

**ANTIBODIES SPECIFICALLY RECOGNIZING GRANULOCYTE-MACROPHAGE
COLONY STIMULATING FACTOR RECEPTOR ALPHA AND USES THEREOF**

SUBMISSION OF SEQUENCE LISTING ON ASCII TEXT FILE

- 5 [0001] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 710262000140SEQLIST.txt, date recorded: November 7, 2018, size: 248 KB).

FIELD OF THE APPLICATION

- 10 [0002] This application pertains to antibodies that specifically recognize granulocyte-macrophage colony stimulating factor receptor alpha (GM-CSFR α), and methods of manufacture and uses thereof, including methods of treating autoimmune and inflammatory conditions, and cancer.

BACKGROUND OF THE APPLICATION

- 15 [0003] Granulocyte-macrophage colony stimulating factor (GM-CSF) is also known as colony-stimulating factor 2 (CSF2). GM-CSF is a type I proinflammatory cytokine which plays a role in exacerbating inflammatory, respiratory and autoimmune diseases. The GM-CSF receptor is a member of the hematopoietic receptor superfamily. It is heterodimeric, consisting of an alpha and a beta subunit. GM-CSF is able to bind with relatively low affinity to the α subunit alone (K_d 1-5nM) but not at all to the β subunit alone. However, the presence of both α and β subunits results in a high affinity ligand-receptor complex ($K_d \approx 100$ pM). Neutralization of GM-CSF binding to GM-CSFR α is therefore a therapeutic approach to treating diseases and conditions mediated through GM-CSFR. An antibody against human GM-CSFR α , designated Mavrimumab (Mab, used as a control in the Examples), is described in WO2007110631.
- 20 [0004] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

BRIEF SUMMARY OF THE APPLICATION

- [0005] In one aspect, the present application provides an isolated anti-GM-CSFR α antibody that specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises one, two, three, four, five, or six amino acid residues selected from the group consisting of Val50, Glu59, Lys194, Lys195, Arg283, and Ile284 of human GM-CSFR α . In some embodiments, the epitope further comprises amino acid residues: (i) Val51, Thr63, and Ile196; (ii) Leu191 and
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Ile196; or (iii) Arg49, Val51, Asn57, and Ser61. In some embodiments, the isolated anti-GM-CSFR α antibody binds to the human GM-CSFR α with a K_d from about 0.1 pM to about 1 nM.

[0006] In some embodiments according to any one of the isolated anti-GM-CSFR α antibodies described above, the isolated anti-GM-CSFR α antibody comprises: a heavy chain variable domain (V_H) comprising a heavy chain complementarity determining region (HC-CDR) 1 comprising $X_1LX_2X_3H$ (SEQ ID NO: 76), wherein X_1 is E, N, G, D, M, S, P, F, Y, A, V, K, W, R or C, X_2 is S, C or P, and X_3 is I or M; an HC-CDR2 comprising $GFDX_1X_2X_3X_4EX_5X_6YAQKX_7QG$ (SEQ ID NO: 77), wherein X_1 is P, G, T, S, or V, X_2 is E, D, G, or A, X_3 is D, G, I, W, S, or V, X_4 is G, E, D, or H, X_5 is T or A, X_6 is N or I, and X_7 is S or F; and an HC-CDR3 comprising $GRYX_1X_2X_3X_4X_5X_6YGFYD$ (SEQ ID NO: 78), wherein X_1 is C, T, S, I, A, or V, X_2 is S, G, E, F, W, H, I, V, N, Y, T, or R, X_3 is T, H, L, F, P, I, S, Y, K, A, D, V, N, or G, X_4 is D, A, M, Y, F, S, T, G, or W, X_5 is T, S, F, Q, A, N, L, E, I, G, or M, and X_6 is C, T, N, S, or A; and a light chain variable domain (V_L) comprising a light chain complementarity determining region (LC-CDR) 1 comprising $RAX_1X_2X_3VX_4X_5X_6LA$ (SEQ ID NO: 293), wherein X_1 is S, L, N, A, K, R, I, Q, G, T, H, M, or C, X_2 is Q, Y, P, A, I, F, T, R, V, L, E, S, or C, X_3 is S, H, W, L, R, K, T, P, I, F, V, E, A, or Q, X_4 is S, L, W, M, A, Y, K, R, G, T, E, V, N, F, or C, X_5 is S, T, R, A, H, Q, P, M, L, or G, and X_6 is Y, L, or F; a LC-CDR2 comprising $X_1X_2X_3SRAT$ (SEQ ID NO: 294), wherein X_1 is G or T, X_2 is A, G, R, H, K, S, T, M, or F, and X_3 is S, A, W, R, L, T, Q, F, Y, H, or N; and a LC-CDR3 comprising $QQYX_1X_2X_3PX_4T$ (SEQ ID NO: 79), wherein X_1 is N, D, S, R, A, T, L, Y, Q, W or G, X_2 is N, D, E, T, Y, G, A, M, F, S, I or L, X_3 is W, S, P, V, G, or R, and X_4 is P, Y, H, S, F, N, D, V, or G.

In some embodiments, the anti-GM-CSFR α antibody comprises: a V_H comprising a HC-CDR1 comprising ELX_1X_2H (SEQ ID NO: 295), wherein X_1 is S, C or P, and X_2 is I or M; an HC-CDR2 comprising $GFDX_1X_2X_3X_4EX_5X_6YAQKX_7QG$ (SEQ ID NO: 77), wherein X_1 is P, G, T, S, or V, X_2 is E, D, G, or A, X_3 is D, G, I, W, S, or V, X_4 is G, E, D, or H, X_5 is T or A, X_6 is N or I, and X_7 is S or F; and an HC-CDR3 comprising $GRYX_1X_2X_3X_4X_5X_6YGFYD$ (SEQ ID NO: 78), wherein X_1 is C, T, S, I, A, or V, X_2 is S, G, E, F, W, H, I, V, N, Y, T, or R, X_3 is T, H, L, F, P, I, S, Y, K, A, D, V, N, or G, X_4 is D, A, M, Y, F, S, T, G, or W, X_5 is T, S, F, Q, A, N, L, E, I, G, or M, and X_6 is C, T, N, S, or A; and a V_L comprising a LC-CDR1 comprising $RASQSVSSYLA$ (SEQ ID NO: 51); a LC-CDR2 comprising $GASSRAT$ (SEQ ID NO: 52); and a LC-CDR3 comprising $QQYX_1X_2X_3PX_4T$ (SEQ ID NO: 79), wherein X_1 is N, D, S, R, A, T, L, Y, Q, W or G, X_2 is N, D, E, T, Y, G, A, M, F, S, I or L, X_3 is W, S, P, V, G, or R, and X_4 is P, Y, H, S, F, N, D, V, or G.

65 [0007] In some embodiments, there is provided an isolated anti-GM-CSFR α antibody
comprises: a V_H comprising an HC-CDR1 comprising the amino acid sequence of any one of
SEQ ID NOs: 1-4, or a variant thereof comprising up to about 3 amino acid substitutions; an HC-
CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, or a variant thereof
70 comprising up to about 3 amino acid substitutions; and an HC-CDR3 comprising the amino acid
sequence of any one of SEQ ID NOs: 17-50, or a variant thereof comprising up to about 3 amino
acid substitutions; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ
ID NO: 51, or a variant thereof comprising up to about 3 amino acid substitutions; a LC-CDR2
comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof comprising up to
about 3 amino acid substitutions; and a LC-CDR3 comprising the amino acid sequence of any
75 one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 amino acid
substitutions.

[0008] In some embodiments, there is provided an isolated anti-GM-CSFR α antibody
comprising a V_H comprising an HC-CDR1, an HC-CDR2, and an HC-CDR3 of a V_H comprising
the amino acid sequence of any one of SEQ ID NOs: 80-121; and a V_L comprising a LC-CDR1,
80 a LC-CDR2, and a LC-CDR3 of a V_L comprising the amino acid sequence of any one of SEQ ID
NOs: 122-144.

[0009] In some embodiments, there is provided an isolated anti-GM-CSFR α antibody
comprises: (i) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID
NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an HC-CDR3
85 comprising the amino acid sequence of SEQ ID NO: 17, or a variant thereof comprising up to
about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising
the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of
SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a
variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs; (ii) a V_H
90 comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2
comprising the amino acid sequence of SEQ ID NO: 8, and an HC-CDR3 comprising the amino
acid sequence of SEQ ID NO: 22, or a variant thereof comprising up to about 5 amino acid
substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid
sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO:
95 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 56, or a variant
thereof comprising up to about 5 amino acid substitutions in the LC-CDRs; (iii) a V_H comprising
an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising
the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid

sequence of SEQ ID NO: 23, or a variant thereof comprising up to about 5 amino acid
100 substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid
sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO:
52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant
thereof comprising up to about 5 amino acid substitutions in the LC-CDRs; (iv) a V_H comprising
an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising
105 the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid
sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 5 amino acid
substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid
sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO:
52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant
110 thereof comprising up to about 5 amino acid substitutions in the LC-CDRs; (v) a V_H comprising
an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising
the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid
sequence of SEQ ID NO: 35, or a variant thereof comprising up to about 5 amino acid
substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid
115 sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO:
52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 53, or a variant
thereof comprising up to about 5 amino acid substitutions in the LC-CDRs; (vi) a V_H comprising
an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising
the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid
120 sequence of SEQ ID NO: 37, or a variant thereof comprising up to about 5 amino acid
substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid
sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO:
52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant
thereof comprising up to about 5 amino acid substitutions in the LC-CDRs; (vii) a V_H
125 comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2
comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino
acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 5 amino acid
substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid
sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO:
130 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a variant
thereof comprising up to about 5 amino acid substitutions in the LC-CDRs; (viii) a V_H
comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2

comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35, or a variant thereof comprising up to about 5 amino acid
 135 substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs; (ix) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising
 140 the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant
 145 thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.

[0010] In some embodiments according to any one of the isolated anti-GM-CSFR α antibodies described above, the isolated anti-GM-CSFR α antibody comprises amino acid residues: (i) E, H, N, G, D, M, S, P, F, Y, A, V, K, W, R, or C at position 31 of the V_H; and/or (ii) S, L, N, A, K, R, I, Q, G, T, H, M, or C at position 26 of the V_L; and/or (iii) Q, Y, P, A, I, F, T, R, V, L, E, S, or C
 150 at position 27 of the V_L; and/or (iv) S, H, W, L, R, K, T, P, I, F, V, E, A, or Q at position 28 of the V_L; and/or (v) S, L, W, M, A, Y, K, R, G, T, E, V, N, F, or C at position 30 of the V_L; and/or (vi) S, T, R, A, H, Q, P, M, L, or G at position 31 of the V_L; and/or (vii) Y, L or F at position 32 of the V_L; and/or (viii) G, or T at position 50 of the V_L; and/or (ix) A, G, R, H, K, S, T, M, F, N, or V at position 51 of the V_L; and/or (x) S, A, W, R, L, T, Q, F, Y, H, or N at position 52 of the
 155 V_L; and/or (xi) D, A, Q, or W at position 92 of the V_L; and/or (xii) N, D, E, T, Y, G, A, M, F, S, I, or L at position 93 of the V_L; and/or (xiii) amino acid residues selected from T, H, V, E, P, L, M, S, W, C, A, G, N, or K at position 28 of the V_H; and/or (xiv) amino acid residues selected from T, P, D, E, Y, W, V, M, N, L, Q, G, S, A, K, or R at position 30 of the V_H, wherein the numbering is according to the EU index of Kabat.

[0011] In some embodiments, according to any one of the isolated anti-GM-CSFR α antibodies described above, the isolated anti-GM-CSFR α antibody comprises: a V_H comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287, or a variant thereof having at least about 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287; and a V_L comprising the amino acid sequence of any one of SEQ ID NOs:
 165 122-144, 150-245, and 288-289, or a variant thereof having at least about 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289. In some

embodiments, the isolated anti-GM-CSFR α antibody comprises: (i) a V_H comprising the amino acid sequence of SEQ ID NO: 80; and a V_L comprising the amino acid sequence of SEQ ID NO: 123; (ii) a V_H comprising the amino acid sequence of SEQ ID NO: 85; and a V_L comprising the amino acid sequence of SEQ ID NO: 125; (iii) a V_H comprising the amino acid sequence of SEQ ID NO: 86; and a V_L comprising the amino acid sequence of SEQ ID NO: 126; (iv) a V_H comprising the amino acid sequence of SEQ ID NO: 91; and a V_L comprising the amino acid sequence of SEQ ID NO: 126; (v) a V_H comprising the amino acid sequence of SEQ ID NO: 99; and a V_L comprising the amino acid sequence of SEQ ID NO: 122; (vi) a V_H comprising the amino acid sequence of SEQ ID NO: 101; and a V_L comprising the amino acid sequence of SEQ ID NO: 126; (vii) a V_H comprising the amino acid sequence of SEQ ID NO: 103; and a V_L comprising the amino acid sequence of SEQ ID NO: 123; (viii) a V_H comprising the amino acid sequence of SEQ ID NO: 99; and a V_L comprising the amino acid sequence of SEQ ID NO: 126; (ix) a V_H comprising the amino acid sequence of SEQ ID NO: 121; and a V_L comprising the amino acid sequence of SEQ ID NO: 126; (x) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 241; (xi) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 193; (xii) a V_H comprising the amino acid sequence of SEQ ID NO: 248; and a V_L comprising the amino acid sequence of SEQ ID NO: 188; (xiii) a V_H comprising the amino acid sequence of SEQ ID NO: 248; and a V_L comprising the amino acid sequence of SEQ ID NO: 193; (xiv) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 288; (xv) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 188; (xvi) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 236; or (xvii) a V_H comprising the amino acid sequence of SEQ ID NO: 91; and a V_L comprising the amino acid sequence of SEQ ID NO: 288.

[0012] In some embodiments, there is provided an isolated anti-GM-CSFR α antibody that specifically binds to GM-CSFR α competitively with any one of the isolated anti-GM-CSFR α antibodies as described above. In some embodiments, there is provided an isolated anti-GM-CSFR α antibody that specifically binds to the same epitope as any one of isolated anti-GM-CSFR α antibodies as described above.

[0013] In some embodiments according to any of the isolated anti-GM-CSFR α antibodies described above, the isolated anti-GM-CSFR α antibody comprises an Fc fragment. In some embodiments, the isolated anti-GM-CSFR α antibody is a full-length IgG antibody. In some embodiments, the isolated anti-GM-CSFR α antibody is a full-length IgG1 or IgG4 antibody. In

some embodiments, the anti-GM-CSFR α antibody is chimeric, human, or humanized. In some embodiments, the anti-GM-CSFR α antibody is an antigen binding fragment selected from the group consisting of a Fab, a Fab', a F(ab')₂, a Fab'-SH, a single-chain Fv (scFv), an Fv fragment, a dAb, a Fd, a nanobody, a diabody, and a linear antibody.

205 [0014] In some embodiments, there is provided isolated nucleic acid molecule(s) that encodes any one of the anti-GM-CSFR α antibodies described above. In some embodiments, there is provided a vector comprising a nucleic acid molecule according to any one of the nucleic acid molecules described above. In some embodiments, there is provided a host cell comprising any one of the anti-GM-CSFR α antibodies described above, any one of the nucleic acid molecules described above, or any one of the vectors described above. In some embodiments, there is provided a method of producing an anti-GM-CSFR α antibody, comprising: a) culturing any one of the host cells described above under conditions effective to express the anti-GM-CSFR α antibody; and b) obtaining the expressed anti-GM-CSFR α antibody from the host cell.

210 [0015] In some embodiments, there is provided a method of treating a disease or condition in an individual in need thereof, comprising administering to the individual an effective amount of an anti-GM-CSFR α antibody according to any one of the anti-GM-CSFR α antibodies described above. In some embodiments, the disease or condition is an inflammatory, respiratory or autoimmune disease or condition. In some embodiments, the disease or condition is selected from the group consisting of rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, 220 allergic response, multiple sclerosis, myeloid leukemia, atherosclerosis.

[0016] Also provided are pharmaceutical compositions, kits and articles of manufacture comprising any one of the anti-GM-CSFR α antibodies described above.

BRIEF DESCRIPTION OF THE DRAWINGS

225 [0017] FIGS. 1A-1C show the binding affinity of exemplary anti-GM-CSFR α antibodies to human GM-CSFR α as analyzed by ELISA. FIG.1A shows the binding curves of T119, E9, E16, E27, E29, E30, E35, E36, E54 and E34 to human GM-CSFR α . FIG.1B shows the binding curves of T119, E108, E105, E113, E87, E85, E39, E40, E1155, E200a, and E1181 to human GM-CSFR α . FIG.1C shows the binding curves of T119, E61, E83, E88, E90, E84, E172, E164, E1 and E31 to human GM-CSFR α .

230 [0018] FIG. 2 shows the binding affinity of E35, E200a, T119, E87, and E108 for cynomolgus monkey GM-CSFR α as analyzed by ELISA.

[0019] FIG. 3 shows the binding affinity of E35, E87, and E108 for IL3RA, IL5RA, and G-CSFR as compared to GM-CSFR α .

235 [0020] FIG. 4 shows the binding affinity of E35-IgG4 to WIL2S cells expressing GM-CSFR α as compared to control WIL2S cells that do not express GM-CSFR α , as analyzed by FACS.

[0021] FIGS. 5A-5D show results of the competitive binding assay for the ability of the parental antibody T119 and lead-optimized antibodies to compete with GM-CSF for binding to GM-CSFR α , as measured using competitive ELISA. FIG. 5A shows results of the competitive binding assay for T119, E01, E09, E194, E27, E29, E34, E35, E40, and E30. FIG. 5B shows

240 results of the competitive binding assay for T119, E83, E87, EII81, E85, E54, EII55, E31, E105, and E84. FIG. 5C shows results of the competitive binding assay for T119, E164, E172, E108, E16, E36, E61, E88, and E39. FIG. 5D shows results of the competitive binding assay for T119, E90, EII33, E200a, E94, E113, and EII52.

[0022] FIGS. 6A and 6B show the thermal melting profiles and the thermal aggregation

245 profiles of the anti-GM-CSFR α antibodies Mab-IgG1, T119-IgG1, E35-IgG1 and E35b-IgG1 as analyzed by UNcle. FIG. 6A shows the thermal melting profiles of the antibodies. FIG. 6B shows the thermal aggregation profiles of the antibodies.

[0023] FIG. 7 shows results of the TF-1 proliferation assay for the parental antibody T119 and lead-optimized antibodies.

250 [0024] FIG. 8 shows results of the human granulocyte shape change assay for E35, E108 and E87b.

[0025] FIG. 9 shows results of the cynomolgus monkey granulocyte shape change assay for E35.

[0026] FIG. 10 shows results of the granulocyte survival assay for E35, E108, and E87b.

255 [0027] FIG. 11 shows results of the CD11b expression assay for E35 and E87b as compared to Mab.

[0028] FIGS. 12A and 12B show results of the TNF α release assays for E35 and E87b as compared to Mab. FIG. 12A shows results of the TNF α release assay for E35 and E87b as compared to Mab, as measured by the Human Macrophage/Microglia Panel. FIG. 12B shows

260 results of the TNF α release assay for E35 and E87b as compared to Mab, as measured by ELISA.

[0029] FIG. 13 shows results of the IL-1 β production assay for E35 and E87b as compared to Mab.

[0030] FIGS. 14A and 14B show results of pharmacokinetics analysis of Mab and E35 in rat as measured by ELISA. FIG. 14A shows antibody serum concentrations of Mab and E35 upon

265 intravenous injection of 2mg/kg of the respective antibodies. FIG. 14B shows pharmacokinetics of Mab and E35 upon intravenous injection of 20mg/kg of the respective antibodies.

- [0031] FIG. 15 shows results of pharmacokinetics analysis of Mab and E35 in cynomolgus monkey as measured by ELISA.
- [0032] FIGS. 16A-D show FACS plots of *in vivo* granulocyte shape change analysis upon administration of Mab-IgG4 or E35-IgG4 in cynomolgus monkey. FIG. 16A shows FACS plots of granulocytes prior to antibody administration. FIG. 16B shows FACS plots of granulocytes 14 days after antibody administration. FIG. 16C shows FACS plots of granulocytes 21 days after antibody administration. FIG. 16D shows results of the *in vivo* granulocyte shape change analysis from prior to antibody administration up to 21 days following antibody administration.
- [0033] FIGS. 17A-17G show results of the inhibitory effect of E35-IgG4 on GM-CSF-induced increase in inflammatory cells. FIG. 17A shows results of the inhibitory effect of E35-IgG4 on GM-CSF-induced increase in white blood cells. FIG. 17B shows results of the inhibitory effect of E35-IgG4 on GM-CSF-induced increase in neutrophils. FIG. 17C shows results of the inhibitory effect of E35-IgG4 on GM-CSF-induced increase in lymphocytes. FIG. 17D shows results of the inhibitory effect of E35-IgG4 on GM-CSF-induced increase in basophils. FIG. 17E shows results of the inhibitory effect of E35-IgG4 on GM-CSF-induced increase in eosinophils. FIG. 17F shows results of the inhibitory effect of E35-IgG4 on GM-CSF-induced increase in monocytes. FIG. 17G shows results of the inhibitory effect of E35-IgG4 on GM-CSF-induced increase in red blood cells.
- [0034] FIGS. 18A-18C show the binding affinity of E35-IgG4, E87b-IgG4 and T119-IgG4 for wild type GMRah and GMRah with mutations at exemplary amino acid residues as measured by ELISA. FIG. 18A shows the binding affinity of E35-IgG4 for wild type GMRah and mutated GMRah. FIG. 18B shows the binding affinity of E87b-IgG4 for wild type GMRah and mutated GMRah. FIG. 18C shows the binding affinity of T119-IgG4 for wild type GMRah and mutated GMRah.
- [0035] FIGS. 19A-19B show the sequence alignments of the variable domain sequences of the anti-GM-CSFR α antibodies. The complementarity determining regions are denoted. FIG. 19A shows the sequence alignments of the heavy chain variable domain sequences. FIG. 19B shows the sequence alignments of the light chain variable domain sequences.
- [0036] FIG. 20 shows the numbering of amino acid residues 16-296 in GM-CSFR α .

DETAILED DESCRIPTION OF THE APPLICATION

[0037] The present application in one aspect provides anti-GM-CSFR α antibodies. By using a combination of selections on naïve scFv phage libraries, affinity maturation and appropriately designed biochemical and biological assays, we have identified highly potent antibody molecules

300 that bind to human GM-CSFR α and inhibit the action of human GM-CSF at its receptor. The results presented herein indicate that our antibodies bind a different region or epitope of GM-CSFR α compared with the known anti-GM-CSFR α antibody Mavrilimumab, and surprisingly are even more potent than Mavrilimumab as demonstrated in a variety of biological assays.

[0038] The anti-GM-CSFR α antibodies provided by the present application include, for
305 example, full-length anti-GM-CSFR α antibodies, anti-GM-CSFR α scFvs, anti-GM-CSFR α Fc fusion proteins, multi-specific (such as bispecific) anti-GM-CSFR α antibodies, anti-GM-CSFR α immunoconjugates, and the like.

[0039] In one aspect, there are provided anti-GM-CSFR α antibodies that specifically bind to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50,
310 Glu59, Lys194, Lys195, Arg283, and Ile284 of human GM-CSFR α .

[0040] In another aspect, there is provided an anti-GM-CSFR α antibody, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain (V_H) comprising a heavy chain variable domain (V_H) comprising an HC-CDR1 comprising X₁LX₂X₃H (SEQ ID NO: 76), wherein X₁ is E, N, G, D, M, S, P, F, Y, A, V, K, W, R or C, X₂ is S, C or P, and X₃ is I or M; an
315 HC-CDR2 comprising GFDX₁X₂X₃X₄EX₅X₆YAQKX₇QG (SEQ ID NO: 77), wherein X₁ is P, G, T, S, or V, X₂ is E, D, G, or A, X₃ is D, G, I, W, S, or V, X₄ is G, E, D, or H, X₅ is T or A, X₆ is N or I, and X₇ is S or F; and an HC-CDR3 comprising GRYX₁X₂X₃X₄X₅X₆YGFDY (SEQ ID NO: 78), wherein X₁ is C, T, S, I, A, or V, X₂ is S, G, E, F, W, H, I, V, N, Y, T, or R, X₃ is T, H, L, F, P, I, S, Y, K, A, D, V, N, or G, X₄ is D, A, M, Y, F, S, T, G, or W, X₅ is T, S, F, Q, A, N, L, E, I, G, or M, and X₆ is C, T, N, S, or A; and a light chain variable domain (V_L) comprising a
320 LC-CDR1 comprising RAX₁X₂X₃VX₄X₅X₆LA (SEQ ID NO: 293), wherein X₁ is S, L, N, A, K, R, I, Q, G, T, H, M, or C, X₂ is Q, Y, P, A, I, F, T, R, V, L, E, S, or C, X₃ is S, H, W, L, R, K, T, P, I, F, V, E, A, or Q, X₄ is S, L, W, M, A, Y, K, R, G, T, E, V, N, F, or C, X₅ is S, T, R, A, H, Q, P, M, L, or G, and X₆ is Y, L, or F; a LC-CDR2 comprising X₁X₂X₃SRAT (SEQ ID NO: 294),
325 wherein X₁ is G or T, X₂ is A, G, R, H, K, S, T, M, or F, and X₃ is S, A, W, R, L, T, Q, F, Y, H, or N; and a LC-CDR3 comprising QQYX₁X₂X₃PX₄T (SEQ ID NO: 79), wherein X₁ is N, D, S, R, A, T, L, Y, Q, W or G, X₂ is N, D, E, T, Y, G, A, M, F, S, I or L, X₃ is W, S, P, V, G, or R, and X₄ is P, Y, H, S, F, N, D, V, or G.

[0041] Also provided are nucleic acids encoding the anti-GM-CSFR α antibodies, compositions
330 comprising the anti-GM-CSFR α antibodies, and methods of making and using the anti-GM-CSFR α antibodies.

Definitions

[0042] As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results, including clinical results. For purposes of this application, beneficial or desired clinical results include, but are not limited to, one or more of the following: alleviating one or more symptoms resulting from the disease, diminishing the extent of the disease, stabilizing the disease (*e.g.*, preventing or delaying the worsening of the disease), preventing or delaying the spread (*e.g.*, metastasis) of the disease, preventing or delaying the recurrence of the disease, delay or slowing the progression of the disease, ameliorating the disease state, providing a remission (partial or total) of the disease, decreasing the dose of one or more other medications required to treat the disease, delaying the progression of the disease, increasing or improving the quality of life, increasing weight gain, and/or prolonging survival. Also encompassed by “treatment” is a reduction of pathological consequence of the disease (such as, for example, tumor volume for cancer). The methods of the application contemplate any one or more of these aspects of treatment.

[0043] The term “antibody” includes full-length antibodies and antigen-binding fragments thereof. A full-length antibody comprises two heavy chains and two light chains. The variable regions of the light and heavy chains are responsible for antigen binding. The variable regions in both chains generally contain three highly variable loops called the complementarity determining regions (CDRs) (light chain (LC) CDRs including LC-CDR1, LC-CDR2, and LC-CDR3, heavy chain (HC) CDRs including HC-CDR1, HC-CDR2, and HC-CDR3). CDR boundaries for the antibodies and antigen-binding fragments disclosed herein may be defined or identified by the conventions of Kabat, Chothia, or Al-Lazikani (Al-Lazikani 1997; Chothia 1985; Chothia 1987; Chothia 1989; Kabat 1987; Kabat 1991). The three CDRs of the heavy or light chains are interposed between flanking stretches known as framework regions (FRs), which are more highly conserved than the CDRs and form a scaffold to support the hypervariable loops. The constant regions of the heavy and light chains are not involved in antigen binding, but exhibit various effector functions. Antibodies are assigned to classes based on the amino acid sequence of the constant region of their heavy chain. The five major classes or isotypes of antibodies are IgA, IgD, IgE, IgG, and IgM, which are characterized by the presence of α , δ , ϵ , γ , and μ heavy chains, respectively. Several of the major antibody classes are divided into subclasses such as IgG1 (γ 1 heavy chain), IgG2 (γ 2 heavy chain), IgG3 (γ 3 heavy chain), IgG4 (γ 4 heavy chain), IgA1 (α 1 heavy chain), or IgA2 (α 2 heavy chain).

