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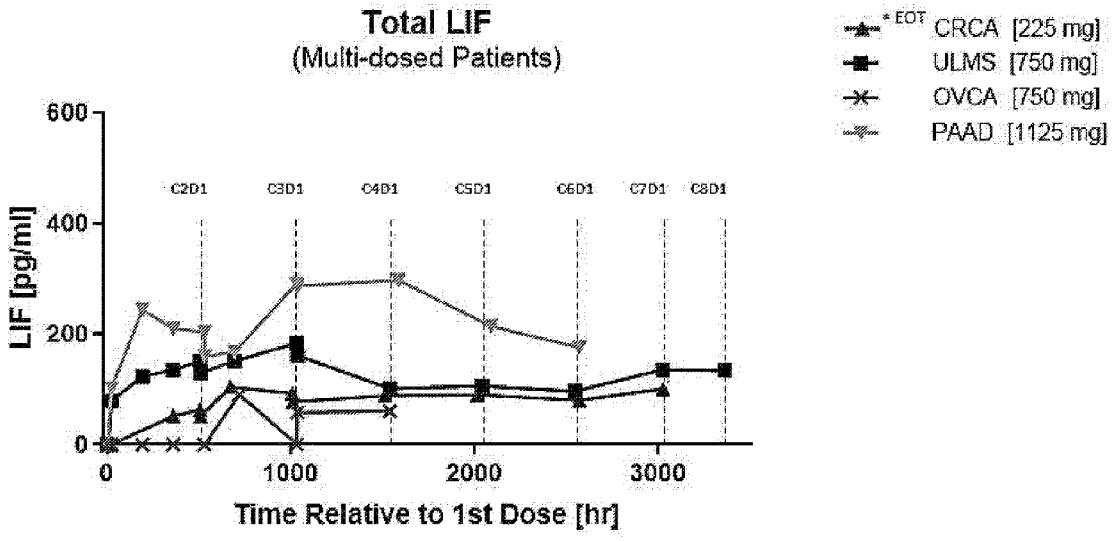

Fig. 27B

(57) Abstract: Described herein are antibodies that target Leukemia Inhibitory Factor (LIF). Also described herein are uses of these antibodies for the treatment of cancer and effective doses of these antibodies.

[Continued on next page]

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ANTIBODIES AGAINST LIF AND DOSAGE FORMS THEREOF

CROSS-REFERENCE

[0001] This application claims priority to and the benefit of European Application Ser. No. 18382327.7, filed on May 14, 2018; European Application Ser. No 18382359.0, filed on May 25, 2018; European Application Ser. No 19382208.7, filed on March 26, 2019; European Application Ser. No 19382331.7, filed on May 3, 2019, each of which is incorporated herein in its entirety.

BACKGROUND

[0002] Leukemia inhibitory factor (LIF) is an Interleukin 6 (IL-6)-type cytokine that is involved in a variety of biological activities including the inhibition of cell differentiation. Human LIF is a polypeptide of 202 amino acids that exerts biological effects via binding to the cell surface LIF receptor (LIFR or CD118) which heterodimerizes with gp130. This leads to activation of pro-growth signaling pathways such as the mitogen activated protein kinase (MAPK) and the Janus activated kinase (JAK/STAT) pathway. High expression levels and high serum levels of LIF have been demonstrated to be associated with a poor prognosis for many types of cancer.

SUMMARY

[0003] Described herein are anti-LIF antibodies that antagonize or block LIF activity. The anti-LIF antibodies described herein are useful for the treatment of cancer. In particular, certain anti-LIF antibodies, when administered at a therapeutically effective dose resulted in superior and surprising efficacy in the reduction of tumor volumes in both mouse and non-human primate cancer models. Thus, the current disclosure includes methods and pharmaceutical compositions of treating cancer using specific anti-LIF antibodies at specific dosages (both weight-based dosing and flat-dosing).

[0004] In one aspect, described herein, is a method of treating an individual with cancer comprising: administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising: (a) an immunoglobulin heavy chain complementarity determining region 1 (VH-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 1-3; (b) an immunoglobulin heavy chain complementarity determining region 2 (VH-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 4 or 5; (c) an immunoglobulin heavy chain complementarity determining region 3 (VH-CDR3) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 6-8; (d) an immunoglobulin light chain complementarity determining region 1 (VL-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 9 or 10; (e) an immunoglobulin

light chain complementarity determining region 2 (VL-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 11or 12; and (5) an immunoglobulin light chain complementarity determining region 3 (VL-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 13; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams. In certain embodiments, the recombinant antibody binds to glycosylated LIF. In certain embodiments, the recombinant antibody comprises at least one framework region derived from a human antibody framework region. In certain embodiments, the recombinant antibody is humanized. In certain embodiments, the recombinant antibody is deimmunized. In certain embodiments, the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains. In certain embodiments, the recombinant antibody is an IgG antibody. In certain embodiments, the recombinant antibody is a Fab, $F(ab)_2$, single-domain antibody, a single chain variable fragment (scFv), or a nanobody. In certain embodiments, the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 200 picomolar. In certain embodiments, the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 100 picomolar. In certain embodiments, the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 1 (GFTFSHAWMH), the VH-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 6 (TCWEWDLDF), the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 11 (SVSNLES), and the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT). In certain embodiments, the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 2 (GFTFSHAW), the VH-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 5 (IKAKSDDYAT), the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 6 (TCWEWDLDF), the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 10 (QSLLDSDGHTYLN), the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 12 (SVS), and the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT). In certain embodiments, the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 3 (HAWMH), the VH-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 7 (WEWDLDF), the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 11 (SVSNLES), and the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT). In certain

embodiments, the recombinant antibody comprises one or more of a heavy chain framework 1 (VH-FR1) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a heavy chain framework 2 (VH-FR2) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a heavy chain framework 3 (VH-FR3) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, and a heavy chain framework 4 (VH-FR4) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the recombinant antibody comprises one or more of a heavy chain framework 1 (VH-FR1) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a heavy chain framework 2 (VH-FR2) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a heavy chain framework 3 (VH-FR3) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, and a heavy chain framework 4 (VH-FR4) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the recombinant antibody comprises one or more of a light chain framework 1 (VL-FR1) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a light chain framework 2 (VL-FR2) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a light chain framework 3 (VL-FR3) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, and a light chain framework 4 (VL-FR4) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the recombinant antibody comprises one or more of a light chain framework 1 (VL-FR1) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a light chain framework 2 (VL-FR2) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a light chain framework 3 (VL-FR3) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, and a light chain framework 4 (VL-FR4) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the recombinant antibody binds to at least one of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or

H138 of SEQ ID NO: 68. In certain embodiments, the recombinant antibody binds to at least five of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the recombinant antibody binds to at least ten of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, H138 of SEQ ID NO: 68. In certain embodiments, the recombinant antibody binds to all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer. In certain embodiments, the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma. In certain embodiments, the recombinant antibody is administered as a component of a pharmaceutical formulation, the pharmaceutical formulation comprising the recombinant antibody and further comprising a pharmaceutically acceptable a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, the pharmaceutical formulation has a pH of about 6.0. In certain embodiments, the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL. In certain embodiments, the recombinant antibody is administered intravenously. In certain embodiments, the recombinant antibody is administered once a week. In certain embodiments, the recombinant antibody is administered about once every two weeks. In certain embodiments, the recombinant antibody is administered about once every three weeks. In certain embodiments, the recombinant antibody is administered about once every four weeks. In certain embodiments, the recombinant antibody is administered at a dose of about 75 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 225 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 750 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1125 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1500 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 2000 milligrams.

[0005] In another aspect, described herein, is a method of treating an individual with cancer comprising administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising: (a) an immunoglobulin heavy chain variable

region (VH) sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 41, 42, 44, or 66; and (b) an immunoglobulin light chain variable region (VL) sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 45-48; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams. In certain embodiments, the VH sequence is at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 42; and the VL sequence is at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 46. In certain embodiments, the VH sequence is identical to the amino acid sequence set forth in SEQ ID NO: 42; and the VL sequence is identical to the amino acid sequence set forth in SEQ ID NO: 46. In certain embodiments, the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains. In certain embodiments, the recombinant antibody is an IgG antibody. In certain embodiments, the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer. In certain embodiments, the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma. In certain embodiments, the recombinant antibody is administered as a component of a pharmaceutical formulation, the pharmaceutical formulation comprising the recombinant antibody and further comprising a pharmaceutically acceptable a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, the pharmaceutical formulation has a pH of about 6.0. In certain embodiments, the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL. In certain embodiments, the recombinant antibody is administered intravenously. In certain embodiments, the recombinant antibody is administered about once a week. In certain embodiments, the recombinant antibody is administered about once every two weeks. In certain embodiments, the recombinant antibody is administered about once every three weeks. In certain embodiments, the recombinant antibody is administered about once every four weeks. In certain embodiments, the recombinant antibody is administered at a dose of about 75 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 225 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 750 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1125 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1500

milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 2000 milligrams.

[0006] In another aspect, described herein, is a method of treating an individual with cancer comprising administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising (a) an immunoglobulin heavy chain sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 57-60 or 67; and (b) an immunoglobulin light chain sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 61-64; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams. In certain embodiments, the immunoglobulin heavy chain sequence is at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 58; and the immunoglobulin light chain sequence is at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 62. In certain embodiments, the immunoglobulin heavy chain sequence is identical to the amino acid sequence set forth in SEQ ID NO: 58; and the immunoglobulin light chain sequence is identical to the amino acid sequence set forth in SEQ ID NO: 62. In certain embodiments, the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains. In certain embodiments, the recombinant antibody is an IgG antibody. In certain embodiments, the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer. In certain embodiments, the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma. In certain embodiments, the recombinant antibody is administered as a component of a pharmaceutical formulation, the pharmaceutical formulation comprising the recombinant antibody and further comprising a pharmaceutically acceptable excipient, carrier, or diluent. In certain embodiments, the pharmaceutical formulation has a pH of about 6.0. In certain embodiments, the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL. In certain embodiments, the recombinant antibody is administered intravenously. In certain embodiments, the recombinant antibody is administered about once a week. In certain embodiments, the recombinant antibody is administered about once every two weeks. In certain embodiments, the recombinant antibody is administered about once every three weeks. In certain embodiments, the recombinant antibody is administered

about once every four weeks. In certain embodiments, the recombinant antibody is administered at a dose of about 75 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 225 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 750 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1125 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1500 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 2000 milligrams.

[0007] In another aspect, described herein, is a pharmaceutical formulation for use in treating a cancer in an individual, wherein the pharmaceutical formulation comprises a pharmaceutically acceptable excipient, carrier, or diluent and a recombinant antibody, wherein the recombinant antibody specifically binds Leukemia Inhibitory Factor (LIF) and comprises: (a) an immunoglobulin heavy chain complementarity determining region 1 (VH-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 1-3; (b) an immunoglobulin heavy chain complementarity determining region 2 (VH-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 4 or 5; (c) an immunoglobulin heavy chain complementarity determining region 3 (VH-CDR3) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 6-8; (d) an immunoglobulin light chain complementarity determining region 1 (VL-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 9 or 10; (e) an immunoglobulin light chain complementarity determining region 2 (VL-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 11or 12; and (f) an immunoglobulin light chain complementarity determining region 3 (VL-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 13; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams. In certain embodiments, the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL. In certain embodiments, the pharmaceutical formulation has a pH of about 6.0. In certain embodiments, the recombinant antibody binds to glycosylated LIF. In certain embodiments, the recombinant antibody comprises at least one framework region derived from a human antibody framework region. In certain embodiments, the recombinant antibody is humanized. In certain embodiments, the recombinant antibody is deimmunized. In certain embodiments, the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains. In certain embodiments, the recombinant antibody is an IgG antibody. In certain embodiments, the recombinant antibody is a Fab, $F(ab)_2$, single-domain antibody, a single chain variable fragment (scFv), or a nanobody. In certain embodiments, the

recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 200 picomolar. In certain embodiments, the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 100 picomolar. In certain embodiments, the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 1 (GFTFSHAWMH), the VH-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 6 (TCWEWDLDF), the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 11 (SVSNLES), and the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT). In certain embodiments, the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 2 (GFTFSHAW), the VH-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 5 (IKAKSDDYAT), the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 6 (TCWEWDLDF), the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 10 (QSLLDSDGHTYLN), the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 12 (SVS), and the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT). In certain embodiments, the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 3 (HAWMH), the VH-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 7 (WEWDLDF), the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 11 (SVSNLES), and the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT). In certain embodiments, the recombinant antibody comprises one or more of a heavy chain framework 1 (VH-FR1) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a heavy chain framework 2 (VH-FR2) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a heavy chain framework 3 (VH-FR3) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, and a heavy chain framework 4 (VH-FR4) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the recombinant antibody comprises one or more of a heavy chain framework 1 (VH-FR1) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a heavy chain framework 2 (VH-FR2) region amino acid sequence

identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a heavy chain framework 3 (VH-FR3) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, and a heavy chain framework 4 (VH-FR4) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the recombinant antibody comprises one or more of a light chain framework 1 (VL-FR1) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a light chain framework 2 (VL-FR2) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a light chain framework 3 (VL-FR3) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, and a light chain framework 4 (VL-FR4) region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the recombinant antibody comprises one or more of a light chain framework 1 (VL-FR1) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a light chain framework 2 (VL-FR2) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a light chain framework 3 (VL-FR3) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, and a light chain framework 4 (VL-FR4) region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the recombinant antibody binds to at least one of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the recombinant antibody binds to at least five of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the recombinant antibody binds to at least ten of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the recombinant antibody binds to all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer. In certain embodiments, the cancer comprises non-small cell lung cancer, epithelial ovarian

carcinoma, or pancreatic adenocarcinoma. In certain embodiments, the recombinant antibody is administered intravenously. In certain embodiments, the recombinant antibody is administered about once a week. In certain embodiments, the recombinant antibody is administered about once every two weeks. In certain embodiments, the recombinant antibody is administered about once every three weeks. In certain embodiments, the recombinant antibody is administered about once every four weeks. In certain embodiments, the recombinant antibody is administered at a dose of about 75 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 225 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 750 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1125 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1500 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 2000 milligrams.

[0008] In another aspect, described herein, is a pharmaceutical formulation for use in treating a cancer in an individual wherein the pharmaceutical formulation comprises a pharmaceutically acceptable excipient, carrier, or diluent and a recombinant antibody, wherein the recombinant antibody specifically binds Leukemia Inhibitory Factor (LIF) and comprises: (a) an immunoglobulin heavy chain variable region (VH) sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 41, 42, 44, or 66; and (b) an immunoglobulin light chain variable region (VL) sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 45-48; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams. In certain embodiments, the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL. In certain embodiments, the pharmaceutical formulation has a pH of about 6.0. In certain embodiments, the recombinant antibody binds to glycosylated LIF. In certain embodiments, the VH sequence is at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 42; and the VL sequence is at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 46. In certain embodiments, the VH sequence is identical to the amino acid sequence set forth in SEQ ID NO: 42; and the VL sequence is identical to the amino acid sequence set forth in SEQ ID NO: 46. In certain embodiments, the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains. In certain embodiments, the recombinant antibody is an IgG antibody. In certain embodiments, the

recombinant antibody is a Fab, $F(ab)_2$, single-domain antibody, a single chain variable fragment (scFv), or a nanobody. In certain embodiments, the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 200 picomolar. In certain embodiments, the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 100 picomolar. In certain embodiments, the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer. In certain embodiments, the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma. In certain embodiments, the recombinant antibody is administered intravenously. In certain embodiments, the recombinant antibody is administered about once a week. In certain embodiments, the recombinant antibody is administered about once every two weeks. In certain embodiments, the recombinant antibody is administered about once every three weeks. In certain embodiments, the recombinant antibody is administered about once every four weeks. In certain embodiments, the recombinant antibody is administered at a dose of about 75 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 225 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 750 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1125 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1500 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 2000 milligrams.

[0009] In another aspect, described herein, is a pharmaceutical formulation for use in treating a cancer in an individual wherein the pharmaceutical formulation comprises a pharmaceutically acceptable excipient, carrier, or diluent and a recombinant antibody, wherein the recombinant antibody specifically binds Leukemia Inhibitory Factor (LIF) and comprises: (a) an immunoglobulin heavy chain sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 57-60 or 67; and (b) an immunoglobulin light chain sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 61-64; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams. In certain embodiments, the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL. In certain embodiments, the pharmaceutical formulation has a pH of about 6.0. In certain embodiments, the recombinant antibody binds to glycosylated LIF. In certain

embodiments, the immunoglobulin heavy chain sequence is at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 58; and the immunoglobulin light chain sequence is at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 62. In certain embodiments, the immunoglobulin heavy chain sequence is identical to the amino acid sequence set forth in SEQ ID NO: 58; and the immunoglobulin light chain sequence is identical to the amino acid sequence set forth in SEQ ID NO: 62. In certain embodiments, the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains. In certain embodiments, the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 200 picomolar. In certain embodiments, the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 100 picomolar. In certain embodiments, the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer. In certain embodiments, the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma. In certain embodiments, the recombinant antibody is administered intravenously. In certain embodiments, the recombinant antibody is administered about once a week. In certain embodiments, the recombinant antibody is administered about once every two weeks. In certain embodiments, the recombinant antibody is administered about once every three weeks. In certain embodiments, the recombinant antibody is administered about once every four weeks. In certain embodiments, the recombinant antibody is administered at a dose of about 75 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 225 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 750 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1125 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 1500 milligrams. In certain embodiments, the recombinant antibody is administered at a dose of about 2000 milligrams.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Fig. 1** depicts a western blot showing inhibition of LIF-induced STAT3 phosphorylation of different anti-LIF humanized antibodies.

[0011] **Fig. 2A** and **2B** depicts a western blot showing inhibition of LIF-induced STAT3 phosphorylation humanized and parental 5D8 antibody.

