at least one mutation selected from R106E, H151R, T152R, Y154R, S155R, W159R, Q171R, S172R, Q173R, G183R, R184E, K185E, E218R, A220R, S228R, H239R, N240R, K259E, G274R, N275R, Y276R, S277R, and N282R is present.

4. The antibody according to any one of claims 1 to 3, wherein said antibody is capable of binding a polypeptide consisting of the amino acid sequence SEQ ID NO:326, wherein said antibody does not bind a polypeptide consisting of amino acids 20-126 of SEQ ID NO:1, and does not bind a polypeptide consisting of amino acids 85-223 of SEQ ID NO:1.

5. The antibody according to claim 2 that comprises two identical VH and two identical VL.

6. The antibody according to claim 2 or claim 5, wherein said antibody comprises a full heavy chain and a full light chain, wherein said full heavy chain and full light chain comprise the amino acid sequences set forth below:

(a) the full heavy chain comprises SEQ ID NO:11 and the full light chain comprises SEQ ID NO:43;
(b) the full heavy chain comprises SEQ ID NO:11 and the full light chain comprises SEQ ID NO:44;
(c) the full heavy chain comprises SEQ ID NO:12 and the full light chain comprises SEQ ID NO:67;
(e) the full heavy chain comprises SEQ ID NO:14 and the full light chain comprises SEQ ID NO:46;
(f) the full heavy chain comprises SEQ ID NO:18 and the full light chain comprises SEQ ID NO:49;
(g) the full heavy chain comprises SEQ ID NO:19 and the full light chain comprises SEQ ID NO:50;
(h) the full heavy chain comprises SEQ ID NO:20 and the full light chain comprises SEQ ID NO:51;
(j) the full heavy chain comprises SEQ ID NO:4 and the full light chain comprises SEQ ID NO:36;
(k) the full heavy chain comprises SEQ ID NO:4 and the full light chain comprises SEQ ID NO:37;
(l) the full heavy chain comprises SEQ ID NO:7 and the full light chain comprises SEQ ID NO:39;
(m) the full heavy chain comprises SEQ ID NO:8 and the full light chain comprises SEQ ID NO:40;
(n) the full heavy chain comprises SEQ ID NO:23 and the full light chain comprises SEQ ID NO:55;
(o) the full heavy chain comprises SEQ ID NO:27 and the full light chain comprises SEQ ID NO:57;
(p) the full heavy chain comprises SEQ ID NO:28 and the full light chain comprises SEQ ID NO:58;
(q) the full heavy chain comprises SEQ ID NO:31 and the full light chain comprises SEQ ID NO:61; or
(r) the full heavy chain comprises SEQ ID NO:32 and the full light chain comprises SEQ ID NO:62.

7. The antibody according to any one of claims 1, 2, 5, or 6, wherein:

(a) CDRH1 comprises SEQ ID NO:147, CDRH2 comprises SEQ ID NO:163, CDRH3 comprises SEQ ID NO:186, CDRL1 comprises SEQ ID NO:193, CDRL2 comprises SEQ ID NO:214, and CDRL3 comprises SEQ ID NO:228;
(b) CDRH1 comprises SEQ ID NO:140, CDRH2 comprises SEQ ID NO:155, CDRH3 comprises SEQ ID NO:169, CDRL1 comprises SEQ ID NO:202, CDRL2 comprises SEQ ID NO:218, and CDRL3 comprises SEQ ID NO:236;
(c) CDRH1 comprises SEQ ID NO:140, CDRH2 comprises SEQ ID NO:155, CDRH3 comprises SEQ ID NO:169, CDRL1 comprises SEQ ID NO:201, CDRL2 comprises SEQ ID NO:218, and CDRL3 comprises SEQ ID NO:236; or
(d) CDRH1 comprises SEQ ID NO:142, CDRH2 comprises SEQ ID NO:157, CDRH3 comprises SEQ ID NO:187, CDRL1 comprises SEQ ID NO:206, CDRL2 comprises SEQ ID NO:221, and CDRL3 comprises SEQ ID NO:242.

8. The antibody according to any one of claims 1, 2, 5, 6, or 7, wherein the antibody is selected from the group consisting of an antibody wherein:

(a) VH comprises SEQ ID NO:77 and VL comprises SEQ ID NO:109,
(b) VH comprises SEQ ID NO:77 and VL comprises SEQ ID NO:110,
(c) VH comprises SEQ ID NO:70 and VL comprises SEQ ID NO:102,
(d) VH comprises SEQ ID NO:70 and VL comprises SEQ ID NO:103,
(e) VH comprises SEQ ID NO:93 and VL comprises SEQ ID NO:123, or
(f) VH comprises SEQ ID NO:94 and VL comprises SEQ ID NO:124.

9. The antibody according to any one of claims 1, 2, 5, 6, 7 or 8, wherein the antibody is selected from the group

consisting of an antibody wherein:

(a) the full heavy chain comprises SEQ ID NO:11 and the full light chain comprises SEQ ID NO:43,
(b) the full heavy chain comprises SEQ ID NO:11 and the full light chain comprises SEQ ID NO:44,
(c) the full heavy chain comprises SEQ ID NO:4 and the full light chain comprises SEQ ID NO:36,
(d) the full heavy chain comprises SEQ ID NO:4 and the full light chain comprises SEQ ID NO:37,
(e) the full heavy chain comprises SEQ ID NO:27 and the full light chain comprises SEQ ID NO:57, or
(f) the full heavy chain comprises SEQ ID NO:28 and the full light chain comprises SEQ ID NO:58.