[0044] The term “antigen-binding fragment” as used herein refers to an antibody fragment including, for example, a diabody, a Fab, a Fab', a F(ab')₂, an Fv fragment, a disulfide stabilized

Fv fragment (dsFv), a (dsFv)₂, a bispecific dsFv (dsFv-dsFv'), a disulfide stabilized diabody (ds diabody), a single-chain Fv (scFv), an scFv dimer (bivalent diabody), a multispecific antibody formed from a portion of an antibody comprising one or more CDRs, a single domain antibody, a nanobody, a domain antibody, a bivalent domain antibody, or any other antibody fragment that
370 binds to an antigen but does not comprise a complete antibody structure. An antigen-binding fragment is capable of binding to the same antigen to which the parent antibody or a parent antibody fragment (*e.g.*, a parent scFv) binds. In some embodiments, an antigen-binding fragment may comprise one or more CDRs from a particular human antibody grafted to a framework region from one or more different human antibodies.

375 **[0045]** The term "epitope" as used herein refers to the specific group of atoms or amino acids on an antigen to which an antibody or antibody moiety binds. Two antibodies or antibody moieties may bind the same epitope within an antigen if they exhibit competitive binding for the antigen.

[0046] As used herein, a first antibody "competes" for binding to a target GM-CSFR α with a
380 second antibody when the first antibody inhibits target GM-CSFR α binding of the second antibody by at least about 50% (such as at least about any of 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99%) in the presence of an equimolar concentration of the first antibody, or *vice versa*. A high throughput process for "binning" antibodies based upon their cross-competition is described in PCT Publication No. WO 03/48731.

385 **[0047]** As use herein, the term "specifically binds," "specifically recognizing," or "is specific for" refers to measurable and reproducible interactions, such as binding between a target and an antibody that is determinative of the presence of the target in the presence of a heterogeneous population of molecules, including biological molecules. For example, an antibody that specifically recognizes a target (which can be an epitope) is an antibody that binds this target
390 with greater affinity, avidity, more readily, and/or with greater duration than its bindings to other targets. In some embodiments, an antibody that specifically recognizes an antigen reacts with one or more antigenic determinants of the antigen with a binding affinity that is at least about 10 times its binding affinity for other targets.

[0048] An "isolated" anti-GM-CSFR α antibody as used herein refers to an anti-GM-CSFR α
395 antibody that (1) is not associated with proteins found in nature, (2) is free of other proteins from the same source, (3) is expressed by a cell from a different species, or, (4) does not occur in nature.

[0049] The term "isolated nucleic acid" as used herein is intended to mean a nucleic acid of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin

400 the “isolated nucleic acid” (1) is not associated with all or a portion of a polynucleotide in which the “isolated nucleic acid” is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence.

[0050] As used herein, the term “CDR” or “complementarity determining region” is intended to mean the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. These particular regions have been described by Kabat *et al.*, J. Biol. Chem. 252:6609-6616 (1977); Kabat *et al.*, U.S. Dept. of Health and Human Services, “Sequences of proteins of immunological interest” (1991); Chothia *et al.*, J. Mol. Biol. 196:901-917 (1987); Al-Lazikani B. *et al.*, J. Mol. Biol., 273: 927-948 (1997); MacCallum *et al.*, J. Mol. Biol. 262:732-745 (1996); Abhinandan and Martin, *Mol. Immunol.*, 45: 3832-3839 (2008); Lefranc M.P. *et al.*, *Dev. Comp. Immunol.*, 27: 55-77 (2003); and Honegger and Plückthun, *J. Mol. Biol.*, 309:657-670 (2001), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or grafted antibodies or variants thereof is intended to be within the scope of the term as defined and used herein. The amino acid residues which encompass the CDRs as defined by each of the above cited references are set forth below in Table 1 as a comparison. CDR prediction algorithms and interfaces are known in the art, including, for example, Abhinandan and Martin, *Mol. Immunol.*, 45: 3832-3839 (2008); Ehrenmann F. *et al.*, *Nucleic Acids Res.*, 38: D301-D307 (2010); and Adolf-Bryfogle J. *et al.*, *Nucleic Acids Res.*, 43: D432-D438 (2015). The contents of the references cited in this paragraph are incorporated herein by reference in their entireties for use in the present application and for possible inclusion in one or more claims herein.

TABLE 1: CDR DEFINITIONS

	Kabat ¹	Chothia ²	MacCallum ³	IMGT ⁴	AHo ⁵
V _H CDR1	31-35	26-32	30-35	27-38	25-40
V _H CDR2	50-65	53-55	47-58	56-65	58-77
V _H CDR3	95-102	96-101	93-101	105-117	109-137
V _L CDR1	24-34	26-32	30-36	27-38	25-40
V _L CDR2	50-56	50-52	46-55	56-65	58-77
V _L CDR3	89-97	91-96	89-96	105-117	109-137

¹Residue numbering follows the nomenclature of Kabat *et al.*, *supra*

²Residue numbering follows the nomenclature of Chothia *et al.*, *supra*

³Residue numbering follows the nomenclature of MacCallum *et al.*, *supra*

⁴Residue numbering follows the nomenclature of Lefranc *et al.*, *supra*

⁵Residue numbering follows the nomenclature of Honegger and Plückthun, *supra*

430 [0051] The term “chimeric antibodies” refer to antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit a biological activity of this application (see U.S. Patent No. 4,816,567; and Morrison *et al.*, Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)).

440 [0052] “Fv” is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the heavy and light chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

445 [0053] “Single-chain Fv,” also abbreviated as “sFv” or “scFv,” are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. In some embodiments, the scFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the scFv to form the desired structure for antigen binding. For a review of scFv, see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

450 [0054] The term “diabodies” refers to small antibody fragments prepared by constructing scFv fragments (see preceding paragraph) typically with short linkers (such as about 5 to about 10 residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, *i.e.*, fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two “crossover” scFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

460 [0055] “Humanized” forms of non-human (*e.g.*, rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region (HVR) of the recipient are replaced by residues from a hypervariable region

of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

[0056] “Percent (%) amino acid sequence identity” or “homology” with respect to the polypeptide and antibody sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the polypeptide being compared, after aligning the sequences considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, Megalign (DNASTAR), or MUSCLE software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program MUSCLE (Edgar, R.C., *Nucleic Acids Research* 32(5):1792-1797, 2004; Edgar, R.C., *BMC Bioinformatics* 5(1):113, 2004).

[0057] The terms “Fc receptor” or “FcR” are used to describe a receptor that binds to the Fc region of an antibody. In some embodiments, an FcR of this application is one that binds an IgG antibody (a γ receptor) and includes receptors of the Fc γ RI, Fc γ RII, and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc γ RII receptors include Fc γ RIIA (an “activating receptor”) and Fc γ RIIB (an “inhibiting receptor”), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc γ RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc γ RIIB contains an immunoreceptor tyrosine-based

inhibition motif (ITIM) in its cytoplasmic domain (*see* review M. in Daëron, *Annu. Rev. Immunol.* 15:203-234 (1997)). The term includes allotypes, such as FcγRIIIA allotypes: FcγRIIIA-Phe158, FcγRIIIA-Val158, FcγRIIA-R131 and/or FcγRIIA-H131. FcRs are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-92 (1991); Capel *et al.*, *Immunomethods* 4:25-34 (1994); and de Haas *et al.*, *J. Lab. Clin. Med.* 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term “FcR” herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer *et al.*, *J. Immunol.* 117:587 (1976) and Kim *et al.*, *J. Immunol.* 24:249 (1994)).

[0058] The term “FcRn” refers to the neonatal Fc receptor (FcRn). FcRn is structurally similar to major histocompatibility complex (MHC) and consists of an α -chain noncovalently bound to β 2-microglobulin. The multiple functions of the neonatal Fc receptor FcRn are reviewed in Ghetie and Ward (2000) *Annu. Rev. Immunol.* 18, 739-766. FcRn plays a role in the passive delivery of immunoglobulin IgGs from mother to young and the regulation of serum IgG levels. FcRn can act as a salvage receptor, binding and transporting pinocytosed IgGs in intact form both within and across cells, and rescuing them from a default degradative pathway.

[0059] The “CH1 domain” of a human IgG Fc region (also referred to as “C1” of “H1” domain) usually extends from about amino acid 118 to about amino acid 215 (EU numbering system).

[0060] “Hinge region” is generally defined as stretching from Glu216 to Pro230 of human IgG1 (Burton, *Molec. Immunol.* 22:161-206 (1985)). Hinge regions of other IgG isotypes may be aligned with the IgG1 sequence by placing the first and last cysteine residues forming inter-heavy chain S-S bonds in the same positions.

[0061] The “CH2 domain” of a human IgG Fc region (also referred to as “C2” of “H2” domain) usually extends from about amino acid 231 to about amino acid 340. The CH2 domain is unique in that it is not closely paired with another domain. Rather, two N-linked branched carbohydrate chains are interposed between the two CH2 domains of an intact native IgG molecule. It has been speculated that the carbohydrate may provide a substitute for the domain-domain pairing and help stabilize the CH2 domain. Burton, *Molec Immunol.* 22:161-206 (1985).

[0062] The “CH3 domain” (also referred to as “C2” or “H3” domain) comprises the stretch of residues C-terminal to a CH2 domain in an Fc region (*i.e.* from about amino acid residue 341 to the C-terminal end of an antibody sequence, typically at amino acid residue 446 or 447 of an IgG).

[0063] A “functional Fc fragment” possesses an “effector function” of a native sequence Fc region. Exemplary “effector functions” include C1q binding; complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC);

530 phagocytosis; down regulation of cell surface receptors (*e.g.* B cell receptor; BCR), etc. Such effector functions generally require the Fc region to be combined with a binding domain (*e.g.* an antibody variable domain) and can be assessed using various assays known in the art.

[0064] An antibody with a variant IgG Fc with “altered” FcR binding affinity or ADCC activity is one which has either enhanced or diminished FcR binding activity (*e.g.*, FcγR or FcRn) 535 and/or ADCC activity compared to a parent polypeptide or to a polypeptide comprising a native sequence Fc region. The variant Fc which “exhibits increased binding” to an FcR binds at least one FcR with higher affinity (*e.g.*, lower apparent K_d or IC_{50} value) than the parent polypeptide or a native sequence IgG Fc. According to some embodiments, the improvement in binding compared to a parent polypeptide is about 3 fold, such as about any of 5, 10, 25, 50, 60, 100, 150, 540 200, or up to 500 fold, or about 25% to 1000% improvement in binding. The polypeptide variant which “exhibits decreased binding” to an FcR, binds at least one FcR with lower affinity (*e.g.*, higher apparent K_d or higher IC_{50} value) than a parent polypeptide. The decrease in binding compared to a parent polypeptide may be about 40% or more decrease in binding.

[0065] “Antibody-dependent cell-mediated cytotoxicity” or “ADCC” refers to a form of 545 cytotoxicity in which secreted Ig bound to Fc receptors (FcRs) present on certain cytotoxic cells (*e.g.*, Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies “arm” the cytotoxic cells and are required for such killing. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express 550 FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or 555 additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.*, in an animal model such as that disclosed in Clynes *et al. PNAS (USA)* 95:652-656 (1998).

[0066] The polypeptide comprising a variant Fc region which “exhibits increased ADCC” or mediates ADCC in the presence of human effector cells more effectively than a polypeptide having wild type IgG Fc or a parent polypeptide is one which *in vitro* or *in vivo* is substantially 560 more effective at mediating ADCC, when the amounts of polypeptide with variant Fc region and the polypeptide with wild type Fc region (or the parent polypeptide) in the assay are essentially the same. Generally, such variants will be identified using any *in vitro* ADCC assay known in the art, such as assays or methods for determining ADCC activity, *e.g.*, in an animal model *etc.*

In some embodiments, the variant is from about 5 fold to about 100 fold, *e.g.* from about 25 to about 50 fold, more effective at mediating ADCC than the wild type Fc (or parent polypeptide).

565 [0067] “Complement dependent cytotoxicity” or “CDC” refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC

570 assay, *e.g.* as described in Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996), may be performed. Polypeptide variants with altered Fc region amino acid sequences and increased or decreased C1q binding capability are described in US patent No. 6,194,551B1 and WO99/51642. The contents of those patent publications are specifically incorporated herein by reference. *See also*, Idusogie *et al. J. Immunol.* 164: 4178-4184 (2000).

575 [0068] Unless otherwise specified, a “nucleotide sequence encoding an amino acid sequence” includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or a RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

580 [0069] The term “operably linked” refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter

585 affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences are contiguous and, where necessary to join two protein coding regions, in the same reading frame.

[0070] “Homologous” refers to the sequence similarity or sequence identity between two polypeptides or between two nucleic acid molecules. When a position in both of the two

590 compared sequences is occupied by the same base or amino acid monomer subunit, *e.g.*, if a position in each of two DNA molecules is occupied by adenine, then the molecules are homologous at that position. The percent of homology between two sequences is a function of the number of matching or homologous positions shared by the two sequences divided by the number of positions compared times 100. For example, if 6 of 10 of the positions in two

595 sequences are matched or homologous then the two sequences are 60% homologous. By way of example, the DNA sequences ATTGCC and TATGGC share 50% homology. Generally, a comparison is made when two sequences are aligned to give maximum homology.

[0071] An “effective amount” of an anti-GM-CSFR α antibody or composition as disclosed herein, is an amount sufficient to carry out a specifically stated purpose. An “effective amount”
600 can be determined empirically and by known methods relating to the stated purpose.

[0072] The term “therapeutically effective amount” refers to an amount of an anti-GM-CSFR α antibody or composition as disclosed herein, effective to “treat” a disease or disorder in an individual. In the case of cancer, the therapeutically effective amount of the anti-GM-CSFR α antibody or composition as disclosed herein can reduce the number of cancer cells; reduce the
605 tumor size or weight; inhibit (*i.e.*, slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (*i.e.*, slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the anti-GM-CSFR α antibody or composition as disclosed herein can prevent growth and/or kill existing cancer cells, it can be
610 cytostatic and/or cytotoxic. In some embodiments, the therapeutically effective amount is a growth inhibitory amount. In some embodiments, the therapeutically effective amount is an amount that extends the survival of a patient. In some embodiments, the therapeutically effective amount is an amount that improves progression free survival of a patient.

[0073] As used herein, by “pharmaceutically acceptable” or “pharmacologically compatible” is
615 meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and
620 manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0074] It is understood that embodiments of the application described herein include “consisting” and/or “consisting essentially of” embodiments.

[0075] Reference to “about” a value or parameter herein includes (and describes) variations
625 that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.

[0076] As used herein, reference to “not” a value or parameter generally means and describes “other than” a value or parameter. For example, the method is not used to treat cancer of type X means the method is used to treat cancer of types other than X.

[0077] As used herein and in the appended claims, the singular forms “a,” “an,” and “the”
630 include plural referents unless the context clearly dictates otherwise.

Anti-GM-CSFR α antibodies

[0078] In one aspect, the present application provides anti-GM-CSFR α antibodies that specifically bind to GM-CSFR α . Anti-GM-CSFR α antibodies include, but are not limited to, humanized antibodies, chimeric antibodies, mouse antibodies, human antibodies, and antibodies comprising the heavy chain and/or light chain CDRs discussed herein. In one aspect, the present application provides isolated antibodies that bind to GM-CSFR α . Contemplated anti-GM-CSFR α antibodies include, for example, full-length anti-GM-CSFR α antibodies (*e.g.*, full-length IgG1 or IgG4), anti-GM-CSFR α scFvs, anti-GM-CSFR α Fc fusion proteins, multi-specific (such as bispecific) anti-GM-CSFR α antibodies, anti-GM-CSFR α immunoconjugates, and the like. In some embodiments, the anti-GM-CSFR α antibody is a full-length antibody (*e.g.*, full-length IgG1 or IgG4) or antigen-binding fragment thereof, which specifically binds to GM-CSFR α . In some embodiments, the anti-GM-CSFR α antibody is a Fab, a Fab', a F(ab')₂, a Fab'-SH, a single-chain Fv (scFv), an Fv fragment, a dAb, a Fd, a nanobody, a diabody, or a linear antibody. In some embodiments, reference to an antibody that specifically binds to GM-CSFR α means that the antibody binds to GM-CSFR α with an affinity that is at least about 10 times (including for example at least about any one of 10, 10², 10³, 10⁴, 10⁵, 10⁶, or 10⁷ times) more tightly than its binding affinity for a non-target. In some embodiments, the non-target is an antigen that is not GM-CSFR α . Binding affinity can be determined by methods known in the art, such as ELISA, fluorescence activated cell sorting (FACS) analysis, or radioimmunoprecipitation assay (RIA). K_d can be determined by methods known in the art, such as surface plasmon resonance (SPR) assay or biolayer interferometry (BLI).

[0079] Although anti-GM-CSFR α antibodies containing human sequences (*e.g.*, human heavy and light chain variable domain sequences comprising human CDR sequences) are extensively discussed herein, non-human anti-GM-CSFR α antibodies are also contemplated. In some embodiments, non-human anti-GM-CSFR α antibodies comprise human CDR sequences from an anti-GM-CSFR α antibody as described herein and non-human framework sequences. Non-human framework sequences include, in some embodiments, any sequence that can be used for generating synthetic heavy and/or light chain variable domains using one or more human CDR sequences as described herein, including, *e.g.*, mammals, *e.g.*, mouse, rat, rabbit, pig, bovine (*e.g.*, cow, bull, buffalo), deer, sheep, goat, chicken, cat, dog, ferret, primate (*e.g.*, marmoset, rhesus monkey), etc. In some embodiments, a non-human anti-GM-CSFR α antibody includes an anti-GM-CSFR α antibody generated by grafting one or more human CDR sequences as described herein onto a non-human framework sequence (*e.g.*, a mouse or chicken framework sequence).

[0080] The complete amino acid sequence of an exemplary human GM-CSFR α comprises or consists of the amino acid sequence of SEQ ID NO: 148.

670
 1 MLLLVTSLLL CELPHPAFLI IPEKSDLRTV APASSLNVRV DSRTMNLSD CQENTTFSKC
 61 FLTDKKNRVV EPRLSNNECS CTFREICLHE GVTFEVHVNT SQRGFQOKLL YPNSGREGTA
 121 AQNFSCFIYN ADLMNCTWAR GPTAPRDVQY FLYIRNSKRR REIRCPYYIQ DSGTHVGCCHL
 181 DNLSGLTSRN YFLVNGTSRE IGIQFFDSL DTKKIERFNP PSNVTVRCNT THCLVRWKQP
 241 RTYQKLSYLD FQYQLDVHRK NTQPGTENLL INVSGDLENR YNFPSEPEA KHSV KIRAAD
 301 VRILNWSWS EAIEFGSDDG NLGVSYYIVL LIVGTLVCGI VLGFLFKRFL RIQRLFPVP
 361 QIKDKLNDNH EVEDEIIWEE FTPEEGKGYR EEVLTVKEIT

675 **[0081]** The amino acid sequence of the extracellular domain of an exemplary human GM-CSFR α comprises or consists of the amino acid sequence of SEQ ID NO: 149.

680
 1 MLLLVTSLLL CELPHPAFLI IPEKSDLRTV APASSLNVRV DSRTMNLSD CQENTTFSKC
 61 FLTDKKNRVV EPRLSNNECS CTFREICLHE GVTFEVHVNT SQRGFQOKLL YPNSGREGTA
 121 AQNFSCFIYN ADLMNCTWAR GPTAPRDVQY FLYIRNSKRR REIRCPYYIQ DSGTHVGCCHL
 181 DNLSGLTSRN YFLVNGTSRE IGIQFFDSL DTKKIERFNP PSNVTVRCNT THCLVRWKQP
 241 RTYQKLSYLD FQYQLDVHRK NTQPGTENLL INVSGDLENR YNFPSEPEA KHSV KIRAAD
 301 VRILNWSWS EAIEFGSDDG

[0082] In some embodiments, the anti-GM-CSFR α antibody described herein specifically
 685 recognizes an epitope within human GM-CSFR α . In some embodiments, the anti-GM-CSFR α antibody cross-reacts with GM-CSFR α from species other than human. In some embodiments, the anti-GM-CSFR α antibody is completely specific for human GM-CSFR α and does not exhibit species or other types of non-human cross-reactivity.

[0083] In some embodiments, the anti-GM-CSFR α antibody described herein specifically
 690 binds to a linear epitope within human GM-CSFR α . In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to a nonlinear epitope within human GM-CSFR α . In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises one, two, three, four, five, or six amino acid residues selected from the group consisting of Val50, Glu59, Lys194, Lys195, Arg283, and Ile284 of human GM-CSFR α . In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises Val50, Glu59, Lys194, Lys195, Arg283, and Ile284 of human GM-CSFR α . In some
 695 embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises one, two, three, four, five, six, seven, eight,
 700 or nine amino acid residues selected from the group consisting of Val50, Glu59, Lys194, Lys195, Arg283, Ile284, Val51, Thr63, and Ile196. In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50, Glu59, Lys194, Lys195, Arg283, Ile284, Val51, Thr63, and Ile196. In some embodiments, the anti-GM-CSFR α antibody described herein specifically
 705 binds to an epitope on human GM-CSFR α , wherein the epitope comprises one, two, three, four, five, six, seven, or eight amino acid residues selected from the group consisting of Val50, Glu59,

Lys194, Lys195, Arg283, Ile284, Leu191 and Ile196. In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50, Glu59, Lys194, Lys195, Arg283, Ile284, Leu191 and Ile196. In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises one, two, three, four, five, six, seven, eight, nine, or ten amino acid residues selected from the group consisting of Val50, Glu59, Lys194, Lys195, Arg283, Ile284, Arg49, Val51, Asn57, and Ser61. In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50, Glu59, Lys194, Lys195, Arg283, Ile284, Arg49, Val51, Asn57, and Ser61.

[0084] In some embodiments, the anti-GM-CSFR α antibody cross-reacts with at least one allelic variant of the GM-CSFR α protein (or fragments thereof). In some embodiments, the allelic variant has up to about 30 (such as about any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, or 30) amino acid substitutions (such as a conservative substitution) when compared to the naturally occurring GM-CSFR α (or fragments thereof). In some embodiments, the anti-GM-CSFR α antibody does not cross-react with any allelic variant of the GM-CSFR α protein (or fragments thereof).

[0085] In some embodiments, the anti-GM-CSFR α antibody cross-reacts with at least one interspecies variant of the GM-CSFR α protein. In some embodiments, for example, the GM-CSFR α protein (or fragments thereof) is human GM-CSFR α and the interspecies variant of the GM-CSFR α protein (or fragments thereof) is a cynomolgus monkey variant thereof. In some embodiments, the anti-GM-CSFR α antibody does not cross-react with any interspecies variant of the GM-CSFR α protein.

[0086] In some embodiments, according to any of the anti-GM-CSFR α antibodies described herein, the anti-GM-CSFR α antibody comprises an antibody heavy chain constant region and an antibody light chain constant region. In some embodiments, the anti-GM-CSFR α antibody comprises an IgG1 heavy chain constant region. In some embodiments, the anti-GM-CSFR α antibody comprises an IgG2 heavy chain constant region. In some embodiments, the anti-GM-CSFR α antibody comprises an IgG3 heavy chain constant region. In some embodiments, the anti-GM-CSFR α antibody comprises an IgG4 heavy chain constant region. In some embodiments, the heavy chain constant region comprises (including consisting of or consisting essentially of) the amino acid sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises (including consisting of or consisting essentially of) the amino acid sequence of SEQ ID NO: 146. In some embodiments, the anti-GM-CSFR α comprises a

lambda light chain constant region. In some embodiments, the anti-GM-CSFR α antibody comprises a kappa light chain constant region. In some embodiments, the light chain constant region comprises (including consisting of or consisting essentially of) the amino acid sequence of SEQ ID NO: 147. In some embodiments, the anti-GM-CSFR α antibody comprises an antibody heavy chain variable domain and an antibody light chain variable domain.

[0087] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising an HC-CDR1 comprising X₁LX₂X₃H (SEQ ID NO: 76), wherein X₁ is E, N, G, D, M, S, P, F, Y, A, V, K, W, R or C, X₂ is S, C or P, and X₃ is I or M; an HC-CDR2 comprising GFDX₁X₂X₃X₄EX₅X₆YAQKX₇QG (SEQ ID NO: 77), wherein X₁ is P, G, T, S, or V, X₂ is E, D, G, or A, X₃ is D, G, I, W, S, or V, X₄ is G, E, D, or H, X₅ is T or A, X₆ is N or I, and X₇ is S or F; and an HC-CDR3 comprising GRYX₁X₂X₃X₄X₅X₆YGFDY (SEQ ID NO: 78), wherein X₁ is C, T, S, I, A, or V, X₂ is S, G, E, F, W, H, I, V, N, Y, T, or R, X₃ is T, H, L, F, P, I, S, Y, K, A, D, V, N, or G, X₄ is D, A, M, Y, F, S, T, G, or W, X₅ is T, S, F, Q, A, N, L, E, I, G, or M, and X₆ is C, T, N, S, or A; and a V_L comprising a LC-CDR1 comprising RAX₁X₂X₃VX₄X₅X₆LA (SEQ ID NO: 293), wherein X₁ is S, L, N, A, K, R, I, Q, G, T, H, M, or C, X₂ is Q, Y, P, A, I, F, T, R, V, L, E, S, or C, X₃ is S, H, W, L, R, K, T, P, I, F, V, E, A, or Q, X₄ is S, L, W, M, A, Y, K, R, G, T, E, V, N, F, or C, X₅ is S, T, R, A, H, Q, P, M, L, or G, and X₆ is Y, L, or F; a LC-CDR2 comprising X₁X₂X₃SRAT (SEQ ID NO: 294), wherein X₁ is G or T, X₂ is A, G, R, H, K, S, T, M, or F, and X₃ is S, A, W, R, L, T, Q, F, Y, H, or N; and a LC-CDR3 comprising QQYX₁X₂X₃PX₄T (SEQ ID NO: 79), wherein X₁ is N, D, S, R, A, T, L, Y, Q, W or G, X₂ is N, D, E, T, Y, G, A, M, F, S, I or L, X₃ is W, S, P, V, G, or R, and X₄ is P, Y, H, S, F, N, D, V, or G.

[0088] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising a HC-CDR1 comprising ELX₁X₂H (SEQ ID NO: 295), wherein X₁ is S, C or P, and X₂ is I or M; an HC-CDR2 comprising GFDX₁X₂X₃X₄EX₅X₆YAQKX₇QG (SEQ ID NO: 77), wherein X₁ is P, G, T, S, or V, X₂ is E, D, G, or A, X₃ is D, G, I, W, S, or V, X₄ is G, E, D, or H, X₅ is T or A, X₆ is N or I, and X₇ is S or F; and an HC-CDR3 comprising GRYX₁X₂X₃X₄X₅X₆YGFDY (SEQ ID NO: 78), wherein X₁ is C, T, S, I, A, or V, X₂ is S, G, E, F, W, H, I, V, N, Y, T, or R, X₃ is T, H, L, F, P, I, S, Y, K, A, D, V, N, or G, X₄ is D, A, M, Y, F, S, T, G, or W, X₅ is T, S, F, Q, A, N, L, E, I, G, or M, and X₆ is C, T, N, S, or A; and a V_L comprising: a LC-CDR1 comprising RASQSVSSYLA (SEQ ID NO: 51); a LC-CDR2 comprising GASSRAT (SEQ ID NO: 52); and a LC-CDR3 comprising QQYX₁X₂X₃PX₄T (SEQ ID NO: 79), wherein X₁ is N, D, S, R, A, T, L, Y, Q, W or G, X₂ is N, D, E, T, Y, G, A, M, F, S, I or L, X₃ is W, S, P, V, G, or R, and X₄ is P, Y, H, S, F, N, D, V, or G.