[0012] **Fig. 3A** shows an IC_{50} for LIF inhibition in U-251 cells using the h5D8 antibody.

[0013] **Fig. 3B** shows representative IC_{50} dose response curves of r5D8 and h5D8 inhibition of

pSTAT3 under endogenous LIF stimulation conditions. Shown are the representative curves (n=1 h5D8, n=2 r5D8).

[0014] **Fig. 4** depicts a western blot showing inhibition of LIF-induced STAT3 phosphorylation of different monoclonal antibodies described in this disclosure.

[0015] **Fig. 5** depicts immunohistochemistry staining and quantitation of LIF expression in glioblastoma multiforme (GBM), NSCLC (non-small cell lung carcinoma), ovarian cancer, and colorectal cancer tumors from human patients. Bars represent mean +/- SEM.

[0016] **Fig. 6** is a graph showing an experiment conducted in a mouse model of non-small cell lung cancer using the humanized 5D8 antibody.

[0017] **Fig. 7A** shows the effect of r5D8 on inhibition of U251 cells in an orthotopic mouse model of GBM. Quantitation shown at day 26.

[0018] **Fig. 7B** shows data from mice inoculated with luciferase expressing human U251 GBM cells and then treated with 100, 200 or 300 μg of h5D8 or vehicle twice a week. Tumor size was determined by bioluminescence (Xenogen IVIS Spectrum) on day 7. The graph shows individual tumor measurements with horizontal bars indicating mean ± SEM. Statistical significance was calculated using the unpaired non-parametric Mann-Whitney U-test.

[0019] **Fig. 8A** shows the effect of r5D8 on inhibition of growth of ovarian cancer cells in an syngeneic mouse model.

[0020] **Fig. 8B** shows the individual measurements of tumors at day 25.

[0021] **Fig. 8C** illustrates that h5D8 shows a significant reduction in tumor growth when administered at 200 μg/mouse twice weekly ($p<0.05$). Symbols are mean + SEM, statistical significance compared with vehicle (with unpaired non-parametric Mann-Whitney U-test).

[0022] **Fig. 9A** shows the effect of r5D8 on inhibition of growth of colorectal cancer cells in a syngeneic mouse model.

[0023] **Fig. 9B** shows the individual measurements of tumors at day 17.

[0024] **Fig. 10A** shows reduction of macrophage infiltration to tumor sites in an orthotopic mouse model of GBM with a representative image and quantitation of CCL22+ cells.

[0025] **Fig. 10B** shows reduction of macrophage infiltration in a human organotypic tissue slice culture model. Shown are a representative image (left) and quantitation (right).

[0026] **Fig. 10C** shows reduction of macrophage infiltration to tumor sites in a syngeneic mouse model of ovarian cancer with a representative image and quantitation of CCL22+ cells.

[0027] **Fig. 10D** shows reduction of macrophage infiltration to tumor sites in a syngeneic mouse model of colorectal cancer with a representative image and quantitation of CCL22+ cells.

[0028] **Fig. 11A** shows increases in non-myeloid effector cells in a syngeneic mouse model of ovarian cancer after treatment with r5D8.

[0029] **Fig. 11B** shows increases in non-myeloid effector cells in a syngeneic mouse model of colorectal cancer after treatment with r5D8.

[0030] **Fig. 11C** shows decreases in percentage of CD4+ T_{REG} cells in a mouse model of NSCLC cancer after treatment with r5D8.

[0031] **Fig. 12** shows data from mice bearing CT26 tumors treated twice weekly with PBS (control) or r5D8 administered intraperitoneally in the presence or absence of anti-CD4 and anti-CD8 depleting antibodies. The graph shows individual tumor measurements at d13 expressed as mean tumor volume + SEM. Statistical differences between groups was determined by unpaired non-parametric Mann-Whitney U-test. R5D8 inhibited the growth of CT26 tumors (*$p<0.05$). The tumor growth inhibition by r5D8 was significantly reduced in the presence of anti-CD4 and anti-CD8 depleting antibodies (****$p<0.0001$).

[0032] **Fig. 13A** illustrates an overview of the co-crystal structure of h5D8 Fab in complex with LIF. The gp130 interacting site is mapped on the surface of LIF (dark shaded).

[0033] **Fig. 13B** illustrates detailed interactions between LIF and h5D8, showing residues forming salt bridges and h5D8 residues with buried surface areas greater than 100 $Å^2$.

[0034] **Fig. 14A** illustrates superposition of the five h5D8 Fab crystal structures and indicates a high degree of similarity despite being crystallized in different chemical conditions.

[0035] **Fig. 14B** illustrates an extensive network of Van der Waals interactions mediated by unpaired Cys100. This residue is well-ordered, partakes in shaping the conformations of HCDR1 and HCDR3 and is not involved in undesired disulfide scrambling. Distances between residues are shown as dashed lines and labeled.

[0036] **Fig. 15A** illustrates binding of h5D8 C100 mutants to human LIF by ELISA.

[0037] **Fig. 15B** illustrates binding of h5D8 C100 mutants to mouse LIF by ELISA.

[0038] **Fig. 16A** illustrates that h5D8 does not block binding between LIF and LIFR by Octet. Sequential binding of h5D8 to LIF followed by LIFR.

[0039] **Fig. 16B** and **16C** illustrate ELISA analysis of LIF/mAb complexes binding to immobilized LIFR or gp130. Signals of species-specific peroxidase conjugated anti-IgG antibodies (anti-human for (-) and h5D8, anti-rat for r5d8 and B09) detecting the antibody portion of mAb/LIF complexes binding immobilized LIFR (**Fig. 16B**) or gp130 (**Fig. 16C**) coated plates.

[0040] **Fig. 17A** and **17B** illustrate mRNA expression of LIF (**Fig. 16A**) or LIFR (**Fig. 16B**) in 72 different human tissues.

[0041] **Figs. 18A** to **C** show images of a patient at Cycle 7 ("C7") of h5D8 (750 mg) treatment on three target lesions, 2 rectus muscle lesions and 1 pelvic cul de sac lesion, and the previous radiation therapy ports. **Fig. 18A** shows Rectus Muscle # 1 – target lesion (**1**) is shown in the left

panel, and the XRT irradiated lesion (**2**) is shown on the right panel, size: 37.8 mm. **Fig. 18B** shows Rectus Muscle #2—target lesion (**3**) is shown in the left panel, and the XRT irradiated lesion (**4**) is shown on the right panel, size: 24.3 mm. **Fig. 18C** shows Pelvic cul de sac – target lesion (**5**) is shown in the right panel, and the XRT irradiated lesion (**6**) is shown on the right panel, size: 25 mm.

[0042] **Fig. 19** shows saturated LIF stabilization relative to time of 1st dose for Subject 0210-003

[0043] **Figs. 20A to C** show evidence of the modulation of biomarkers that are indicative of the potential mechanism of action of LIF inhibition in tumor biopsy from 0201-003. Data shows results pre-h5D8 treatment compared to on-h5D8 treatment. **Fig. 20A** shows anti-tumor immunity as percent (%) change in CD68 frequency; % change in CD8 frequency; and % change in Foxp3 frequency. **Fig. 20B** shows macrophage phenotype characterization as a % change in CD163 frequency; % change in CD206 frequency; and a % change in MHCII frequency. **Fig. 20C** shows h5D8 treatment effect on pSTAT3 as a % change in nuclei stained for pSTAT3+.

[0044] **Figs. 21A to C** show evidence of the modulation of biomarkers that are indicative of the potential mechanism of action of LIF inhibition in tumor biopsy from Subject 0301-003. Data shows results pre-h5D8 treatment compared to on-h5D8 treatment. **Fig. 21A** shows anti-tumor immunity as percent (%) change in CD68 frequency; % change in CD8 frequency; and % change in Foxp3 frequency. **Fig. 21B** shows macrophage phenotype characterization as a % change in CD163 frequency; % change in CD205 frequency; and a % change in MHCII frequency. **Fig. 21C** shows h5D8 treatment's effects of pSTAT3 as a % change in nuclei stained for pSTAT3+.

[0045] **Fig. 22** shows evidence of the modulation of biomarkers that are indicative of the potential mechanism of action of LIF inhibition in tumor biopsy from Subject 0301-004. Data shows results pre-h5D8 treatment compared to on-h5D8 treatment. **Fig. 22** shows anti-tumor immunity as percent (%) change in CD68 frequency; % change in CD8 frequency; and % change in Foxp3 frequency.

[0046] **Fig. 23** shows the LIF stabilization pattern relative to time of 1st dose for Subject 0201-004.

[0047] **Fig. 24** shows evidence of the modulation of biomarkers that are indicative of the potential mechanism of action of LIF inhibition in tumor biopsy from Subject 0201-004. Data shows results pre-h5D8 treatment compared to on-h5D8 treatment. **Fig. 24** shows macrophage phenotype characterization as a % change in CD163 frequency; % change in CD205 frequency; and a % change in MHCII frequency.

[0048] **Fig. 25** shows saturated LIF stabilization relative to time of 1st dose for Subject 0301-002.

[0049] **Fig. 26** shows h5D8 exposure in patients of dose cohorts 1-5. Shown is the geometric mean of h5D8 plasma levels in patients relative to start of the 1st infusion in dose cohort 1-5. Additional treatment cycles are indicated (mg q3weeks). The number of patients analyzed in each cohort was: cohort 1 n=2, cohort 2 n=1, cohort 3 n=10, cohort 4 n=8, and cohort 5 n=3.

[0050] **Figs. 27A** and **B** show LIF stabilization in patients after treatment with h5D8 in dose cohorts 1-5 relative to time of first infusion. **Fig. 27B** shows total LIF levels in patients after the first two cycles of h5D8 in dose cohort 1-4.

DETAILED DESCRIPTION

[0051] Unless otherwise defined, all technical terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. Any reference to “or” herein is intended to encompass “and/or” unless otherwise stated.

[0052] In one aspect, described herein, is a method of treating an individual with cancer comprising: administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising: (a) an immunoglobulin heavy chain complementarity determining region 1 (VH-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 1-3; (b) an immunoglobulin heavy chain complementarity determining region 2 (VH-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 4 or 5; (c) an immunoglobulin heavy chain complementarity determining region 3 (VH-CDR3) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 6-8; (d) an immunoglobulin light chain complementarity determining region 1 (VL-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 9 or 10; (e) an immunoglobulin light chain complementarity determining region 2 (VL-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 11or 12; and (5) an immunoglobulin light chain complementarity determining region 3 (VL-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 13; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

[0053] In another aspect, described herein, is a method of treating an individual with cancer comprising administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising: (a) an immunoglobulin heavy chain variable region (VH) sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%,

or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 41, 42, 44, or 66; and (b) an immunoglobulin light chain variable region (VL) sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 45-48; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

[0054] In another aspect, described herein, is a method of treating an individual with cancer comprising administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising (a) an immunoglobulin heavy chain sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 57-60 or 67; and (b) an immunoglobulin light chain sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 61-64; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

[0055] In another aspect, described herein, is a pharmaceutical formulation for use in treating a cancer in an individual, wherein the pharmaceutical formulation comprises a pharmaceutically acceptable excipient, carrier, or diluent and a recombinant antibody, wherein the recombinant antibody specifically binds Leukemia Inhibitory Factor (LIF) and comprises: (a) an immunoglobulin heavy chain complementarity determining region 1 (VH-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 1-3; (b) an immunoglobulin heavy chain complementarity determining region 2 (VH-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 4 or 5; (c) an immunoglobulin heavy chain complementarity determining region 3 (VH-CDR3) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 6-8; (d) an immunoglobulin light chain complementarity determining region 1 (VL-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 9 or 10; (e) an immunoglobulin light chain complementarity determining region 2 (VL-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 11or 12; and (f) an immunoglobulin light chain complementarity determining region 3 (VL-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 13; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

[0056] In another aspect, described herein, is a pharmaceutical formulation for use in treating a cancer in an individual wherein the pharmaceutical formulation comprises a pharmaceutically acceptable excipient, carrier, or diluent and a recombinant antibody, wherein the recombinant antibody specifically binds Leukemia Inhibitory Factor (LIF) and comprises: (a) an immunoglobulin heavy chain variable region (VH) sequence with an amino acid sequence at

least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 41, 42, 44, or 66; and (b) an immunoglobulin light chain variable region (VL) sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 45-48; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

[0057] In another aspect, described herein, is a pharmaceutical formulation for use in treating a cancer in an individual wherein the pharmaceutical formulation comprises a pharmaceutically acceptable excipient, carrier, or diluent and a recombinant antibody, wherein the recombinant antibody specifically binds Leukemia Inhibitory Factor (LIF) and comprises: (a) an immunoglobulin heavy chain sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 57-60 or 67; and (b) an immunoglobulin light chain sequence with an amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 61-64; wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

[0058] As used herein, unless otherwise indicated, the term "about" refers to an amount that is near the stated amount by at least 10%.

[0059] As used herein the terms "individual," "subject," and "patient" are used interchangeably and include humans diagnosed with or suspected of being afflicted with a tumor, a cancer, or other neoplasm.

[0060] As used herein the term "treat" or "treating" refers to interventions to a physiological or disease state of an individual designed or intended to ameliorate at least one sign or symptom associated with said physiological or disease state. Described herein treat or treating with respect to cancer refers to interventions intended to induce a complete response, a partial response, a delay of progression of the cancer or tumor being treated, a decrease in tumor size or tumor burden, or a delay in growth of tumor or tumor burden. Treating also refers to interventions intended to reduce metastases or malignancy of a cancer or a tumor. The skilled artisan will recognize that given a heterogeneous population of individuals afflicted with a disease, not all individuals will respond equally, or at all, to a given treatment. Nevertheless, these individuals are considered treated. Unsuccessful treatments generally result in progression of disease, and a necessity for additional treatment with a different therapeutic. In certain aspects the antibodies and methods described herein can be used to maintain remission of a cancer or prevent reoccurrence of the same cancer or a different cancer related to the treated cancer.

[0061] As used herein "checkpoint inhibitor" refers to a drug that inhibits a biological molecule

("checkpoint molecule") produced by an organism that negatively regulates the anti-tumor/cancer activity of T cells in the organism. The checkpoint molecule can be produced by the tumor, an immune cell in the tumor microenvironment, or by an immune cell not in the tumor microenvironment but existing in the blood stream or lymphatic system. Checkpoint molecules include without limitation PD-1, PDL-1, PDL-2, CTLA4, TIM-3, LAG-3, VISTA, SIGLEC7, PVR, TIGIT, IDO, KIR, A2AR, B7-H3, B7H4, and NOX2.

[0062] As used herein, unless otherwise indicated, the term "antibody" includes antigen binding fragments of antibodies, i.e. antibody fragments that retain the ability to bind specifically to the antigen bound by the full-length antibody, e.g. fragments that retain one or more CDR regions. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies; heavy chain antibodies, single-chain antibody molecules, e.g. single-chain variable region fragments (scFv), nanobodies and multispecific antibodies formed from antibody fragments with separate specificities, such as a bispecific antibody. In certain embodiments, the antibodies are humanized in such a way as to reduce an individual's immune response to the antibody. For example, the antibodies may be chimeric, e.g. non-human variable region with human constant region, or CDR grafted, e.g. non-human CDR regions with human constant region and variable region framework sequences. In certain embodiments, antibodies are deimmunized after humanization. Deimmunization involves removing or mutating one or more T-cell epitopes in the constant region of the antibody. In certain embodiments, the antibodies described herein are monoclonal. As used herein a "recombinant antibody" is an antibody that comprises an amino acid sequence derived from two different species or, or two different sources, and includes synthetic molecules, for example, an antibody that comprises a non-human CDR and a human framework or constant region. In certain embodiments, recombinant antibodies of the present invention are produced from a recombinant DNA molecule or synthesized.

[0063] The terms "cancer" and "tumor" relate to the physiological condition in mammals characterized by deregulated cell growth. Cancer is a class of diseases in which a group of cells display uncontrolled growth or unwanted growth. Cancer cells can also spread to other locations, which can lead to the formation of metastases. Spreading of cancer cells in the body can, for example, occur via lymph or blood. Uncontrolled growth, intrusion, and metastasis formation are also termed malignant properties of cancers. These malignant properties differentiate cancers from benign tumors, which typically do not invade or metastasize.

[0064] Percent (%) sequence identity with respect to a reference polypeptide or antibody sequence is the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide or antibody sequence, after aligning the

sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not 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 known for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, or Megalign (DNASTAR) software. Appropriate parameters for aligning sequences are able to be determined, including 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 ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, Calif., or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0065] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y, where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0066] The term “epitope” includes any determinant capable of being bound by an antigen binding protein, such as an antibody. An epitope is a region of an antigen that is bound by an antigen binding protein that targets that antigen, and when the antigen is a protein, includes specific amino acids that directly contact the antigen binding protein. Most often, epitopes reside on proteins, but in some instances can reside on other kinds of molecules, such as saccharides or lipids. Epitope determinants can include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and can have specific three dimensional structural characteristics, and/or specific charge characteristics. Generally,

antibodies specific for a particular target antigen will preferentially recognize an epitope on the target antigen in a complex mixture of proteins and/or macromolecules.