10. The antibody of any one of claims 1 to 9 which:

(a) is a monoclonal antibody, a recombinant antibody, a human antibody, a chimeric antibody, a bispecific antibody, a multispecific antibody, or a fragment thereof;
(b) is of the IgG1, IgG2, IgG3, or the IgG4 subtype;
(c) is a human antibody of the IgG1, IgG2, IgG3, or the IgG4 subtype;
(d) is an Fab fragment, an Fab' fragment, an $F(ab')_2$ fragment, an Fv fragment, a diabody, a domain antibody, or a single chain antibody molecule; or
(e) is an immunologically functional immunoglobulin fragment and derived from a human source.

11. A nucleic acid encoding the antibody according to any one of claims 1 to 10, optionally wherein said nucleic acid is operably linked to a control sequence.

12. A vector comprising the nucleic acid according to claim 11.

13. A host cell comprising the vector according to claim 12 and/or the nucleic acid according to claim 11.

14. A pharmaceutical composition comprising at least one antibody according to any one of claims 1 to 10, and a pharmaceutically acceptable excipient.

15. The pharmaceutical composition of claim 14, further comprising:

(a) an additional active agent; or
(b) an additional active agent selected from the group consisting of a radioisotope, a radionuclide, a toxin, a therapeutic and a chemotherapeutic group.

16. The antibody of any one of claims 1 to 10 for use in therapy.

17. Use of the antibody of any one of claims 1 to 10 in the manufacture of a medicament for treating or preventing a condition associated with c-fms in a patient, wherein the condition is selected from cancer, bone disease, and inflammatory disease.

18. The use according to claim 17, wherein the inflammatory disease is selected from the group consisting of inflammatory arthritis, atherosclerosis, multiple sclerosis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid spondylitis, ankylosing spondylitis, arthritis, psoriatic arthritis, rheumatoid arthritis, osteoarthritis, eczema, contact dermatitis, psoriasis, toxic shock syndrome, sepsis, septic shock, endotoxic shock, asthma, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerularonephritis, diabetes, graft vs. host reaction, allograft rejection, multiple sclerosis, muscle degeneration, muscular dystrophy, Alzheimer's disease, stroke, and cachexia.

19. The use according to claim 17, wherein the cancer is selected from the group consisting of breast cancer, prostate cancer, colorectal cancer, endometrial adenocarcinoma, leukemia, lymphoma, melanoma, esophageal squamous cell cancer, gastric cancer, astrocytic cancer, endometrial cancer, cervical cancer, bladder cancer, renal cancer, lung cancer and ovarian cancer.

20. The use according to claim 17, wherein the bone disease is selected from the group consisting of:

(a) medical disorders that involve excessive bone loss;
(b) medical disorders that require the formation of new bone;
(c) osteopenic disorders that involve excessive osteoclast activity;
(d) systemic bone loss associated with arthritis; and
(e) bone disease associated with renal failure.

21. The use according to claim 20, wherein:

(a) the antibody is for use according to claim 20(a), and wherein the medical disorder is selected from breast cancer, prostate cancer, multiple myeloma and osteosarcoma; or
(b) the antibody is for use according to claim 20(c), wherein the osteopenic disorder is selected from the group consisting of osteopenia, osteoporosis, periodontitis, Paget's disease, bone loss due to immobilization, lytic bone metastases, and arthritis.

22. The use according to claim 20(d) or claim 21(b), wherein the arthritis is selected from the group consisting of osteoarthritis, rheumatoid arthritis, psoriatic arthritis, and inflammatory arthritis.

23. The use according to claim 17, wherein the condition is bone disease, and wherein the bone disease is a bone disorder; wherein the antibody is administered in combination with:

(a) a further therapeutic agent; or
(b) a further therapeutic agent selected from a cancer therapy agent, an agent that inhibits osteoclast activity, and an agent that enhances osteoblast activity.

24. The use according to claim 23, wherein the patient is a cancer patient undergoing radiation therapy or chemotherapy.

25. The use according to any one of claims 17 and 19-23, wherein the condition is cancer or bone disease; wherein the antibody is administered in combination with a cancer therapy agent.

26. The use according to any one of claims 17, 20, and 21, wherein the condition is bone disease resulting in loss of bone mass, and wherein the antibody is administered in combination with a further therapeutic agent selected from a bone growth promoting (anabolic) agent and a bone anti-resorptive agent.

27. The use according to any one of claims 17, 18, and 22, wherein the condition is inflammatory disease; and wherein the antibody is administered in combination with an anti-inflammatory agent.

28. The pharmaceutical composition according to claim 14 or claim 15 for use in treating a patient, wherein the pharmaceutically acceptable excipient is selected from a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant; and wherein the patient is a human patient.

29. An *in vitro* method of preparing the antibody of any one of claims 1 to 10, comprising the step of preparing said antibody from a host cell that secretes said antibody.