[0089] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
775 HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, or a variant
thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an
HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, or a variant
thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, and
an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50, or a
780 variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid
substitutions.

[0090] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, an HC-CDR2
comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, and an HC-CDR3
785 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50.

[0091] In some embodiments, the anti-GM-CSFR α antibody comprises a V_L comprising: an
LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, or a variant thereof
comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an LC-CDR2
comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof comprising up to
790 about 3 (such as about any of 1, 2, or 3) amino acid substitutions, and an LC-CDR3 comprising
the amino acid sequence of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to
about 3 (such as about any of 1, 2, or 3) amino acid substitutions.

[0092] In some embodiments, the anti-GM-CSFR α antibody comprises a V_L comprising: an
LC-CDR1 comprising the amino acid sequence of SEQ ID NOs: 51, an LC-CDR2 comprising
795 the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid
sequence of any one of SEQ ID NOs: 53-75.

[0093] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, or a variant
thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an
800 HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, or a variant
thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, and
an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50, or a
variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid
substitutions; and a V_L comprising: an LC-CDR1 comprising the amino acid sequence of SEQ
805 ID NO: 51, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino
acid substitutions, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, or a
variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid

substitutions, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions.

[0094] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, and an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50; and a V_L comprising: an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 53-75.

[0095] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 17, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising: an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.

[0096] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 17; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54.

[0097] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 56, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.

[0098] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the

amino acid sequence of SEQ ID NO: 8, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an
845 LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 56.

[0099] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 23, or a variant thereof comprising up to about 5 amino acid substitutions in the
850 HC-CDRs; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.

[00100] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising an
855 HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 23; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57.

[00101] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
860 HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID
865 NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.

[00102] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
870 HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57.

[00103] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
875 HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the

amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 53, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.

[00104] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 53.

[00105] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 37, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.

[00106] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 37; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57.

[00107] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.

910 [00108] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2 comprising the
amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence
of SEQ ID NO: 39; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of
915 LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54.

[00109] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the
amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence
of SEQ ID NO: 35, or a variant thereof comprising up to about 5 amino acid substitutions in the
920 HC-CDRs; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID
NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3
comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to
about 5 amino acid substitutions in the LC-CDRs.

[00110] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
925 HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the
amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence
of SEQ ID NO: 35; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of
SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an
LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57.

930 [00111] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the
amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence
of SEQ ID NO: 50, or a variant thereof comprising up to about 5 amino acid substitutions in the
HC-CDRs; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID
935 NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3
comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to
about 5 amino acid substitutions in the LC-CDRs.

[00112] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising: an
HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the
940 amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence
of SEQ ID NO: 50; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of
SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an
LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57.

945 [00113] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1-50, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51-75, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1-50; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51-75.

950 [00114] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 5 and 17, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 54, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 5 and 17; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 54.

960 [00115] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 8 and 22, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 56, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 8 and 22; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 56.

965 [00116] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 23, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 23; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57.

970 [00117] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 6 and 27, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 6 and 27; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57.

980 [00118] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 35, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 53, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 35; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 53.

985 [00119] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 37, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 37; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57.

995 [00120] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 3, 6 and 39, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 54, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 3, 6 and 39; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 54.

1000 [00121] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 35, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57, or a variant thereof comprising up to about 5 amino acid substitutions. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 35; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57.

1005 [00122] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequences of SEQ ID NOs: 1, 7 and 50, or a variant thereof comprising up to about 5 amino acid substitutions; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57, or a variant thereof comprising up to about 5 amino acid substitutions. In some
1010 embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid

sequences of SEQ ID NOs: 1, 7 and 50; and a V_L comprising the amino acid sequences of SEQ ID NOs: 51, 52 and 57.

1015 [00123] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising an HC-CDR1, an HC-CDR2 and an HC-CDR3 of the V_H comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287; and a V_L comprising a LC-CDR1, a LC-CDR2, and a LC-CDR3 of the V_L comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289.

1020 [00124] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising one, two or three HC-CDRs of SEQ ID NO: 80. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising one, two or three HC-CDRs of SEQ ID NO: 85. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising one, two or three HC-CDRs of SEQ ID NO: 86. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising one, two or three HC-CDRs of SEQ ID NO: 91. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising one, two or three HC-CDRs of SEQ ID NO: 99. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising one, two or three HC-CDRs of SEQ ID NO: 101. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising one, two or three HC-CDRs of SEQ ID NO: 103. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising one, two or three HC-CDRs of SEQ ID NO: 121.

1030 [00125] In some embodiments, the anti-GM-CSFR α antibody comprises a V_L comprising one, two or three LC-CDRs of SEQ ID NO: 123. In some embodiments, the anti-GM-CSFR α antibody comprises a V_L comprising one, two or three LC-CDRs of SEQ ID NO: 125. In some embodiments, the anti-GM-CSFR α antibody comprises a V_L comprising one, two or three LC-CDRs of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody comprises a V_L comprising one, two or three LC-CDRs of SEQ ID NO: 122.

1040 [00126] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of SEQ ID NO: 80, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 123. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of SEQ ID NO: 85, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 125. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of SEQ ID NO: 86, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of

1045 SEQ ID NO: 91, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of SEQ ID NO: 99, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 122. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of SEQ ID NO: 101, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of SEQ ID NO: 103, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 123. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of SEQ ID NO: 99, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising HC-CDR1, HC-CDR2 and HC-CDR3 of the V_H of SEQ ID NO: 121, and a V_L comprising LC-CDR1, LC-CDR2 and LC-CDR3 of the V_L of SEQ ID NO: 126.

1055 [00127] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of any one of SEQ ID NOs: 80-121 and 246-287, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of any one of SEQ ID NOs: 80-121 and 246-287, and a V_L comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289.

1065 [00128] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 123, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 80 and a V_L comprising the amino acid sequence of SEQ ID NO: 123.

1070 [00129] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 85, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 125, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α

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antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 85 and a V_L comprising the amino acid sequence of SEQ ID NO: 125.

[00130] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 86, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 126, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 86 and a V_L comprising the amino acid sequence of SEQ ID NO: 126.

[00131] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 91, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 126, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 91 and a V_L comprising the amino acid sequence of SEQ ID NO: 126.

[00132] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 122, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 99 and a V_L comprising the amino acid sequence of SEQ ID NO: 122.

[00133] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 101, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 126, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 101 and a V_L comprising the amino acid sequence of SEQ ID NO: 126.

[00134] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 123, or a variant thereof

having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 103 and a V_L comprising the amino acid sequence of SEQ ID NO: 123.

[00135] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 126, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 99 and a V_L comprising the amino acid sequence of SEQ ID NO: 126.

[00136] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 121, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 126, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 121 and a V_L comprising the amino acid sequence of SEQ ID NO: 126.

[00137] In some embodiments, functional epitopes can be mapped by combinatorial alanine scanning. In this process, a combinatorial alanine-scanning strategy can be used to identify amino acids in the GM-CSFR α protein that are necessary for interaction with GM-CSFR α antibodies. In some embodiments, the epitope is conformational and crystal structure of anti-GM-CSFR α antibodies bound to GM-CSFR α may be employed to identify the epitopes.

[00138] In some embodiments, the present application provides antibodies which compete with any one of the GM-CSFR α antibodies described herein for binding to GM-CSFR α . In some embodiments, the present application provides antibodies which compete with any one of the anti-GM-CSFR α antibodies provided herein for binding to an epitope on the GM-CSFR α . In some embodiments, an anti-GM-CSFR α antibody is provided that binds to the same epitope as an anti-GM-CSFR α antibody comprising a V_H comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287, and a V_L comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289. In some embodiments, an anti-GM-CSFR α antibody is provided that specifically binds to GM-CSFR α competitively with an anti-GM-CSFR α antibody comprising a V_H comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287 and a V_L comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289.

[00139] In some embodiments, competition assays may be used to identify a monoclonal antibody that competes with an anti-GM-CSFR α antibody described herein for binding to GM-CSFR α . Competition assays can be used to determine whether two antibodies bind the same epitope by recognizing identical or sterically overlapping epitopes or one antibody competitively inhibits binding of another antibody to the antigen. In certain embodiments, such a competing antibody binds to the same epitope that is bound by an antibody described herein. Exemplary competition assays include, but are not limited to, routine assays such as those provided in Harlow and Lane (1988) Antibodies: A Laboratory Manual ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.). Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in Methods in Molecular Biology vol. 66 (Humana Press, Totowa, N.J.). In some embodiments, two antibodies are said to bind to the same epitope if each blocks binding of the other by 50% or more. In some embodiments, the antibody that competes with an anti-GM-CSFR α antibody described herein is a chimeric, humanized or human antibody.

[00140] Exemplary anti-GM-CSFR α antibody sequences are shown in Tables 2, 3 and 18, and in FIGS. 19A, 19B. Those skilled in the art will recognize that many algorithms are known for prediction of CDR positions and for delimitation of antibody heavy chain and light chain variable regions. Anti-GM-CSFR α antibodies comprising CDRs, V_H and/or V_L sequences from antibodies described herein, but based on prediction algorithms other than those exemplified in the tables below, are within the scope of this invention.

Table 2. Exemplary anti-GM-CSFR α antibody CDR sequences.

Antibody Name	HC-CDR1	HC-CDR2	HC-CDR3
T119	ELSIH (SEQ ID NO: 1)	GFDPEDGETNYAQKSQG (SEQ ID NO: 5)	GRYCSTDTCYGFDY (SEQ ID NO: 17)
E01	ELSIH (SEQ ID NO: 1)	GFDPEDGETNYAQKSQG (SEQ ID NO: 5)	GRYCSTDTCYGFDY (SEQ ID NO: 17)
E09	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYCGHASCYGFYD (SEQ ID NO: 18)
E105	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLMFTYGFDY (SEQ ID NO: 19)
E108	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTELYQNYGFDY (SEQ ID NO: 20)
E113	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYTELFASYGFYD (SEQ ID NO: 21)
E16	ELSIH (SEQ ID NO: 1)	GFDPEDGEAIYAQKSQG (SEQ ID NO: 8)	GRYSEHSTSYGFDY (SEQ ID NO: 22)
E194	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYTGLMNSYGFYD (SEQ ID NO: 23)
E27	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYISFMFTYGFDY (SEQ ID NO: 24)
E29	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG	GRYCFPDTCYGFDY (SEQ ID NO: 25)

		(SEQ ID NO: 6)	NO: 25)
E30	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYCSTDTCYGFDY(SEQ ID NO: 17)
E34	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYSFTDLAYGFDY(SEQ ID NO: 26)
E35	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLATTYGFDY(SEQ ID NO: 27)
E36	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYAFIDTAYGFDY(SEQ ID NO: 28)
E39	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYCSSLDCYGFDY(SEQ ID NO: 29)
E40	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLDESYGFDY(SEQ ID NO: 30)
E54	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYSSYDIAYGFDY(SEQ ID NO: 31)
E61	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYAWTDIAYGFDY(SEQ ID NO: 32)
E83	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYCFYDLCYGFDY(SEQ ID NO: 33)
E85	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYSSYFTNYGFDY(SEQ ID NO: 34)
E87	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYVSLFFNYGFDY(SEQ ID NO: 35)
E88	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYCHKDGCYGFDY(SEQ ID NO: 36)
E90	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYTGLYASYGFDY(SEQ ID NO: 37)
E94	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYCETDICYGFDY(SEQ ID NO: 38)
E200a	ELPMH (SEQ ID NO: 3)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTIITTNYGFDY(SEQ ID NO: 39)
EII33	ELSIH (SEQ ID NO: 1)	GFDGDGEETIYAQKFQG (SEQ ID NO: 9)	GRYTSLAATYGFDY(SEQ ID NO: 40)
EII52	ELSIH (SEQ ID NO: 1)	GFDGDIEETIYAQKFQG (SEQ ID NO: 10)	GRYTSLATTYGFDY(SEQ ID NO: 27)
EII81	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLAATYGFDY(SEQ ID NO: 40)
E161	ELCMH (SEQ ID NO: 4)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYAVTDMAYGFDY(SEQ ID NO: 41)
E163	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYAFAGLAYGFDY(SEQ ID NO: 42)
E164	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYTNDFANYGFDY(SEQ ID NO: 43)
E170	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYSSVGSTYGFDY(SEQ ID NO: 44)
E172	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYANLYNNYGFDY(SEQ ID NO: 45)
E174	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYVYLASNYGFDY(SEQ ID NO: 46)
E181	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYSTNFSNYGFDY(SEQ ID NO: 47)
E84	ELSMH (SEQ ID NO: 2)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYTRGWFNYGFDY(SEQ ID NO: 48)
EII55	ELSIH (SEQ ID NO: 1)	GFDGDWHETIYAQKFQG (SEQ ID NO: 14)	GRYTSLDATYGFDY(SEQ ID NO: 49)
E87b	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKSQG (SEQ ID NO: 7)	GRYVSLFFNYGFDY(SEQ ID NO: 35)
E31	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKSQG	GRYSESFASYGFDY(SEQ ID

		(SEQ ID NO: 7)	NO: 50)
E41	ELSIH (SEQ ID NO: 1)	GFDPAWGETIYAQKFQG (SEQ ID NO: 15)	GRYTSLATTYGFDY(SEQ ID NO: 27)
EII41	ELSIH (SEQ ID NO: 1)	GFDTGDDGETIYAQKFQG (SEQ ID NO: 11)	GRYTSLDATYGFDY(SEQ ID NO: 49)
EII46	ELSIH (SEQ ID NO: 1)	GFDSEWGETIYAQKFQG (SEQ ID NO: 12)	GRYTSLATTYGFDY(SEQ ID NO: 27)
EII49	ELSIH (SEQ ID NO: 1)	GFDVASGETIYAQKFQG (SEQ ID NO: 13)	GRYTSLDATYGFDY(SEQ ID NO: 49)
EII7	ELSIH (SEQ ID NO: 1)	GFDSEVGETIYAQKFQG (SEQ ID NO: 16)	GRYTSLAATYGFDY(SEQ ID NO: 40)
E35a	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLATTYGFDY(SEQ ID NO: 27)
E35b	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLATTYGFDY(SEQ ID NO: 27)
E35c	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLATTYGFDY(SEQ ID NO: 27)
E35d	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLATTYGFDY(SEQ ID NO: 27)
E35e	ELSIH (SEQ ID NO: 1)	GFDPEDGETIYAQKFQG (SEQ ID NO: 6)	GRYTSLATTYGFDY(SEQ ID NO: 27)
Antibody Name	LC-CDR1	LC-CDR2	LC-CDR3
T119	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E01	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPPT (SEQ ID NO: 54)
E09	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E105	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E108	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E113	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPYT (SEQ ID NO: 55)
E16	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDSWPYT (SEQ ID NO: 56)
E194	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPYT (SEQ ID NO: 57)
E27	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E29	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPHT (SEQ ID NO: 58)
E30	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPHT (SEQ ID NO: 58)
E34	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDSSPPT (SEQ ID NO: 59)
E35	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPYT (SEQ ID NO: 57)
E36	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYSNSPPT (SEQ ID NO: 60)
E39	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPHT (SEQ ID NO: 58)
E40	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPYT (SEQ ID NO: 61)
E54	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNSPPT (SEQ ID NO: 62)

E61	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPST (SEQ ID NO: 63)
E83	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYSNSPPT (SEQ ID NO: 60)
E85	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPYT (SEQ ID NO: 55)
E87	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E88	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDSSPHT (SEQ ID NO: 64)
E90	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPYT (SEQ ID NO: 57)
E94	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E200a	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPPT (SEQ ID NO: 54)
EII33	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYRNWPFT (SEQ ID NO: 65)
EII52	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYANPPNT (SEQ ID NO: 66)
EII81	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYTNVPDT (SEQ ID NO: 67)
E161	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNSPPT (SEQ ID NO: 68)
E163	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPPT (SEQ ID NO: 69)
E164	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPYT (SEQ ID NO: 55)
E170	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPYT (SEQ ID NO: 61)
E172	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E174	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPPT (SEQ ID NO: 53)
E181	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPYT (SEQ ID NO: 57)
E84	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYNNWPYT (SEQ ID NO: 55)
EII55	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYGNRPDT (SEQ ID NO: 73)
E87b	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPYT (SEQ ID NO: 57)
E31	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPYT (SEQ ID NO: 57)
E41	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNGPET (SEQ ID NO: 74)
EII41	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYLNSPFT (SEQ ID NO: 70)
EII46	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYSNVPVT (SEQ ID NO: 71)
EII49	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYYNGPGT (SEQ ID NO: 72)
EII7	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYRNGPPT (SEQ ID NO: 75)
E35a	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPHT (SEQ ID NO: 58)
E35b	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNSPYT (SEQ ID NO: 61)

E35c	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDSSPHT (SEQ ID NO: 64)
E35d	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYDNWPPT (SEQ ID NO: 54)
E35e	RASQSVSSYLA (SEQ ID NO: 51)	GASSRAT (SEQ ID NO: 52)	QQYSNSPPT (SEQ ID NO: 60)

Table 3. Exemplary sequences.

SEQ ID NO	Description	Sequence
148	hGM-CSFR α	MLLLVTSLLLCELPHPAFLLIPEKSDLRTVAPASSLNVRFDSTMTNLSWDCQENT TFSKCFLTDKKNRVVEPRLSNNECSCTFREICLHEGVTFEVHVNTSQRGFQKLL YPNSGREGTAAQNFSFCFIYNADLMNCTWARGPTAPRDVQYFLYIRNSKRREIR CPYYIQDSGTHVGCHLDNLSGLTSRNYFLVNGTSREIGIQFFDSLDTKKIERFNP PSNVTVRCNTTHCLVRWKQPRTYQKLSYLDYQYQLDVHRKNTQPGTENLLINV SGDLENRYNFPSEPRAKHSVKIRAADVRLNWSSWSEAIEFGSDDGNLGSVYTY VLLIVGTLVCGIVLGLFLKFRFLRIQRLFPVPQIKDKLNDNHEVEDEIWEFTPEE GKGYREEVLTVEIT
80	E01, T119 V _H	QMLVQSGAEVKKPGASVKVSKVSGHTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKSQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYCSTDT CYGFDYWGQGTLLTVSS
81	E09 V _H	QMLVQSGAEVKKPGASVKVSKVSGHTLTLSMHVVRQAPGKGLEWMGGF DPEDGETIYAQKFQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYCGHA SCYGFDYWGQGTLLTVSS
82	E105 V _H	QMLVQSGAEVKKPGASVKVSKVSGYTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKFQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYTSMLF TYGFDYWGQGTLLTVSS
83	E108 V _H	QMLVQSGAEVKKPGASVKVSKVSGHTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKFQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYTELYQ NYGFDYWGQGTLLTVSS
84	E113 V _H	QMLVQSGAEVKKPGASVKVSKVSGYTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKSQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYTELFA SYGFDYWGQGTLLTVSS
85	E16 V _H	QMLVQSGAEVKKPGASVKVSKVSGYTLTLSIHVVRQAPGKGLEWMGGFD PEDGEAIYAQKSQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYSEHST SYGFDYWGQGTLLTVSS
86	E194 V _H	QMLVQSGAEVKKPGASVKVSKVSGYTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKSQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYTGLMN SYGFDYWGQGTLLTVSS
87	E27 V _H	QMLVQSGAEVKKPGASVKVSKVSGYTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKFQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYISFMFT YGFYWGQGTLLTVSS
88	E29 V _H	QMLVQSGAEVKKPGASVKVSKVSGHTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKFQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYCFPDT CYGFDYWGQGTLLTVSS
89	E30 V _H	QMLVQSGAEVKKPGASVKVSKVSGHTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKFQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYCSTDT CYGFDYWGQGTLLTVSS
90	E34 V _H	QMLVQSGAEVKKPGASVKVSKVSGYTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKFQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYSFTDL AYGFDYWGQGTLLTVSS
91	E35, E35a-e V _H	QMLVQSGAEVKKPGASVKVSKVSGYTLTLSIHVVRQAPGKGLEWMGGFD PEDGETIYAQKFQGRVTMTGDTSTDTAYLESSLRSEDTALYYCATGRYTSLAT TYGFDYWGQGTLLTVSS

SEQ ID NO	Description	Sequence
92	E36 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYAFIDTAYGFDYWGQGTLLTVSS
93	E39 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLSIHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYCSSLCYGFDYWGQGTLLTVSS
94	E40 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLSIHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYTSLDESYGFDYWGQGTLLTVSS
95	E54 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYSSYDIAYGFDYWGQGTLLTVSS
96	E61 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYAWTDIAYGFDYWGQGTLLTVSS
97	E83 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFDPEDGETIYAQKSQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYCFYDLCYGFDYWGQGTLLTVSS
98	E85 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFDPEDGETIYAQKSQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYSSYFTNYGFDYWGQGTLLTVSS
99	E87, E87b V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFDPEDGETIYAQKSQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYVSLFFNYGFDYWGQGTLLTVSS
100	E88 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYCHKDGCYGFDYWGQGTLLTVSS
101	E90 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFDPEDGETIYAQKSQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYTGLYASYGFDYWGQGTLLTVSS
102	E94 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYCETDICYGFDYWGQGTLLTVSS
103	E200a V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTELPMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYTIITNYGFDYWGQGTLLTVSS
104	EII33 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFDDGEETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYTSLAA TYGFDYWGQGTLLTVSS
105	EII52 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFDDIEETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYTSLATTYGFDYWGQGTLLTVSS
106	EII81 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYTSLAA TYGFDYWGQGTLLTVSS
107	E161 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLCMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYWATGRYAVTD MAYGFDYWGQETLVSVSS
108	E163 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYAFAGLAYGFDYWGQGTLLTVSS
109	E164 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKSQGRVTMTGDTSTDYAYLESSLRSEDTALYYCATGRYTNDFANYGFDYWGQGTLLTVSS

SEQ ID NO	Description	Sequence
110	E170 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLSMHWVRQAPGKGLEWMGGF DPEDGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYSSVG STYGFDYWGQGLTVTVSS
111	E172 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSMHWVRQAPGKGLEWMGGF DPEDGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYANLY NNYGFDYWGQGLTVTVSS
112	E174 V _H	QMLVQSGAEVKKPGASVKVSCKVSGHTLTLSIHWVRQAPGKGLEWMGGFD PEDGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYVYLAS NYGFDYWGQGLTVTVSS
113	E181 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSMHWVRQAPGKGLEWMGGF DPEDGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYSTNF SNYGFDYWGQGLTVTVSS
114	E84 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSMHWVRQAPGKGLEWMGGF DPEDGETIYAQKSQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYTRG WFNYGFDYWGQGLTVTVSS
115	EII41 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFD TGDDGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYTS LDA TYGFDYWGQGLTVTVSS
116	EII46 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFD SEWGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYTS LAT TYGFDYWGQGLTVTVSS
117	EII49 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFD VASGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYTS LDA TYGFDYWGQGLTVTVSS
118	EII55 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFD GDWHETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYTS LD ATYGFDYWGQGLTVTVSS
119	E41 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFD PAWGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYTS LAT TYGFDYWGQGLTVTVSS
120	EII7 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFD SEVGETIYAQKFQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYTS LAA TYGFDYWGQGLTVTVSS
121	E31 V _H	QMLVQSGAEVKKPGASVKVSCKVSGYTLTLSIHWVRQAPGKGLEWMGGFD PEDGETIYAQKSQGRVTMTGDTSTDTAYLELSSLRSEDTALYYCATGRYSES FAS YGFDYWGQGLTVTVSS
122	T119, E87, E09, E105, E108, E27, E94, E172, E174, V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYNNWPPTFGQGTKLEIK
123	E01, E200a, E35d V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDNWPPTFGQGTKLEIK
124	E113, E85, E164, E84, V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYNNWPPTFGQGTKLEIK
125	E16 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDSWPPTFGQGTKLEIK
126	E194, E35, E90, E181, E87b, E31 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDNWPPTFGQGTKLEIK
127	E29, E30, E39, E35a V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDNSPPTFGQGTKLEIK
128	E34 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDSSPPTFGQGTKLEIK

SEQ ID NO	Description	Sequence
129	E36, E83, E35e V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSNSPPTFGQGTKLEIK
130	E40, E170, E35b V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDNSPYTFGQGTKLEIK
131	E54 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYNSSPPTFGQGTKLEIK
132	E61 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDNSPSTFGQGTKLEIK
133	E88, E35c V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDSSPHTFGQGTKLEIK
134	EII33 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYRNWPFTFGQGTKLEIK
135	EII52 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYANPPNTFGQGTKLEIK
136	EII81 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYTNVPDFTFGQGTKLEIK
137	E161 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYNNSPPTFGQGTKLEIK
138	E163 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDNSPPTFGQGTKLEIK
139	EII41 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYLNPSPTFGQGTKLEIK
140	EII46 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSNPVPTFGQGTKLEIK
141	EII49 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYYNGPPTFGQGTKLEIK
142	EII55 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGNRPDFTFGQGTKLEIK
143	E41 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDNGPETFGQGTKLEIK
144	EII7 V _L	EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYRNGPPTFGQGTKLEIK
145	IgG1 heavy chain constant region	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLS LSPGK
146	IgG4 heavy chain constant region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPCP APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFCFSVMHEALHNHYTQKSLSLSLG K
147	Light chain constant region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDYSLSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

GM-CSF

1170 **[00141]** Granulocyte-macrophage colony stimulating factor (GM-CSF), also known as colony-stimulating factor 2 (CSF2), is produced by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts. GM-CSF is a type I proinflammatory cytokine which enhances survival, proliferation, and/or differentiation of a broad range of hematopoietic cell types including neutrophils, eosinophils, monocytes, and macrophages, such as, myeloid

1175 differentiation, recruitment and differentiation of monocyte-derived dendritic cells, initiation and activation of neutrophils. It is also involved in promoting formation of blood vessels as well as tumor growth. Clinically, GM-CSF is often used to enhance the restoration of bone marrow following radiation procedures.

[00142] GM-CSF is one of the first proinflammatory cytokines that are present at the

1180 inflammation sites and is critical in the regulation of the inflammatory process, by for example, enhancing the differentiation of hematopoietic cell types into neutrophils, eosinophils, monocytes, and macrophages (Nature Reviews Rheumatology 2015; 7(11):415-430). By activating the vascular endothelial cells, GM-CSF promotes the recruitment of monocytes and macrophages. GM-CSF also enhances the proliferation of monocytes and macrophages, such as

1185 macrophages of the synovial joints in rheumatoid arthritis; as well as promoting cytokine production from macrophages, including GM-CSF and other inflammatory cytokines such as TNF- α , IL-6, IL-1 and chemokines. GM-CSF is further involved in modulating antigen-presenting cells in the inflammatory tissues, and promoting IL-23 production by macrophages and dendritic cells, which together with IL-6 and IL-1, modulates T cell differentiation.