Structural attributes of the antibodies described herein

[0067] A complementarity determining region ("CDR") is a part of an immunoglobulin (antibody) variable region that is primarily responsible for the antigen binding specificity of the antibody. CDR regions are highly variable from one antibody to the next even when the antibody specifically binds the same target or epitope. A heavy chain variable region comprises three CDR regions, abbreviated VH-CDR1, VH-CDR2, and VH-CDR3; and a light chain variable region comprises three CDR regions, abbreviated VL-CDR1, VL-CDR2, and VL-CDR3. These CDR regions are ordered consecutively in the variable region with the CDR1 being the most N-terminal and the CDR3 being the most C-terminal. Interspersed between the CDRs are framework regions which contribute to the structure and display much less variability than the CDR regions. A heavy chain variable region comprises four framework regions, abbreviated VH-FR1, VH-FR2, VH-FR3, and VH-FR4; and a light chain variable region comprises four framework regions, abbreviated VL-FR1, VL-FR2, VL-FR3, and VL-FR4. Complete full-sized bivalent antibodies comprising two heavy and light chains will comprise: 12 CDRs, with three unique heavy chain CDRs and three unique light chain CDRs; 16 FR regions, with four unique heavy chain FR regions and four unique light chain FR regions. In certain embodiments, the antibodies described herein minimally comprise three heavy chain CDRs. In certain embodiments, the antibodies described herein minimally comprise three light chain CDRs. In certain embodiments, the antibodies described herein minimally comprise three heavy chain CDRs and three light chain CDRs. The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme); Al-Lazikani et al., (1997) *JMB* 273,927-948 ("Chothia" numbering scheme); MacCallum et al., J. *Mol. Biol.* 262:732-745 (1996), "Antibody-antigen interactions: Contact analysis and binding site topography," ("Contact" numbering scheme); Lefranc MP et al.,"IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains," Dev Comp *Immunol*, 2003 Jan;27(1):55-77 ("IMGT" numbering scheme); and Honegger A and Plückthun A, "Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool," *J Mol Biol*, 2001 Jun 8;309(3):657-70, ("Aho" numbering scheme). CDRs are identified herein from variable sequences provided using different numbering systems, herein with the Kabat, the IMGT, the Chothia numbering system, or any combination of the three. The boundaries of a given CDR or

FR may vary depending on the scheme used for identification. For example, the Kabat scheme is based on structural alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, "30a," and deletions appearing in some antibodies. The two schemes place certain insertions and deletions ("indels") at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme. In certain embodiments, the CDRs can be defined by any combination of the IMGT, Chothia, Kabat, Contact, and Aho methods.

[0068] The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three CDRs (*See e.g.*, Kindt et al. Kuby *Immunology, 6th ed.*, W.H. Freeman and Co., page 91(2007)). A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively (*See e.g.*, Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., Nature 352:624-628 (1991)). In certain embodiments, the antibodies described herein comprise variable regions of rat origin. In certain embodiments, the antibodies described herein comprise CDRs of rat origin. In certain embodiments, the antibodies described herein comprise variable regions of mouse origin. In certain embodiments, the antibodies described herein comprise CDRs of mouse origin.

[0069] Alterations (*e.g.,* substitutions) may be made in CDRs, *e.g.,* to improve antibody affinity. Such alterations may be made in CDR encoding codons with a high mutation rate during somatic maturation (*See e.g.*, Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and the resulting variant can be tested for binding affinity. Affinity maturation (e.g., using error-prone PCR, chain shuffling, randomization of CDRs, or oligonucleotide-directed mutagenesis) can be used to improve antibody affinity (*See e.g.*, Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (2001)). CDR residues involved in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling (*See e.g.*, Cunningham and Wells *Science*, 244:1081-1085 (1989)). CDR-H3 and CDR-L3 in particular are often targeted. Alternatively, or additionally, a crystal structure of an antigen-antibody complex is analyzed 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.

[0070] In certain embodiments, the antibodies described herein comprise a constant region in addition to a variable region. The heavy chain constant region (C_H) comprises four domains abbreviated C_H1, C_H2, C_H3, and C_H4, located at the C-terminal end of the full heavy chain polypeptide, C-terminal to the variable region. The light chain constant region (C_L) is much smaller than the C_H and is located at the C-terminal end of the full light chain polypeptide, C-terminal to the variable region. The constant region is highly conserved and comprises different isotypes that are associated with slightly different functions and properties. In certain embodiments, the constant region is dispensable for antibody binding to a target antigen. In certain embodiments, the constant regions of the antibody, both heavy and light chains are dispensable for antibody binding. In certain embodiments, the antibodies described herein lack one or more of a light chain constant region, heavy chain constant region, or both. Most monoclonal antibodies are of an IgG isotype; which is further divided into four subclasses IgG_1, IgG_2, IgG_3, and IgG_4. In certain embodiments, the antibodies described herein comprise any IgG subclass. In certain embodiments, the IgG subclass comprises IgG_1. In certain embodiments, the IgG subclass comprises IgG_2. In certain embodiments, the IgG subclass comprises IgG_3. In certain embodiments, the IgG subclass comprises IgG_4.

[0071] Antibodies comprise a fragment crystallizable region (Fc region) that is responsible for binding to complement and Fc receptors. The Fc region comprises the C_H2, C_H3, and C_H4 regions of the antibody molecule. The Fc region of an antibody is responsible for activating complement and antibody dependent cell cytotoxicity (ADCC). The Fc region also contributes to an antibody's serum half-life. In certain embodiments, the Fc region of the antibodies described herein comprise one or more amino acid substitutions that promote complement mediated cell lysis. In certain embodiments, the Fc region of antibodies described herein comprises one or more amino acid substitutions that promote ADCC. In certain embodiments, the Fc region of antibodies described herein comprises one or more amino acid substitutions that reduce complement mediated cell lysis. In certain embodiments, the Fc region of antibodies described herein comprises one or more amino acid substitutions that increase binding of the antibody to an Fc receptor. In certain embodiments, the Fc receptor comprises FcγRI (CD64), FcγRIIA (CD32), FcγRIIIA (CD16a), FcγRIIIB (CD16b), or any combination thereof. In certain embodiments, the Fc region of the antibodies described herein comprise one or more amino acid substitutions that increase the serum half-life of the antibody. In certain embodiments, the one or more amino acid substitutions that increase the serum half-life of the antibody increase affinity of the antibody to the neonatal Fc receptor (FcRn).

[0072] In some embodiments, the antibodies of this disclosure are variants that possesses

some but not all effector functions, which make it a desirable candidate for applications in which the half-life of the antibody in vivo is important yet certain effector functions (such as complement 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 FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. Non-limiting examples of in vitro assays to assess ADCC activity of a molecule of interest are described in U.S. Pat. No. 5,500,362 and 5,821,337. Alternatively, non-radioactive assays methods may be employed (e.g., ACTI™ and CytoTox 96® non-radioactive cytotoxicity assays). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC), monocytes, macrophages, and Natural Killer (NK) cells.

[0073] Antibodies can have increased half-lives and improved binding to the neonatal Fc receptor (FcRn) (*See e.g.*, US 2005/0014934). Such antibodies can comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn, and 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 according to the EU numbering system (See e.g., U.S. Pat. No. 7,371,826). Other examples of Fc region variants are also contemplated (*See e.g.*, Duncan & Winter, Nature 322:738-40 (1988); U.S. Pat. Nos. 5,648,260 and 5,624,821; and WO94/29351).

[0074] Antibodies useful in the clinic are often "humanized" to reduce immunogenicity in human individuals. Humanized antibodies improve safety and efficacy of monoclonal antibody therapy. One common method of humanization is to produce a monoclonal antibody in any suitable animal (e.g., mouse, rat, hamster) and replace the constant region with a human constant region, antibodies engineered in this way are termed "chimeric". Another common method is "CDR grafting" which replaces the non-human V-FRs with human V-FRs. In the CDR grafting method all residues except for the CDR region are of human origin. In certain embodiments, the antibodies described herein are humanized. In certain embodiments, the antibodies described herein are chimeric. In certain embodiments, the antibodies described herein are CDR grafted.

[0075] Humanization generally reduces or has little effect on the overall affinity of the antibody. Described herein are antibodies that unexpectedly possess greater affinity for their target after humanization. In certain embodiments, humanization increases the affinity for the antibody by 10%. In certain embodiments, humanization increases the affinity for the antibody by 25%. In certain embodiments, humanization increases the affinity for the antibody by 35%. In certain embodiments, humanization increases the affinity for the antibody by 50%. In certain embodiments, humanization increases the affinity for the antibody by 60%. In certain

embodiments, humanization increases the affinity for the antibody by 75%. In certain embodiments, humanization increases the affinity for the antibody by 100%. Affinity is suitably measured using surface plasmon resonance (SPR). In certain embodiments, affinity is measured using glycosylated human LIF. In certain embodiments, the glycosylated human LIF is immobilized to the surface of the SPR chip. In certain embodiments, the antibody binds with a K_D of less than about 300 nanomolar, 200 nanomolar,150 nanomolar, 125 nanomolar 100 nanomolar, 90 nanomolar, 80 nanomolar, 70 nanomolar, 60 nanomolar, 50 nanomolar, 40 nanomolar, or less.

Antibodies of the current disclosure

[0076] The antibodies described herein were generated from rats immunized with DNA encoding human LIF.

[0077] In certain embodiments, described herein, is an antibody (5D8) that specifically binds LIF comprising a VH-CDR1 set forth in any one of SEQ ID NOs: 1-3, a VH-CDR2 set forth in any one of SEQ ID NOs: 4 or 5, and a VH-CDR3 set forth in any one of SEQ ID NOs: 6 to 8. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a VL-CDR1 set forth in any one of SEQ ID NOs: 9 or 10, a VL-CDR2 set forth in SEQ ID NOs: 11 or 12, and a VL-CDR3 set forth in SEQ ID NO: 13. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a VH-CDR1 set forth in any one of SEQ ID NOs: 1-3, a VH-CDR2 set forth in any one of SEQ ID NOs: 4 or 5, and a VH-CDR3 set forth in any one of SEQ ID NOs: 6-8, a VL-CDR1 set forth in any one of SEQ ID NOs: 9 or 10, a VL-CDR2 set forth in SEQ ID NOs: 11 or 12, and a VL-CDR3 set forth in SEQ ID NO: 13. In certain embodiments, the antibody specifically binds to human LIF.

[0078] In certain embodiments, the antibody that specifically binds LIF comprises one or more human heavy chain framework regions comprising: a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a VH-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, or a VH-FR4 region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the one or more human heavy chain framework regions comprise a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid

sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 20, and a VH-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 24. In certain embodiments, the antibody that specifically binds LIF comprises one or more human light chain framework regions comprising: a VL-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, or a VL-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the one or more human light chain framework regions comprise a VL-FR1 amino acid sequence at least about 80%, about 90%, or about 95% identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the one or more human heavy chain framework regions and the one or more human light chain regions comprise a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 20, a VH-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 24, a VL-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence at least 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the antibody that specifically binds LIF comprises one or more human heavy chain framework regions comprising: a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ

ID NOs: 14-17, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, or a VH-FR4 region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the one or more human heavy chain framework regions comprise a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 20, and a VH-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 24. In certain embodiments, the antibody that specifically binds LIF comprises one or more human light chain framework regions comprising: a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, or a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the one or more human light chain framework regions comprise a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the one or more human heavy chain framework regions and the one or more human light chain regions comprise a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 20, a VH-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 24, a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the antibody specifically binds human LIF.

5D8

[0079] The antibodies described herein were generated from rats immunized with DNA encoding human LIF. One such antibody (5D8) was cloned and sequenced and comprises CDRs

(using the combination of the Kabat and IMGT CDR numbering methods) with the following amino acid sequences: a VH-CDR1 corresponding to SEQ ID NO: 1 (GFTFSHAWMH), a VH-CDR2 corresponding to SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), a VH-CDR3 corresponding to SEQ ID NO: 6 (TCWEWDLDF), a VL-CDR1 corresponding to SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), a VL-CDR2 corresponding to SEQ ID NO: 11 (SVSNLES), and a VL-CDR3 corresponding to SEQ ID NO: 13 (MQATHAPPYT). This antibody has been humanized by CDR grafting and the humanized version is referred to as h5D8.

[0080] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a VH-CDR1at least 80% or 90% identical to that set forth in SEQ ID NO: 1 (GFTFSHAWMH), a VH-CDR2 at least 80%, 90%, or 95% identical to that set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), and a VH-CDR3 at least 80% or 90% identical to that set forth in SEQ ID NO: 6 (TCWEWDLDF). In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a VL-CDR1 at least 80% or 90% identical to that set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), a VL-CDR2 at least 80% identical to that set forth in SEQ ID NO: 11 (SVSNLES), and a VL-CDR3 at least 80% or 90% identical to that set forth in SEQ ID NO: 13 (MQATHAPPYT). In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a VH-CDR1 set forth in SEQ ID NO: 1 (GFTFSHAWMH), a VH-CDR2 set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), a VH-CDR3 set forth in SEQ ID NO: 6 (TCWEWDLDF), a VL-CDR1 set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), a VL-CDR2 set forth in SEQ ID NO: 11 (SVSNLES), and a VL-CDR3 set forth in SEQ ID NO: 13 (MQATHAPPYT). Certain conservative amino acid substitutions are envisioned in the amino acid sequences of the CDRs of this disclosure. In certain embodiments, the antibody comprises CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 6, 9, 11, and 13 by 1, 2, 3, or 4 amino acids. In certain embodiments, the antibody comprises CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 6, 9, 11, and 13 by 1, 2, 3, or 4 amino acids and does not affect the binding affinity by greater than 10%, 20%, or 30%. In certain embodiments, antibodies that specifically bind LIF comprise one or more human heavy chain framework regions comprising: a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a VH-FR3 amino acid sequence at least 90% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, or a VH-FR4 region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the

one or more human heavy chain framework regions comprises a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 20, and a VH-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 24. In certain embodiments, the antibody that specifically binds LIF comprises one or more human light chain framework regions comprising: a VL-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, or a VL-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the one or more human light chain framework regions comprise a VL-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% % identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the one or more human heavy chain framework regions and the one or more human light chain regions comprise all of a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 20, a VH-FR4 amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 24, a VL-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid

sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the antibody specifically binds human LIF. In certain embodiments, the antibody that specifically binds LIF comprises one or more human heavy chain framework regions comprising: a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, or a VH-FR4 region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the one or more human heavy chain framework regions comprise a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 20, and a VH-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 24. In certain embodiments, the antibody that specifically binds LIF comprises one or more human light chain framework regions comprising: a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, or a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the one or more human light chain framework regions comprise a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the one or more human heavy chain framework regions and the one or more human light chain regions comprise a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 20, a VH-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 24, a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 38.

In certain embodiments, the antibody specifically binds human LIF.

[0081] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a VH-CDR1 amino acid sequence at least 80% or 90% identical to that set forth in SEQ ID NO: 1 (GFTFSHAWMH), a VH-CDR2 amino acid sequence at least 80%, 90%, or 95% identical to that set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), and a VH-CDR3 amino acid sequence at least 80% or 90% identical to that set forth in SEQ ID NO: 8 (TSWEWDLDF). In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a VL-CDR1 amino acid sequence at least 80% or 90% identical to that set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), a VL-CDR2 amino acid sequence at least 80% identical to that set forth in SEQ ID NO: 11 (SVSNLES), and a VL-CDR3 amino acid sequence at least 80% or 90% identical to that set forth in SEQ ID NO: 13 (MQATHAPPYT). In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a VH-CDR1 amino acid sequence set forth in SEQ ID NO: 1 (GFTFSHAWMH), a VH-CDR2 amino acid sequence set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), a VH-CDR3 amino acid sequence set forth in SEQ ID NO: 8 (TSWEWDLDF), a VL-CDR1 amino acid sequence set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), a VL-CDR2 amino acid sequence set forth in SEQ ID NO: 11 (SVSNLES), and a VL-CDR3 amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT). Certain conservative amino acid substitutions are envisioned in the amino acid sequences of the CDRs of this disclosure. In certain embodiments, the antibody comprises CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 8, 9, 11, and 13 by 1, 2, 3, or 4 amino acids. In certain embodiments, the antibody comprises CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 8, 9, 11, and 13 by 1, 2, 3, or 4 amino acids and does not affect the binding affinity by greater than 10%, 20%, or 30%. In certain embodiments, antibodies that specifically bind LIF comprise one or more human heavy chain framework regions comprising: a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a VH-FR3 amino acid sequence at least 90% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, or a VH-FR4 region amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the one or more human heavy chain framework regions comprises a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino

acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 20, and a VH-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 24. In certain embodiments, the antibody that specifically binds LIF comprises one or more human light chain framework regions comprising: a VL-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, or a VL-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the one or more human light chain framework regions comprise a VL-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the one or more human heavy chain framework regions and the one or more human light chain regions comprise all of a VH-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 20, a VH-FR4 amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 24, a VL-FR1 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence at least about 80%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the antibody specifically binds human LIF. In certain embodiments, the antibody that specifically binds LIF comprises one or more human heavy chain framework regions comprising:

a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 14-17, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 18 or 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-22, or a VH-FR4 region amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 23-25. In certain embodiments, the one or more human heavy chain framework regions comprise a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 20, and a VH-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 24. In certain embodiments, the antibody that specifically binds LIF comprises one or more human light chain framework regions comprising: a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 26-29, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 30-33, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 34-37, or a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in any one of SEQ ID NOs: 38-40. In certain embodiments, the one or more human light chain framework regions comprise a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the one or more human heavy chain framework regions and the one or more human light chain regions comprise a VH-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 15, a VH-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 19, a VH-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 20, a VH-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 24, a VL-FR1 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 27, a VL-FR2 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 31, a VL-FR3 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 35, and a VL-FR4 amino acid sequence identical to the amino acid sequence set forth in SEQ ID NO: 38. In certain embodiments, the antibody specifically binds human LIF.

[0082] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region comprising an amino acid sequence at least

about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 41, 42, and 44. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region comprising an amino acid sequence set forth in any one of SEQ ID NOs: 41, 42, and 44. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized light chain variable region comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 45-48. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized light chain variable region comprising an amino acid sequence set forth in any one of SEQ ID NOs: 45-48. In certain embodiments, the antibody specifically binds human LIF.

[0083] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO:42; and a humanized light chain variable region comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 46. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 42; and a humanized light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 46.

[0084] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 66; and a humanized light chain variable region comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 46. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 66; and a humanized light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 46.