1190 Endogenous GM-CSF modulates sensory neurons by relying pain signals and promoting sensitivity to pain. In GM-CSF knockout mice, myeloid cell development was not affected, suggesting a limited role for GM-CSF in promoting myeloid cell development (Stanley et al. PNAS 1994; 91(12): 5592-5594). However, due to the lack of appropriate inflammatory reactions, GM-CSF knockout mice were more prone to infections (Trapnell et al. N Engl J Med

1195 2003; 349:2527-2539; Dranoff et al. Science 1994; 264:713-716). Lack of GM-CSF reduced the occurrence of rheumatoid arthritis, encephalomyelitis, and autoimmune myocarditis, suggesting that GM-CSF is primarily involved in the inflammatory process (Lawlor et al. Arthritis & Rheumatism 2005; (52) 3749-3754; McQualter et al. Journal of Experimental Medicine 2001; 194(7): 873-882; Sonderegger et al. Journal of Experimental Medicine 2008;

1200 205(10): 2281-2294).

GM-CSFR

[00143] The GM-CSF receptor is a member of the hematopoietic receptor superfamily. It is heterodimeric, consisting of an alpha and a beta subunit. The alpha subunit is highly specific for GM-CSF whereas the beta subunit is shared with other cytokine receptors, including IL3 and IL5.

1205 This is reflected in a broader tissue distribution of the beta receptor subunit. The alpha subunit, GM-CSFR α , is primarily expressed on myeloid cells and non-hematopoietic cells, such as neutrophils, macrophages, eosinophils, dendritic cells, endothelial cells and respiratory epithelial cells. Full length GM-CSFR α is a 400 amino acid type I membrane glycoprotein that belongs to the type I cytokine receptor family, and consists of a 22 amino acid signal peptide (positions 1-
1210 22), a 298 amino acid extracellular domain (positions 23-320), a transmembrane domain from positions 321-345 and a short 55 amino acid intra-cellular domain. The signal peptide is cleaved to provide the mature form of GM-CSFR α as a 378 amino acid protein. cDNA clones of the human and murine GM-CSFR α are available and, at the protein level, the receptor subunits have 36% identity. GM-CSF is able to bind with relatively low affinity to the α subunit alone (Kd 1-
1215 5nM) but not at all to the β subunit alone. However, the presence of both α and β subunits results in a high affinity ligand-receptor complex (Kd $\approx$ 100pM). GM-CSF signaling occurs through its initial binding to the GM-CSFR α chain and then cross-linking with a larger subunit the common β chain to generate the high affinity interaction, which phosphorylates the JAK-STAT pathway. GM-CSFR binding to GM-CSF is reviewed in Haman *et al. Journal of Biological Chemistry*
1220 1999; 274(48). This interaction is also capable of signaling through tyrosine phosphorylation and activation of the MAP kinase pathway. Pathologically, GM-CSF has been shown to play a role in exacerbating inflammatory, respiratory and autoimmune diseases. Neutralization of GM-CSF binding to GM-CSFR α is therefore a therapeutic approach to treating diseases and conditions mediated through GM-CSFR.

1225 ***Full-length anti-GM-CSFR α antibody***

[00144] The anti-GM-CSFR α antibody in some embodiments is a full-length anti-GM-CSFR α antibody. In some embodiments, the full-length anti-GM-CSFR α antibody is an IgA, IgD, IgE, IgG, or IgM. In some embodiments, the full-length anti-GM-CSFR α antibody comprises IgG constant domains, such as constant domains of any of IgG1, IgG2, IgG3, and IgG4 including
1230 variants thereof. In some embodiments, the full-length anti-GM-CSFR α antibody comprises a lambda light chain constant region. In some embodiments, the full-length anti-GM-CSFR α antibody comprises a kappa light chain constant region. In some embodiments, the full-length anti-GM-CSFR α antibody is a full-length human anti-GM-CSFR α antibody. In some embodiments, the full-length anti-GM-CSFR α antibody comprises an Fc sequence of a mouse

1235 immunoglobulin. In some embodiments, the full-length anti-GM-CSFR α antibody comprises an Fc sequence that has been altered or otherwise changed so that it has enhanced antibody dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) effector function.

[00145] Thus, for example, in some embodiments, there is provided a full-length anti-GM-
1240 CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody specifically binds to GM-CSFR α . In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant
1245 region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00146] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG2 constant domains, wherein the anti-GM-CSFR α antibody specifically binds to GM-CSFR α . In some embodiments, the IgG2 is human IgG2. In some embodiments, the light
1250 chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00147] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG3 constant domains, wherein the anti-GM-CSFR α antibody specifically binds to GM-CSFR α . In some embodiments, the IgG3 is human IgG3. In some embodiments, the light
chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00148] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody specifically binds to GM-CSFR α . In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy
1255 chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region
1260 comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00149] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy
1265 chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3)

1270 amino acid substitutions, and an HC-CDR3 comprising the amino acid sequence of any one of
SEQ ID NOs: 17-50, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or
3) amino acid substitutions; and b) a light chain variable domain comprising an LC-CDR1
comprising the amino acid sequence of SEQ ID NO: 51, or a variant thereof comprising up to
about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an LC-CDR2 comprising the
amino acid sequence of SEQ ID NO: 52, or a variant thereof comprising up to about 3 (such as
1275 about any of 1, 2, or 3) amino acid substitutions, and an LC-CDR3 comprising the amino acid
sequence of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 (such
as about any of 1, 2, or 3) amino acid substitutions. In some embodiments, the IgG1 is human
IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino
acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region
1280 comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments,
the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO:
145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ
ID NO: 147.

[00150] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody
1285 comprising IgG2 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy
chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of any one
of SEQ ID NOs: 1-4, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or
3) amino acid substitutions, an HC-CDR2 comprising the amino acid sequence of any one of
SEQ ID NOs: 5-16, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3)
1290 amino acid substitutions, and an HC-CDR3 comprising the amino acid sequence of any one of
SEQ ID NOs: 17-50, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or
3) amino acid substitutions; and b) a light chain variable domain comprising an LC-CDR1
comprising the amino acid sequence of SEQ ID NO: 51, or a variant thereof comprising up to
about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an LC-CDR2 comprising the
1295 amino acid sequence of SEQ ID NO: 52, or a variant thereof comprising up to about 3 (such as
about any of 1, 2, or 3) amino acid substitutions, and an LC-CDR3 comprising the amino acid
sequence of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 (such
as about any of 1, 2, or 3) amino acid substitutions. In some embodiments, the IgG2 is human
IgG2. In some embodiments, the light chain constant region comprises or consists of the amino
1300 acid sequence of SEQ ID NO: 147.

[00151] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody
comprising IgG3 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy

chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, and an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions. In some embodiments, the IgG3 is human IgG3. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00152] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, and an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO:

146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00153] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody

1340 comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, and an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid
1345 substitutions in the HC-CDR sequences; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions in the LC-CDR sequences. In some embodiments, the
1350 IgG1 is human IgG1. In some embodiments, the anti-GM-CSFR α heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the anti-GM-CSFR α light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region
1355 comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00154] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody

comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID
1360 NOs: 5-16, and an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions in the HC-CDR sequences; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence
1365 of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions in the LC-CDR sequences. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some
1370 embodiments, the heavy chain constant region comprises or consists of the amino acid sequence

of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

1375 **[00155]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, and an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 53-75. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

1390 **[00156]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, and an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 53-75. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

1400 **[00157]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an HC-CDR3

1405 comprising the amino acid sequence of SEQ ID NO: 17; and b) a light chain variable domain
comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2
comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino
acid sequence of SEQ ID NO: 54. In some embodiments, the IgG1 is human IgG1. In some
embodiments, the heavy chain constant region comprises or consists of the amino acid sequence
1410 of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists
of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant
region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain
constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00158] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody
1415 comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy
chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID
NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, and an HC-CDR3
comprising the amino acid sequence of SEQ ID NO: 22; and b) a light chain variable domain
comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2
1420 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino
acid sequence of SEQ ID NO: 56. In some embodiments, the IgG1 is human IgG1. In some
embodiments, the heavy chain constant region comprises or consists of the amino acid sequence
of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists
of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant
1425 region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain
constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00159] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody
comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy
chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID
1430 NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3
comprising the amino acid sequence of SEQ ID NO: 23; and b) a light chain variable domain
comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2
comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino
acid sequence of SEQ ID NO: 57. In some embodiments, the IgG1 is human IgG1. In some
1435 embodiments, the heavy chain constant region comprises or consists of the amino acid sequence
of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists
of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant

region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

1440 **[00160]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27; and b) a light chain variable domain
1445 comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00161] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy
1455 chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 53. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00162] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3
1470 comprising the amino acid sequence of SEQ ID NO: 37; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2

comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00163] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 39; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00164] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

1505 [00165] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 50; and b) a light chain variable domain
1510 comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00166] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy
1520 chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 17; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain
1525 constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00167] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, and an HC-CDR3
1530 comprising the amino acid sequence of SEQ ID NO: 22; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 56. In some embodiments, the IgG4 is human IgG4. In some

embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00168] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 23; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00169] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00170] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID

NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 53. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00171] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 37; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00172] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 39; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant

region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

1610 [00173] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

1620 [00174] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a) a heavy chain variable domain comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 50; and b) a light chain variable domain comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

1630 [00175] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a light chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-

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245, and 288-289, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00176] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG2 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a light chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some embodiments, the IgG2 is human IgG2. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00177] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG3 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a light chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some embodiments, the IgG3 is human IgG3. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00178] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a light chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-

1675 245, and 288-289, or a variant thereof having at least about 90% (for example at least about any
of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some
embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region
comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments,
the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO:
1680 147. In some embodiments, the heavy chain constant region comprises or consists of the amino
acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of
the amino acid sequence of SEQ ID NO: 147.

[00179] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody
comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy
1685 chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 80-121,
and 246-287, and a light chain variable domain comprising the amino acid sequence of any one
of SEQ ID NOs: 122-144, 150-245, and 288-289. In some embodiments, the IgG1 is human
IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino
acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region
1690 comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments,
the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO:
145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ
ID NO: 147.

[00180] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody
comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy
1695 chain variable domain comprising the amino acid sequence of any one of SEQ ID NOs: 80-121,
and 246-287, and a light chain variable domain comprising the amino acid sequence of any one
of SEQ ID NOs: 122-144, 150-245, and 288-289. In some embodiments, the IgG4 is human
IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino
1700 acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region
comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments,
the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID
NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of
SEQ ID NO: 147.

1705 **[00181]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody
comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy
chain variable domain comprising the amino acid sequence of SEQ ID NO: 80 and a light chain
variable domain comprising the amino acid sequence of SEQ ID NO: 123. In some embodiments,

- the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1715 **[00182]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 85 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 125. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
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- 1725 **[00183]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 86 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
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- 1735 **[00184]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence
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of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

- 1745 **[00185]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 99 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 122. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or
- 1750 consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1755 **[00186]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or
- 1760 consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1765 **[00187]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 103 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 123. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or
- 1770 consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1775 **[00188]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy

- chain variable domain comprising the amino acid sequence of SEQ ID NO: 99 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
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- 1785 **[00189]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG1 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 121 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG1 is human IgG1. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
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- 1795 **[00190]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 80 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 123. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
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- 1805 **[00191]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 85 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 125. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain
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constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO:146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

- 1815 **[00192]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 86 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or
- 1820 consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO:146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1825 **[00193]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or
- 1830 consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO:146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1835 **[00194]** In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 99 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 122. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or
- 1840 consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO:146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

- 1845 [00195] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or
1850 consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1855 [00196] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 103 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 123. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or
1860 consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1865 [00197] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 99 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or
1870 consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- 1875 [00198] In some embodiments, there is provided a full-length anti-GM-CSFR α antibody comprising IgG4 constant domains, wherein the anti-GM-CSFR α antibody comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 121 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments,

the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146 and the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

Binding affinity

[00199] Binding affinity can be indicated by K_d , K_{off} , K_{on} , or K_a . The term “ K_{off} ”, as used herein, is intended to refer to the off-rate constant for dissociation of an antibody from the antibody/antigen complex, as determined from a kinetic selection set up. The term “ K_{on} ”, as used herein, is intended to refer to the on-rate constant for association of an antibody to the antigen to form the antibody/antigen complex. The term equilibrium dissociation constant “ K_d ”, as used herein, refers to the dissociation constant of a particular antibody-antigen interaction, and describes the concentration of antigen required to occupy one half of all of the antibody-binding domains present in a solution of antibody molecules at equilibrium, and is equal to K_{off}/K_{on} . The measurement of K_d presupposes that all binding agents are in solution. In the case where the antibody is tethered to a cell wall, *e.g.*, in a yeast expression system, the corresponding equilibrium rate constant is expressed as EC50, which gives a good approximation of K_d . The affinity constant, K_a , is the inverse of the dissociation constant, K_d .

[00200] The dissociation constant (K_d) is used as an indicator showing affinity of antibody moieties to antigens. For example, easy analysis is possible by the Scatchard method using antibodies marked with a variety of marker agents, as well as by using Biacore (made by Amersham Biosciences), analysis of biomolecular interactions by surface plasmon resonance, according to the user's manual and attached kit. The K_d value that can be derived using these methods is expressed in units of M (Mols). An antibody that specifically binds to a target may have a K_d of, for example, $\leq 10^{-7}$ M, $\leq 10^{-8}$ M, $\leq 10^{-9}$ M, $\leq 10^{-10}$ M, $\leq 10^{-11}$ M, $\leq 10^{-12}$ M, or $\leq 10^{-13}$ M.

[00201] Binding specificity of the antibody can be determined experimentally by methods known in the art. Such methods comprise, but are not limited to, Western blots, ELISA-, RIA-, ECL-, IRMA-, EIA-, BIAcore-tests and peptide scans.

[00202] In some embodiments, the anti-GM-CSFR α antibody specifically binds to a target GM-CSFR α with a K_d of about 10^{-7} M to about 10^{-13} M (such as about 10^{-7} M to about 10^{-13} M, about 10^{-8} M to about 10^{-13} M, about 10^{-9} M to about 10^{-13} M, or about 10^{-10} M to about 10^{-12} M). Thus

in some embodiments, the K_d of the binding between the anti-GM-CSFR α antibody and GM-CSFR α , is about 10^{-7} M to about 10^{-13} M, about 1×10^{-7} M to about 5×10^{-13} M, about 10^{-7} M to about 10^{-12} M, about 10^{-7} M to about 10^{-11} M, about 10^{-7} M to about 10^{-10} M, about 10^{-7} M to about 10^{-9} M, about 10^{-8} M to about 10^{-13} M, about 1×10^{-8} M to about 5×10^{-13} M, about 10^{-8} M to about 10^{-12} M, about 10^{-8} M to about 10^{-11} M, about 10^{-8} M to about 10^{-10} M, about 10^{-8} M to about 10^{-9} M, about 5×10^{-9} M to about 1×10^{-13} M, about 5×10^{-9} M to about 1×10^{-12} M, about 5×10^{-9} M to about 1×10^{-11} M, about 5×10^{-9} M to about 1×10^{-10} M, about 10^{-9} M to about 10^{-13} M, about 10^{-9} M to about 10^{-12} M, about 10^{-9} M to about 10^{-11} M, about 10^{-9} M to about 10^{-10} M, about 5×10^{-10} M to about 1×10^{-13} M, about 5×10^{-10} M to about 1×10^{-12} M, about 5×10^{-10} M to about 1×10^{-11} M, about 10^{-10} M to about 10^{-13} M, about 1×10^{-10} M to about 5×10^{-13} M, about 1×10^{-10} M to about 1×10^{-12} M, about 1×10^{-10} M to about 5×10^{-12} M, about 1×10^{-10} M to about 1×10^{-11} M, about 10^{-11} M to about 10^{-13} M, about 1×10^{-11} M to about 5×10^{-13} M, about 10^{-11} M to about 10^{-12} M, or about 10^{-12} M to about 10^{-13} M. In some embodiments, the K_d of the binding between the anti-GM-CSFR α antibody and a GM-CSFR α is about 10^{-7} M to about 10^{-13} M.

[00203] In some embodiments, the K_d of the binding between the anti-GM-CSFR α antibody and a non-target is more than the K_d of the binding between the anti-GM-CSFR α antibody and the target, and is herein referred to in some embodiments as the binding affinity of the anti-GM-CSFR α antibody to the target (*e.g.*, GM-CSFR α) is higher than that to a non-target. In some embodiments, the non-target is an antigen that is not GM-CSFR α . In some embodiments, the K_d of the binding between the anti-GM-CSFR α antibody (against GM-CSFR α) and a non-GM-CSFR α target can be at least about 10 times, such as about 10-100 times, about 100-1000 times, about 10^3 - 10^4 times, about 10^4 - 10^5 times, about 10^5 - 10^6 times, about 10^6 - 10^7 times, about 10^7 - 10^8 times, about 10^8 - 10^9 times, about 10^9 - 10^{10} times, about 10^{10} - 10^{11} times, or about 10^{11} - 10^{12} times of the K_d of the binding between the anti-GM-CSFR α antibody and a target GM-CSFR α .

[00204] In some embodiments, the anti-GM-CSFR α antibody binds to a non-target with a K_d of about 10^{-1} M to about 10^{-6} M (such as about 10^{-1} M to about 10^{-6} M, about 10^{-1} M to about 10^{-5} M, or about 10^{-2} M to about 10^{-4} M). In some embodiments, the non-target is an antigen that is not GM-CSFR α . Thus in some embodiments, the K_d of the binding between the anti-GM-CSFR α antibody and a non-GM-CSFR α target is about 10^{-1} M to about 10^{-6} M, about 1×10^{-1} M to about 5×10^{-6} M, about 10^{-1} M to about 10^{-5} M, about 1×10^{-1} M to about 5×10^{-5} M, about 10^{-1} M to about 10^{-4} M, about 1×10^{-1} M to about 5×10^{-4} M, about 10^{-1} M to about 10^{-3} M, about 1×10^{-1} M to about 5×10^{-3} M, about 10^{-1} M to about 10^{-2} M, about 10^{-2} M to about 10^{-6} M, about 1×10^{-2} M to about 5×10^{-6} M, about 10^{-2} M to about 10^{-5} M, about 1×10^{-2} M to about 5×10^{-5} M, about 10^{-2}

M to about 10^{-4} M, about 1×10^{-2} M to about 5×10^{-4} M, about 10^{-2} M to about 10^{-3} M, about 10^{-3} M to about 10^{-6} M, about 1×10^{-3} M to about 5×10^{-6} M, about 10^{-3} M to about 10^{-5} M, about 1×10^{-3} M to about 5×10^{-5} M, about 10^{-3} M to about 10^{-4} M, about 10^{-4} M to about 10^{-6} M, about 1×10^{-4} M to about 5×10^{-6} M, about 10^{-4} M to about 10^{-5} M, or about 10^{-5} M to about 10^{-6} M.

1950 **[00205]** In some embodiments, when referring to that the anti-GM-CSFR α antibody specifically recognizes a target GM-CSFR α at a high binding affinity, and binds to a non-target at a low binding affinity, the anti-GM-CSFR α antibody will bind to the target GM-CSFR α with a K_d of about 10^{-7} M to about 10^{-13} M (such as about 10^{-7} M to about 10^{-13} M, about 10^{-8} M to about 10^{-13} M, about 10^{-9} M to about 10^{-13} M, or about 10^{-10} M to about 10^{-12} M), and will bind to the non-
1955 target with a K_d of about 10^{-1} M to about 10^{-6} M (such as about 10^{-1} M to about 10^{-6} M, about 10^{-1} M to about 10^{-5} M, or about 10^{-2} M to about 10^{-4} M).

[00206] In some embodiments, when referring to that the anti-GM-CSFR α antibody specifically recognizes GM-CSFR α , the binding affinity of the anti-GM-CSFR α antibody is compared to a control anti-GM-CSFR α antibody (such as Mavrilimumab). In some embodiments, the K_d of the
1960 binding between the control anti-GM-CSFR α antibody and GM-CSFR α can be at least about 2 times, such as about 2 times, about 3 times, about 4 times, about 5 times, about 6 times, about 7 times, about 8 times, about 9 times, about 10 times, about 10-100 times, about 100-1000 times, about 10^3 - 10^4 times of the K_d of the binding between the anti-GM-CSFR α antibody described herein and GM-CSFR α .

1965 **Nucleic Acids**

[00207] Nucleic acid molecules encoding the anti-GM-CSFR α antibodies are also contemplated. In some embodiments, there is provided a nucleic acid (or a set of nucleic acids) encoding a full-length anti-GM-CSFR α antibody, including any of the full-length anti-GM-CSFR α antibodies described herein. In some embodiments, the nucleic acid (or a set of nucleic acids) encoding the
1970 anti-GM-CSFR α antibody described herein may further comprises a nucleic acid sequence encoding a peptide tag (such as protein purification tag, *e.g.*, His-tag, HA tag).

[00208] Also contemplated here are isolated host cells comprising an anti-GM-CSFR α antibody, an isolated nucleic acid encoding the polypeptide components of the anti-GM-CSFR α antibody, or a vector comprising a nucleic acid encoding the polypeptide components of the anti-GM-
1975 CSFR α antibody described herein.

[00209] The present application also includes variants to these nucleic acid sequences. For example, the variants include nucleotide sequences that hybridize to the nucleic acid sequences

encoding the anti-GM-CSFR α antibodies of the present application under at least moderately stringent hybridization conditions.

1980 [00210] The present application also provides vectors in which a nucleic acid of the present application is inserted.

[00211] In brief summary, the expression of an anti-GM-CSFR α antibody (*e.g.*, full-length anti-GM-CSFR α antibody) by a natural or synthetic nucleic acid encoding the anti-GM-CSFR α antibody can be achieved by inserting the nucleic acid into an appropriate expression vector, 1985 such that the nucleic acid is operably linked to 5' and 3' regulatory elements, including for example a promoter (*e.g.*, a lymphocyte-specific promoter) and a 3' untranslated region (UTR). The vectors can be suitable for replication and integration in eukaryotic host cells. Typical cloning and expression vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid 1990 sequence.

[00212] The nucleic acids of the present application may also be used for nucleic acid immunization and gene therapy, using standard gene delivery protocols. Methods for gene delivery are known in the art. See, *e.g.*, U.S. Pat. Nos. 5,399,346, 5,580,859, 5,589,466, incorporated by reference herein in their entireties. In some embodiments, the application 1995 provides a gene therapy vector.

[00213] The nucleic acid can be cloned into a number of types of vectors. For example, the nucleic acid can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

2000 [00214] Further, the expression vector may be provided to a cell in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Green and Sambrook (2013, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, New York), and in other virology and molecular biology manuals. Viruses which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, 2005 herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers (*see, e.g.*, WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

[00215] A number of viral based systems have been developed for gene transfer into 2010 mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. A selected gene can be inserted into a vector and packaged in retroviral particles using

techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either *in vivo* or *ex vivo*. A number of retroviral systems are known in the art. In some embodiments, adenovirus vectors are used. A number of adenovirus vectors are known in the art.

2015 In some embodiments, lentivirus vectors are used. Vectors derived from retroviruses such as the lentivirus are suitable tools to achieve long-term gene transfer since they allow long-term, stable integration of a transgene and its propagation in daughter cells. Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses such as murine leukemia viruses in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added
2020 advantage of low immunogenicity.

[00216] Additional promoter elements, *e.g.*, enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have recently been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that
2025 promoter function is preserved when elements are inverted or moved relative to one another. In the thymidine kinase (tk) promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline.

[00217] One example of a suitable promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable
2030 of driving high levels of expression of any polynucleotide sequence operatively linked thereto. Another example of a suitable promoter is Elongation Growth Factor-1 α (EF-1 α). However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an
2035 avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter. Further, the application should not be limited to the use of constitutive promoters. Inducible promoters are also contemplated as part of the application. The use of an inducible promoter provides a
2040 molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionein promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

2045 [00218] In some embodiments, the expression of the anti-GM-CSFR α antibody is inducible. In some embodiments, a nucleic acid sequence encoding the anti-GM-CSFR α antibody is operably linked to an inducible promoter, including any inducible promoter described herein.

Inducible promoters

2050 [00219] The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Exemplary inducible promoter systems for use in eukaryotic cells include, but are not limited to, hormone-regulated elements (e.g., *see* Mader, S. and White, J. H. (1993) Proc. Natl. Acad. Sci. USA 90:5603-5607), synthetic ligand-regulated elements (*see, e.g.,* Spencer, D. M. et al 1993) Science 262: 1019-
2055 1024) and ionizing radiation-regulated elements (*e.g., see* Manome, Y. et al. (1993) Biochemistry 32: 10607-10613; Datta, R. et al. (1992) Proc. Natl. Acad. Sci. USA 89: 1014-10153). Further exemplary inducible promoter systems for use in in vitro or in vivo mammalian systems are reviewed in Gingrich et al. (1998) Annual Rev. Neurosci 21:377-405. In some embodiments, the inducible promoter system for use to express the anti-GM-CSFR α antibody is the Tet system. In some embodiments, the inducible promoter system for use to express the anti-GM-CSFR α antibody is the lac repressor system from *E. coli*.

[00220] An exemplary inducible promoter system for use in the present application is the Tet system. Such systems are based on the Tet system described by Gossen et al. (1993). In an exemplary embodiment, a polynucleotide of interest is under the control of a promoter that
2065 comprises one or more Tet operator (TetO) sites. In the inactive state, Tet repressor (TetR) will bind to the TetO sites and repress transcription from the promoter. In the active state, *e.g.,* in the presence of an inducing agent such as tetracycline (Tc), anhydrotetracycline, doxycycline (Dox), or an active analog thereof, the inducing agent causes release of TetR from TetO, thereby allowing transcription to take place. Doxycycline is a member of the tetracycline family of
2070 antibiotics having the chemical name of 1-dimethylamino-2,4a,5,7,12-pentahydroxy-11-methyl-4,6-dioxo-1,4a,11,11a,12,12a-hexahydrotetracene-3-carboxamide.

[00221] In one embodiment, a TetR is codon-optimized for expression in mammalian cells, *e.g.,* murine or human cells. Most amino acids are encoded by more than one codon due to the degeneracy of the genetic code, allowing for substantial variations in the nucleotide sequence of
2075 a given nucleic acid without any alteration in the amino acid sequence encoded by the nucleic acid. However, many organisms display differences in codon usage, also known as “codon bias” (*i.e.,* bias for use of a particular codon(s) for a given amino acid). Codon bias often correlates with the presence of a predominant species of tRNA for a particular codon, which in turn

increases efficiency of mRNA translation. Accordingly, a coding sequence derived from a particular organism (*e.g.*, a prokaryote) may be tailored for improved expression in a different organism (*e.g.*, a eukaryote) through codon optimization.

[00222] Other specific variations of the Tet system include the following “Tet-Off” and “Tet-On” systems. In the Tet-Off system, transcription is inactive in the presence of Tc or Dox. In that system, a tetracycline-controlled transactivator protein (tTA), which is composed of TetR fused to the strong transactivating domain of VP16 from Herpes simplex virus, regulates expression of a target nucleic acid that is under transcriptional control of a tetracycline-responsive promoter element (TRE). The TRE is made up of TetO sequence concatamers fused to a promoter (commonly the minimal promoter sequence derived from the human cytomegalovirus (hCMV) immediate-early promoter). In the absence of Tc or Dox, tTA binds to the TRE and activates transcription of the target gene. In the presence of Tc or Dox, tTA cannot bind to the TRE, and expression from the target gene remains inactive.

[00223] Conversely, in the Tet-On system, transcription is active in the presence of Tc or Dox. The Tet-On system is based on a reverse tetracycline-controlled transactivator, rtTA. Like tTA, rtTA is a fusion protein comprised of the TetR repressor and the VP16 transactivation domain. However, a four amino acid change in the TetR DNA binding moiety alters rtTA's binding characteristics such that it can only recognize the tetO sequences in the TRE of the target transgene in the presence of Dox. Thus, in the Tet-On system, transcription of the TRE-regulated target gene is stimulated by rtTA only in the presence of Dox.

[00224] Another inducible promoter system is the lac repressor system from *E. coli* (See Brown et al., Cell 49:603-612 (1987)). The lac repressor system functions by regulating transcription of a polynucleotide of interest operably linked to a promoter comprising the lac operator (lacO). The lac repressor (lacR) binds to LacO, thus preventing transcription of the polynucleotide of interest. Expression of the polynucleotide of interest is induced by a suitable inducing agent, *e.g.*, isopropyl- β -D-thiogalactopyranoside (IPTG).

[00225] In order to assess the expression of a polypeptide or portions thereof, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co-transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and the like.

[00226] Reporter genes are used for identifying potentially transfected cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, *e.g.*, enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells. Suitable reporter genes may include genes encoding luciferase, β -galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (*e.g.*, Ui-Tel *et al.*, 2000 *FEBS Letters* 479: 79-82). Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter-driven transcription.

[00227] In some embodiments, there is provided nucleic acid encoding a full-length anti-GM-CSFR α antibody according to any of the full-length anti-GM-CSFR α antibodies described herein. In some embodiments, the nucleic acid comprises one or more nucleic acid sequences encoding the heavy and light chains of the full-length anti-GM-CSFR α antibody. In some embodiments, each of the one or more nucleic acid sequences are contained in separate vectors. In some embodiments, at least some of the nucleic acid sequences are contained in the same vector. In some embodiments, all of the nucleic acid sequences are contained in the same vector. Vectors may be selected, for example, from the group consisting of mammalian expression vectors and viral vectors (such as those derived from retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses).

[00228] Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, *e.g.*, mammalian, bacterial, yeast, or insect cell by any method in the art. For example, the expression vector can be transferred into a host cell by physical, chemical, or biological means.

[00229] Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. See, for example, Green and Sambrook (2013, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, New York). In some embodiments, the introduction of a polynucleotide into a host cell is carried out by calcium phosphate transfection.

[00230] Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become

the most widely used method of inserting genes into mammalian, *e.g.*, human cells. Other viral vectors can be derived from lentivirus, poxviruses, herpes simplex virus 1, adenoviruses and adeno-associated viruses, and the like. *See*, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362.

2150 **[00231]** Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*e.g.*, an artificial membrane vesicle).

2155 **[00232]** In the case where a non-viral delivery system is utilized, an exemplary delivery vehicle is a liposome. The use of lipid formulations is contemplated for the introduction of the nucleic acids into a host cell (*in vitro*, *ex vivo* or *in vivo*). In another aspect, the nucleic acid may be associated with a lipid. The nucleic acid associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a
2160 liposome via a linking molecule that is associated with both the liposome and the oligonucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid. Lipid, lipid/DNA or lipid/expression vector associated compositions are not limited to any particular structure in
2165 solution. For example, they may be present in a bilayer structure, as micelles, or with a “collapsed” structure. They may also simply be interspersed in a solution, possibly forming aggregates that are not uniform in size or shape. Lipids are fatty substances which may be naturally occurring or synthetic lipids. For example, lipids include the fatty droplets that naturally occur in the cytoplasm as well as the class of compounds which contain long-chain
2170 aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes.

[00233] Regardless of the method used to introduce exogenous nucleic acids into a host cell or otherwise expose a cell to the inhibitor of the present application, in order to confirm the presence of the recombinant DNA sequence in the host cell, a variety of assays may be
2175 performed. Such assays include, for example, “molecular biological” assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR and PCR; “biochemical” assays, such as detecting the presence or absence of a particular peptide, *e.g.*, by immunological means (ELISAs and Western blots) or by assays described herein to identify agents falling within the scope of the application.

2180 **Preparation of anti-GM-CSFR α antibodies**

[00234] In some embodiments, the anti-GM-CSFR α antibody is a monoclonal antibody or derived from a monoclonal antibody. In some embodiments, the anti-GM-CSFR α antibody comprises V_H and V_L domains, or variants thereof, from the monoclonal antibody. In some embodiments, the anti-GM-CSFR α antibody further comprises C_H1 and C_L domains, or variants thereof, from the monoclonal antibody. Monoclonal antibodies can be prepared, *e.g.*, using known methods in the art, including hybridoma methods, phage display methods, or using recombinant DNA methods. Additionally, exemplary phage display methods are described herein and in the Examples below.

[00235] In a hybridoma method, a hamster, mouse, or other appropriate host animal is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized *in vitro*. The immunizing agent can include a polypeptide or a fusion protein of the protein of interest. Generally, peripheral blood lymphocytes (“PBLs”) are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine, and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (“HAT medium”), which prevents the growth of HGPRT-deficient cells.

[00236] In some embodiments, the immortalized cell lines fuse efficiently, support stable high-level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. In some embodiments, the immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies.

[00237] The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the polypeptide. The binding specificity

of monoclonal antibodies produced by the hybridoma cells can be determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, *Anal. Biochem.*, 107:220 (1980).

[00238] After the desired hybridoma cells are identified, the clones can be sub cloned by limiting dilution procedures and grown by standard methods. Goding, *supra*. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown *in vivo* as ascites in a mammal.

[00239] The monoclonal antibodies secreted by the sub clones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

[00240] In some embodiments, according to any of the anti-GM-CSFR α antibodies described herein, the anti-GM-CSFR α antibody comprises sequences from a clone selected from an antibody library (such as a phage library presenting scFv or Fab fragments). The clone may be identified by screening combinatorial libraries for antibody fragments with the desired activity or activities. For example, a variety of methods are known in the art for generating phage display libraries and screening such libraries for antibodies possessing the desired binding characteristics. Such methods are reviewed, *e.g.*, in Hoogenboom *et al.*, *Methods in Molecular Biology* 178:1-37 (O'Brien *et al.*, ed., Human Press, Totowa, N.J., 2001) and further described, *e.g.*, in McCafferty *et al.*, *Nature* 348:552-554; Clackson *et al.*, *Nature* 352: 624-628 (1991); Marks *et al.*, *J. Mol. Biol.* 222: 581-597 (1992); Marks and Bradbury, *Methods in Molecular Biology* 248:161-175 (Lo, ed., Human Press, Totowa, N.J., 2003); Sidhu *et al.*, *J. Mol. Biol.* 338(2): 299-310 (2004); Lee *et al.*, *J. Mol. Biol.* 340(5): 1073-1093 (2004); Fellouse, *Proc. Natl. Acad. Sci. USA* 101(34): 12467-12472 (2004); and Lee *et al.*, *J. Immunol. Methods* 284(1-2): 119-132(2004).

[00241] In certain phage display methods, repertoires of V_H and V_L genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter *et al.*, *Ann. Rev. Immunol.*, 12: 433-455 (1994). Phage typically display antibody fragments, either as scFv fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (*e.g.*, from human) to provide a single source of antibodies to a wide range of non-self and also self-antigens without any immunization as described by Griffiths *et al.*, *EMBO J*, 12:

725-734 (1993). Finally, naive libraries can also be made synthetically by cloning unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement *in vitro*, as described by Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: U.S. Pat. No. 5,750,373, and US Patent Publication Nos. 2005/0079574, 2005/0119455, 2005/0266000, 2007/0117126, 2007/0160598, 2007/0237764, 2007/0292936, and 2009/0002360.

[00242] The anti-GM-CSFR α antibodies can be prepared using phage display to screen libraries for anti-GM-CSFR α antibody moieties specific to the target GM-CSFR α . The library can be a human scFv phage display library having a diversity of at least one $\times 10^9$ (such as at least about any of 1×10^9 , 2.5×10^9 , 5×10^9 , 7.5×10^9 , 1×10^{10} , 2.5×10^{10} , 5×10^{10} , 7.5×10^{10} , or 1×10^{11}) unique human antibody fragments. In some embodiments, the library is a naïve human library constructed from DNA extracted from human PMBCs and spleens from healthy donors, encompassing all human heavy and light chain subfamilies. In some embodiments, the library is a naïve human library constructed from DNA extracted from PBMCs isolated from patients with various diseases, such as patients with autoimmune diseases, cancer patients, and patients with infectious diseases. In some embodiments, the library is a semi-synthetic human library, wherein heavy chain CDR3 is completely randomized, with all amino acids (with the exception of cysteine) equally likely to be present at any given position (*see, e.g.*, Hoet, R.M. *et al.*, *Nat. Biotechnol.* 23(3):344-348, 2005). In some embodiments, the heavy chain CDR3 of the semi-synthetic human library has a length from about 5 to about 24 (such as about any of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24) amino acids. In some embodiments, the library is a fully-synthetic phage display library. In some embodiments, the library is a non-human phage display library.

[00243] Phage clones that bind to the target GM-CSFR α with high affinity can be selected by iterative binding of phage to the target GM-CSFR α , which is bound to a solid support (such as, for example, beads for solution panning or mammalian cells for cell panning), followed by removal of non-bound phage and by elution of specifically bound phage. The bound phage clones are then eluted and used to infect an appropriate host cell, such as *E. coli* XL1-Blue, for expression and purification. The panning can be performed for multiple (such as about any of 2, 3, 4, 5, 6 or more) rounds with solution panning, cell panning, or a combination of both, to enrich for phage clones binding specifically to the target GM-CSFR α . Enriched phage clones can be tested for specific binding to the target GM-CSFR α by any methods known in the art, including for example ELISA and FACS.

[00244] Monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the application can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). Hybridoma cells as described above or GM-CSFR α -specific phage clones of the application can serve as a source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains and/or framework regions in place of the homologous non-human sequences (U.S. Patent No. 4,816,567; Morrison *et al.*, *supra*) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the application, or can be substituted for the variable domains of one antigen-combining site of an antibody of the application to create a chimeric bivalent antibody.

[00245] The antibodies can be monovalent antibodies. Methods for preparing monovalent antibodies are known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy-chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

[00246] *In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly Fab fragments, can be accomplished using any method known in the art.

[00247] Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant-domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. In some embodiments, the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding is present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism.

Human and Humanized Antibodies

[00248] The anti-GM-CSFR α antibodies (*e.g.*, full-length anti-GM-CSFR α antibodies) can be humanized antibodies or human antibodies. Humanized forms of non-human (*e.g.*, murine) antibody moieties are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')₂, scFv, or other antigen-binding subsequences of antibodies) that typically contain minimal sequence derived from non-human immunoglobulin. Humanized antibody moieties include human immunoglobulins, immunoglobulin chains, or fragments thereof (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibody moieties can also comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody can comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin, and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence.

[00249] Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. According to some embodiments, humanization can be essentially performed following the method of Winter and co-workers (Jones *et al.*, *Nature*, 321: 522-525 (1986); Riechmann *et al.*, *Nature*, 332: 323-327 (1988); Verhoeven *et al.*, *Science*, 239: 1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibody moieties are antibody moieties (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibody moieties are typically human antibody moieties in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[00250] As an alternative to humanization, human antibody moieties can be generated. For example, it is now possible to produce transgenic animals (*e.g.*, mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (JH) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line

2350 immunoglobulin gene array into such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits *et al.*, *PNAS USA*, 90:2551 (1993); Jakobovits *et al.*, *Nature*, 362:255-258 (1993); Bruggemann *et al.*, *Year in Immunol.*, 7:33 (1993); U.S. Patent Nos. 5,545,806, 5,569,825, 5,591,669; 5,545,807; and WO 97/17852. Alternatively, human antibodies can be made by introducing human immunoglobulin loci into
2355 transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed that closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016, and Marks *et al.*, *Bio/Technology*,
2360 10: 779-783 (1992); Lonberg *et al.*, *Nature*, 368: 856-859 (1994); Morrison, *Nature*, 368: 812-813 (1994); Fishwild *et al.*, *Nature Biotechnology*, 14: 845-851 (1996); Neuberger, *Nature Biotechnology*, 14: 826 (1996); Lonberg and Huszar, *Intern. Rev. Immunol.*, 13: 65-93 (1995).
[00251] Human antibodies may also be generated by *in vitro* activated B cells (see U.S. Patents 5,567,610 and 5,229,275) or by using various techniques known in the art, including phage
2365 display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks *et al.*, *J. Mol. Biol.*, 222:581 (1991). The techniques of Cole *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies. Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985) and Boerner *et al.*, *J. Immunol.*, 147(1): 86-95 (1991).

Anti-GM-CSFR α antibody variants

2370 [00252] In some embodiments, amino acid sequence variants of the anti-GM-CSFR α antibodies (e.g., full-length anti-GM-CSFR α antibody) provided herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide
2375 synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, e.g., antigen-binding.
[00253] In some embodiments, anti-GM-CSFR α antibody variants having one or more amino
2380 acid substitutions are provided. Sites of interest for substitutional mutagenesis include the HVRs and FRs. Amino acid substitutions may be introduced into an antibody of interest and the

products screened for a desired activity, *e.g.*, improved bioactivity, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

[00254] Conservative substitutions are shown in Table 4 below.

2385

TABLE 4: CONSERVATIVE SUBSTITUTIONS

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

[00255] Amino acids may be grouped into different classes according to common side-chain properties:

- a. hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;
- 2390 b. neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
- c. acidic: Asp, Glu;
- d. basic: His, Lys, Arg;
- e. residues that influence chain orientation: Gly, Pro;
- f. aromatic: Trp, Tyr, Phe.

2395 [00256] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[00257] An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, *e.g.*, using phage display-based affinity maturation techniques. Briefly, one or more CDR residues are mutated and the variant antibody moieties displayed on phage and

2400 screened for a particular biological activity (*e.g.*, bioactivity based on TF-1 cell proliferation assay or binding affinity). Alterations (*e.g.*, substitutions) may be made in HVRs, *e.g.*, to improve bioactivity based on TF-1 cell proliferation assay or antibody affinity. Such alterations may be made in HVR “hotspots,” *i.e.*, residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (*see, e.g.*, Chowdhury, *Methods Mol. Biol.* 2405 207:179-196 (2008)), and/or specificity determining residues (SDRs), with the resulting variant V_H or V_L being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, *e.g.*, in Hoogenboom *et al.* in *Methods in Molecular Biology* 178:1-37 (O'Brien *et al.*, ed., Human Press, Totowa, NJ, (2001)).

[00258] In some embodiments of affinity maturation, diversity is introduced into the variable 2410 genes chosen for maturation by any of a variety of methods (*e.g.*, error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves HVR-directed approaches, in which several HVR residues (*e.g.*, 4-6 residues at a time) are randomized. HVR residues involved in antigen binding 2415 may be specifically identified, *e.g.*, using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[00259] In some embodiments, substitutions, insertions, or deletions may occur within one or more HVRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (*e.g.*, conservative substitutions as provided 2420 herein) that do not substantially reduce binding affinity may be made in HVRs. Such alterations may be outside of HVR “hotspots” or SDRs. In some embodiments of the variant V_H and V_L sequences provided above, each HVR either is unaltered, or contains no more than one, two or three amino acid substitutions.

[00260] A useful method for identification of residues or regions of an antibody that may be 2425 targeted for mutagenesis is called “alanine scanning mutagenesis” as described by Cunningham and Wells (1989) *Science*, 244:1081-1085. In this method, a residue or group of target residues (*e.g.*, charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (*e.g.*, alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at 2430 the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex can be determined to identify contact points between the antibody and antigen. Such contact residues

and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

2435 **[00261]** Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (e.g. for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

2440 **[00262]** In some embodiments, provided herein are anti-GM-CSFR α antibodies comprising a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 5 amino acid substitutions in the V_H; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the V_L.

2450 **[00263]** In some embodiments, provided herein are anti-GM-CSFR α antibodies comprising a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27, wherein the V_H comprises amino acid substitutions comprising amino acid residues E, H, N, G, D, M, S, P, F, Y, A, V, K, W, R, or C at position 31.

2455 **[00264]** In some embodiments, provided herein are anti-GM-CSFR α antibodies comprising a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27, wherein the V_H comprises amino acid residues selected from T, H, V, E, P, L, M, S, W, C, A, G, N, or K at position 28, and/or amino acid residues selected from T, P, D, E, Y, W, V, M, N, L, Q, G, S, A, K, or R at position 30.

2460 **[00265]** In some embodiments, provided herein are anti-GM-CSFR α antibodies comprising a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, wherein the V_L comprises amino acid substitutions comprising S, L, N, A, K, R, I, Q, G, T, H, M, or C at position 26; and/or Q, Y, P, A, I, F, T, R, V, L, E, S, or C at position 27; and/or S, H, W, L, R, K, T, P, I, F, V, E, A, or Q at position 28; and/or S, L, W, M, A, Y, K, R, G, T, E, V, N, F, or C at position 30; and/or S, T, R, A, H, Q, P, M, L, or G at

position 31; and/or Y, L or F at position 32; and/or G or T at position 50; and/or A, G, R, H, K, S, T, M, F, N, or V at position 51; and/or S, A, W, R, L, T, Q, F, Y, H, or N at position 52; and/or D, A, Q, or W at position 92; and/or N, D, E, T, Y, G, A, M, F, S, I, or L at position 93.

2470 [00266] In some embodiments, any one or combination of the amino acid substitutions as shown in Table 15 is contemplated.

[00267] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence
2475 identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 241, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250 and a V_L comprising the amino acid sequence of SEQ ID NO: 241.

[00268] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250, or a variant thereof having at least about 90% (for
2480 example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 193, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250 and a V_L
2485 comprising the amino acid sequence of SEQ ID NO: 193.

[00269] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 248, or a variant thereof having at least about 90% (for
example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence
2490 identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 188, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 248 and a V_L comprising the amino acid sequence of SEQ ID NO: 188.

[00270] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 248, or a variant thereof having at least about 90% (for
2495 example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 193, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 248 and a V_L comprising the amino acid sequence of SEQ ID NO: 193.

2500 [00271] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 288, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250 and a V_L comprising the amino acid sequence of SEQ ID NO: 288.

2505 [00272] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 188, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250 and a V_L comprising the amino acid sequence of SEQ ID NO: 188.

2510 [00273] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 236, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 250 and a V_L comprising the amino acid sequence of SEQ ID NO: 236.

2515 [00274] In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 91, or a variant thereof having at least about 90% (for example at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and a V_L comprising the amino acid sequence of SEQ ID NO: 288, or a variant thereof having at least about 90% sequence identity. In some embodiments, the anti-GM-CSFR α antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 91 and a V_L comprising the amino acid sequence of SEQ ID NO: 288.

Fc Region Variants

2520 [00275] In some embodiments, one or more amino acid modifications may be introduced into the Fc region of an antibody (e.g., a full-length anti-GM-CSFR α antibody or anti-GM-CSFR α Fc fusion protein) provided herein, thereby generating an Fc region variant. In some embodiments, the Fc region variant has enhanced ADCC effector function, often related to binding to Fc receptors (FcRs). In some embodiments, the Fc region variant has decreased ADCC effector

function. There are many examples of changes or mutations to Fc sequences that can alter effector function. For example, WO 00/42072 and Shields *et al. J Biol. Chem.* 9(2): 6591-6604 (2001) describe antibody variants with improved or diminished binding to FcRs. The contents of those publications are specifically incorporated herein by reference.

[00276] Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) is a mechanism of action of therapeutic antibodies against tumor cells. ADCC is a cell-mediated immune defense whereby an effector cell of the immune system actively lyses a target cell (*e.g.*, a cancer cell), whose membrane-surface antigens have been bound by specific antibodies (*e.g.*, an anti-GM-CSFR α antibody). The typical ADCC involves activation of NK cells by antibodies. An NK cell expresses CD16 which is an Fc receptor. This receptor recognizes, and binds to, the Fc portion of an antibody bound to the surface of a target cell. The most common Fc receptor on the surface of an NK cell is called CD16 or Fc γ RIII. Binding of the Fc receptor to the Fc region of an antibody results in NK cell activation, release of cytolytic granules and consequent target cell apoptosis. The contribution of ADCC to tumor cell killing can be measured with a specific test that uses NK-92 cells that have been transfected with a high-affinity FcR. Results are compared to wild-type NK-92 cells that do not express the FcR.

[00277] In some embodiments, the application contemplates an anti-GM-CSFR α antibody variant (such as a full-length anti-GM-CSFR α antibody variant) comprising an Fc region that possesses some but not all effector functions, which makes it a desirable candidate for applications in which the half-life of the anti-GM-CSFR α antibody *in vivo* is important yet certain effector functions (such as CDC and ADCC) are unnecessary or deleterious. *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks Fc γ R binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express Fc γ RIII only, whereas monocytes express Fc γ RI, Fc γ RII and Fc γ RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is described in U.S. Pat. No. 5,500,362 (see, *e.g.* Hellstrom, I. *et al. Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I *et al., Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985); U.S. Pat. No. 5,821,337 (see Bruggemann, M. *et al., J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assay methods may be employed (see, for example, ACTITM non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, Calif.; and CYTOTOX 96TM non-radioactive cytotoxicity assay (Promega, Madison, Wis.).

Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.*, in an animal model such as that disclosed in Clynes *et al.* *Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. See, *e.g.*, C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996); Cragg, M. S. *et al.*, *Blood* 101:1045-1052 (2003); and Cragg, M. S. and M. J. Glennie, *Blood* 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half-life determinations can also be performed using methods known in the art (see, *e.g.*, Petkova, S. B. *et al.*, *Int'l. Immunol.* 18(12):1759-1769 (2006)).

[00278] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Pat. No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (U.S. Pat. No. 7,332,581).

[00279] Certain antibody variants with improved or diminished binding to FcRs are described. (See, *e.g.*, U.S. Pat. No. 6,737,056; WO 2004/056312, and Shields *et al.*, *J. Biol. Chem.* 9(2): 6591-6604 (2001).)

[00280] In some embodiments, there is provided an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) variant comprising a variant Fc region comprising one or more amino acid substitutions which improve ADCC. In some embodiments, the variant Fc region comprises one or more amino acid substitutions which improve ADCC, wherein the substitutions are at positions 298, 333, and/or 334 of the variant Fc region (EU numbering of residues). In some embodiments, the anti-GM-CSFR α antibody (*e.g.*, full-length anti-GM-CSFR α antibody) variant comprises the following amino acid substitution in its variant Fc region: S298A, E333A, and K334A.

[00281] In some embodiments, alterations are made in the Fc region that result in altered (*i.e.*, either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), *e.g.*, as described in U.S. Pat. No. 6,194,551, WO 99/51642, and Idusogie *et al.*, *J. Immunol.* 164: 4178-4184 (2000).

[00282] In some embodiments, there is provided an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) variant comprising a variant Fc region comprising one or more amino acid substitutions which increase half-life and/or improve binding to the neonatal Fc

receptor (FcRn). Antibodies with increased half-lives and improved binding to FcRn are described in US2005/0014934A1 (Hinton *et al.*). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, *e.g.*, substitution of Fc region residue 434 (U.S. Pat. No. 7,371,826).

[00283] See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Pat. No. 5,648,260; U.S. Pat. No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

[00284] Anti-GM-CSFR α antibodies (such as full-length anti-GM-CSFR α antibodies) comprising any of the Fc variants described herein, or combinations thereof, are contemplated.

Glycosylation Variants

[00285] In some embodiments, an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) provided herein is altered to increase or decrease the extent to which the anti-GM-CSFR α antibody is glycosylated. Addition or deletion of glycosylation sites to an anti-GM-CSFR α antibody may be conveniently accomplished by altering the amino acid sequence of the anti-GM-CSFR α antibody or polypeptide portion thereof such that one or more glycosylation sites is created or removed.

[00286] Wherein the anti-GM-CSFR α antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, *e.g.*, Wright *et al.*, *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, *e.g.*, mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an anti-GM-CSFR α antibody of the application may be made in order to create anti-GM-CSFR α antibody variants with certain improved properties.

[00287] The N-glycans attached to the CH2 domain of Fc is heterogeneous. Antibodies or Fc fusion proteins generated in CHO cells are fucosylated by fucosyltransferase activity. See Shoji-Hosaka *et al.*, *J. Biochem.* 2006, 140:777- 83. Normally, a small percentage of naturally occurring afucosylated IgGs may be detected in human serum. N-glycosylation of the Fc is important for binding to Fc γ R; and afucosylation of the N-glycan increases Fc's binding capacity to Fc γ RIIIa. Increased Fc γ RIIIa binding can enhance ADCC, which can be advantageous in certain antibody therapeutic applications in which cytotoxicity is desirable.

2635 [00288] In some embodiments, an enhanced effector function can be detrimental when Fc-mediated cytotoxicity is undesirable. In some embodiments, the Fc fragment or CH2 domain is not glycosylated. In some embodiments, the N-glycosylation site in the CH2 domain is mutated to prevent from glycosylation.

2640 [00289] In some embodiments, anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) variants are provided comprising an Fc region wherein a carbohydrate structure attached to the Fc region has reduced fucose or lacks fucose, which may improve ADCC function. Specifically, anti-GM-CSFR α antibodies are contemplated herein that have reduced fucose relative to the amount of fucose on the same anti-GM-CSFR α antibody produced in a wild-type CHO cell. That is, they are characterized by having a lower amount of fucose than

2645 they would otherwise have if produced by native CHO cells (*e.g.*, a CHO cell that produce a native glycosylation pattern, such as, a CHO cell containing a native FUT8 gene). In some embodiments, the anti-GM-CSFR α antibody is one wherein less than about 50%, 40%, 30%, 20%, 10%, or 5% of the N-linked glycans thereon comprise fucose. For example, the amount of fucose in such an anti-GM-CSFR α antibody may be from 1% to 80%, from 1% to 65%, from 5%

2650 to 65% or from 20% to 40%. In some embodiments, the anti-GM-CSFR α antibody is one wherein none of the N-linked glycans thereon comprise fucose, *i.e.*, wherein the anti-GM-CSFR α antibody is completely without fucose, or has no fucose or is afucosylated. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (*e.g.* complex, hybrid and

2655 high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (EU numbering of Fc region residues); however, Asn297 may also be located about ± 3 amino acids upstream or downstream of position 297, *i.e.*, between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have

2660 improved ADCC function. See, *e.g.*, US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to “defucosylated” or “fucose-deficient” antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119;

2665 WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki *et al. J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki *et al. Biotech. Bioeng.* 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka *et al. Arch. Biochem. Biophys.* 249:533-545

(1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams *et al.*, especially at Example 11), and knockout cell lines, such as α -1,6-fucosyltransferase gene, FUT8, knockout CHO cells (see, *e.g.*, Yamane-Ohnuki *et al. Biotech. Bioeng.* 87: 614 (2004); Kanda, Y. *et al., Biotechnol. Bioeng.*, 94(4):680-688 (2006); and WO2003/085107).

[00290] Anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) variants are further provided with bisected oligosaccharides, *e.g.*, in which a biantennary oligosaccharide attached to the Fc region of the anti-GM-CSFR α antibody is bisected by GlcNAc. Such anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, *e.g.*, in WO 2003/011878 (Jean-Mairet *et al.*); U.S. Pat. No. 6,602,684 (Umana *et al.*); US 2005/0123546 (Umana *et al.*), and Ferrara *et al., Biotechnology and Bioengineering*, 93(5): 851-861 (2006). Anti-GM-CSFR α antibody (such as full-length anti-GM-CSFR α antibody) variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such anti-GM-CSFR α antibody variants may have improved CDC function. Such antibody variants are described, *e.g.*, in WO 1997/30087 (Patel *et al.*); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

[00291] In some embodiments, the anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) variants comprising an Fc region are capable of binding to an Fc γ RIII. In some embodiments, the anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) variants comprising an Fc region have ADCC activity in the presence of human effector cells (*e.g.*, T cell) or have increased ADCC activity in the presence of human effector cells compared to the otherwise same anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) comprising a human wild-type IgG1Fc region.