[0085] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 57-60; and a humanized light chain comprising

an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 61-64. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 57-60; and a humanized light chain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 61-64.

[0086] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 58; and a humanized light chain comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 62. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 58; and a humanized light chain comprising an amino acid sequence set forth in SEQ ID NO: 62. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO:67; and a humanized light chain comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 62. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 67; and a humanized light chain comprising an amino acid sequence set forth in SEQ ID NO: 62.

[0087] In a certain embodiments, described herein, is a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising: a heavy chain complementarity determining region 1 (VH-CDR1) comprising an amino acid sequence set forth in SEQ ID NO: 3; a heavy chain complementarity determining region 2 (VH-CDR2) comprising an amino acid sequence set forth in SEQ ID NO: 4; a heavy chain complementarity determining region 3 (VH-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 7; a light chain complementarity determining region 1 (VL-CDR1) comprising an amino acid sequence set forth in SEQ ID NO: 9; and a light chain complementarity determining region 2 (VL-CDR2) comprising an amino acid sequence set forth in SEQ ID NO: 11; and a light chain complementarity determining region 3 (VL-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 13.

[0088] In a certain embodiments, described herein, is a recombinant antibody that specifically

binds Leukemia Inhibitory Factor (LIF) comprising: a heavy chain complementarity determining region 1 (VH-CDR1) comprising an amino acid sequence set forth in SEQ ID NO: 2; a heavy chain complementarity determining region 2 (VH-CDR2) comprising an amino acid sequence set forth in SEQ ID NO: 5; a heavy chain complementarity determining region 3 (VH-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 6; a light chain complementarity determining region 1 (VL-CDR1) comprising an amino acid sequence set forth in SEQ ID NO: 10; and a light chain complementarity determining region 2 (VL-CDR2) comprising an amino acid sequence set forth in SEQ ID NO: 12; and a light chain complementarity determining region 3 (VL-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 13. Certain conservative amino acid substitutions are envisioned in the amino acid sequences of the CDRs of this disclosure. In certain embodiments, the antibody comprises CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 2, 5, 6, 10, 12, and 13 by 1, 2, 3, or 4 amino acids. In certain embodiments, the antibody comprises CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 2, 5, 6, 10, 12, and 13 by 1, 2, 3, or 4 amino acids and does not affect the binding affinity by greater than 10%, 20%, or 30%.

[0089] In a certain embodiments, described herein, is a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising: a heavy chain complementarity determining region 1 (VH-CDR1) comprising an amino acid sequence set forth in SEQ ID NO: 3; a heavy chain complementarity determining region 2 (VH-CDR2) comprising an amino acid sequence set forth in SEQ ID NO: 4; a heavy chain complementarity determining region 3 (VH-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 7; a light chain complementarity determining region 1 (VL-CDR1) comprising an amino acid sequence set forth in SEQ ID NO: 9; and a light chain complementarity determining region 2 (VL-CDR2) comprising an amino acid sequence set forth in SEQ ID NO: 11; and a light chain complementarity determining region 3 (VL-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 13. Certain conservative amino acid substitutions are envisioned in the amino acid sequences of the CDRs of this disclosure. In certain embodiments, the antibody comprises CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 3, 4, 7, 9, 11, and 13 by 1, 2, 3, or 4 amino acids. In certain embodiments, the antibody comprises CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 3, 4, 7, 9, 11, and 13 by 1, 2, 3, or 4 amino acids and does not affect the binding affinity by greater than 10%, 20%, or 30%.

[0090] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 49-52; and a humanized light chain comprising

an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 53-56. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 49-52; and a humanized light chain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 53-56.

[0091] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 50; and a humanized light chain comprising an amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in of SEQ ID NO: 54. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 50; and a humanized light chain comprising an amino acid sequence set forth in any one of SEQ ID NO: 54.

Epitopes bound by therapeutically useful LIF antibodies

[0092] Described herein is a unique epitope of human LIF that when bound inhibits LIF biological activity (e.g., STAT3 phosphorylation) and inhibits tumor growth *in vivo*. The epitope described herein consists of two discontinuous stretches of amino acids (from residue 13 to residue 32 and from residue 120 to 138 of human LIF), that are present in two distinct topological domains (alpha helixes A and C) of the human LIF protein. This binding is a combination of weak (Van der Waals attraction), medium (hydrogen binding), and strong (salt bridge) interactions. In certain embodiments, a contact residue is a residue on LIF that forms a hydrogen bond with a residue on an anti-LIF antibody. In certain embodiments, a contact residue is a residue on LIF that forms a salt bridge with a residue on an anti-LIF antibody. In certain embodiments, a contact residue is a residue on LIF that results in a Van der Waals attraction with and is within at least 5, 4, or 3 angstroms of a residue on an anti-LIF antibody.

[0093] In certain embodiments, described herein is an isolated antibody that binds any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, described herein is an isolated antibody that binds all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, described herein is an isolated antibody that binds all of the following residues:

A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the antibody only binds residues that participate with the antibody in strong or medium interactions. In certain embodiments, the antibody only binds residues that participate with the antibody in strong interactions. In a certain embodiment, the antibody interacts with helix A and C of LIF. In a certain embodiment, the antibody blocks LIF interaction with gp130.

[0094] In certain embodiments, described herein is an antibody comprising CDRs with an amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 6, 9, 11, and 13 that binds any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, described herein is an antibody comprising CDRs with an amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 6, 9, 11, and 13 that binds to all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the antibody only binds residues that participate with the antibody in strong or medium interactions. In certain embodiments, the antibody only binds residues that participate with the antibody in strong interactions.

[0095] In certain embodiments, described herein is an antibody comprising CDRs with an amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 8, 9, 11, and 13 that binds any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, described herein is an antibody comprising CDRs with an amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 8, 9, 11, and 13 that binds to all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the antibody only binds residues that participate with the antibody in strong or medium interactions. In certain embodiments, the antibody only binds residues that participate with the antibody in strong interactions.

[0096] In certain embodiments, described herein is an antibody comprising CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 6, 9, 11, and 13 by 1, 2, 3, 4, or 5 amino acids and binds any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123,

S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, described herein is an antibody comprising CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 6, 9, 11, and 13 by 1, 2, 3, 4, or 5 amino acids and binds to all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the antibody only binds residues that participate with the antibody in strong or medium interactions. In certain embodiments, the antibody only binds residues that participate with the antibody in strong interactions.

[0097] In certain embodiments, described herein is an antibody comprising CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 8, 9, 11, and 13 by 1, 2, 3, 4, or 5 amino acids and binds any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, described herein is an antibody comprising CDRs that differ from the amino acid sequence set forth in any one of SEQ ID NOs: 1, 4, 8, 9, 11, and 13 by 1, 2, 3, 4, or 5 amino acids and bind to all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the antibody only binds residues that that participate with the antibody in strong or medium interactions. In certain embodiments, the antibody only binds residues that that participate with the antibody in strong interactions.

[0098] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO:42; and a humanized light chain variable region amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 46 and binds any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO:42; and a humanized light chain variable region amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99%

identical to the amino acid sequence set forth in SEQ ID NO: 46 and binds all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the antibody only binds residues that that participate with the antibody in strong or medium interactions. In certain embodiments, the antibody only binds residues that that participate with the antibody in strong interactions.

[0099] In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 66; and a humanized light chain variable region amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 46 and binds any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, described herein, is an antibody that specifically binds LIF comprising a humanized heavy chain variable region amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 66; and a humanized light chain variable region amino acid sequence at least about 80%, about 90%, about 95%, about 97%, about 98%, or about 99% identical to the amino acid sequence set forth in SEQ ID NO: 46 and binds all of the following residues: A13, I14, R15, H16, P17, C18, H19, N20, Q25, Q29, Q32, D120, R123, S127, N128, L130, C131, C134, S135, or H138 of SEQ ID NO: 68. In certain embodiments, the antibody only binds residues that that participate with the antibody in strong or medium interactions. In certain embodiments, the antibody only binds residues that that participate with the antibody in strong interactions.

Therapeutic indications

[00100] In certain embodiments, the antibodies disclosed herein inhibit LIF signaling in cells. In certain embodiments, the IC_{50} for biological inhibition of the antibody under serum starved conditions in U-251 cells is less than or equal to about 100, 75, 50, 40, 30, 20, 10, 5, or 1 nanomolar. In certain embodiments, the IC_{50} for biological inhibition of the antibody under serum starved conditions in U-251 cells is less than or equal to about 900, 800, 700, 600, 500, 400, 300, 200, or 100 nanomolar.

[00101] In certain embodiments, h5D8 and the dosages of h5D8 described herein are useful for treating tumors and cancers that express LIF. In certain embodiments, an individual treated with

the antibodies of this disclosure has been selected for treatment as having a LIF positive tumor/cancer. In certain embodiments, the tumor is LIF positive or produces elevated levels of LIF. In certain embodiments, LIF positivity is determined in comparison to a reference value or a set pathological criteria. In certain embodiments, a LIF positive tumor expresses greater than 2-fold, 3- fold, 5-fold, 10-fold, 100-fold or more LIF than a non-transformed cell from which the tumor is derived. In certain embodiments, the tumor has acquired ectopic expression of LIF. A LIF positive tumor can be determined histologically using, for example, immunohistochemistry with an anti-LIF antibody; by commonly used molecular biology methods such as, for example, mRNA quantitation by real-time PCR or RNA-seq; or protein quantitation, for example, by western blot, flow cytometry, ELISA, or a homogenous protein quantitation assays (e.g., AlphaLISA®). In certain embodiments, the antibodies can be used to treat patients diagnosed with cancer. In certain embodiments, the cancer comprises one or more cancer stem cells or is one or more cancer stem cells.

[00102] In certain embodiments, h5D8 and the dosages of h5D8 described herein are useful for treating tumors in cancers that express the LIF receptor (CD118). A LIF receptor positive tumor can be determined by histopathology or flow cytometry, and, in certain embodiments, comprises a cell that binds a LIF receptor antibody greater than 2x, 3x, 4x, 5x, 10x or more than an isotype control. In certain embodiments, the tumor has acquired ectopic expression of the LIF receptor. In a certain embodiment, the cancer is a cancer stem cell. In a certain embodiment, a LIF positive tumor or cancer can be determined by immunohistochemistry using anti-LIF an anti-LIF antibody. In a certain embodiment, a LIF positive tumor is determined by IHC analysis with a LIF Level in the top 10%, 20%, 30%, 40%, or top 50% of tumors.

[00103] H5D8 and the dosages of h5D8 described herein influence numerous outcomes. In a certain embodiment, the antibodies described herein can reduce the presence of M2 macrophages in tumors by at least 10%, 20%, 30%, 40%, 50%, 60 %, 70%, 80%, 90% or more in a tumor model compared to a control antibody (e.g., isotype control). M2 macrophages can be identified by staining for CCL22 and/or CD206 in IHC sections or by flow cytometry of tumor infiltrating immune or myeloid cells. In a certain embodiment, the antibodies described herein can reduce the binding of LIF to gp130 tumors by at least 10%, 20%, 30%, 40%, 50%, 60 %, 70%, 80%, 90% or more when compared to a control antibody (e.g., isotype control). In a certain embodiment, the antibodies described herein can reduce LIF signaling by at least 10%, 20%, 30%, 40%, 50%, 60 %, 70%, 80%, 90% or more in a LIF responsive cell line compared to a control antibody (e.g., isotype control). LIF signaling can be measured by, for example, western blot for phosphorylated STAT3 (a downstream target of LIF signaling). The antibodies here are also highly specific for LIF compared to other IL-6 family member cytokines. In certain

embodiments, the antibodies bind human LIF with an affinity about 10x, about 50x, or about 100x greater than that of any other IL-6 family member cytokine. In certain embodiments, the LIF antibodies do not bind to other IL-6 family member cytokines that are produced in a mammalian system. In certain embodiments, the antibodies do not bind to Oncostatin M that has been produced in a mammalian system.

[00104] H5D8 and the dosages of h5D8 described herein are useful in methods to improve the levels of biomarkers that are prognostic indicators of tumor or cancer burden. Tumor markers such as carbohydrate antigen-125 (CA-125), carbohydrate antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA), are positive prognostic indicators. Generally, low-levels of these antigens correlate with treatment success. In certain embodiments, h5D8 reduces serum CEA, CA 19-9, CA-125 or combinations thereof, when administered at a dose of about 1125 or 1500 about once every 2, 3, or 4 weeks, including increments therein. In certain embodiments, the tumor associated marker comprises CA 19-9, CA-125, CEA or a combination thereof. In certain embodiments, the tumor associated marker comprises CEA. In certain embodiments, the tumor associated marker comprises CA-125. In certain embodiments, the tumor associated marker comprises CA 19-9. The levels of CA 19-9, CA-125, CEA or a combination thereof can be reduced by about 10%, 20%, 25%, 30%, 35%, 40%, or 50% as a result of the treatment described herein.

[00105] H5D8 and the dosages of h5D8 described herein can also be used to improve other prognostic indicators of tumor/cancer burden, or disease impact. In certain embodiments, the prognostic indicator is the Eastern Cooperative Oncology Group ("ECOG") status. ECOG status is scaled 0 to 5 as follows: 0, fully active, able to carry on all pre-disease performance without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2, ambulatory and capable of all self-care but unable to carry out any work activities; up to and about more than 50% of waking hours; 3, capable of only limited self-care; confined to bed or chair more than 50% of waking hours; 4, completely disabled; cannot carry on any self-care; totally confined to bed or chair; 5, dead. In certain embodiments, the methods and dosages decrease an ECOG score by 1, 2, 3, or 4. In certain embodiments, an ECOG status of an individual is reduced to 0, 1, 2, or 3. In certain embodiments, an ECOG status of an individual does not increase for at least 3, 6, 9, or 12 months. In certain embodiments, an ECOG status of an individual is reduced to 0 or 1 when h5D8 is administered at a dose of about 1125 or 1500 about once every 2, 3, or 4 weeks, including increments therein. This improvement or delay in progression will be seen after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more treatments.

[00106] In certain embodiments, h5D8 treatment leads to stable-disease. In certain

embodiments, h5D8 and the dosages of h5D8 described herein result in stable disease for at least 3, 6, 12, 15, 18, 24, 30, or 36 months during treatment. In certain embodiments, the antibodies and dosages described herein result in stable disease for at least 3, 6, 12, 15, 18, 24, 30, or 36 months during treatment with h5d8 administered at a dose of about 1125 or 1500 about once every 2, 3, or 4 weeks, including increments therein. In certain embodiments, the antibodies and dosages described herein result in stable disease for at least12 months during treatment with h5d8 administered at a dose of about 1125 or 1500 about once every 2, 3, or 4 weeks, including increments therein. This delay in progression will be seen after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more treatments.

[00107] In certain embodiments, h5D8 and the dosages of h5D8 described herein are useful for the treatment of a cancer or tumor. In certain embodiments, h5D8 is useful for the treatment of a cancer that is refractory with at least one other treatment. In certain embodiments, the treatment is a chemotherapeutic or an immunotherapy (e.g., immune checkpoint inhibitor therapy). In certain embodiments, the immunotherapy is one that targets PD-1, PDL-1, PDL-2 or any combination thereof. In certain embodiments, the immunotherapy is one that targets polio virus receptor (PVR), TIGIT, or any combination thereof. In certain embodiments, the cancer comprises breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head, neck, ovarian, prostate, brain, pancreatic, skin, bone, bone marrow, blood, thymus, uterine, testicular, and liver tumors. In certain embodiments, tumors which can be treated with the antibodies of the invention comprise adenoma, adenocarcinoma, angiosarcoma, astrocytoma, epithelial carcinoma, germinoma, glioblastoma, glioma, hemangioendothelioma, hemangiosarcoma, hematoma, hepatoblastoma, leukemia, lymphoma, medulloblastoma, melanoma, neuroblastoma, osteosarcoma, retinoblastoma, rhabdomyosarcoma, sarcoma and/or teratoma. In certain embodiments, the tumor/cancer is selected from the group of acral lentiginous melanoma, actinic keratosis, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, Bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinoma, capillary carcinoid, carcinoma, carcinosarcoma, cholangiocarcinoma, chondrosarcoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal sarcoma, Swing's sarcoma, focal nodular hyperplasia, gastronoma, germ line tumors, glioblastoma, glucagonoma, hemangioblastoma, hemangioendothelioma, hemangioma, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinite, intraepithelial neoplasia, intraepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, liposarcoma, lung carcinoma, lymphoblastic leukemia, lymphocytic leukemia, leiomyosarcoma, melanoma, malignant melanoma, malignant mesothelial tumor, nerve sheath tumor, medulloblastoma,

medulloepithelioma, mesothelioma, mucoepidermoid carcinoma, myeloid leukemia, neuroblastoma, neuroepithelial adenocarcinoma, nodular melanoma, osteosarcoma, ovarian carcinoma, papillary serous adenocarcinoma, pituitary tumors, plasmacytoma, pseudosarcoma, prostate carcinoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, squamous cell carcinoma, small cell carcinoma, soft tissue carcinoma, somatostatin secreting tumor, squamous carcinoma, squamous cell carcinoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vagina/vulva carcinoma, VIPpoma, and Wilm's tumor. In certain embodiments, the tumor/cancer to be treated with one or more antibodies of the invention comprise brain cancer, head and neck cancer, colorectal carcinoma, acute myeloid leukemia, pre-B-cell acute lymphoblastic leukemia, bladder cancer, astrocytoma, preferably grade II, III or IV astrocytoma, glioblastoma, glioblastoma multiforme, small cell cancer, and non-small cell cancer, preferably non-small cell lung cancer, lung adenocarcinoma, metastatic melanoma, androgen-independent metastatic prostate cancer, androgen-dependent metastatic prostate cancer, prostate adenocarcinoma, and breast cancer, preferably breast ductal cancer, and/or breast carcinoma. In certain embodiments, the cancer treated with the antibodies of this disclosure comprises glioblastoma. In certain embodiments, the cancer treated with one or more antibodies of this disclosure comprises pancreatic cancer. In certain embodiments, the cancer treated with one or more antibodies of this disclosure comprises ovarian cancer. In certain embodiments, the cancer treated with one or more antibodies of this disclosure comprises lung cancer. In certain embodiments, the cancer treated with one or more antibodies of this disclosure comprises prostate cancer. In certain embodiments, the cancer treated with one or more antibodies of this disclosure comprises colon cancer. In certain embodiments, the cancer treated comprises glioblastoma, pancreatic cancer, ovarian cancer, colon cancer, prostate cancer, or lung cancer. In a certain embodiment, the cancer is refractory to other treatment. In a certain embodiment, the cancer treated is relapsed. In a certain embodiment, the cancer is a relapsed/refractory glioblastoma, pancreatic cancer, ovarian cancer, colon cancer, prostate cancer, or lung cancer. In certain embodiments, the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer. In certain embodiments, the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma. In certain embodiments, the cancer comprises an advanced solid tumor. In certain embodiments, the cancer comprises appendiceal cancer, rectal cancer, metastatic mixoid liposarcoma, and paraganglioma.