Cysteine Engineered Variants

[00292] In some embodiments, it may be desirable to create cysteine engineered anti-GM-CSFR α antibodies (such as a full-length anti-GM-CSFR α antibody) in which one or more amino acid residues are substituted with cysteine residues. In some embodiments, the substituted residues occur at accessible sites of the anti-GM-CSFR α antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the anti-GM-CSFR α antibody and may be used to conjugate the anti-GM-CSFR α antibody to other moieties, such as drug moieties or linker-drug moieties, to create an anti-GM-CSFR α immunoconjugate, as described further herein. Cysteine engineered anti-GM-CSFR α antibodies (*e.g.*, full-length anti-GM-CSFR α antibodies) may be generated as described, *e.g.*, in U.S. Pat. No. 7,521,541.

Derivatives

[00293] In some embodiments, an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) provided herein may be further modified to contain additional non-

2705 proteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the anti-GM-CSFR α antibody include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane,

2710 poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The

2715 polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the anti-GM-CSFR α antibody may vary, and if more than one polymer are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of anti-GM-CSFR α antibody to be improved,

2720 whether the anti-GM-CSFR α antibody derivative will be used in a therapy under defined conditions, etc.

Pharmaceutical Compositions

[00294] Also provided herein are compositions (such as pharmaceutical compositions, also referred to herein as formulations) comprising any of the anti-GM-CSFR α antibodies (such as a

2725 full-length anti-GM-CSFR α antibody), nucleic acids encoding the antibodies, vectors comprising the nucleic acids encoding the antibodies, or host cells comprising the nucleic acids or vectors described herein. In some embodiments, there is provided a pharmaceutical composition comprising any one of the anti-GM-CSFR α antibodies described herein and a pharmaceutically acceptable carrier.

2730 [00295] Suitable formulations of the anti-GM-CSFR α antibodies are obtained by mixing an anti-GM-CSFR α antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations

2735 employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propylparaben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10
2740 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal
2745 complexes (*e.g.* Zn-protein complexes); and/or non-ionic surfactants such as TWEENTM, PLURONICSM or polyethylene glycol (PEG). Exemplary formulations are described in WO98/56418, expressly incorporated herein by reference. Lyophilized formulations adapted for subcutaneous administration are described in WO97/04801. Such lyophilized formulations may be reconstituted with a suitable diluent to a high protein concentration and the reconstituted
2750 formulation may be administered subcutaneously to the individual to be treated herein. Lipofectins or liposomes can be used to deliver the anti-GM-CSFR α antibodies of this application into cells.

[00296] The formulation herein may also contain one or more active compounds in addition to the anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) as necessary for
2755 the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide an anti-neoplastic agent, a growth inhibitory agent, a cytotoxic agent, or a chemotherapeutic agent in addition to the anti-GM-CSFR α antibody. Such molecules are suitably present in combination in amounts that are effective for the purpose intended. The effective amount of such other agents
2760 depends on the amount of anti-GM-CSFR α antibody present in the formulation, the type of disease or disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein or about from 1 to 99% of the heretofore employed dosages.

[00297] The anti-GM-CSFR α antibodies (*e.g.*, full-length anti-GM-CSFR α antibodies) may also
2765 be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for

example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Sustained-release preparations may be prepared.

2770 **[00298]** Sustained-release preparations of the anti-GM-CSFR α antibodies (*e.g.*, full-length anti-GM-CSFR α antibodies) can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody (or fragment thereof), which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D (-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydro gels release proteins for shorter time periods. When encapsulated antibody remain in the body for a long time, they can denature or aggregate as a result of exposure to moisture at 37 °C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization of anti-GM-CSFR α antibodies depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization can be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

2785 **[00299]** In some embodiments, the anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) is formulated in a buffer comprising a citrate, NaCl, acetate, succinate, glycine, polysorbate 80 (Tween 80), or any combination of the foregoing.

[00300] The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by, *e.g.*, filtration through sterile filtration membranes.

Methods of treatment using anti-GM-CSFR α antibodies

2795 **[00301]** The anti-GM-CSFR α antibodies (*e.g.*, full-length anti-GM-CSFR α antibodies) and/or compositions of the application can be administered to individuals (*e.g.*, mammals such as humans) to treat a disease and/or disorder associated with high expression levels of GM-CSF and/or GM-CSFR α , and disease and/or disorder with deregulated GM-CSF and/or GM-CSFR α function, such as autoimmune and/or inflammatory conditions or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function, for

example, rheumatoid arthritis, asthma, and myeloid leukemia pulmonary disease. The present application thus in some embodiments provides a method of treating an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) in an individual comprising administering to the individual an effective amount of a composition (such as a pharmaceutical composition) comprising an anti-GM-CSFR α antibody (*e.g.*, a full-length anti-GM-CSFR α antibody), such as any one of the anti-GM-CSFR α antibodies (*e.g.*, full-length anti-GM-CSFR α antibodies) described herein.

[00302] In some embodiments, the disease or condition is selected, for example, from the group consisting of rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, allergic response, multiple sclerosis, myeloid leukemia, and atherosclerosis. In some embodiments, the individual is human.

[00303] For example, in some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a pharmaceutical composition comprising an anti-GM-CSFR α antibody (*e.g.*, full-length anti-GM-CSFR α antibody) specifically binding to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50, Glu59, Lys194, Lys195, Arg283, and Ile284 of human GM-CSFR α . In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50, Glu59, Lys194, Lys195, Arg283, Ile284, Val51, Thr63, and Ile196. In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50, Glu59, Lys194, Lys195, Arg283, Ile284, Leu191 and Ile196. In some embodiments, the anti-GM-CSFR α antibody described herein specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50, Glu59, Lys194, Lys195, Arg283, Ile284, Arg49, Val51, Asn57, and Ser61. In some embodiments, the anti-GM-CSFR α antibody is a full-length antibody. In some embodiments, the full-length anti-GM-CSFR α antibody is an IgG1 or IgG4 antibody. In some embodiments, the disease or condition is selected from the group consisting of rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, allergic response, multiple sclerosis, myeloid leukemia, and atherosclerosis. In some embodiments, the individual is human.

2835 [00304] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a pharmaceutical composition comprising an anti-GM-CSFR α antibody (*e.g.*, full-length anti-GM-CSFR α antibody) comprising a heavy chain variable domain (V_H) comprising an HC-CDR1 comprising X₁LX₂X₃H (SEQ ID NO: 76), wherein X₁ is E, N, G, D, M, S, P, F, Y, A, V, K, W, R or C, X₂ is S, C or P, and X₃ is I or M; an HC-CDR2 comprising GFDX₁X₂X₃X₄EX₅X₆YAQKX₇QG (SEQ ID NO: 77), wherein X₁ is P, G, T, S, or V, X₂ is E, D, G, or A, X₃ is D, G, I, W, S, or V, X₄ is G, E, D, or H, X₅ is T or A, X₆ is N or I, and X₇ is S or F; and an HC-CDR3 comprising GRYX₁X₂X₃X₄X₅X₆YGFDY (SEQ ID NO: 78), wherein X₁ is C, 2845 T, S, I, A, or V, X₂ is S, G, E, F, W, H, I, V, N, Y, T, or R, X₃ is T, H, L, F, P, I, S, Y, K, A, D, V, N, or G, X₄ is D, A, M, Y, F, S, T, G, or W, X₅ is T, S, F, Q, A, N, L, E, I, G, or M, and X₆ is C, T, N, S, or A; and a V_L comprising a LC-CDR1 comprising RAX₁X₂X₃VX₄X₅X₆LA (SEQ ID NO: 293), wherein X₁ is S, L, N, A, K, R, I, Q, G, T, H, M, or C, X₂ is Q, Y, P, A, I, F, T, R, V, L, E, S, or C, X₃ is S, H, W, L, R, K, T, P, I, F, V, E, A, or Q, X₄ is S, L, W, M, A, Y, K, R, G, T, 2850 E, V, N, F, or C, X₅ is S, T, R, A, H, Q, P, M, L, or G, and X₆ is Y, L, or F; a LC-CDR2 comprising X₁X₂X₃SRAT (SEQ ID NO: 294), wherein X₁ is G or T, X₂ is A, G, R, H, K, S, T, M, or F, and X₃ is S, A, W, R, L, T, Q, F, Y, H, or N; and a LC-CDR3 comprising QQYX₁X₂X₃PX₄T (SEQ ID NO: 79), wherein X₁ is N, D, S, R, A, T, L, Y, Q, W or G, X₂ is N, D, E, T, Y, G, A, M, F, S, I or L, X₃ is W, S, P, V, G, or R, and X₄ is P, Y, H, S, F, N, D, V, or G.

2855 [00305] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising 2860 an HC-CDR1 comprising the amino acid sequence of SEQ ID NOs: 1-4, an HC-CDR2 comprising the amino acid sequence of SEQ ID NOs: 5-16, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NOs: 17-50, or a variant thereof comprising up to 5 amino acid substitutions; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NOs: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NOs: 52, and an LC- 2865 CDR3 comprising the amino acid sequence of SEQ ID NOs: 53-75, or a variant thereof comprising up to 5 amino acid substitutions.

[00306] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a composition comprising an anti-GM-CSFR α antibody comprising a V_H comprising the amino acid sequence of SEQ ID NOs: 80-121, and 246-287 or a variant thereof having at least about 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-287, and a V_L comprising the amino acid sequence of SEQ ID NOs: 122-144, 150-245, and 288-289, or a variant thereof having at least about 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289.

[00307] In some embodiments, the anti-GM-CSFR α antibody provided herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00308] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 17, or a variant thereof comprising up to 5 amino acid substitutions; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a variant thereof comprising up to 5 amino acid substitutions.

[00309] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H comprising the amino acid sequence of SEQ ID NO: 80 and a V_L comprising the amino acid sequence of SEQ ID NO: 123. In some embodiments, the anti-GM-CSFR α antibody provided herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4.

some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

2905 **[00310]** In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising
2910 an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof comprising up to 5 amino acid substitutions; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3
2915 comprising the amino acid sequence of SEQ ID NO: 56, or a variant thereof comprising up to 5 amino acid substitutions.

[00311] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H comprising the amino acid sequence of SEQ ID NO: 85 and a V_L comprising the amino acid sequence of SEQ ID NO: 125. In some embodiments, the anti-GM-CSFR α antibody provided
2920 herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light
2925 chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00312] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective
2930 amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 23, or a variant thereof comprising up to 5 amino acid substitutions; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an

2935 LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3
comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to 5
amino acid substitutions.

[00313] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H
comprising the amino acid sequence of SEQ ID NO: 86 and a V_L comprising the amino acid
2940 sequence of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody provided
herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In
some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In
some embodiments, the heavy chain constant region comprises or consists of the amino acid
sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises
2945 or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light
chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00314] In some embodiments, there is provided a method of treating an individual having an
autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or
GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid
2950 arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective
amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising
an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising
the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid
sequence of SEQ ID NO: 27, or a variant thereof comprising up to 5 amino acid substitutions;
2955 and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an
LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3
comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to 5
amino acid substitutions.

[00315] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H
comprising the amino acid sequence of SEQ ID NO: 91 and a V_L comprising the amino acid
2960 sequence of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody provided
herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In
some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In
some embodiments, the heavy chain constant region comprises or consists of the amino acid
2965 sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises
or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light
chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

2970 [00316] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35, or a variant thereof comprising up to 5 amino acid substitutions; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 53, or a variant thereof comprising up to 5 amino acid substitutions.

2980 [00317] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H comprising the amino acid sequence of SEQ ID NO: 99 and a V_L comprising the amino acid sequence of SEQ ID NO: 122. In some embodiments, the anti-GM-CSFR α antibody provided herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

2990 [00318] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 37, or a variant thereof comprising up to 5 amino acid substitutions; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to 5 amino acid substitutions.

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- [00319] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H comprising the amino acid sequence of SEQ ID NO: 101 and a V_L comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody provided herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- [00320] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to 5 amino acid substitutions; and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a variant thereof comprising up to 5 amino acid substitutions.
- [00321] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H comprising the amino acid sequence of SEQ ID NO: 103 and a V_L comprising the amino acid sequence of SEQ ID NO: 123. In some embodiments, the anti-GM-CSFR α antibody provided herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.
- [00322] In some embodiments, there is provided a method of treating an individual having an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective

3035 amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising
an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising
the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid
sequence of SEQ ID NO: 35, or a variant thereof comprising up to 5 amino acid substitutions;
and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an
3040 LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3
comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to 5
amino acid substitutions.

[00323] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H
comprising the amino acid sequence of SEQ ID NO: 99 and a V_L comprising the amino acid
3045 sequence of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody provided
herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In
some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In
some embodiments, the heavy chain constant region comprises or consists of the amino acid
sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises
3050 or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light
chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00324] In some embodiments, there is provided a method of treating an individual having an
autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or
GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid
3055 arthritis, asthma, or myeloid leukemia) comprising administering to the individual an effective
amount of a composition comprising an anti-GM-CSFR α antibody comprising: a V_H comprising
an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising
the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid
sequence of SEQ ID NO: 50, or a variant thereof comprising up to 5 amino acid substitutions;
3060 and a V_L comprising an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, an
LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and an LC-CDR3
comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to 5
amino acid substitutions.

[00325] In some embodiments, the anti-GM-CSFR α antibody provided herein comprises a V_H
3065 comprising the amino acid sequence of SEQ ID NO: 121 and a V_L comprising the amino acid
sequence of SEQ ID NO: 126. In some embodiments, the anti-GM-CSFR α antibody provided
herein is a full-length anti-GM-CSFR α antibody comprising IgG1 or IgG4 constant domains. In
some embodiments, the IgG1 is human IgG1. In some embodiments, the IgG4 is human IgG4. In

some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 145. In some embodiments, the heavy chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 146. In some embodiments, the light chain constant region comprises or consists of the amino acid sequence of SEQ ID NO: 147.

[00326] In some embodiments, the individual is a mammal (*e.g.*, human, non-human primate, rat, mouse, cow, horse, pig, sheep, goat, dog, cat, *etc.*). In some embodiments, the individual is a human. In some embodiments, the individual is a clinical patient, a clinical trial volunteer, an experimental animal, *etc.* In some embodiments, the individual is younger than about 60 years old (including for example younger than about any of 50, 40, 30, 25, 20, 15, or 10 years old). In some embodiments, the individual is older than about 60 years old (including for example older than about any of 70, 80, 90, or 100 years old). In some embodiments, the individual is diagnosed with or genetically prone to one or more of the diseases or disorders described herein (such as rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, allergic response, multiple sclerosis, myeloid leukemia, or atherosclerosis). In some embodiments, the individual has one or more risk factors associated with one or more diseases or disorders described herein.

[00327] The present application in some embodiments provides a method of delivering an anti-GM-CSFR α antibody (such as any one of the anti-GM-CSFR α antibodies described herein, *e.g.*, an isolated anti-GM-CSFR α antibody) to a cell expressing GM-CSFR α on its surface in an individual, the method comprising administering to the individual a composition comprising the anti-GM-CSFR α antibody.

[00328] Many diagnostic methods for cancer or any other disease exhibiting abnormal GM-CSF and/or GM-CSFR α expression and the clinical delineation of those diseases are known in the art. Such methods include, but are not limited to, *e.g.*, immunohistochemistry, PCR, and fluorescent in situ hybridization (FISH).

[00329] In some embodiments, the anti-GM-CSFR α antibodies (*e.g.*, full-length anti-GM-CSFR α antibodies) and/or compositions of the application are administered in combination with a second, third, or fourth agent (including, *e.g.*, an antineoplastic agent, a growth inhibitory agent, a cytotoxic agent, or a chemotherapeutic agent) to treat diseases or disorders involving abnormal GM-CSF/GM-CSFR α expression.

[00330] Cancer treatments can be evaluated by, *e.g.*, tumor regression, tumor weight or size shrinkage, time to progression, duration of survival, progression free survival, overall response rate, duration of response, quality of life, protein expression and/or activity. Approaches to determining efficacy of the therapy can be employed, including for example, measurement of response through radiological imaging.

3105 [00331] In some embodiments, the efficacy of treatment is measured as the percentage tumor growth inhibition (% TGI), calculated using the equation $100 - (T/C \times 100)$, where T is the mean relative tumor volume of the treated tumor, and C is the mean relative tumor volume of a non-treated tumor. In some embodiments, the %TGI is about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, or more than 95%. In some embodiments, the efficacy of treatment is measured using shape change of granulocytes and/or increase in the survival of granulocytes.

3110 In some embodiments, the efficacy of treatment is measured by the increase of cytokine secretion by monocytes.

[00332] Dosing and method of administering the anti-GM-CSFR α antibodies

3115 [00333] The dose of the anti-GM-CSFR α antibody (such as isolated anti-GM-CSFR α antibody) compositions administered to an individual (such as a human) may vary with the particular composition, the mode of administration, and the type of disease being treated. In some embodiments, the amount of the composition (such as composition comprising isolated anti-GM-CSFR α antibody) is effective to result in an objective response (such as a partial response or a complete response) in the treatment of cancer. In some embodiments, the amount of the anti-GM-CSFR α antibody composition is sufficient to result in a complete response in the individual.

3120 In some embodiments, the amount of the anti-GM-CSFR α antibody composition is sufficient to result in a partial response in the individual. In some embodiments, the amount of the anti-GM-CSFR α antibody composition administered (for example when administered alone) is sufficient to produce an overall response rate of more than about any of 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 64%, 65%, 70%, 75%, 80%, 85%, or 90% among a population of individuals

3125 treated with the anti-GM-CSFR α antibody composition. Responses of an individual to the treatment of the methods described herein can be determined, for example, based on RECIST levels.

[00334] In some embodiments, the amount of the composition (such as composition comprising isolated anti-GM-CSFR α antibody) is sufficient to prolong progress-free survival of the

3130 individual. In some embodiments, the amount of the composition is sufficient to prolong overall survival of the individual. In some embodiments, the amount of the composition (for example when administered alone) is sufficient to produce clinical benefit of more than about any of 50%, 60%, 70%, or 77% among a population of individuals treated with the anti-GM-CSFR α antibody composition.

3135 [00335] In some embodiments, the amount of the composition (such as composition comprising isolated anti-GM-CSFR α antibody), alone or in combination with a second, third, and/or fourth

agent, is an amount sufficient to decrease the size of a tumor, decrease the number of cancer cells, or decrease the growth rate of a tumor by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% compared to the corresponding tumor size, number of cancer cells, or tumor growth rate in the same subject prior to treatment or compared to the corresponding activity in other subjects not receiving the treatment. Standard methods can be used to measure the magnitude of this effect, such as *in vitro* assays with purified enzyme, cell-based assays, animal models, or human testing.

[00336] In some embodiments, the amount of the anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) in the composition is below the level that induces a toxicological effect (*i.e.*, an effect above a clinically acceptable level of toxicity) or is at a level where a potential side effect can be controlled or tolerated when the composition is administered to the individual.

[00337] In some embodiments, the amount of the composition is close to a maximum tolerated dose (MTD) of the composition following the same dosing regimen. In some embodiments, the amount of the composition is more than about any of 80%, 90%, 95%, or 98% of the MTD.

[00338] In some embodiments, the amount of an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) in the composition is included in a range of about 0.001 μ g to about 1000 μ g.

[00339] In some embodiments of any of the above aspects, the effective amount of anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) in the composition is in the range of about 0.1 μ g/kg to about 100 mg/kg of total body weight.

[00340] The anti-GM-CSFR α antibody compositions can be administered to an individual (such as human) via various routes, including, for example, intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, intraocular, intrathecal, transmucosal, and transdermal. In some embodiments, sustained continuous release formulation of the composition may be used. In some embodiments, the composition is administered intravenously. In some embodiments, the composition is administered intraportally. In some embodiments, the composition is administered intraarterially. In some embodiments, the composition is administered intraperitoneally. In some embodiments, the composition is administered intrahepatically. In some embodiments, the composition is administered by hepatic arterial infusion. In some embodiments, the administration is to an injection site distal to a first disease site.

Articles of Manufacture and Kits

3170 **[00341]** In some embodiments of the application, there is provided an article of manufacture
containing materials useful for the treatment of autoimmune and/or inflammatory condition or
cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-
CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia), or for
3175 delivering an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) to a
cell expressing GM-CSFR α on its surface. The article of manufacture can comprise a container
and a label or package insert on or associated with the container. Suitable containers include, for
example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials
such as glass or plastic. Generally, the container holds a composition which is effective for
treating a disease or disorder described herein, and may have a sterile access port (for example
3180 the container may be an intravenous solution bag or a vial having a stopper pierceable by a
hypodermic injection needle). At least one active agent in the composition is an anti-GM-CSFR α
antibody of the application. The label or package insert indicates that the composition is used for
treating the particular condition. The label or package insert will further comprise instructions
for administering the anti-GM-CSFR α antibody composition to the patient. Articles of
3185 manufacture and kits comprising combinatorial therapies described herein are also contemplated.
[00342] Package insert refers to instructions customarily included in commercial packages of
therapeutic products that contain information about the indications, usage, dosage, administration,
contraindications and/or warnings concerning the use of such therapeutic products. In some
embodiments, the package insert indicates that the composition is used for treating autoimmune
3190 and/or inflammatory conditions (such as rheumatoid arthritis, asthma, chronic obstructive
pulmonary disease, allergic response, multiple sclerosis, myeloid leukemia, and atherosclerosis).
In some embodiments, the package insert indicates that the composition is used for treating
cancer (*e.g.* myeloid leukemia).
[00343] Additionally, the article of manufacture may further comprise a second container
3195 comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection
(BWI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further
include other materials desirable from a commercial and user standpoint, including other buffers,
diluent, filters, needles, and syringes.
[00344] Kits are also provided that are useful for various purposes, *e.g.*, for treatment of an
3200 autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or
GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid
arthritis, asthma, or myeloid leukemia), or for delivering an anti-GM-CSFR α antibody (such as a

full-length anti-GM-CSFR α antibody) to a cell expressing GM-CSFR α on its surface, optionally in combination with the articles of manufacture. Kits of the application include one or more
3205 containers comprising anti-GM-CSFR α antibody composition (or unit dosage form and/or article of manufacture), and in some embodiments, further comprise another agent (such as the agents described herein) and/or instructions for use in accordance with any of the methods described herein. The kit may further comprise a description of selection of individuals suitable for treatment. Instructions supplied in the kits of the application are typically written instructions on
3210 a label or package insert (*e.g.*, a paper sheet included in the kit), but machine-readable instructions (*e.g.*, instructions carried on a magnetic or optical storage disk) are also acceptable.

[00345] For example, in some embodiments, the kit comprises a composition comprising an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody). In some
3215 embodiments, the kit comprises a) a composition comprising any one of the anti-GM-CSFR α antibodies described herein, and b) an effective amount of at least one other agent, wherein the other agent enhances the effect (*e.g.*, treatment effect, detecting effect) of the anti-GM-CSFR α antibody. In some embodiments, the kit comprises a) a composition comprising any one of the anti-GM-CSFR α antibodies described herein, and b) instructions for administering the anti-GM-CSFR α antibody composition to an individual for treatment of an autoimmune and/or
3220 inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia). In some embodiments, the kit comprises a) a composition comprising any one of the anti-GM-CSFR α antibodies described herein, b) an effective amount of at least one other agent, wherein the other agent enhances the effect (*e.g.*, treatment effect, detecting effect) of the anti-
3225 GM-CSFR α antibody, and c) instructions for administering the anti-GM-CSFR α antibody composition and the other agent(s) to an individual for treatment of an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia). The anti-GM-CSFR α antibody and the other agent(s) can be present in separate
3230 containers or in a single container. For example, the kit may comprise one distinct composition or two or more compositions wherein one composition comprises an anti-GM-CSFR α antibody and another composition comprises another agent.

[00346] In some embodiments, the kit comprises a nucleic acid (or set of nucleic acids) encoding an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody). In
3235 some embodiments, the kit comprises a) a nucleic acid (or set of nucleic acids) encoding an anti-GM-CSFR α antibody, and b) a host cell for expressing the nucleic acid (or set of nucleic acids).

In some embodiments, the kit comprises a) a nucleic acid (or set of nucleic acids) encoding an anti-GM-CSFR α antibody, and b) instructions for i) expressing the anti-GM-CSFR α antibody in a host cell, ii) preparing a composition comprising the anti-GM-CSFR α antibody, and iii) administering the composition comprising the anti-GM-CSFR α antibody to an individual for the treatment of an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia). In some embodiments, the kit comprises a) a nucleic acid (or set of nucleic acids) encoding an anti-GM-CSFR α antibody, b) a host cell for expressing the nucleic acid (or set of nucleic acids), and c) instructions for i) expressing the anti-GM-CSFR α antibody in the host cell, ii) preparing a composition comprising the anti-GM-CSFR α antibody, and iii) administering the composition comprising the anti-GM-CSFR α antibody to an individual for the treatment of an autoimmune and/or inflammatory condition or cancer characterized by high GM-CSF and/or GM-CSFR α expression and/or abnormal GM-CSF/GM-CSFR α function (*e.g.*, rheumatoid arthritis, asthma, or myeloid leukemia).

[00347] The kits of the application are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (*e.g.*, sealed Mylar or plastic bags), and the like. Kits may optionally provide additional components such as buffers and interpretative information. The present application thus also provides articles of manufacture, which include vials (such as sealed vials), bottles, jars, flexible packaging, and the like.

[00348] The instructions relating to the use of the anti-GM-CSFR α antibody compositions generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of an anti-GM-CSFR α antibody (such as a full-length anti-GM-CSFR α antibody) as disclosed herein to provide effective treatment of an individual for an extended period, such as any of a week, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the anti-GM-CSFR α antibody and pharmaceutical compositions and instructions for use and packaged in quantities sufficient for storage and use in pharmacies, for example, hospital pharmacies and compounding pharmacies.

[00349] Those skilled in the art will recognize that several embodiments are possible within the scope and spirit of this application. The application will now be described in greater detail by reference to the following non-limiting examples. The following examples further illustrate the application but, of course, should not be construed as in any way limiting its scope.

EXAMPLES

[00350] In the experimental disclosure which follows, the following abbreviations apply: GMF (human GM-CSF); GMRa (human GM-CSFR α); GMRb (human GM-CSFR β); Mab (Mavrilimumab); GMRah (human GM-CSFR α -6His); BGMRa (Biotin-Avi- GM-CSFR α); mGMRa(cynomolgus monkey GM- CSFR α); mGMRah (cynomolgus monkey GM-CSFR α -6His).

Example 1: Generation of recombinant human GM-CSFR α and selection of anti-GM-CSFR α scFv antibodies

Generation of recombinant GM-CSFR α

[00351] The full-length sequence of human GM-CSFR α (hereon referred to as GMRa) was subcloned from the vector pSC- GM-CSFR α (Generay, Shanghai) into the expression vector pTT5 using restriction enzyme recognition sites HindIII and XhoI. His-tag or other conventionally used tags were used to tag GMRa. Expression vectors pTT5-GMRa-6his (ECD), pTT5-Avi-10His-GMRa (ECD), and pTT5-GMRa (400a.a) were generated. “ECD” stands for extracellular domain, “his or His” stands for His-tag, and “Avi” stands for Avidin tag.

[00352] Additionally, recombinant cynomolgus monkey GM-CSFR α construct was cloned. Primers were designed based on the sequence of cynomolgus monkey GM-CSFR α in NCBI database (XM_024791666.1), and used to obtain GM-CSFR α cDNA by reverse transcription of RNA from peripheral blood mononuclear cells (PBMC) of cynomolgus monkeys. The ECD-encoding sequence was amplified from the GM-CSFR α cDNA and cloned into an eukaryotic expression vector pTT5 to generate pTT5-mGMRa-6his(ECD).