Therapeutic methods

[00108] In certain embodiments, the antibodies can be administered by any route suitable for the administration of antibody-containing pharmaceutical compositions, such as, for example, subcutaneous, intraperitoneal, intravenous, intramuscular, intratumoral, or intracerebral, etc. In certain embodiments, the antibodies are administered intravenously. In certain embodiments, the antibodies are administered on a suitable dosage schedule, for example, weekly, twice weekly, monthly, twice monthly, etc. In certain embodiments, the antibodies are administered about once every three weeks. The antibodies can be administered in any therapeutically effective amount. In certain embodiments, the therapeutically acceptable amount is between about 0.1 mg/kg and about 50 mg/kg. In certain embodiments, the therapeutically acceptable amount is between about 1 mg/kg and about 40 mg/kg. In certain embodiments, the therapeutically acceptable amount is between about 5 mg/kg and about 30 mg/kg. The h5D8 antibody can be administered at a flat dose regardless of the weight or mass of the individual to whom the h5D8 antibody is administered. The h5D8 antibody can be administered at a flat dose regardless of the weight or mass of the individual to whom the h5D8 antibody is administered, provided that the individual has a mass of at least about 37.5 kilograms. A flat dose of h5D8 can be administered from about 75 milligrams to about 2000 milligrams. A flat dose of h5D8 can be administered from about 225 milligrams to about 2000 milligrams, from about 750 milligrams to about 2000 milligrams, from about 1125 milligrams to about 2000 milligrams, or from about 1500 milligrams to about 2000 milligrams. A flat dose of h5D8 can be administered at about 75 milligrams. A flat dose of h5D8 can be administered at about 225 milligrams. A flat dose of h5D8 can be administered at about 750 milligrams. A flat dose of h5D8 can be administered at about 1125 milligrams. A flat dose of h5D8 can be administered at about 1500 milligrams. A flat dose of h5D8 can be administered at about 2000 milligrams.

[00109] Other dosages of h5D8 are contemplated. A flat dose of h5D8 can be administered at about 50, 100, 150, 175, 200, 250, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1025, 1050, 1075, 1100, 1150, 1175, 1200, 1225, 1250, 1275, 1300, 1325, 1350, 1375, 1400, 1425, 1450, 1475, 1525, 1550, 1575, 1600, 1625, 1650, 1675, 1700, 1725, 1750, 1775, 1800, 1825, 1850, 1875, 1900, 1925, 1950, 1975, 2025, 2050, 2075, or 2100 milligrams. Any of these doses can be administered about once a week, about once every two weeks, about once every three weeks, or about once every four weeks.

[00110] A flat dose of h5D8 can be administered from about 75 milligrams to about 2000 milligrams about once a week. A flat dose of h5D8 can be administered from about 75 milligrams to about 1500 milligrams about once a week. A flat dose of h5D8 can be administered from about 225 milligrams to about 1500 milligrams, from about 750 milligrams to

about 1500 milligrams, from about 1125 milligrams to about 1500 milligrams about once a week. A flat dose of h5D8 can be administered at about 75 milligrams about once a week. A flat dose of h5D8 can be administered at about 225 milligrams about once a week. A flat dose of h5D8 can be administered at about 750 milligrams about once a week. A flat dose of h5D8 can be administered at about 1125 milligrams about once a week. A flat dose of h5D8 can be administered at about 1500 milligrams about once a week. A flat dose of h5D8 can be administered at about 2000 milligrams about once a week.

[00111] A flat dose of h5D8 can be administered from about 75 milligrams to about 2000 milligrams about once every two weeks. A flat dose of h5D8 can be administered from about 75 milligrams to about 1500 milligrams about once every two weeks. A flat dose of h5D8 can be administered from about 225 milligrams to about 1500 milligrams, from about 750 milligrams to about 1500 milligrams, from about 1125 milligrams to about 1500 milligrams about once every two weeks. A flat dose of h5D8 can be administered at about 75 milligrams about once every two weeks. A flat dose of h5D8 can be administered at about 225 milligrams about once every two weeks. A flat dose of h5D8 can be administered at about 750 milligrams about once every two weeks. A flat dose of h5D8 can be administered at about 1125 milligrams about once every two weeks. A flat dose of h5D8 can be administered at about 1500 milligrams about once every two weeks. A flat dose of h5D8 can be administered at about 2000 milligrams about once every two weeks.

[00112] A flat dose of h5D8 can be administered from about 75 milligrams to about 2000 milligrams about once every three weeks. A flat dose of h5D8 can be administered from about 75 milligrams to about 1500 milligrams about once every three weeks. A flat dose of h5D8 can be administered from about 225 milligrams to about 1500 milligrams, from about 750 milligrams to about 1500 milligrams, from about 1125 milligrams to about 1500 milligrams about once every three weeks. A flat dose of h5D8 can be administered at about 75 milligrams about once every three weeks. A flat dose of h5D8 can be administered at about 225 milligrams about once every three weeks. A flat dose of h5D8 can be administered at about 750 milligrams about once every three weeks. A flat dose of h5D8 can be administered at about 1125 milligrams about once every three weeks. A flat dose of h5D8 can be administered at about 1500 milligrams about once every three weeks. A flat dose of h5D8 can be administered at about 2000 milligrams about once every three weeks.

[00113] A flat dose of h5D8 can be administered from about 75 milligrams to about 2000 milligrams about once every four weeks. A flat dose of h5D8 can be administered from about 75 milligrams to about 1500 milligrams about once every four weeks. A flat dose of h5D8 can be administered from about 225 milligrams to about 1500 milligrams, from about 750 milligrams to

about 1500 milligrams, from about 1125 milligrams to about 1500 milligrams about once every four weeks. A flat dose of h5D8 can be administered at about 75 milligrams about once every four weeks. A flat dose of h5D8 can be administered at about 225 milligrams about once every four weeks. A flat dose of h5D8 can be administered at about 750 milligrams about once every four weeks. A flat dose of h5D8 can be administered at about 1125 milligrams about once every four weeks. A flat dose of h5D8 can be administered at about 1500 milligrams about once every four weeks. A flat dose of h5D8 can be administered at about 2000 milligrams about once every four weeks.

[00114] The h5D8 antibody can be administered at a dose based on the bodyweight or mass of the individual to whom the h5D8 antibody is administered. A body weight adjusted dose of h5D8 can be administered from about 1 mg/kg to about 25 mg/kg. A body weight adjusted dose of h5D8 can be administered from about 3 mg/kg to about 25 mg/kg, from about 10 mg/kg to about 25 mg/kg, from about 15 mg/kg to about 25 mg/kg, or from about 20 mg/kg to about 25 mg/kg. A body weight adjusted dose of h5D8 can be administered at about 1 mg/kg. A body weight adjusted dose of h5D8 can be administered at about 3 mg/kg. A body weight adjusted dose of h5D8 can be administered at about 10 mg/kg. A body weight adjusted dose of h5D8 can be administered at about 15 mg/kg. A body weight adjusted dose of h5D8 can be administered at about 20 mg/kg. A body weight adjusted dose of h5D8 can be administered at about 25 mg/kg.

[00115] A body weight adjusted dose of h5D8 can be administered from about 1 mg/kg to about 25 mg/kg about once every three weeks. A body weight adjusted dose of h5D8 can be administered from about 3 mg/kg to about 25 mg/kg, from about 10 mg/kg to about 20 mg/kg, from about 15 mg/kg to about 25 mg/kg, or from about 20 mg/kg to about 25 mg/kg about once every one, two, three, or four weeks.

[00116] Other bodyweight adjusted doses of h5D8 are contemplated. A body weight adjusted dose of h5D8 can be administered at about 2 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, or 30 mg/kg. Any of these doses can be administered once a week, about once every two weeks, about once every three weeks, or about once every four weeks.

[00117] A body weight adjusted dose of h5D8 can be administered at about 1 mg/kg once a week. A body weight adjusted dose of h5D8 can be administered at about 3 mg/kg once a week. A body weight adjusted dose of h5D8 can be administered at about 10 mg/kg once a week. A body weight adjusted dose of h5D8 can be administered at about 15 mg/kg once a week. A body weight adjusted dose of h5D8 can be administered at about 20 mg/kg once a week. A body weight adjusted dose of h5D8 can be administered at about 25 mg/kg once a week.

[00118] A body weight adjusted dose of h5D8 can be administered at about 1 mg/kg about once every two weeks. A body weight adjusted dose of h5D8 can be administered at about 3 mg/kg about once every two weeks. A body weight adjusted dose of h5D8 can be administered at about 10 mg/kg about once every two weeks. A body weight adjusted dose of h5D8 can be administered at about 15 mg/kg about once every two weeks. A body weight adjusted dose of h5D8 can be administered at about 20 mg/kg about once every two weeks. A body weight adjusted dose of h5D8 can be administered at about 25 mg/kg about once every two weeks.

[00119] A body weight adjusted dose of h5D8 can be administered at about 1 mg/kg about once every three weeks. A body weight adjusted dose of h5D8 can be administered at about 3 mg/kg about once every three weeks. A body weight adjusted dose of h5D8 can be administered at about 10 mg/kg about once every three weeks. A body weight adjusted dose of h5D8 can be administered at about 15 mg/kg about once every three weeks. A body weight adjusted dose of h5D8 can be administered at about 20 mg/kg about once every three weeks. A body weight adjusted dose of h5D8 can be administered at about 25 mg/kg about once every three weeks.

[00120] A body weight adjusted dose of h5D8 can be administered at about 1 mg/kg about once every four weeks. A body weight adjusted dose of h5D8 can be administered at about 3 mg/kg about once every four weeks. A body weight adjusted dose of h5D8 can be administered at about 10 mg/kg about once every four weeks. A body weight adjusted dose of h5D8 can be administered at about 15 mg/kg about once every four weeks. A body weight adjusted dose of h5D8 can be administered at about 20 mg/kg about once every four weeks. A body weight adjusted dose of h5D8 can be administered at about 25 mg/kg about once every four weeks.

[00121] Any of the doses detailed herein can be administered i.v. over a time period of at least about 60 minutes; however, this period can vary somewhat based upon conditions relevant to each individual administration.

[00122] The doses described herein can result in a serum/plasma half-life of h5D8 between about 15 and about 20 days. In certain embodiments, the dosages result in a serum half-life of about 16 to 19 days. In certain embodiments, the dosages result in a serum half-life of about 17 to 18 days. In certain embodiments, dosages of h5D8 administered at 750 milligrams, 1125 milligrams, or 1500 milligrams result in a serum half-life of about 17 or 18 days.

[00123] Any of the dosage amounts described herein can be formulated as a composition for the treatment of a cancer/tumor described herein.

Pharmaceutically acceptable excipients, carriers and diluents

[00124] In certain embodiments, the antibodies of the current disclosure are administered suspended in a sterile solution. In certain embodiments, the solution comprises a physiologically appropriate salt concentration (e.g., NaCl). In certain embodiments, the solution comprises

between about 0.6% and 1.2% NaCl. In certain embodiments, the solution comprises between about 0.7% and 1.1% NaCl. In certain embodiments, the solution comprises between about 0.8% and 1.0% NaCl. In certain embodiments, a highly concentrated stock solution of antibody may be diluted in about 0.9% NaCl. In certain embodiments, the solution comprises about 0.9% NaCl. In certain embodiments, the solution further comprises one or more of: buffers, for example, acetate, citrate, histidine, succinate, phosphate, bicarbonate and hydroxymethylaminomethane (Tris); surfactants, for example, polysorbate 80 (Tween 80), polysorbate 20 (Tween 20),polysorbate and poloxamer 188; polyol/disaccharide/polysaccharides, for example, glucose, dextrose, mannose, mannitol, sorbitol, sucrose, trehalose, and dextran 40; amino acids, for example, histidine, glycine or arginine; antioxidants, for example, ascorbic acid, methionine; and chelating agents, for example, EGTA or EGTA. In certain embodiments, the antibodies of the current disclosure are shipped/stored lyophilized and reconstituted before administration. In certain embodiments, lyophilized antibody formulations comprise a bulking agent such as, mannitol, sorbitol, sucrose, trehalose, and dextran 40. In a certain embodiment, anti-LIF antibodies of this disclosure can be shipped and stored as a concentrated stock solution to be diluted at the treatment site of use. In certain embodiments, the stock solution comprises about 25mM histidine, about 6% sucrose, about 0.01% polysorbate, and about 20mg/mL of anti-LIF antibody. In certain embodiments, the pH of the solution is about 6.0. In certain embodiments, the form administered to an individual is an aqueous solution comprising about 25mM histidine, about 6% sucrose, about 0.01% polysorbate 80, and about 20mg/mL of h5D8 antibody. In certain embodiments, the pH of the solution is about 6.0.

[00125] The h5D8 antibody, described herein, can be included in a kit comprising a vial filled with a sterile solution comprising the h5D8 antibody at a concentration of about 20 mg/mL, about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80. The vial can be a single-use glass vial. The single-use glass vial can be filled with about 10 milliliters of 5D8 antibody at a concentration of about 20 mg/mL h5D8 antibody, about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80. In certain embodiments, the pH of the solution is about 6.0. The h5D8 antibody, described herein, can be included in a kit comprising a vial filled with a lyophilized composition comprising the h5D8 antibody that when reconstituted in an appropriate amount of sterile diluent yields a concentration of about 20 mg/mL h5D8 antibody, about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80. The vial can be a single-use glass vial.

[00126] The antibodies described herein can be administered or prepared or diluted for administration in different ways depending upon the dosage level that is ultimately to be delivered to the patient. This can be done to optimize for example the pharmaceutical properties

of the patient dosage for example to reduce particulate matter. H5D8 can be prepared at a concentration of about 8 mg/mL regardless of ultimate dose delivered to the patient. In certain embodiments, the h5D8 can be prepared at a level of no more than about 10, 9, 8, 7, 6, 5 or 4 mg/mL. In certain embodiments, the h5D8 can be prepared at a level of greater than about 1, 2, 3, 4, 5, 6, or 7 mg/mL.

EXAMPLES

[00127] The following illustrative examples are representative of embodiments of the compositions and methods described herein and are not meant to be limiting in any way.

Example 1-Generation of rat antibodies specific for LIF

[00128] A cDNA encoding amino acids 23-202 of human LIF was cloned into expression plasmids (Aldevron GmbH, Freiburg, Germany). Groups of laboratory rats (Wistar) were immunized by intradermal application of DNA-coated gold-particles using a hand-held device for particle-bombardment ("gene gun"). Cell surface expression on transiently transfected HEK cells was confirmed with anti-tag antibodies recognizing a tag added to the N-terminus of the LIF protein. Serum samples were collected after a series of immunizations and tested in flow cytometry on HEK cells transiently transfected with the aforementioned expression plasmids. Antibody-producing cells were isolated and fused with mouse myeloma cells (Ag8) according to standard procedures. Hybridomas producing antibodies specific for LIF were identified by screening in a flow cytometry assay as described above. Cell pellets of positive hybridoma cells were prepared using an RNA protection agent (RNAlater, cat. #AM7020 by ThermoFisher Scientific) and further processed for sequencing of the variable domains of the antibodies.

Example 2-Generation of mouse antibodies specific for LIF

[00129] A cDNA encoding amino acids 23-202 of human LIF was cloned into expression plasmids (Aldevron GmbH, Freiburg, Germany). Groups of laboratory mice (NMRI) were immunized by intradermal application of DNA-coated gold-particles using a hand-held device for particle-bombardment ("gene gun"). Cell surface expression on transiently transfected HEK cells was confirmed with anti-tag antibodies recognizing a tag added to the N-terminus of the LIF protein. Serum samples were collected after a series of immunizations and tested in flow cytometry on HEK cells transiently transfected with the aforementioned expression plasmids. Antibody-producing cells were isolated and fused with mouse myeloma cells (Ag8) according to standard procedures. Hybridomas producing antibodies specific for LIF were identified by screening in a flow cytometry assay as described above. Cell pellets of positive hybridoma cells were prepared using an RNA protection agent (RNAlater, cat. #AM7020 by ThermoFisher Scientific) and further processed for sequencing of the variable domains of the antibodies.

Example 3-Humanization of rat antibodies specific for LIF

[00130] One clone from the rat immunization (5D8) was chosen for subsequent humanization. Humanization was conducted using standard CDR grafting methods. The heavy chain and light chain regions were cloned from the 5D8 hybridoma using standard molecular cloning techniques and sequenced by the Sanger method. A BLAST search was then conducted against human heavy chain and light chain variable sequences and 4 sequences from each were chosen as acceptor frameworks for humanization. These acceptor frameworks were deimmunized to remove T cell response epitopes. The heavy chain and light chain CDR1, CDR2 and CDR3 of 5D8 were cloned into the 4 different heavy chain acceptor frameworks (H1 to H4), and 4 different light chain frameworks (L1 to L4). Then all 16 different antibodies were tested for: expression in CHO-S cells (Selexis); inhibition of LIF-induced STAT3 phosphorylation; and binding affinity by Surface Plasmon Resonance (SPR). These experiments are summarized in **table 1**.