[00353] The expression and purification of recombinant human GM-CSFR α , including GMRa-6his(ECD), Avi-10His-GMRa(ECD), and mGMRa-6his(ECD) were carried out according to manufacturer’s protocol. Briefly, 293F cells were transfected with the expression vectors, and the cells were cultured at 37°C, under 8% CO₂ and 120rpm for 5 days. The culture media was collected and proteins expressing His-tag were purified using Ni Sepharose purification according to manufacturer’s protocol. Specifically, the Qiagen Ni-NTA superflow cartridges were used for immobilized metal affinity chromatography (IMAC) analysis. The cartridges were first equilibrated with buffer A1 (50mM Na₃PO₄, 0.15M NaCl, pH 7.2) with a flow rate of 150cm/h. The pH of the supernatant of the culture media was adjusted to 7.2 and flown through the cartridges at room temperature at 150cm/h. Next, buffer A1 (6 times the volume of that of the cartridges) was used to equilibrate the cartridges at 150cm/h. A 50mM PB solution (0.15M NaCl and 0.2M Imidazole, pH 7.2) with a volume that is 10 times that of the cartridges was used to wash the cartridges and the elution was collected.

3305 *Generation of biotinylated GM-CSFR α antigen*

[00354] Biotinylation of Avi-10His-GMR α using the biotin ligase B0101A (GeneCopoeia) was carried out according to the manufacturer's protocol. Briefly, buffer A/B and BirA ligase were added to Avi-10His-GMR α , followed by 2 hours of incubation at 30°C. The biotinylated GMR α is referred to as Bavih-GMR α . The efficiency of biotinylation was measured using ELISA.

3310 Briefly, Bavih-GMR α was serially diluted at a 1:2 ratio, from a starting concentration of 500ng/mL, before being used to coat the ELISA plate. SA-HRP was used for detection and standard biotinylation products were used as control. The biotinylation efficiency was determined to be 70%. The bioactivity of Bavih-GMR α was confirmed using TF-1 cell proliferation assay.

3315 *Selection of anti-GM-CSFR α scFv antibodies*

[00355] *Generation of yeast scFv antibody display library:* RNA collected from 2000 human blood samples was reverse-transcribed into cDNA, and the V_H and V_K fragments were amplified using V_H- and V_K-specific primers. Upon gel extraction and purification, scFvs were generated by linking V_H and V_K, and were cloned into the yeast display plasmid PYD1, which were then electroporated into yeast to generate the yeast scFv antibody display library.

3320 **[00356]** *Selection of anti-GM-CSFR α scFv antibodies:* scFvs which recognized GM-CSFR α were isolated from the yeast display library. Briefly, magnetic-activated cell sorting (MACS) was used to enrich for cells expressing anti-GM-CSFR α scFv antibodies. 1000 OD yeast cells were subjected to centrifugation for 5 minutes at 2500g. Cell pellet was obtained and resuspended in 1L of SGCAA culture media with OD₆₀₀=1 as the starting concentration. Expression was induced for 40-48 hours at 20°C and 250rpm. After centrifugation and washing with PBSM, the pellet was resuspended in 5-10 times volume of 1 μ M Bavih-GMR α (in PBSM), and incubated for an hour at 4°C. After centrifugation and washing with PBSM, unbound antigens were washed off with PBSM. Magnetic beads were added and mixed thoroughly before incubation for 30 minutes at 4°C on a rotator. The supernatant was discarded after centrifugation at 2500g for 5 minutes, and the pellet was resuspended in PBSM with 5-10 times the volume. 7mL of cells was added to the column at a time until all cells were passed through the column. Bound cells were collected and upon further culturing and centrifugation were subjected to plasmid isolation.

3335 **[00357]** *Generation of phage display library and selection of scFv antibodies:* scFv antibody fragments from the selected yeast cells were PCR amplified using scFv-F and scFv-R primers. To generate phage display libraries, the scFv fragments were then cloned into the phage display vector pDAN5 using SfiI. Upon ligation, the vector was used to transduce TG1 phage display

electroporation-competent cells to obtain the phage scFv antibody display library. scFv antibodies specific to GM-CSFR α were isolated from the phage display library in a series of repeated selection cycles. Briefly, phage scFv library (2×10^{11} PFU) was added to biotinylated GM-CSFR α , and incubated for 2 hours at 37°C. GM-CSFR α with phage bound was captured on streptavidin coated magnetic beads. Unbound phage were washed away. After washing with TBST for 8-15 times (increasing number of washes for every round of selection), phage that specifically bound to GM-CSFR α were washed off with Glycine-HCl (pH2.2). These phages were used to transduce TG1 cells in log phase, with the addition of Ampicillin, and cultured for an hour. Upon the addition of helper phage, the cells were cultured on a rocking bed for overnight at 200rpm at 28°C. Culture media was collected the next day, centrifuged to obtain the supernatant, and was subjected to the next round of selection. A panel of positive scFv antibodies was obtained at the end of the selection process.

[00358] Monoclonal scFv antibodies were selected and subjected to ligand binding assays. The first assay was designed to identify scFv antibodies that bound human GM-CSFR α and/or cynomolgus monkey GM-CSFR α . Briefly, a 96-well plate was coated with GMRAh (human GM-CSFR α -6His) or mGMRAh (cynomolgus monkey GM-CSFR α -6His) in PBS at 0.2 μ g/well and left overnight at 4°C. Before loading the scFv antibodies, the plates were washed with TBST, blocked for 1-2 hours at 37°C using 5% milk and washed again with TBST. Each scFv sample was first diluted to 40 μ g/mL, and 150 μ L was added to the first row of wells. The 40 μ g/mL scFv samples were then serially diluted at a 1:3 ratio and added to the remaining wells. After incubating for an hour at 37°C, followed by washing with TBST for 6 times, 100 μ L of the primary antibody and secondary antibody mixture (mouse anti-flag (1:2500) and anti-mouse FC-AP (1:2000)) was added to each well. After incubation for an hour under 37°C, the plate was washed for 3 times using TBST. pNPP was then added at 50 μ L/well and incubated for 10-20 minutes at 37°C. 3M NaOH was used to stop the reaction. The ELISA results (OD410) were then analyzed and the binding curves were generated by PRISM.

[00359] The second assay was designed to identify scFv antibodies that were capable of inhibiting binding of GM-CSF to GM-CSFR α , as measured by competitive ELISA. Briefly, a 96-well plate was coated with 0.5 μ g/well of GM-CSF and 5% milk, incubated for 1-2 hours at 37°C, and followed by washing with TBST. Each scFv antibody sample was first diluted to 40 μ g/mL, and 100 μ L was added to the first row of wells. The 40 μ g/mL scFv antibody samples were then serially diluted at a 1:2 ratio and added to the remaining wells. 50 μ L of 2.5 μ g/mL Bavih-GMRA in PBS was added to each well. After incubating for an hour at 37°C, the wells were washed with TBST for 6 times. 100 μ L of SA-HRP (1:20,000) was then added to each well

and incubated for an hour at 37°C. The wells were washed with TBST for 6 times before adding 50µL/well of TMB, and incubated for 5-10 minutes at 37°C. 2M H₂SO₄ was used to stop the reaction. The ELISA results (OD450) were analyzed, and the binding curves were generated by PRISM.

[00360] *TF-1 proliferation assay:* scFv antibodies able to inhibit binding between GM-CSF and GM-CSFR α were assessed for biological activity in a TF-1 proliferation assay, which analyzed the ability of the antibodies to inhibit the proliferation of TF-1 cells stimulated with GM-CSF.

TF-1 is a human premyeloid cell line established from a patient with erythroleukemia. This cell line is factor-dependent for survival and proliferation, and is routinely maintained in human GM-CSF. Briefly, TF-1 cells were maintained in RPMI1640, 10%FBS, 10ng/mL GM-CSF media, and were passaged twice every week. Cells were washed with media without GM-CSF (RPMI1640, 10%FBS) for three times, and resuspended in the same media. Approximately 10,000 cells were added to each well of a 96-well plate and cultured overnight. The following day, the scFv antibodies were serially diluted at a 1:10 ratio (from 10µg/mL to 0.0001µg/mL), and were added to the cells. After incubating at 37°C for an hour, GM-CSF (Peprotech) was added at a final concentration of 200pg/mL. The following day, cell survival was analyzed using the Celltiter-glo assay kit (Promega). IC₅₀ was calculated by PRISM.

Example 2: Generation and characterization of full-length human anti-GM-CSFR α antibodies

Generation of full-length anti-GM-CSFR α antibodies

[00361] The most potent scFv antibodies were reformatted as human IgG1 or IgG4 antibody molecules with a human IgG1 or IgG4 heavy chain constant domain, and a human kappa light chain constant domain. VL and VH were amplified from the prokaryotic expression vector and introduced into eukaryotic expression vectors pTT5-L (containing kappa constant domain) and pTT5-H1 (containing IgG1 heavy chain constant domain), or pTT5-H4 (containing IgG4 heavy chain constant domain). Plasmids expressing the light and heavy chains were extracted and used to transform 293F cells. After the cells were cultured at 37°C, 8% CO₂ and 120rpm for five days, the culture media was purified using Protein A affinity chromatography. Briefly, Protein A column was first equilibrated with a PBS buffer containing 50mM PBS and 0.15M NaCl (pH7.2), at a flow rate of 150cm/h and with a volume that is six times the volume of the column. The supernatant of the culture media (pH was adjusted to 7.2) was passed through the column at 150cm/h. Upon further equilibration, the column was washed off using 50mM sodium citrate (pH3.5) and the elution was collected. Out of the full-length antibodies that were generated, T119 was selected as the lead parent antibody. Using the scFv of T119, a phage scFv display

library containing mutations in the CDR regions was generated. Variants that were able to bind human GM-CSFR α with high affinity, and with low dissociation rate were assessed for biological activity in the TF-1 proliferation assay. scFv antibodies that showed improved biological activity as compared to the scFv of T119 were used to generate full-length antibodies. A further round of selection of the full-length antibodies using the TF-1 proliferation assay was carried out. The selected lead-optimized antibodies were then subjected to further biochemical and biological analysis.

Affinity of anti-GM-CSFR α antibodies

[00362] The affinity of the parent antibody T119 and the lead-optimized antibodies (reformatted as human IgG1) for human GM-CSFR α was evaluated using ELISA. As shown in FIGS. 1A-1C, the lead-optimized antibodies exhibited improved binding affinity as compared to T119. Next, the affinity of the parent antibody T119 and lead-optimized antibodies E35, E200a, E87, and E108 (reformatted as human IgG4) for cynomolgus monkey GM-CSFR α (mGMRah) was evaluated using ELISA. As shown in FIG. 2, the anti-GM-CSFR α antibodies cross-reacted with cynomolgus monkey GM-CSFR α .

Specificity of anti-GM-CSFR α antibodies

[00363] *Cross-reactivity to homologous proteins:* Using ELISA, antibodies E35, E87, and E108 (reformatted as human IgG4) were tested for cross-reactivity to homologous proteins of GM-CSFR α , including IL3RA, IL5RA, and G-CSFR. As shown in FIG. 3, the antibodies bound specifically to GMRAh as compared to the other homologous proteins tested, suggesting that the anti-GM-CSFR α antibodies have specificity for GM-CSFR α .

[00364] *Binding specificity to GM-CSFR α -expressing WIL2S cells:* The anti-GM-CSFR α antibody E35-IgG4 was further assessed for binding to WIL2S cells expressing GM-CSFR α .

Anti-GM-CSFR α antibody E35-IgG4 was fluorescently labeled with GYL-650 (Dylight Amine-Reactive Dyes, Thermo Fisher) according to manufacturer's protocol. WIL2S cells expressing GM-CSFR α were generated via electroporation with an expression vector containing the full-length GM-CSFR α , and untreated WIL2S were used as controls. 48 hours after electroporation, both electroporated and untreated cells were transferred into 15mL conical tubes, centrifuged for 5 minutes at 1000rpm, and resuspended in DPBS. 1×10^6 cells were then added to each Eppendorf tube and centrifuged for 5 minutes at 1000g. GM-CSFR α -expressing WIL2S cells were treated with 15 μ g/mL of E35-IgG4 in 100 μ L 1%BSA (GMRa-E35), and control WIL2S cells were treated with either 100 μ L of 1%BSA (CK) or 5 μ g/mL of E35-IgG4 in 100 μ L 1%BSA (NC-E35). Cells from all three groups were incubated for 40 minutes at 37°C, washed with 1mL PBS twice, resuspended in 0.2mL PBS, and subjected to FACS analysis. As shown in FIG. 4, E35-IgG4 did

not bind to control WIL2S cells but showed strong binding to WIL2S cells expressing GM-CSFR α .

Characterization of binding affinity and dissociation constant (K_d)

[00365] The binding affinity of anti-GM-CSFR α antibodies E35, and E87b (reformatted as human IgG4) were characterized using Biacore T200 (GE). Antibodies E35 and E87b were stabilized on sensor chip CM5. The affinities for GM-Rah at various concentrations were measured. The range of concentrations included 10, 5, 2.5, 1.25, 0.625, 0.3125, 0.15625, 0.078, 0.039, 0.0195, and 0 nM. The concentrations of 0.625 and 0 nM were repeated once. Using the SPR technology, the association and dissociation rates were measured, and binding affinity was determined. Table 5 shows the K_{on} , K_{off} , and K_d of E35 and E87b.

Table 5

Antibody	k_{on} (1/Ms)	k_{off} (1/s)	K_d (M)
E35	5.37E+06	4.78E-05	8.90E-12
E87b	3.58E+06	2.42E-05	6.75E-12

Anti-GM-CSFR α antibodies compete with GM-CSF for binding to GM-CSFR α

[00366] Competitive ELISA experiments were carried out as described in Example 1 to assess the ability of the anti-GM-CSFR α antibodies to recognize the ligand-binding site on GM-CSFR α and compete with GM-CSF for binding to GM-CSFR α . As shown in FIGS. 5A-5D, the parent antibody T119 and lead-optimized antibodies (reformatted as human IgG4) were able to block GM-CSF from binding to human GM-CSFR α , suggesting competitive binding of the antibodies to the ligand-binding site on GM-CSFR α .

Anti-GM-CSFR α antibody stability assays

[00367] *Thermal stability analysis:* The thermal stability of T119-IgG1, E35-IgG1, E35b-IgG1, and Mab-IgG1 were analyzed using the UNcle platform. The thermal melting (T_m) and thermal aggregation (T_{agg}) values for each antibody were measured. T_m indicates the unfolding temperature of the antibody during a thermal ramp, and T_{agg} indicates the aggregation temperature of the antibody during a thermal ramp. As shown in Table 6 and FIGS. 6A-6B, T119-IgG1, E35-IgG1 and E35b-IgG1 showed increased thermal melting temperature as compared to Mab-IgG1, with E35-IgG1 and E35b-IgG1 exhibiting higher melting temperature than the parent T119-IgG1. T119-IgG1, E35-IgG1 and E35b-IgG1 also showed increased thermal aggregation temperature as compared to Mab-IgG1, with E35-IgG1 and E35b-IgG1 exhibiting higher aggregation temperature than the parent T119-IgG1. These results suggest that

E35-IgG1 and E35b-IgG1 exhibited improved thermal stability as compared to the parental T119-IgG1 antibody, as well as the control Mab-IgG1 antibody.

Table 6

Well	Sample	T _m 1 (°C)	T _{agg} 266 (°C)	T _{agg} 473 (°C)
H1	2 mg/ml Mab-IgG1	67.8	64.56	65.6
I1	2 mg/ml T119-IgG1	69.53	56.65	70.01
J1	2 mg/ml E35-IgG1	73.52	67.15	77.37
K1	2 mg/ml E35b-IgG1	70.42	69.01	77.64

3475 *TF-1 proliferation assay*

[00368] TF-1 proliferation assay was performed as described in Example 1. The parent antibody T119 and lead-optimized antibodies (reformatted as human IgG4) were tested for their abilities to inhibit TF-1 cell proliferation. As shown in FIG. 7, the lead-optimized antibodies showed comparable or improved ability to inhibit TF-1 cell proliferation as compared to the parental T119 antibody.

Granulocyte shape change assay

[00369] The anti-GM-CSFR α antibodies were further evaluated using human granulocyte shape change assays. Briefly, PBMCs were removed from 10mL human peripheral blood using Ficoll gradient. Upon removal of PBMCs and the Ficoll buffer, red blood cells were lysed using cell lysis buffer. The remaining cells were washed with PBS and cell culture media. 100,000 cells were added to each well of a 96-well plate, and incubated for 30 minutes at 37°C. Cells were then treated with 100pg/mL GM-CSF, as well as serially diluted antibodies (1:10 dilution; 10 μ g/mL to 0.0001 μ g/mL). After incubation for 3 hours at 37°C, the cells were subjected to FACS analysis, and the shape change of the granulocytes was evaluated based on the GEO mean of the forward scatter. As shown in FIG. 8, E35, E108 and E87b (reformatted as human IgG4) prevented granulocyte shape change. The IC₅₀ of each antibody is shown in Table 7 below.

Table 7

Antibody	E35	E108	E87b
IC ₅₀ (μ g/mL)	0.002050	0.002066	0.001505

3495 [00370] The anti-GM-CSFR α antibody E35(reformatted as human IgG4) was further evaluated using cynomolgus monkey granulocyte shape change assays. Cynomolgus monkey granulocytes were purified from whole blood, and treated with 100pg/mL GM-CSF, as well as serially diluted E35 (1:10 dilution; 10 μ g/mL to 0.0001 μ g/mL). The cells were subjected to FACS analysis, and the shape change of the granulocytes was evaluated based on the GEO mean of the forward scatter. The results showed that E35 prevented cynomolgus monkey granulocyte shape change 3500 (FIG. 9), with an IC₅₀ of 0.002527 μ g/mL.

Human granulocyte survival assay

[00371] Granulocytes are able to survive for longer in the presence of GM-CSF. In the human granulocyte survival assay, the ability of the anti-GM-CSFR α antibodies to inhibit this response was assessed. Briefly, granulocytes were isolated from human peripheral blood and treated with 3505 100pg/mL GM-CSF. Antibodies were serially diluted at a 1:10 ratio (10 μ g/mL to 0.0001 μ g/mL) and were added to the cells. After incubation for 48 hours, cell survival was analyzed using the Celltiter-glo assay kit (Promega). As shown in FIG. 10, E35, E108, and E87b effectively inhibited granulocyte survival. Table 8 shows the IC₅₀ of each antibody for inhibiting human granulocyte survival.

3510

Table 8

Antibody	E35-IgG4	E108-IgG4	E87b-IgG4
IC ₅₀ (μ g/mL)	0.004200	0.005521	0.002528

Inhibitory effect on cytokine release

[00372] *Inhibitory effect on CD11b expression:* Anti-GM-CSFR α antibodies E35 and E87b, as well as Mab were evaluated for their abilities to inhibit the expression of CD11b from cells in the human peripheral blood. Briefly, 50 μ L of human peripheral blood was added to each well of a 3515 96-well plate, and incubated with serially diluted antibodies (1:10 dilution; 10 μ g/mL to 0.0001 μ g/mL). After incubating for 1 hour at 37°C, 10ng/mL GM-CSF was added, and followed by incubation for an additional hour. FITC conjugated anti-CD11b antibody (BD53310) was used to label CD11b by incubating for 30 minutes at 4°C. Red blood cells were then lysed using 1mL red blood cell lysis buffer (BD349202), and after two washes with PBS, the expression of 3520 CD11b was analyzed using FACS. As shown in FIG. 11 and Table 9, E35 and E87b showed improved abilities to inhibit CD11b expression as compared to Mab. The IC₅₀ of the antibodies are shown in Table 9.

Table 9

Antibody	Mab-IgG4	E35-IgG4	E87b-IgG4
IC50($\mu\text{g/mL}$)	0.1813	0.1111	0.1439

3525 [00373] *Inhibitory effects on cytokine production:* To evaluate the inhibitory effects of anti-GM-CSFR α antibodies on cytokine production, PBMCs were isolated from 10mL human peripheral blood using Ficoll gradient, washed with PBS twice, and resuspended in the cell culture media. 1,000,000 cells (100 μL) were added to each well of a 96-well plate, and 50 μL of serially diluted antibodies (100-0.001 $\mu\text{g/mL}$) were added to the wells and incubated for an hour at 37°C. LPS and GM-CSF were then added to a final concentration of 100ng/mL and 50ng/mL, respectively. After incubating at 37°C for 48 hours, the supernatant was collected and the levels of TNF α and IL-1 β were analyzed using the Human Macrophage/Microglia Panel (Biolegend, 740503). As shown in FIG. 12A and Table 10, E35 and E87b (reformatted as human IgG4) showed improved inhibitory effect on TNF α secretion as compared to Mab-IgG4. As shown in 3530 FIG. 13 and Table 11, E35 and E87b (reformatted as human IgG4) both exhibited improved inhibitory effect on IL-1 β secretion as compared to Mab-IgG4.

Table 10

Antibody	Mab	E35	E87b
IC50($\mu\text{g/mL}$)	3.094	0.2777	0.06664

Table 11

Antibody	Mab	E35	E87b
IC50($\mu\text{g/mL}$)	0.01263	0.003535	0.01333

3540

[00374] The supernatant was further analyzed for levels of TNF α using ELISA. The ELISA results confirmed that E35 and E87b exhibited improved inhibitory effect on TNF α secretion as compared to Mab (FIG. 12B and Table 12).

Table 12

Antibody	Mab	E35	E87b
IC50($\mu\text{g/mL}$)	1.741	0.3290	0.09349

3545 *Pharmacokinetics of anti-GM-CSFR α antibodies*

[00375] *PK values in rat*: 10 healthy adult rats (approximately 0.2kg by weight) were separated into two groups by weight, with 5 in each group. Rat in the first group were injected intravenously with 20mg/kg of Mab-IgG4 or E35-IgG4, while rat in the second group were injected intravenously with 2mg/kg of Mab-IgG4 or E35-IgG4. Blood was collected first at one hour after injection, and subsequently at 2 days, 3 days, 5 days, 9 days, and 15 days after injection. After centrifugation, the plasma was used for analyzing antibody concentration using ELISA. Briefly, synthetic GM-CSFR α was used to cover the wells of a 96-well plate. On the following day, after washing with PBST, blocking with 200 μ L PBS-milk for an hour, followed by another wash with PBST, the plasma was added and incubated for an hour at 37°C. The plate was washed with 0.1% TBST for 6 times before 100 μ L of Goat-anti-human Fc antibody-AP (1:3000 in PBS) was added to each well and incubated for an hour. After washing with 0.1% TBST for 6 times, 50 μ L of pNPP was added to each well and color was developed for 10-20 minutes at 37°C. The results were read by a microplate reader at 410nm which suggested that the half-life of E35-IgG4 was longer than that of Mab-IgG4 (FIGS. 14A-14B and Table 13).

3560

Table 13

Antibody	Mab-IgG4	E35-IgG4
T1/2		
T1/2 (20mg/kg)	129h	190.9h
T1/2 (2mg/kg)	53.09h	186.7h

[00376] *PK and PD studies in cynomolgus monkey*: Four cynomolgus monkeys (approximately 3kg by weight) were injected with either E35-IgG4 or the control antibody Mab-IgG4 at a concentration of 10mg/kg. Specifically, Animal #1 and #2 were injected with Mab-IgG4, and Animal #3 and #4 were injected with E35-IgG4. 6mL of blood was collected from each animal the day before injection (D-1), one hour after injection (D1), and subsequently at D2, D4, D8, D15, D22, D29, and D36. To evaluate the pharmacokinetics of the antibodies, plasma was collected from 1mL of the blood sample collected at each time point by centrifuging for 15 minutes at 5000g, and stored at -80°C as 50 μ L aliquots. The concentrations of E35-IgG4 and Mab-IgG4 were analyzed using ELISA performed as described above for the pharmacokinetics study in rats. As shown in FIG. 15 and Table 14, the half-life of E35-IgG4 was longer than that of Mab-IgG4. To evaluate the pharmacodynamics of the antibodies, granulocytes were isolated from 5mL of the blood sample collected at each time point and subjected to granulocyte shape

change analysis. Briefly, 100 μ L of granulocytes (2×10^6 /mL) were added to each well of a 96-well plate, and incubated for 30 minutes at 37°C, followed by incubation with 100pg/mL GM-CSF for 3 hours. The cells were then subjected to shape change analysis using FACS as described above for the granulocyte shape change assay. The results showed that E35-IgG4 and Mab-IgG4 both prevented granulocyte shape change. Surprisingly, the effect of Mab-IgG4 only lasted for 14 days after the injection, while the effect of E35-IgG4 lasted for at least 21 days (FIGS. 16A-16D).

Table 14:

Antibody	Animal No.	T1/2(h)	Average T1/2 (h)	T _{max} (h)	C _{max} (ng/ml)	AUC
Mab-IgG4	1	44.86346	69.41	1	95783.719	17340604
	2	93.956602		1	76499.663	14508393
E35-IgG4	3	104.10626	106.4	1	73486.786	14118941
	4	108.76885		1	77001.042	15830767

Inhibitory effects on GM-CSF-induced increase of inflammatory cells

[00377] To examine the inhibitory effects of anti-GM-CSFR α antibodies on GM-CSF-induced increase of inflammatory cells, GM-CSF was administered to cynomolgus monkeys previously injected with E35-IgG4 or NaCl solution as a control, and the levels of white blood cells, neutrophils, lymphocytes, basophils, eosinophils, monocytes, and red blood cells were evaluated following GM-CSF administration. Briefly, 4 cynomolgus monkeys were assigned to two groups, with 2 in each group. E35-IgG4 was administered to one group via intraperitoneal injections on Day 1 and Day 3. The other group was injected with NaCl solution as control. On Day 3, 4 and 5, both groups were injected with 5.0 μ g/kg of GM-CSF (twice a day, approximately 8 hours in between injections). Blood samples were collected prior to the first GM-CSF injection and subsequently at 0.5h, 4.0h, 28.0h, 52.0h, 76.0h, 124.0h, and 176.0h after the first injection, and the levels of various cells types at each time point were analyzed.

[00378] The results showed that as compared to the control group, E35-IgG4 completely repressed GM-CSF-induced increase in white blood cells, neutrophils, lymphocytes, basophils, eosinophils, and monocytes. In contrast, the levels of red blood cells remained constant before and after GM-CSF treatment for both groups (FIGS. 17A-17G).

Example 3: Identification of E35 variants that retain biological activity

[00379] The sequence of his-tagged E35-scFv was cloned into a prokaryotic expression vector.

3600 Selected residues in the CDR regions were subjected to saturation mutagenesis and screening. The mutated versions were inserted into prokaryotic expression vectors and used to transfect BL21. After plating, 60 clones were randomly selected for sequencing, and 14-19 distinct mutations at each position were obtained. scFvs containing these mutations were generated, purified and subjected to TF-1 proliferation assay to assess their biological activity. The

3605 mutations and corresponding IC₅₀ for reducing TF-1 cell proliferation are shown in Table 15 below (numbering is according to the EU index of Kabat):

Table 15: The unit for IC₅₀ values indicated is µg/mL

Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀
HE31N	0.11	E35	0.12	HT28H	0.06	LS26L	0.044	LQ27Y	0.065	LS31T	0.060	LS28H	0.058
HE31G	0.116	HT30P	0.126	HT28V	0.08	LS26N	0.054	LQ27P	0.097	LS31R	0.069	LS28W	0.060
E35	0.12	HT30D	0.132	HT28E	0.091	LS26A	0.062	LQ27A	0.104	LS31A	0.078	LS28L	0.067
HE31D	0.13	HT30E	0.132	HT28P	0.093	LS26K	0.069	LQ27I	0.105	LS31H	0.106	LS28R	0.077
HE31M	0.13	HT30Y	0.142	HT28L	0.100	LS26R	0.072	LQ27F	0.113	LS31Q	0.117	LS28K	0.082
HE31S	0.14	HT30W	0.151	HT28M	0.11	LS26I	0.073	LQ27T	0.113	E35	0.12	LS28T	0.088
HE31P	0.17	HT30V	0.158	HT28S	0.11	LS26Q	0.075	LQ27R	0.117	LS31P	0.139	LS28P	0.089
HE31F	0.18	HT30M	0.174	HT28W	0.11	LS26G	0.078	E35	0.12	LS31M	0.156	LS28I	0.091
HE31Y	0.2	HT30N	0.178	HT28C	0.12	LS26T	0.081	LQ27V	0.120	LS31L	0.235	LS28F	0.100
HE31A	0.21	HT30L	0.181	E35	0.12	LS26H	0.089	LQ27L	0.128	LS31G	0.279	LS28V	0.104
HE31V	0.22	HT30Q	0.192	HT28A	0.13	LS26M	0.089	LQ27E	0.135	LS31W	0.649	LS28E	0.111
HE31K	0.23	HT30G	0.199	HT28G	0.16	LS26C	0.114	LQ27S	0.138	LS31I	0.681	LS28A	0.116
HE31W	0.26	HT30S	0.213	HT28N	0.17	E35	0.12	LQ27C	0.142	LS31E	0.832	E35	0.12
HE31R	0.31	HT30A	0.215	HT28K	0.217					LS31D	1.34	LS28Q	0.154
HE31C	0.36	HT30K	0.325										
		HT30R	0.350										
Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀	Mut.	IC ₅₀
LS30L	0.069	LY32L	0.07	LS52A	0.068	LA51G	0.12	E35	0.12	E35	0.12	LN93D	0.045
LS30W	0.071	E35	0.12	LS52W	0.073	LA51R	0.12	LG50T	0.25	LD92A	0.282	LN93E	0.081
LS30M	0.073	LY32F	0.21	LS52R	0.089	E35	0.12	LG50A	0.5	LD92Q	0.328	E35	0.12
LS30A	0.078	LY32M	0.42	LS52L	0.115	LA51H	0.162	LG50D	0.88	LD92W	0.342	LN93T	0.14
LS30Y	0.082	LY32T	0.51	E35	0.12	LA51K	0.168	LG50Q	0.93	LD92V	0.387	LN93Y	0.156
LS30K	0.083	LY32Q	0.87	LS52T	0.136	LA51S	0.18	LG50I	1.08	LD92L	0.420	LN93G	0.205
LS30R	0.088	LY32W	1.17	LS52Q	0.138	LA51T	0.18	LG50S	1.3	LD92T	0.494	LN93A	0.21
LS30G	0.092	LY32V	1.23	LS52F	0.167	LA51M	0.264	LG50V	1.4	LD92R	0.495	LN93M	0.27
LS30T	0.092	LY32A	1.35	LS52Y	0.181	LA51F	0.294	LG50N	1.59	LD92M	0.507	LN93F	0.3
LS30E	0.100	LY32G	1.35	LS52H	0.192	LA51N	0.36	LG50P	1.86	LD92G	0.522	LN93S	0.3
E35	0.12	LY32C	1.9	LS52N	0.253	LA51V	0.36	LG50R	2.79	LD92H	0.530	LN93I	0.33
LS30V	0.124	LY32N	2.05	LS52P	1.055	LA51C	0.37	LG50L	3.9	LD92I	0.597	LN93L	0.33

LS30N	0.132	LY32R	3.12	LS52D	1.751	LA51L	0.5	LG50H	4.29	LD92S	0.598	LN93H	0.45
LS30F	0.160	LY32E	3.75			LA51E	0.81	LG50C	25.7	LD92K	0.640	LN93R	0.6
LS30C	0.221	LY32P	5.15			LA51W	1.59	LG50E	29.85	LD92P	0.881	LN93P	0.66
		LY32K	9.6			LA51P	2.1	LG50Y	32			LN93K	0.78
		LY32S	NA			LA51Q	18.17	LG50W	NA				

[00380] Based on these results, it was determined that scFv antibodies having the following

3610 amino acid sequences derived from the E35 scFv retained their biological activities as evaluated by the TF-1 proliferation assay:

(i) E, H, N, G, D, M, S, P, F, Y, A, V, K, W, R, or C at position 31 of the V_H;

(ii) S, L, N, A, K, R, I, Q, G, T, H, M, or C at position 26 of the V_L;

(iii) Q, Y, P, A, I, F, T, R, V, L, E, S, or C at position 27 of the V_L;

3615 (iv) S, H, W, L, R, K, T, P, I, F, V, E, A, or Q at position 28 of the V_L;

(v) S, L, W, M, A, Y, K, R, G, T, E, V, N, F, or C at position 30 of the V_L;

(vi) S, T, R, A, H, Q, P, M, L, or G at position 31 of the V_L;

(vii) Y, L or F at position 32 of the V_L;

(viii) G, or T at position 50 of the V_L;

3620 (ix) A, G, R, H, K, S, T, M, F, N, or V at position 51 of the V_L;

(x) S, A, W, R, L, T, Q, F, Y, H, or N at position 52 of the V_L;

(xi) D, A, Q, or W at position 92 of the V_L;

(xii) N, D, E, T, Y, G, A, M, F, S, I, or L at position 93 of the V_L;

(xiii) amino acid residues selected from T, H, V, E, P, L, M, S, W, C, A, G, N, or K at position

3625 28 of the V_H;

(xiv) amino acid residues selected from T, P, D, E, Y, W, V, M, N, L, Q, G, S, A, K, or R at position 30 of the V_H.

[00381] E35 variants containing combinatorial mutations were also generated. The IC₅₀ for

reducing TF-1 cell proliferation of full-length IgG4 antibodies containing the E35 variants were

3630 analyzed and are shown in Table 16 below. These results suggested that E35 variants containing combinatorial mutations exhibited improved efficacy for reducing TF-1 cell proliferation.

Table 16

Antibody	IC ₅₀ (μg/mL)	Normalization
E35-IG4	0.0474	1.0000
E35-VL93D-IG4	0.03714	0.7835

E35-VH28H-IG4	0.05693	1.2011
E35-VH28E-IG4	0.03073	0.6483
E35-VH28H-VL93L-IG4	0.01628	0.3435
E35-VH28H-VL93D-IG4	0.02783	0.5871
E35-VH28H-VL30L-IG4	0.02959	0.6243
E35-VH28H-VL30C-IG4	0.04306	0.9084
E35-VH28E-VL30L-IG4	0.02682	0.5658
E35-VH28E-VL30C-IG4	0.02077	0.4382
E35-VH28H-VL30L-93D-IG4	0.02414	0.5093

3635 [00382] The exemplary heavy chain variable domain and light chain variable domain sequences of E35 variants are shown in Table 17 below.

Table 17

Antibody	Substitution	V _H SEQ ID NO	V _L SEQ ID NO	Antibody	Substitution	V _H SEQ ID NO	V _L SEQ ID NO
AbM-1	LS26A	91	150	AbM-74	LS52H	91	222
AbM-2	LS26C	91	151	AbM-75	LS52L	91	223
AbM-3	LS26G	91	152	AbM-76	LS52N	91	224
AbM-4	LS26H	91	153	AbM-77	LS52Q	91	225
AbM-5	LS26I	91	154	AbM-78	LS52R	91	226
AbM-6	LS26K	91	155	AbM-79	LS52T	91	227
AbM-7	LS26L	91	156	AbM-81	LS52W	91	229
AbM-8	LS26M	91	157	AbM-83	LS52Y	91	231
AbM-9	LS26N	91	158	AbM-84	LD92A	91	232
AbM-10	LS26Q	91	159	AbM-85	LD92Q	91	233
AbM-11	LS26R	91	160	AbM-86	LD92W	91	234
AbM-12	LS26T	91	161	AbM-87	LN93A	91	235
AbM-13	LQ27A	91	162	AbM-88	LN93D	91	236
AbM-14	LQ27C	91	163	AbM-89	LN93E	91	237
AbM-15	LQ27E	91	164	AbM-90	LN93F	91	238
AbM-16	LQ27F	91	165	AbM-91	LN93G	91	239
AbM-17	LQ27I	91	166	AbM-92	LN93I	91	240
AbM-18	LQ27L	91	167	AbM-93	LN93L	91	241
AbM-19	LQ27P	91	168	AbM-94	LN93M	91	242
AbM-20	LQ27R	91	169	AbM-95	LN93S	91	243
AbM-21	LQ27S	91	170	AbM-96	LN93T	91	244
AbM-22	LQ27T	91	171	AbM-97	LN93Y	91	245
AbM-23	LQ27V	91	172	AbM-98	HT28A	246	126
AbM-24	LQ27Y	91	173	AbM-99	HT28C	247	126
AbM-25	LS28A	91	174	AbM-100	HT28E	248	126
AbM-26	LS28E	91	175	AbM-101	HT28G	249	126
AbM-27	LS28F	91	176	AbM-102	HT28H	250	126
AbM-28	LS28H	91	177	AbM-103	HT28K	251	126
AbM-29	LS28I	91	178	AbM-104	HT28L	252	126
AbM-30	LS28K	91	179	AbM-105	HT28M	253	126
AbM-31	LS28L	91	180	AbM-106	HT28N	254	126
AbM-32	LS28P	91	181	AbM-107	HT28P	255	126
AbM-33	LS28Q	91	182	AbM-108	HT28S	256	126
AbM-34	LS28R	91	183	AbM-109	HT28V	257	126

AbM-35	LS28T	91	184	AbM-110	HT28W	258	126
AbM-36	LS28V	91	185	AbM-111	HT30A	259	126
AbM-37	LS28W	91	186	AbM-112	HT30D	260	126
AbM-38	LS30A	91	187	AbM-113	HT30E	261	126
AbM-39	LS30C	91	188	AbM-114	HT30G	262	126
AbM-40	LS30E	91	189	AbM-115	HT30K	263	126
AbM-41	LS30F	91	190	AbM-116	HT30L	264	126
AbM-42	LS30G	91	191	AbM-117	HT30M	265	126
AbM-43	LS30K	91	192	AbM-118	HT30N	266	126
AbM-44	LS30L	91	193	AbM-119	HT30P	267	126
AbM-45	LS30M	91	194	AbM-120	HT30Q	268	126
AbM-46	LS30N	91	195	AbM-121	HT30R	269	126
AbM-47	LS30R	91	196	AbM-122	HT30S	270	126
AbM-48	LS30T	91	197	AbM-123	HT30V	271	126
AbM-49	LS30V	91	198	AbM-124	HT30W	272	126
AbM-50	LS30W	91	199	AbM-125	HT30Y	273	126
AbM-51	LS30Y	91	200	AbM-126	HE31A	274	126
AbM-52	LS31A	91	201	AbM-127	HE31C	275	126
AbM-53	LS31G	91	202	AbM-128	HE31D	276	126
AbM-54	LS31H	91	203	AbM-129	HE31F	277	126
AbM-55	LS31L	91	204	AbM-130	HE31G	278	126
AbM-56	LS31M	91	205	AbM-131	HE31K	279	126
AbM-57	LS31P	91	206	AbM-132	HE31M	280	126
AbM-58	LS31Q	91	207	AbM-133	HE31N	281	126
AbM-59	LS31R	91	208	AbM-134	HE31P	282	126
AbM-60	LS31T	91	209	AbM-135	HE31R	283	126
AbM-61	LY32F	91	210	AbM-136	HE31S	284	126
AbM-62	LY32L	91	211	AbM-137	HE31V	285	126
AbM-63	LG50T	91	212	AbM-138	HE31W	286	126
AbM-64	LA51F	91	289	AbM-139	HE31Y	287	126
AbM-65	LA51G	91	213	AbM-140	E35-28H-93L-IG4	250	241
AbM-66	LA51H	91	214	AbM-141	E35-28H-30L-IG4	250	193
AbM-67	LA51K	91	215	AbM-142	E35-28E-30C-IG4	248	188
AbM-68	LA51M	91	216	AbM-143	E35-28E-30L-IG4	248	193
AbM-69	LA51R	91	217	AbM-144	E35-28H-30L93D-IG4	250	288
AbM-70	LA51S	91	218	AbM-145	E35-28H-30C-IG4	250	188
AbM-71	LA51T	91	219	AbM-146	E35HT28H-LN93D-IG4	250	236
AbM-72	LS52A	91	220	AbM-147	E35-LS30L-LN93D-IG4	91	288
AbM-73	LS52F	91	221				

Example 4: Epitope mapping of anti-GM-CSFR α antibodies

3640 **[00383]** Amino acid residues in proximity to the binding sites of GM-CSF on GM-CSFR α were identified based on their crystal structures, the numbering of GM-CSFR α is according to the crystal structure (PDB id: 4RS1) as shown in FIG. 20. Using the Discovery Studio software, the predicted binding sites for E35 were identified, and the amino acid residues within the binding

sites and in proximity to the binding sites were selected and subjected to alanine scanning. GM-CSFR α proteins with these selected mutations were expressed. The binding affinity of E35-IgG4, E87b-IgG4 and T119-IgG4 for each mutated GM-CSFR α protein was analyzed using ELISA. FIGS. 18A-18C show the ELISA binding curves of the antibodies for mutated GM-CSFR α . As used herein, GMRah represents His-tagged wild-type human GM-CSFR α (GM-CSFR α -6His). Mutations at various positions of the amino acid sequence of the wild type GM-CSFR α were generated using alanine scanning as described above. As shown in FIGS. 18A-18C, mutation at position C60 significantly affected the binding affinity E35, E87b, and T119 and was determined to be a mutation that affected the protein structure of GM-CSFR α . Based on these results, exemplary epitopes of antibodies E35, E87b, and T119 were identified as comprising amino acid residues as shown in Table 18. The numbering of the amino acid residues in GM-CSFR α (SEQ ID NO: 292) is shown in FIG. 20.

Table 18

Antibody	R49	V50	V51	N57	E59	S61	T63	L191	K194	K195	I196	R283	I284
E35		GMR-V50	GMR-V51		GMR-E59		GMR-T63		GMR-K194	GMR-K195	GMR-I196	GMR-R283	GMR-I284
E87b		GMR-V50			GMR-E59			GMR-L191	GMR-K194	GMR-K195	GMR-I196	GMR-R283	GMR-I284
T119	GMR-R49	GMR-V50	GMR-V51	GMR-N57	GMR-E59	GMR-S61			GMR-K194	GMR-K195		GMR-R283	GMR-I284

CLAIMS

1. An isolated anti-GM-CSFR α antibody that specifically binds to an epitope on human GM-CSFR α , wherein the epitope comprises amino acid residues Val50, Glu59, Lys194, Lys195, Arg283, and Ile284 of human GM-CSFR α .
2. The isolated anti-GM-CSFR α antibody of claim 1, wherein the epitope further comprises amino acid residues:
 - (i) Val51, Thr63, and Ile196; or
 - (ii) Leu191 and Ile196; or
 - (iii) Arg49, Val51, Asn57, and Ser61.
3. The isolated anti-GM-CSFR α antibody of claims 1 or 2, wherein the anti-GM-CSFR α antibody has a T_m of at least about 69°C.
4. The isolated anti-GM-CSFR α antibody of any one of claims 1-3, wherein the anti-GM-CSFR α antibody binds to the human GM-CSFR α with a K_d from about 0.1 pM to about 1 nM.
5. An isolated anti-GM-CSFR α antibody, wherein the anti-GM-CSFR α antibody comprises:
 - a heavy chain variable domain (V_H) comprising a heavy chain complementarity determining region (HC-CDR) 1 comprising X₁LX₂X₃H (SEQ ID NO: 76), wherein X₁ is E, N, G, D, M, S, P, F, Y, A, V, K, W, R or C, X₂ is S, C or P, and X₃ is I or M; an HC-CDR2 comprising GFDX₁X₂X₃X₄EX₅X₆YAQKX₇QG (SEQ ID NO: 77), wherein X₁ is P, G, T, S, or V, X₂ is E, D, G, or A, X₃ is D, G, I, W, S, or V, X₄ is G, E, D, or H, X₅ is T or A, X₆ is N or I, and X₇ is S or F; and
 - an HC-CDR3 comprising GRYX₁X₂X₃X₄X₅X₆YGFDY (SEQ ID NO: 78), wherein X₁ is C, T, S, I, A, or V, X₂ is S, G, E, F, W, H, I, V, N, Y, T, or R, X₃ is T, H, L, F, P, I, S, Y, K, A, D, V, N, or G, X₄ is D, A, M, Y, F, S, T, G, or W, X₅ is T, S, F, Q, A, N, L, E, I, G, or M, and X₆ is C, T, N, S, or A;
 - and a light chain variable domain (V_L) comprising a light chain complementarity determining region (LC-CDR) 1 comprising RAX₁X₂X₃VX₄X₅X₆LA (SEQ ID NO: 293), wherein X₁ is S, L, N, A, K, R, I, Q, G, T, H, M, or C, X₂ is Q, Y, P, A, I, F, T, R, V, L, E, S, or C, X₃ is S, H, W, L, R, K, T, P, I, F, V, E, A, or Q, X₄ is S, L, W, M, A, Y, K, R, G, T, E, V, N, F, or C, X₅ is S, T, R, A, H, Q, P, M, L, or G, and X₆ is Y, L, or F;

35 a LC-CDR2 comprising $X_1X_2X_3SRAT$ (SEQ ID NO: 294), wherein X_1 is G or T, X_2 is A, G, R, H, K, S, T, M, or F, and X_3 is S, A, W, R, L, T, Q, F, Y, H, or N; and
 a LC-CDR3 comprising $QQYX_1X_2X_3PX_4T$ (SEQ ID NO: 79), wherein X_1 is N, D, S, R, A, T, L, Y, Q, W or G, X_2 is N, D, E, T, Y, G, A, M, F, S, I or L, X_3 is W, S, P, V, G, or R, and X_4 is P, Y, H, S, F, N, D, V, or G.

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6. The isolated anti-GM-CSFR α antibody of claim 5, wherein the anti-GM-CSFR α antibody comprises:

a V_H comprising a HC-CDR1 comprising ELX_1X_2H (SEQ ID NO: 295), wherein X_1 is S, C or P, and X_2 is I or M; an HC-CDR2 comprising
 45 $GFDX_1X_2X_3X_4EX_5X_6YAQKX_7QG$ (SEQ ID NO: 77), wherein X_1 is P, G, T, S, or V, X_2 is E, D, G, or A, X_3 is D, G, I, W, S, or V, X_4 is G, E, D, or H, X_5 is T or A, X_6 is N or I, and X_7 is S or F; and an HC-CDR3 comprising $GRYX_1X_2X_3X_4X_5X_6YGFDY$ (SEQ ID NO: 78), wherein X_1 is C, T, S, I, A, or V, X_2 is S, G, E, F, W, H, I, V, N, Y, T, or R, X_3 is T, H, L, F, P, I, S, Y, K, A, D, V, N, or G, X_4 is D, A, M, Y, F, S, T, G, or W,
 50 X_5 is T, S, F, Q, A, N, L, E, I, G, or M, and X_6 is C, T, N, S, or A;
 and a V_L comprising a LC-CDR1 comprising $RASQSVSSYLA$ (SEQ ID NO: 51); a LC-CDR2 comprising $GASSRAT$ (SEQ ID NO: 52); and a LC-CDR3 comprising
 55 $QQYX_1X_2X_3PX_4T$ (SEQ ID NO: 79), wherein X_1 is N, D, S, R, A, T, L, Y, Q, W or G, X_2 is N, D, E, T, Y, G, A, M, F, S, I or L, X_3 is W, S, P, V, G, or R, and X_4 is P, Y, H, S, F, N, D, V, or G.

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7. An isolated anti-GM-CSFR α antibody, comprising:

a V_H comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-4, or a variant thereof comprising up to about 3 amino acid substitutions; an
 60 HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 5-16, or a variant thereof comprising up to about 3 amino acid substitutions; and an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 17-50, or a variant thereof comprising up to about 3 amino acid substitutions; and
 a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, or
 65 a variant thereof comprising up to about 3 amino acid substitutions; a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof comprising up to about 3 amino acid substitutions; and a LC-CDR3 comprising the amino acid

sequence of any one of SEQ ID NOs: 53-75, or a variant thereof comprising up to about 3 amino acid substitutions.

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8. An isolated anti-GM-CSFR α antibody, comprising a V_H comprising an HC-CDR1, an HC-CDR2, and an HC-CDR3 of a V_H comprising the amino acid sequence of any one of SEQ ID NOs: 80-121; and a V_L comprising a LC-CDR1, a LC-CDR2, and a LC-CDR3 of a V_L comprising the amino acid sequence of any one of SEQ ID NOs: 122-144.

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9. The isolated anti-GM-CSFR α antibody of any one of claims 1-8, comprising:

- (i) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 17, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs;
- (ii) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 56, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs;
- (iii) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 23, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs;

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- 105 (iv) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs;
- 110 (v) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 53, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs;
- 115 (vi) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 37, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs;
- 120 (vii) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs;
- 125 (viii) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and
- 130
- 135

- an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs;
- (ix) a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; and a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.
10. The isolated anti-GM-CSFR α antibody of any one of claims 1-9, comprising a V_H comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 5 amino acid substitutions in the HC-CDRs; a V_L comprising a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 51, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 5 amino acid substitutions in the LC-CDRs.
11. The isolated anti-GM-CSFR α antibody of any one of claims 5-10, comprising amino acid residues:
- (i) E, H, N, G, D, M, S, P, F, Y, A, V, K, W, R, or C at position 31 of the V_H; and/or
 - (ii) S, L, N, A, K, R, I, Q, G, T, H, M, or C at position 26 of the V_L; and/or
 - (iii) Q, Y, P, A, I, F, T, R, V, L, E, S, or C at position 27 of the V_L; and/or
 - (iv) S, H, W, L, R, K, T, P, I, F, V, E, A, or Q at position 28 of the V_L; and/or
 - (v) S, L, W, M, A, Y, K, R, G, T, E, V, N, F, or C at position 30 of the V_L; and/or
 - (vi) S, T, R, A, H, Q, P, M, L, or G at position 31 of the V_L; and/or
 - (vii) Y, L or F at position 32 of the V_L; and/or

- 170 (viii) G, or T at position 50 of the V_L; and/or
 (ix) A, G, R, H, K, S, T, M, F, N, or V at position 51 of the V_L; and/or
 (x) S, A, W, R, L, T, Q, F, Y, H, or N at position 52 of the V_L; and/or
 (xi) D, A, Q, or W at position 92 of the V_L; and/or
 (xii) N, D, E, T, Y, G, A, M, F, S, I, or L at position 93 of the V_L; and/or
 175 (xiii) amino acid residues selected from T, H, V, E, P, L, M, S, W, C, A, G, N, or K at
 position 28 of the V_H; and/or
 (xiv) amino acid residues selected from T, P, D, E, Y, W, V, M, N, L, Q, G, S, A, K, or R
 at position 30 of the V_H,
 wherein the numbering is according to the EU index of Kabat.

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12. The isolated anti-GM-CSFR α antibody of any one of claims 1-11, comprising:
 a V_H comprising the amino acid sequence of any one of SEQ ID NOs: 80-121, and 246-
 287, or a variant thereof having at least about 90% sequence identity to the amino acid
 sequence of any one of SEQ ID NOs: 80-121, and 246-287; and
 185 a V_L comprising the amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245,
 and 288-289, or a variant thereof having at least about 90% sequence identity to the
 amino acid sequence of any one of SEQ ID NOs: 122-144, 150-245, and 288-289.

13. The isolated anti-GM-CSFR α antibody of claim 12, comprising:

- 190 (i) a V_H comprising the amino acid sequence of SEQ ID NO: 80; and a V_L
 comprising the amino acid sequence of SEQ ID NO: 123;
 (ii) a V_H comprising the amino acid sequence of SEQ ID NO: 85; and a V_L
 comprising the amino acid sequence of SEQ ID NO: 125;
 (iii) a V_H comprising the amino acid sequence of SEQ ID NO: 86; and a V_L
 195 comprising the amino acid sequence of SEQ ID NO: 126;
 (iv) a V_H comprising the amino acid sequence of SEQ ID NO: 91; and a V_L
 comprising the amino acid sequence of SEQ ID NO: 126;
 (v) a V_H comprising the amino acid sequence of SEQ ID NO: 99; and a V_L
 comprising the amino acid sequence of SEQ ID NO: 122;
 200 (vi) a V_H comprising the amino acid sequence of SEQ ID NO: 101; and a V_L
 comprising the amino acid sequence of SEQ ID NO: 126;
 (vii) a V_H comprising the amino acid sequence of SEQ ID NO: 103; and a V_L
 comprising the amino acid sequence of SEQ ID NO: 123;

- 205 (viii) a V_H comprising the amino acid sequence of SEQ ID NO: 99; and a V_L comprising the amino acid sequence of SEQ ID NO: 126; or
- (ix) a V_H comprising the amino acid sequence of SEQ ID NO: 121; and a V_L comprising the amino acid sequence of SEQ ID NO: 126.
- (x) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 241;
- 210 (xi) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 193;
- (xii) a V_H comprising the amino acid sequence of SEQ ID NO: 248; and a V_L comprising the amino acid sequence of SEQ ID NO: 188;
- 215 (xiii) a V_H comprising the amino acid sequence of SEQ ID NO: 248; and a V_L comprising the amino acid sequence of SEQ ID NO: 193;
- (xiv) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 288;
- (xv) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 188;
- 220 (xvi) a V_H comprising the amino acid sequence of SEQ ID NO: 250; and a V_L comprising the amino acid sequence of SEQ ID NO: 236; or
- (xvii) a V_H comprising the amino acid sequence of SEQ ID NO: 91; and a V_L comprising the amino acid sequence of SEQ ID NO: 288.
- 225 14. An isolated anti-GM-CSFR α antibody that specifically binds to GM-CSFR α competitively with the isolated anti-GM-CSFR α antibody of any one of claims 1-13, or specifically binds to the same epitope as the isolated anti-GM-CSFR α antibody of any one of claims 1-13.
- 230 15. The isolated anti-GM-CSFR α antibody according to any one of claims 1-14, wherein the anti-GM-CSFR α antibody comprises an Fc fragment.
16. The isolated anti-GM-CSFR α antibody of claim 15, wherein the anti-GM-CSFR α antibody is a full-length IgG antibody.
- 235 17. The isolated anti-GM-CSFR α antibody of claim 16, wherein the anti-GM-CSFR α antibody is a full-length IgG1 or IgG4 antibody.

- 240 18. The isolated anti-GM-CSFR α antibody of any one of claims 1-17, wherein the anti-GM-CSFR α antibody is chimeric, human, or humanized.
- 245 19. The isolated anti-GM-CSFR α antibody according to any one of claims 1-14, wherein the anti-GM-CSFR α antibody is an antigen binding fragment selected from the group consisting of a Fab, a Fab', a F(ab')₂, a Fab'-SH, a single-chain Fv (scFv), an Fv fragment, a dAb, a Fd, a nanobody, a diabody, and a linear antibody.
20. An isolated nucleic acid molecule that encodes the anti-GM-CSFR α antibody according to any one of claims 1-19.
- 250 21. A vector comprising the nucleic acid molecule of claim 20.
22. An isolated host cell comprising the anti-GM-CSFR α antibody of any one of claims 1-18, the nucleic acid of claim 20, or the vector of claim 21.
- 255 23. A method of producing an anti-GM-CSFR α antibody, comprising:
a) culturing the host cell of claim 22 under conditions effective to express the anti-GM-CSFR α antibody; and
b) obtaining the expressed anti-GM-CSFR α antibody from the host cell.
- 260 24. A pharmaceutical composition comprising the anti-GM-CSFR α antibody according to any one of claims 1-19, the nucleic acid of claim 20, the vector of claim 21, or the isolated host cell of claim 22, and a pharmaceutically acceptable carrier.
- 265 25. A method of treating a disease or condition in an individual in need thereof, comprising administering to the individual an effective amount of the pharmaceutical composition of claim 24.
- 270 26. The method of claim 25, wherein the disease or condition is an inflammatory, respiratory or autoimmune disease or condition.

27. The method of claim 26, wherein the disease or condition is selected from the group consisting of rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, allergic response, multiple sclerosis, myeloid leukemia, atherosclerosis.