Table 1 Summary of 5D8 humanization

Heavy chain light chain combination	Inhibition of LIF-induced pSTAT3 from **Fig. 1**	Affinity by SPR K_{D1} (pM)	Expression (ug/mL)
H0L0	+++	133±46	393
H1L1	-	N/A	627
H1L2	+++	55±23	260
H1L3	+++	54±31	70
H1L4	-	N/A	560
H2L1	-	N/A	369
H2L2	+++	52±22	392
H2L3	++	136±19	185
H2L4	-	N/A	78
H3L1	N/A	N/A	No expression
H3L2	N/A	N/A	No expression
H3L3	N/A	N/A	No expression
H3L4	N/A	N/A	No expression
H4L1	-	N/A	259
H4L2	++	913±308	308

H4L3	+		252
H4L4	-	N/A	186
N/A= Not attempted; H0L0=chimeric antibody with full rat heavy and light chain variable regions			

[00131] The expression performance of the transfected cells was compared in Erlenmeyer flasks (seeding $3x10^5$ cells/mL, 200 mL culture volume) within fed-batch cultivation after 10 days of cell culture. At this point cells were harvested and the secreted antibody purified using a Protein A column and then quantitated. All humanized antibodies expressed except those using the H3 heavy chain. The H2 and L2 variable regions performed well compared to other variable regions (SEQ ID NO: 42 and SEQ ID NO: 46).

[00132] Inhibition of LIF-induced STAT3 phosphorylation at tyrosine 705 was determined by western blot. U251 glioma cells were plated in 6-well plates at a density of 100.000 cells/well. Cells were cultured in complete medium for 24 hours before any treatment and after that, cells were serum starved for 8 hours. After that, cells with the indicated antibodies over night at a concentration of 10 µg/ml. After treatment, proteins were obtained in radio-immunoprecipitation assay (RIPA) lysis buffer containing phosphatase and protease inhibitors, quantified (BCA-protein assay, Thermo Fisher Scientific) and used in western blot. For western blot, membranes were blocked for 1 hour in 5% non-fat dried milk - TBST and incubated with the primary antibody overnight (p-STAT3, catalog #9145, Cell Signaling or STAT3, catalog #9132, Cell Signaling) or 30 minutes (β-actin-peroxidase, catalog #A3854, Sigma-Aldrich). Membranes were then washed with TBST, incubated with secondary and washed again. Proteins were detected by chemiluminescence (SuperSignal Substrate, catalog #34076, Thermo Fisher Scientific). These results are shown in **Fig. 1**. The darker the pSTAT3 band the less inhibition is present. Inhibition was high in lanes labeled 5D8 (non-humanized rat), A(H0L0), C (H1L2), D (H1L3), and G (H2L2); inhibition was moderate in H (H2L3), O (H4L2), and P (H4L3); inhibition was absent in B (H1L1), E (H1L4), F (H2L1), I (H2L4), N (H4L1) and Q (H4L4).

[00133] Antibodies that exhibited inhibition of LIF-induced STAT3 phosphorylation were then analyzed by SPR to determine binding affinity. Briefly, binding of the A(H0L0), C (H1L2), D (H1L3), and G (H2L2), H (H2L3) and O (H4L2) humanized antibodies to amine coupled hLIF was observed using a Biacore™ 2002 Instrument. Kinetic constants and affinities were determined by mathematical sensorgram fitting (Langmuir interaction model [A + B = AB]) of all sensorgrams generated on all sensor chip surfaces at six ligand concentrations. The best fitted curves (minimal Chi2) of each concentration were used for calculation of kinetic constants and affinities. *See* **table 1.**

[00134] Since the experimental setup used bivalent antibodies as analytes, best fitted sensorgrams, were also analyzed on basis of a bivalent analyte fitting model [A+B = AB; AB+B = AB2] in order to obtain a more detailed insight into the target binding mechanism of the humanized antibodies. Kinetic sensorgram analysis using a bivalent fitting model [A+B = AB; AB+B = AB2] confirmed the relative affinity ranking of the mAb samples.

[00135] The humanized 5D8 comprising H2 and L2 was selected for more in-depth analysis due to its high binding affinity and high yield from batch culture.

Example 4-Humanization of clone 5D8 improves binding to LIF

[00136] We selected the H2L2 clone (h5D8) for further analysis and compared binding by SPR to the parental rat 5D8 (r5D8) and a mouse clone 1B2. The 1B2 antibody is a previously disclosed mouse anti-LIF antibody previously deposited at the Deutsche Sammlung von Mikroorganismen and Zellkulturen GmbH (DSM ACC3054) and was included for comparison purposes. Recombinant human LIF purified from *E.coli* and HEK-293 cells, respectively, were used as ligands. The LIF from human or *E. coli* sources was covalently coupled to the surface of Biacore optical sensor chips using amine coupling chemistry, and binding affinities were calculated from the kinetic constants.

Materials and methods

[00137] Human LIF from E.coli was obtained from Millipore; reference LIF 1010; human LIF from HEK-293 cells was obtained from ACRO Biosystems, reference LIF-H521b. LIF was coupled to the sensor chips using the Biacore Amine Coupling Kit (BR-1000-50; GE-Healthcare, Uppsala). Samples were run on a Biacore™ 2002 Instrument using CM5 optical sensor chips (BR-1000-12; GE-Healthcare, Uppsala). Biacore HBS-EP buffer was used during the machine runs (BR-1001-88; GE-Healthcare, Uppsala). Kinetic analysis of binding sensorgrams was performed using BIAevaluation 4.1 software. Kinetic constants and affinities were determined by mathematical sensorgram fitting (Langmuir interaction model [A + B = AB]) of all sensorgrams generated on all sensor chip surfaces at increasing analyte concentrations. Sensorgrams were also analyzed on the basis of a bivalent analyte sensorgram fitting model [A+B = AB; AB+B = AB_2], including component analysis, in order to generate an estimate on the bivalent contribution to the determined Langmuir antibody – target affinities (e.g., avidity contribution). The best fitted curves (minimal Chi^2) of each concentration were used for calculation of kinetic constants and affinities. Summaries of these affinity experiments are shown in **table 2** (human LIF made in *E.coli*) and **table 3** (human LIF made in HEK 293 cells).

Table 2 Improved binding of 5D8 after humanization	K_D [pM]	
hLIF (*E. coli*)	Langmuir 1:1 sensorgram fitting	Bivalent analyte fitting

Mouse 1B2	400±210	1500±200
r5D8 (Rat)	130±30	780±130
h5D8 (humanized)	26±14	82±25

Table 3 Improved binding of 5D8 after humanization	K_D [pM]	
hLIF (HEK 293)	Langmuir 1:1 sensorgram fitting	Bivalent analyte fitting
Mouse 1B2	320±150	3900±900
r5D8 (rat)	135±100	410±360
h5D8 (humanized)	13±6	63±30

[00138] The Langmuir 1:1 sensorgram fitting model from this set of experiments indicates that the humanized 5D8 (h5D8) antibody bound with ~10 - 25 times higher affinity to human LIF than mouse 1B2 and r5D8.

[00139] Next, the h5D8 antibody was tested against LIF of multiple species by SPR. h5D8 SPR binding kinetics were performed for recombinant LIF analytes derived from different species and expression systems: human LIF (E.coli, HEK293 cells); mouse LIF (E.coli, CHO cells); rat LIF (E.coli); cynomolgus monkey LIF (yeast, HEK293 cells).

Materials and Methods

[00140] The h5D8 antibody was immobilized to the sensor chip surface by non-covalent, Fc specific capturing. Recombinant, Ig(Fc) specific *S. aureus* Protein A/G was used as capturing agent, allowing sterically uniform and flexible presentation of the anti-LIF antibody to the LIF analytes. Sources of the LIF analytes are as follows: Human LIF (from *E.coli*; Millipore reference LIF 1050); Human LIF (from HEK cells ACRO Biosystems LIF-H521); Mouse LIF (*E. coli*; Millipore Cat. No NF-LIF2010); Mouse LIF (from CHO cells; Reprokine Catalog # RCP09056); Monkey LIF (yeast Kingfisher Biotech Catalog # RP1074Y); Monkey LIF produced in HEK-293 cell. Overall h5D8 exhibited binding to LIF from several species. A summary of this affinity experiment is shown in **table 4.**

Table 4 Broad species reactivity of humanized 5D8	Langmuir 1:1 sensorgram fitting		
Analyte	mean K_a (1/Ms)[10^5]	mean K_d (1/S) [10^{-5}]	mean K_D [pM]
Human LIF (*E.coli*)	8.5 ± 0.7	7.2 ± 0.7	86 ± 9

Human LIF (HEK-293)	5.5 ± 0.02	3.1 ± 0.7	56 ± 13
Mouse LIF (*E.coli*)	21.4 ± 3.7	5.7 ± 1.0	27 ± 6
Mouse LIF(CHO cells)	6.5 ± 0.7	1.1 ± 0.3	17 ± 4
Cyno Monkey LIF (yeast)	6.3 ± 0.8	5.4± 0.7	89 ± 10
Cyno Monkey LIF (HEK-293)	2.4 ± 0.2	3.3± 0.3	134 ± 6

Example 5-Humanized clone 5D8 inhibits LIF-induced phosphorylation of STAT3 in vitro

[00141] To determine the biological activity of h5D8, the humanized and parental versions were tested in a cell culture model of LIF activation. **Fig. 2A** shows that the humanized clone exhibited increased inhibition of STAT3 phosphorylation (Tyr 705) when a glioma cell line was incubated with human LIF. **Fig. 2B** shows an experiment with the same set up of **Fig. 2A** repeated with different dilutions of the h5D8 antibody.

Methods

[00142] U251 glioma cells were plated in 6-well plates at a density of 150,000 cells/well. Cells were cultured in complete medium for 24 hours before any treatment. After that, cells were treated over night or not (control cells) with r5D8 anti-LIF antibody or h5D8 anti-LIF antibody at a concentration of 10 µg/ml.

[00143] After treatment, proteins were obtained in radio-immunoprecipitation assay (RIPA) lysis buffer containing phosphatase and protease inhibitors, quantified (BCA-protein assay, Thermo Fisher Scientific) and used in western blot. For western blot, membranes were blocked for 1 hour in 5% non-fatty milk - TBST and incubated with the primary antibody overnight (p-STAT3, catalog #9145, Cell Signaling or STAT3, catalog #9132, Cell Signaling) or 30 minutes (β-actin-peroxidase, catalog #A3854, Sigma-Aldrich). Membranes were then washed with TBST, incubated with secondary antibody if necessary, and washed again. Proteins were detected by chemiluminescence (SuperSignal Substrate, catalog #34076, Thermo Fisher Scientific).

Example 6-IC_{50} value of h5D8 antibody treatment on endogenous levels of LIF in U-251 cells.

[00144] We also determined an IC_{50} of as low as 490 picomolar (**Fig. 3A**) for biological inhibition for h5D8 under serum starved conditions in U-251 cells. *See* representative results **Fig. 3A** and **3B** and **table 5**.

Table 5

Cell Line Tissue	Cell Line Name	Treatment	IC_{50} (nM)				IC_{90} (nM)	JAK inhibition (%)
Endogenous LIF Condition			n=1	n=2	Mean	SD	Mean	Mean
GBM	U251	h5D8	0.78	0.54	0.66	0.12	4.1	84%
		r5D8	1.6	1.5	1.4	0.15	8.5	86%
			1.2	1.4				

Methods

[00145] The U-251 cells were seeded at 600,000 cells per 6cm plate (per condition). Cells were treated with h5D8 in corresponding concentration (titration) overnight at 37°C, under serum starvation (0.1% FBS). As a positive control for pSTAT3, recombinant LIF (R&D #7734-LF/CF) was used to stimulate the cells at 1.79 nM for 10min at 37°C. As a negative control of pSTAT3, the JAK I inhibitor (Calbiochem #420099) was used at 1uM for 30min at 37°C. Cells were then harvested on ice for lysates following the Meso Scale Discovery Multi-Spot Assay System Total STAT3 (Cat# K150SND-2) and Phospho-STAT3 (Tyr705) (Cat# K150SVD-2) kits' protocol, to measure protein levels detectable by the MSD Meso Sector S600.

Example 7-Additonal antibodies that specifically bind to human LIF

[00146] Other rat antibody clones (10G7 and 6B5) that specifically bind human LIF were identified and a summary of their binding characteristics are shown below in **table 6,** clone 1B2 served as a comparison.

Methods

[00147] Kinetic real time binding analysis was performed for anti-LIF mAbs 1B2, 10G7 and 6B5, immobilized on the surface of CM5 optical sensor chips, applying recombinant LIF target proteins [human LIF (*E.coli*); Millipore Cat. No. LIF 1010 and human LIF (HEK293 cells); ACRO Biosystems Cat. No. LIF-H521b] as analytes.

[00148] Kinetic constants and affinities were obtained by mathematical sensorgram fitting using a Langmuir 1:1 binding model applying global (simultaneous fitting of sensorgram sets) as well as single curve fitting algorithms. Plausibility of global fits was assessed by k_{obs} analysis.

Table 6 Affinity measurements of additional anti-LIF antibodies		Langmuir 1:1 sensorgram fitting		
Analyte	clone	mean K_a (1/Ms)	mean K_d (1/S)	mean K_D [nM]
Human LIF (*E.coli*)	1B2	1.1 ± 0.4E5	1.1 ± 0.3E-3	9.7 ± 1.4
Human LIF (HEK-293)	1B2	2.0 ± 0.04E6	1.4 ± 0.2E-3	0.7 ± 0.03
Human LIF (*E.coli*)	10G7	7.9 ± 5.8E4	6.0 ± 2.3E-4	12.6 ± 9.5
Human LIF (HEK-293)	10G7	3.6 ± 1.75E5	3.1 ± 0.5E-4	1.1 ± 0.6
Human LIF (*E.coli*)	6B5	N/A	N/A	N/A
Human LIF (HEK-293)	6B5	3.6 ± 1.7E5	3.1± 0.5E-4	62 ± 6

Example 8-Additional anti LIF antibodies inhibit LIF-induced phosphorylation of STAT3in vitro

[00149] Additional clones were tested for their ability to inhibit LIF-induced phosphorylation of STAT3 in cell culture. As shown in **Fig. 4** clones 10G7 and the previously detailed r5D8 exhibited high inhibition of LIF-induced STAT3 phosphorylation, compared to the 1B2 clone. Anti-LIF polyclonal anti-sera (pos.) was included as a positive control While 6B5 exhibited no inhibition, this may be explained by a possible lack of 6B5 binding to non-glycosylated LIF which was used in this experiment.

Methods

[00150] Patient derived glioma cells were plated in 6-well plates at a density of 150,000 cells/well. Cells were cultured in GBM medium that consisted of Neurobasal medium (Life Technologies) supplemented with B27 (Life Technologies), penicillin/streptomycin and growth factors (20 ng/ml EGF and 20 ng/ml FGF-2 [PeproTech]) for 24 hours before any treatment. The following day, cells were treated or not with recombinant LIF produced in E. coli or a mix of recombinant LIF plus the indicated antibodies for 15 minutes (final concentration of 10 µg/ml

for the antibodies and 20 ng/ml of recombinant LIF). After treatment, proteins were obtained in radio-immunoprecipitation assay (RIPA) lysis buffer containing phosphatase and protease inhibitors, quantified (BCA-protein assay, Thermo Fisher Scientific) and used in western blot. For western blot, membranes were blocked for 1 hour in 5% non-fatty milk - TBST and incubated with the primary antibody overnight (p-STAT3, catalog #9145, Cell Signaling) or 30 minutes (β-actin-peroxidase, catalog #A3854, Sigma-Aldrich). Membranes were then washed with TBST, incubated with secondary antibody if necessary, and washed again. Proteins were detected by chemiluminescence (SuperSignal Substrate, catalog #34076, Thermo Fisher Scientific).

Example 9- LIF is highly overexpressed across multiple tumor types

[00151] Immunohistochemistry was conducted on multiple human tumor types to determine the degree of LIF expression. As shown in **Fig. 5** LIF is highly expressed in glioblastoma multiforme (GBM), non-small cell lung cancer (NSCLC), ovarian cancer, and colorectal cancer (CRC).

Example 10-Humanized clone h5D8 inhibits tumor growth in a mouse model of non-small cell lung carcinoma

[00152] To determine the ability of the humanized 5D8 clone to inhibit a LIF positive cancer *in vivo* this antibody was tested in a mouse model of non-small cell lung carcinoma (NSCLC). **Fig. 6** shows reduced tumor growth in mice treated with this antibody compared to a vehicle negative control.

Methods

[00153] The murine non-small cell lung cancer (NSCLC) cell line KLN205 with high LIF levels was stably infected with lentivirus expressing the firefly luciferase gene for in vivo bioluminescence monitoring. To develop the mouse model, $5x10^5$ KLN205 non-small cell lung cancer (NSCLC) cells were orthotopically implanted into the left lung of 8-week-old immunocompetent syngeneic DBA/2 mice by intercostal puncture. Mice were treated with a control vehicle or with 15 mg/kg or 30 mg/kg of the h5D8 antibody intraperitoneally twice a week and tumor growth was monitored by bioluminescence. For the bioluminescence imaging, mice received an intraperitoneal injection of 0.2 mL of 15 mg/mL D-luciferin under 1–2% inhaled isoflurane anesthesia. The bioluminescence signals were monitored using the IVIS system 2000 series (Xenogen Corp., Alameda, CA, USA) consisting of a highly sensitive cooled CCD camera. Living Image software (Xenogen Corp.) was used to grid the imaging data and integrate the total bioluminescence signals in each boxed region. Data were analyzed using the total photon flux emission (photons/second) in the regions of interest (ROI). The results demonstrate that treatment with the h5D8 antibody promote tumor regression. Data are

presented as mean ± SEM.

Example 11- h5D8 inhibits tumor growth in a mouse model of glioblastoma multiforme

[00154] In an orthotopic GBM tumor model using a luciferase expressing human cell line U251, r5D8 significantly reduced tumor volumes in mice administered 300 µg r5D8 and h5D8 by intraperitoneal (IP) injection twice a week. Results of this study are shown in **Fig. 7A** (quantitation at day 26 post treatment). This experiment was also conducted using humanized h5D8 mice treated with 200 µg or 300µg showed a statistically significant reduction in tumor after 7 days of treatment.

Methods

[00155] U251 cells stably expressing luciferase were harvested, washed in PBS, centrifuged at 400g for 5min, resuspended in PBS and counted with an automated cell counter (Countess, Invitrogen). Cells were kept on ice to maintain optimal viability. Mice were anaesthetized with intraperitoneal administration of Ketamine (Ketolar50®) / Xylacine (Rompún®) (75 mg/kg and 10 mg/kg respectively). Each mouse was carefully placed in the stereotactic device and immobilized. Hair from the head was removed with depilatory cream, and the head skin was cut with a scalpel to expose the skull. A small incision was carefully made with a drill in the coordinates 1.8 mm lateral and 1mm anterior to the Lambda. 5 µL of cells were inoculated using a Hamilton 30G syringe into the right corpus striatum, at 2.5 mm of depth. Head incision was closed with Hystoacryl tissue adhesive (Braun) and mice were injected with subcutaneous analgesic Meloxicam (Metacam®) (1 mg/kg). The final cell number implanted into each mouse was $3x10^5$.

[00156] Mice were treated twice a week with h5D8 administered intraperitoneally. Treatment was initiated on day 0, immediately after tumor cell inoculation. Mice received a total of 2 doses of h5D8 or vehicle control.

[00157] Body weight and tumor volume: Body weight was measured 2 times/week and tumor growth was quantified by bioluminescence on day 7 (Xenogen IVIS Spectrum). To quantify bioluminescence activity in vivo, mice were anaesthetized using isofluorane, and injected intraperitoneally with luciferin substrate (PerkinElmer) (167 µg/kg).

[00158] Tumor size as determined by bioluminescence (Xenogen IVIS Spectrum) was evaluated at day 7. The individual tumor measurements and mean ± SEM for each treatment group were calculated. Statistical significance was determined by the unpaired non-parametric Mann-Whitney U-test.

Example 12- h5D8 inhibits tumor growth in a mouse model of ovarian cancer

[00159] The efficacy of r5D8 was evaluated in two other syngeneic tumor models. In the ovarian orthotopic tumor model ID8, IP administration of 300 µg r5D8 twice weekly

significantly inhibited tumor growth as measured by abdominal volume (**Fig. 8A** and **8B**). Results in **Fig. 8C** show that h5D8 also reduced tumor volume at a dose of 200 µg and above.

Methods

[00160] ID8 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Gibco, Invitrogen), supplemented with 10% Fetal Bovine Serum (FBS) (Gibco, Invitrogen), 40 U/mL Penicillin and 40 µg/mL Streptomycin (PenStrep) (Gibco, Invitrogen) and 0.25 µg/mL Plasmocin (Invivogen).

[00161] The ID8 cells were harvested, washed in PBS, centrifuged at 400 g for 5min and resuspended in PBS. Cells were kept on ice to maintain optimal viability and 200 µL of the cell suspension was injected intraperitoneally with a 27G needle. The final cell number implanted into mice was $5x10^6$.

[00162] Mice were treated twice weekly with h5D8 administered ip at different doses as indicated. Body weights were measured 2 times/week and tumor progression was monitored by measuring abdominal girth using a caliper (Fisher Scientific).

Example 13- r5D8 inhibits tumor growth in a mouse model of colorectal cancer

[00163] In mice with subcutaneous colon CT26 tumors, r5D8 (administered 300 µg IP twice weekly) significantly inhibited tumor growth (**Fig. 9A** and **9B**).

Methods

[00164] CT26 cells were cultured in Roswell Park Memorial Institute medium (RPMI [Gibco, Invitrogen]), supplemented with 10% Fetal Bovine Serum (FBS), 40 U/mL penicillin and 40 µg/mL streptomycin (PenStrep) and 0.25 µg/mL Plasmocin.

[00165] CT26 cells (8×10^5)were trypsinized, rinsed with PBS, centrifuged at 400 g for 5 minutes and resuspended in 100 µL PBS. Cells were kept on ice to avoid cell death. The CT26 cells were administered to mice via subcutaneous injection using a 27G needle.

[00166] 300 µg r5D8, or vehicle control, was administered to the mice via intraperitoneal injection (IP) twice weekly from day 3 post CT26 cell implant.

[00167] Body weight and tumor volumes were measured three times per week. Tumor volume was measured using a caliper (Fisher Scientific).

Example 14- r5D8 reduces inflammatory infiltration in tumor models

[00168] In the U251 GBM orthotopic model, expression of CCL22, a marker of M2 polarized macrophages, was significantly decreased in tumors treated with r5D8 as shown in **Fig. 10A**. This finding was also confirmed in a physiologically relevant organotypic tissue slice culture model using r5D8 in which three patient samples showed a significant decrease in CCL22 and CD206 (MRC1) expression (also a marker of M2 macrophages) after treatment, as shown in **Fig. 10B** (compare upper, control, to lower, treated, for both MRC1 and CCL22**)**. Furthermore, r5D8

also decreased $CCL22^{+}M2$ macrophages in syngeneic ID8 (**Fig. 10C**) and CT26 (**Fig. 10D**) tumors in immunocompetent mice.

Example 15- r5D8 increases non-myeloid effector cells

[00169] To investigate additional immune mechanisms, the effect of r5D8 on T cells and other non-myeloid immune effector cells within the tumor microenvironment were evaluated. In the ovarian orthotopic ID8 syngeneic model, r5D8 treatment resulted in an increase in intratumoral NK cells and an increase in total and activated $CD4^{+}$and $CD8^{+}$T cells as shown in **Fig. 11A**. Similarly, in the colon syngeneic CT26 tumor model, r5D8 increased intratumoral NK cells, increased CD4+and CD8+T cells and trended to decrease $CD4^{+}CD25^{+}FoxP3^{+}$T-reg cells as shown in **Fig. 11B**. A trend for a decrease in $CD4^{+}CD25^{+}FoxP3^{+}$T-reg cells was also observed in the syngeneic orthotopic KLN205 tumor model following r5D8treatment as shown in **Fig. 11C**. Consistent with a requirement for T cells to mediate efficacy, depletion of $CD4^{+}$and $CD8^{+}$T cells in the CT26 model inhibited the anti-tumor efficacy of r5D8 as shown in **Fig. 12**.

Methods for T cell depletion

[00170] CT26 cells were cultured in RPMI culture medium (Gibco, Invitrogen), supplemented with 10% Fetal Bovine Serum (FBS [Gibco, Invitrogen]), 40 U/mL penicillin and 40 µg/mL streptomycin (PenStrep [Gibco, Invitrogen]) and 0.25 µg/mL Plasmocin (Invivogen). CT26 cells (5×10^5) were collected, rinsed with PBS, centrifuged at 400 g for 5 minutes and resuspended in 100 µL PBS. Cells were kept on ice to avoid cell death. The CT26 cells were administered in both flanks to mice via subcutaneous injection using a 27G syringe. Mice were treated twice weekly with r5D8 administered intraperitoneally as indicated in the study design. Vehicle control (PBS), rat r5D8, and/or anti-CD4 and anti-CD8 was administered to the mice via intraperitoneal injection (IP) twice weekly as stated in the study design. All antibody treatments were administered concomitantly.

Example 16-Crystal structure of h5D8 in complex with human LIF

[00171] The crystal structure of h5D8 was solved to a resolution of 3.1 angstroms in order to determine the epitope on LIF that h5D8 was bound to and to determine residues of h5D8 that participate in binding. The co-crystal structure revealed that the N-terminal loop of LIF is centrally positioned between the light and heavy chain variable regions of h5D8 (**Fig. 13A**). In addition, h5D8 interacts with residues on helix A and C of LIF, thereby forming a discontinuous and conformational epitope. Binding is driven by several salt-bridges, H-bonds and Van der Waals interactions (**Table 7**, **Fig. 13B**). The h5D8 epitope of LIF spans the region of interaction with gp130. *See* Boulanger, M.J., Bankovich, A.J., Kortemme, T., Baker, D. & Garcia, K.C. Convergent mechanisms for recognition of divergent cytokines by the shared signaling receptor gp130. *Molecular cell* 12, 577-589 (2003). The results are summarized below in **table 7** and

depicted in **Fig. 13**.

Table 7 Summary of X-Ray crystal structure for h5D8 in complex with human LIF		
LIF Residue (epitope)	Interaction type	h5D8 Residue (paratope, Kabat numbering)
Ala13	VDW	L-Tyr49, L-Asn53
Ile14-O	HB	L-Ser50-OG
Ile	VDW	L-His30, L-Tyr32, L-Tyr49, L-Ser50
		H-Trp97
Arg15-NE	SB	L-Glu55-OE1, L-Glu55-OE2
Arg15-NH1	SB	L-Glu55-OE1, L-Glu55-OE2
Arg15-NH2	SB	L-Glu55-OE1, L-Glu55-OE2
Arg15-O	HB	L-Asn34-ND2
Arg15	VDW	L-Asn34, L-Leu46, L-Tyr49, L-Glu55, L-Ser56
		H-Glu96, H-Trp97, H-Asp98, H-Leu99, H-Asp101
His16-NE2	SB	H-Asp101-OD2
His16	VDW	L-Tyr32, L-Asn34, L-Met89
		H-Trp95, H-Glu96, H-Trp97, H-Asp101
Pro17	VDW	L-Tyr32, L-Ala91
		H-Trp97
Cys18	VDW	L-Tyr32
		H-Trp33, H-Trp97
His19-NE2	SB	H-Glu96-OE1, H-Glu96-OE2
His19	VDW	H-His31, H-Trp33, H-Glu96
Asn20-OD1	HB	H-Lys52-NZ
Asn20-ND2	HB	H-Asp53-OD1
Asn20	VDW	H-Trp33, H-Lys52, H-Asp53
Gln25-NE2	HB	H-Asp53-OD2
Gln25	VDW	H-His31, H-Ser52C, H-Asp53
Gln29	VDW	H-His31
Gln32	VDW	H-Lys52B
Asp120-OD2	HB	H-Ser30-OG
Asp120	VDW	H-Thr28, H-Ser30
Arg123-NE	HB	H-Thr28-OG
Arg123	VDW	H-Thr28
Gly124	VDW	H-His31
Leu125	VDW	H-His31
Ser127-OG	HB	H-Asp98-OD2
Ser127-O	HB	H-Trp97-NE1
Ser127	VDW	H-His31, H-Trp97, H-Asp98
Asn128-OD1	HB	H-His31-NE2

Asn128	VDW	H-His31
Leu130	VDW	H-Trp97
Cys131	VDW	H-Trp97
Cys134	VDW	H-Trp97
Ser135-O	HB	L-His30-NE2
Ser135	VDW	L-His30
His138	VDW	L-His30
VDW, Van der Waals low energy binding; **HB**, hydrogen bond (medium energy binding); **SB**, salt bridge (high energy binding)		

Methods

[00172] LIF was transiently expressed in HEK 293S (Gnt I$^{-/-}$) cells and purified using Ni-NTA affinity chromatography, followed by gel-filtration chromatography in 20 mM Tris pH 8.0 and 150 mM NaCl. The recombinant h5D8 Fab was transiently expressed in HEK 293F cells and purified using KappaSelect affinity chromatography, followed by cation exchange chromatography. Purified h5D8 Fab and LIF were mixed at a 1:2.5 molar ratio and incubated at room temperature for 30 min prior to deglycosylation using EndoH. Gel-filtration chromatography was subsequently used to purify the complex. The complex was concentrated to 20 mg/mL and set up for crystallization trials using sparse matrix screens. Crystals formed at 4°C in a condition containing 19% (v/v) isopropanol, 19% (w/v) PEG 4000, 5% (v/v) glycerol, 0.095 M sodium citrate pH 5.6. The crystal diffracted to a resolution of 3.1 Å at the 08ID-1 beamline at the Canadian Light Source (CLS). Data were collected, processed and scaled using XDS as per Kabsch et al. Xds. *Acta crystallographica. Section D, Biological crystallography* 66, 125-132 (2010).Structures were determined by molecular replacement using Phaser as per McCoy et al. Phaser crystallographic software. *J Appl Crystallogr* 40, 658-674 (2007). Several iterations of model building and refinement were performed using Coot and phenix.refine until the structures converged to an acceptable R_{work} and R_{free}. *See* Emsley et al. Features and development of Coot. *Acta crystallographica. Section D, Biological crystallography* 66, 486-501 (2010); and Adams, et al. PHENIX: a comprehensive Python-based system for macromolecular structure solution. *Acta crystallographica. Section D, Biological crystallography* 66, 213-221 (2010) respectively. The figures were generated in PyMOL (The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC).

Example 17- h5D8 has high specificity for LIF

[00173] We sought to test binding of h5D8 to other LIF family members to determine the binding specificity. Using Octet96 analysis h5D8 binding to human LIF is approximately 100-fold greater than binding to LIFs highest homology IL-6 family member Oncostatin M (OSM) when both proteins are produced in *E. coli*. When both proteins are produced in a mammalian

system h5D8 exhibits no binding to OSM. Data are summarized in **table 8**.

Table 8 Summary of h5D8 Affinity Measurements for Cytokines as Measured by Octet

	KD [M]	kon [1/Ms]	kdis [1/s]
h5D8 + huLIF (E. coli)	4.3E-10 +/- 2.0E-11	3.1E+05 +/- 3.1E+03	1.3E-04 +/- 5.8E-06
h5D8 + huLIF (mammalian)	1.3E-09 +/- 7.2E-11	1.2E+05 +/- 1.3E+03	1.5E-04 +/- 8.5E-06
h5D8 + huOSM (E. coli)	3.6E-08 +/- 1.4E-09	8.5E+04 +/- 3.1E+03	3.1E-03 +/- 4.1E-05
h5D8 + huOSM (mammalian)	ND	ND	ND
h5D8 + huIL-6 (E. coli)	ND	ND	ND

ND = no binding

Methods

[00174] Octet Binding Experiments: Reagents were used and prepared as per manufacturer's provided manual. A Basic Kinetics Experiment was performed using Octet Data Acquisition software ver. 9.0.0.26 as follows: Setup of sensors/program: i) Equilibration (60 seconds); ii) Loading (15 seconds); iii) Baseline (60 seconds); iv) Association (180 seconds); and v) Dissociation (600 seconds)

[00175] Octet Affinity of h5D8 for cytokines: A Basic Kinetics Experiment was performed using Octet Data Acquisition software ver. 9.0.0.26 as follows: Amine Reactive 2ndGeneration Biosensors (AR2G) were hydrated for a minimum of 15 minutes in water. Amine conjugation of h5D8 to the biosensors was performed according to ForteBio Technical Note 26 (please see References) using the Amine Coupling Second Generation Kit. Dip steps were as performed at 30°C, 1000rpm as follows: i) 60 seconds Equilibration in water; ii) 300 seconds Activation in 20mM ECD, 10mM sulfo-NHS in water; iii) 600 second Immobilization of 10 µg/ml h5D8 in 10mM Sodium Acetate, pH 6.0; iv) 300 seconds Quench in 1M Ethanolamine, pH 8.5; v) 120 seconds Baseline in water. Kinetics experiments were then performed with the following Dip and Read steps at 30°C, 1000rpm: vi) 60 seconds Baseline in 1X kinetics buffer; vii) 180 seconds Association of appropriate serial dilutions of a cytokine in 1X kinetics buffer; viii) 300 seconds Dissociation in 1X kinetics buffer; ix) Three Regeneration/Neutralization cycles alternating between 10mM glycine pH 2.0 and 1X kinetics buffer respectively (5 seconds in each for 3 cycles). Following regeneration, the biosensors were reused for subsequent binding analyses.

[00176] Human recombinant LIF produced from mammalian cells was from ACROBiosystems

(LIF-H521b); human recombinant OSM produced in mammalian cells was from R & D (8475-OM/CF); and human recombinant OSM produced in *E. coli* cells was from R & D (295-OM-050/CF).

Example 18- Crystal structure of h5D8 fab

[00177] Five crystal structures of the h5D8 Fab under a wide spectrum of chemical conditions were determined. The high resolutions of these structures indicate that the conformations of CDR residues are associated with minor flexibility, and are highly similar in different chemical environments. A unique feature of this antibody is the presence of a non-canonical cysteine in position 100 of the variable heavy region. Structure analysis shows that the cysteine is unpaired and largely inaccessible to the solvent.

[00178] H5D8 Fab was obtained by papain digestion of its IgG, followed by purification using standard affinity, ion exchange and size chromatography techniques. Crystals were obtained using vapor diffusion methods and allowed to determine five crystal structures ranging between 1.65 Å to 2.0 Å in resolution. All structures were solved in the same crystallographic space group and with similar unit cell dimensions (P212121, a~53.8 Å, b~66.5 Å, c~143.3 Å), despite crystallization conditions ranging across five different pH levels: 5.6, 6.0, 6.5, 7.5 and 8.5. As such, these crystal structures allow for comparison of the three-dimensional disposition of h5D8 Fab unimpeded by crystal packing artefacts and across a wide spectrum of chemical conditions.

[00179] Electron density was observed for all complementarity determining region (CDR) residues, which were subsequently modeled. Noticeably, LCDR1 and HCDR2 adopted elongated conformations that together with shallow LCDR3 and HCDR3 regions formed a binding groove at the center of the paratope (**Fig. 14A**). The five structures were highly similar across all residues, with all-atoms root mean square deviations ranging between 0.197 Å and 0.327 Å (**Fig. 14A**). These results indicated that the conformations of CDR residues were maintained in various chemical environments, including pH levels ranging between 5.6 and 8.5 and ionic strengths ranging between 150 mM and 1 M. Analysis of the electrostatic surface of the h5D8 paratope revealed that positively and negatively charged regions equally contributed to hydrophilic properties, with no prevalent hydrophobic patches. h5D8 has the uncommon feature of a non-canonical cysteine at the base of HCDR3 (Cys100). In all five structures, this free cysteine is ordered and does not form any disulfide scrambles. Additionally, it is not modified by the addition of Cys (cysteinylation) or glutathione (glutathiolation) and makes Van der Waals interactions (3.5-4.3 Å distances) with main chain and side chain atoms of Leu4, Phe27, Trp33, Met34, Glu102 and Leu105 of the heavy chain (**Fig. 14B**). Finally, Cys100 is a predominantly buried structural residue that appears to be involved in mediating the conformations of CDR1 and HCDR3. It is thus unlikely to have reactivity with other cysteines, as observed by a

homogeneous disposition of this region in our five crystal structures.

Methods

[00180] H5D8-1 IgG was obtained from Catalent Biologics and was formulated in 25 mM histidine, 6% sucrose, 0.01% polysorbate 80, at pH 6.0. The formulated IgG was extensively buffer-exchanged into PBS using a 10K MWCO concentrator (Millipore) prior to digestion with 1:100 microgram papain (Sigma) for 1 hour at 37°C in PBS, 1.25 mM EDTA, 10 mM cysteine. The papain-digested IgG was flown through a Protein A column (GE Healthcare) using an AKTA Start chromatography system (GE Healthcare). The Protein A flow-through, which contained the h5D8 Fab was recovered and buffer-exchanged into 20 mM sodium acetate, pH 5.6 using a 10K MWCO concentrator (Millipore). The resulting sample was loaded onto a Mono S cation exchange column (GE Healthcare) using an AKTA Pure chromatography system (GE Healthcare). Elution with a gradient of 1 M potassium chloride resulted in a predominant h5D8 Fab peak that was recovered, concentrated and purified to size homogeneity using a Superdex 200 Increase gel filtration column (GE Healthcare) in 20 mM Tris-HCl, 150 mM sodium chloride, at pH 8.0. The high purity of the h5D8 Fab was confirmed by SDS-PAGE under reducing and non-reducing conditions.

[00181] Purified h5D8 Fab was concentrated to 25 mg/mL using a 10K MWCO concentrator (Millipore). An Oryx 4 dispenser (Douglas Instruments) was used to set up vapor diffusion crystallization experiments with sparse matrix 96-conditions commercial screens JCSG TOP96 (Rigaku Reagents) and MCSG-1 (Anatrace) at 20°C. Crystals were obtained and harvested after four days in the following five crystallization conditions: 1) 0.085 M sodium citrate, 25.5% (w/v) PEG 4000, 0.17 M ammonium acetate, 15% (v/v) glycerol, pH 5.6; 2) 0.1 M MES, 20% (w/v) PEG 6000, 1 M lithium chloride, pH 6.0; 3) 0.1 M MES, 20% (w/v) PEG 4000, 0.6 M sodium chloride, pH 6.5; 4) 0.085 M sodium HEPES, 17% (w/v) PEG 4000, 8.5% (v/v) 2-propanol, 15% (v/v) glycerol, pH 7.5; and 5) 0.08 M Tris, 24% (w/v) PEG 4000, 0.16 M magnesium chloride, 20% (v/v) glycerol, pH 8.5. Prior to flash-freezing in liquid nitrogen, mother liquors containing the crystals were supplemented with 5-15% (v/v) glycerol or 10% (v/v) ethylene glycol, as required. Crystals were subjected to X-ray synchrotron radiation at the Advanced Photon Source, beamline 23-ID-D (Chicago, IL) and diffraction patterns were recorded on a Pilatus3 6M detector. Data were processed using XDS and structures were determined by molecular replacement using Phaser. Refinement was carried out in PHENIX with iterative model building in Coot. Figures were generated in PyMOL. All software were accessed through SBGrid.

Example 19- Mutations at Cysteine 100 of h5D8 preserve binding

[00182] Analysis of h5D8 revealed a free cysteine residue at position 100 (C100) in the

variable region of the heavy chain. H5D8 variants were generated by substituting C100 with each naturally occurring amino acid in order to characterize binding to and affinity for human and mouse LIF. Binding was characterized using ELISA and Octet assay. Results are summarized in **table 9.** ELISA EC50 curves are shown in **Fig. 15** (**Fig.15A** human LIF and **Fig. 15B** Mouse LIF).

Table 9 Summary of affinities determined by Octet assay and EC50 determined by ELISA

Mutation	Affinity/ k_D (M)		Binding EC50 (nM)	
	human LIF	mouse LIF	human LIF	mouse LIF
C100	<1.0E-12 ± 2.252E-11	9.946E-11 ± 8.272E-12	0.09878	0.1605
C100S	8.311E-10 ± 5.886E-11	2.793E-09 ± 5.925E-11	n.d.	n.d.
C100Q	3.87E-09 ± 1.55E-10	2.84E-09 ± 4.85E-11	10.18	26.33
C100N	5.59E-09 ± 1.01E-10	6.68E-09 ± 9.8E-11	13.18	45.87
C100E	2.67E-09 ± 4.64E-11	4.1E-09 ± 7.56E-11	7.179	25.3
C100D	2.02E-09 ± 8.08E-11	6.49E-09 ± 7.16E-11	11.89	22.88
C100T	4.36E-10 ± 2.1E-11	1.02E-09 ± 1.77E-11	5.575	8.753
C100G	2.49E-09 ± 4.2E-11	3.33E-09 ± 5.42E-11	21.94	40.17
C100P	2.74E-10 ± 2.97E-10	<1.0E-12 ± 7.64E-10	34.44	101.9
C100A	<1.0E-12 ± 2.713E-11	<1.0E-12 ± 1.512E-11	0.6705	0.9532
C100V	<1.0E-12 ± 1.805E-11	<1.0E-12 ± 8.086E-12	0.2785	0.3647
C100L	<1.0E-12 ± 1.963E-11	1.998E-10 ± 1.055E-11	0.454	0.547
C100I	<1.0E-12 ± 1.424E-11	3.361E-11 ± 7.545E-12	0.299	0.3916
C100M	1.155E-09 ± 3.400E-11	2.676E-09 ± 2.449E-11	0.7852	1.563
C100F	4.376E-09 ± 1.127E-10	1.147E-08 ± 9.099E-11	8.932	21.53
C100Y	1.444E-08 ± 1.159E-09	2.514E-08 ± 2.047E-09	n.d.	n.d.
C100W	2.508E-08 ± 7.036E-09	4.819E-08 ± 4.388E-09	n.d.	n.d.
C100H	1.304E-10 ± 1.416E-10	4.284E-09 ± 1.231E-10	8.254	n.d.
C100K	7.477E-08 ± 1.581E-09	6.053E-08 ± 2.589E-09	n.d.	n.d.
C100R	1.455E-07 ± 6.964E-09	5.142E-08 ± 3.247E-09	n.d.	n.d.

Methods

ELISA: Binding of h5D8 C100 variants to human and mouse LIF was determined by ELISA. Recombinant human or mouse LIF protein was coated on Maxisorp 384-well plates at 1 ug/mL overnight at 4°C. Plates were blocked with 1x blocking buffer for 2 hours at room temperature. Titrations of each h5D8 C100 variants were added and allowed to bind for 1 hour at room temperature. Plates were washed three times with PBS+0.05% Tween-20. HRP-conjugated anti-human IgG was added and allowed to bind for 30 min at room temperature. Plates were washed three times with PBS+0.05% Tween-20 and developed using 1x TMB substrate. The reaction was stopped with 1M HCl and absorbance at 450 nm was measured. Generation of figures and non-linear regression analysis was performed using Graphpad Prism.

[00183] Octet RED96: The affinity of h5D8 C100 variants to human and mouse LIF was

determined by BLI using the Octet RED96 system. h5D8 C100 variants were loaded onto Anti-Human Fc biosensors at 7.5 ug/mL following a 30 second baseline in 1x kinetics buffer. Titrations of human or mouse LIF protein were associated to the loaded biosensors for 90 seconds and allowed to dissociate in 1x kinetics buffer for 300 seconds. KDs were calculated by the data analysis software using a 1:1 global fit model.

Example 20- h5D8 blocks binding of LIF to gp130 in vitro

[00184] To determine whether h5D8 prevented LIF from binding to LIFR, a molecular binding assay using the Octet RED 96 platform was performed. H5D8 was loaded onto AHC biosensors by anti-human Fc capture. Then, the biosensors were dipped in LIF and, as expected, association was observed (**Fig. 16A**, middle third). Subsequently, the biosensors were dipped in different concentrations of LIFR. A dose-dependent association was observed (**Fig. 16A,** right third). The control experiment demonstrated that this association was LIF-specific (not shown), and not due to a non-specific interaction of LIFR with h5D8 or with the biosensors.

[00185] To further characterize the binding of h5D8 and LIF, a series of ELISA binding experiments was conducted. H5D8 and LIF were pre-incubated and were then introduced to plates coated with either recombinant human LIFR (hLIFR) or gp130. The lack of binding between the h5D8/LIF complex and the coated substrate would indicate that h5D8 in some way disrupted the binding of LIF to the receptor. Additionally, control antibodies that either did not bind LIF (isotype control, indicated by (-)) or that bind LIF at known binding sites (B09 does not compete with either gp130 or LIFR for LIF binding; r5D8 is the rat parental version of h5D8) were also used. The ELISA results demonstrated that the h5D8/LIF complex was able to bind hLIFR (as was r5D8/LIF complex), indicating that these antibodies did not prevent the LIF/LIFR association (**Fig. 16A**). In contrast, the h5D8/LIF complex (and a r5D8/LIF complex) was not able to bind recombinant human gp130 (**Fig. 16B**). This indicates that the gp130 binding site of LIF was affected when LIF was bound to h5D8.

Example 21- LIF and LIFR expression in human tissues

[00186] Quantitative real-time PCR was performed on many different types of human tissue in order to determine expression levels of LIF and LIFR. The mean expression levels shown in **Fig. 17A** and **17B** are given as copies per 100ng of total RNA. Most tissues expressed at least 100 copies per 100ng of total RNA. LIF mRNA expression was highest in human adipose tissue (mesenteric-ileum [1]), blood-vessel tissue (choroid-plexus [6] and mesenteric [8]) and umbilical cord [68] tissue and lowest in brain tissue (cortex [20] and substantia-nigra [28]). LIFR mRNA expression was highest in human adipose tissue (mesenteric-ileum [1]), blood vessel tissue (pulmonary [9]), brain tissue [11-28] and thyroid [66] tissue and was lowest in PBMCs [31]. LIF and LIFR mRNA expression levels in cynomolgus tissues were similar to

those observed in human tissues, wherein LIF expression was high in adipose tissue and LIFR expression was high in adipose tissue and low in PBMCs (data not shown).

[00187] The tissue numbering for **Fig. 17A** and **Fig. 17B** is: 1 – adipose (mesenteric-ileum); 2 - adrenal gland; 3 - bladder; 4 - bladder (trigone); 5 - blood-vessel (cerebral: middle-cerebral-artery); 6 – blood vessel (choroid-plexus); 7 – blood vessel (coronary artery); 8 – blood vessel (mesenteric (colon)); 9 – blood vessel (pulmonary); 10 – blood vessel (renal); 11 – brain (amygdala); 12 - brain (caudate); 13 - brain (cerebellum); 14 brain – (cortex: cingulate-anterior); 15 - brain (cortex: cingulate-posterior); 16 - brain (cortex: frontal-lateral); 17 - brain (cortex: frontal-medial); 18 - brain (cortex: occipital); 19 - brain (cortex: parietal); 20 – brain (cortex: temporal); 21 - brain (dorsal-raphe-nucleus); 22 - brain (hippocampus); 23 - brain (hypothalamus: anterior); 24 - brain (hypothalamus: posterior); 25 - brain (locus coeruleus); 26 - brain (medulla oblongata); 27 – brain (nucleus accumbens); 28 - brain (substantia nigra); 29 - breast; 30 - caecum; 31- peripheral blood mononuclear cell (PBMCs); 32 - colon; 33 – dorsal root ganlia (DRG); 34 - duodenum; 35 – fallopian tube; 36 - gallbladder; 37 – heart (left atrium); 38 - heart (left ventricle); 39 - ileum;40 - jejunum;41 – kidney (cortex); 42 - kidney (medulla);43 - kidney (pelvis); 44 - liver (parenchyma); 45 - liver (bronchus: primary); 46 - liver (bronchus: tertiary); 47 - lung (parenchyma); 48 – lymph gland (tonsil); 49 - muscle (skeletal); 50 - esophagus; 51 - ovary; 52 - pancreas; 53 - pineal gland; 54 – pituitary gland; 55 - placenta; 56 - prostate; 57 - rectum; 58 - skin (foreskin); 69 – spinal cord; 60 - spleen (parenchyma); 61 - stomach (antrum); 62 - stomach (body); 63 - stomach (fundus); 64 - stomach (pyloric canal); 65 - testis; 66 – thyroid gland; 67 - trachea; 68 – umbilical cord; 69 - ureter; 70 – uterus (cervix); 71 - uterus (myometrium); and 72 – vas deferens.

Example 22-Dose selection, dose increments, and flat dosing

[00188] Anti-LIF antibody dose selection, dose increments and flat dosing are described below. Mice and cynomolgus monkeys were used for the safety evaluation of h5D8.

[00189] No treatment-related adverse effects were observed in 4-week GLP toxicity studies in mice and monkeys which received weekly IV dosing up to 100 mg/kg. Thus, the highest non-severely toxic dose (HNSTD) is >100 mg/kg and the no-observed-adverse-effect-level (NOAEL) was established as 100 mg/kg IV in both species under the conditions of the studies. The dosage was scaled to establish a human equivalent dose (HED). A body surface area (BSA)-based scaling approach was adopted for the estimation of the HED. Based on these GLP toxicology studies a maximum recommended starting dose (MRSD) was estimated as shown below:

- 0.81 mg/kg IV HED from mouse NOAEL with 10-fold safety factor
- >10 mg/kg IV based on 1/10 the severely toxic dose in mice
- 3.2 mg/kg IV HED from cynomolgus monkey NOAEL with 10-fold safety factor

- >16.7 mg/kg IV based on 1/6 the HNSTD

Based on the toxicology studies, and taking a conservative approach for an advanced cancer patient population in the Phase 1 study, a MRSD of 1 mg/kg (or 75 mg flat dose) IV was supported by the data.

[00190] The pharmacologically active dose (PAD) has also been considered in setting the MRSD. Based on pharmacology, PK and LIF stabilization data in mouse pharmacology models available to date, the following approach was used to estimate the PAD. Based on the dose-*response in the U251 mouse xenograft model, the optimal efficacious dose was considered to be* about 300 μg IP twice weekly; this dose level was associated with a trough serum level before the last dose of about 230 μg/mL. There was evidence that maximal stabilization of serum LIF levels had been achieved at this 300 μg dose in this model, which was also supported by serum LIF stabilization data in the mouse GLP toxicity study at doses of 10, 30 and 100 mg/kg. Using a PK model based on a 2-compartmental model fitted to the monkey PK data and scaled for humans, a clinical dose of 1500 mg every 3 weeks would provide a C_{trough} of about 500 μg/mL. Similarly, the minimally effective dose of 20 μg twice weekly in this U251 mouse xenograft model was associated with a trough serum level before the last dose of about 20 μg/mL; there was evidence that only about 50% of maximal serum LIF stabilization was achieved at this 20-μg dose, supported by evidence of minimal LIF stabilization at a dose of 0.5 mg/kg IV in the mouse PK-tolerability study. A clinical dose of 75 mg every 3 weeks would provide a C_{trough} of about 25 μg/mL. Additional PK-PD (LIF stabilization) data available from mouse syngeneic models supported the PAD derived from the U251 mouse xenograft model.

[00191] Thus, a starting dose of 75 mg i.v. was considered appropriate based on both the toxicology data in mice and monkeys and the minimal effective dose in a mouse xenograft model. A maximum clinical dose of 1500 to 2000 mg was supported by the toxicology data. A flat-dosing approach was appropriate based on the observation of a linear PK in animal models, in conjunction with the absence of test-article related adverse findings.

Example 23-Phase 1 dose escalation and dose expansion study for h5D8

[00192] A phase 1 clinical study was instituted to establish a safety profile and proper dosing of h5D8 in monotherapy against a cross-section of cancers. Primary objectives were to: 1) evaluate the safety and tolerability of h5D8 in patients with advanced solid tumors; 2) determine the recommended dose for h5D8 monotherapy; and 3) assess the preliminary anti-tumor activity, as measured by Overall Response Rate (ORR), of h5D8 according to RECIST 1.1 criteria. Secondary objectives were to: characterize the PK and immunogenicity of h5D8; and 2) assess efficacy parameters in patients with advanced solid tumors, including Disease Control Rate (DCR) and Progression Free Survival (PFS) by RECIST 1.1. Exploratory objectives were to: 1)

explore the relationships between pharmacokinetics, pharmacodynamics and h5D8 exposure to patient safety and anti-tumor activity; b) assess whether high tumor LIF expression correlates with anti-tumor activity of h5D8; c) characterize pharmacodynamic effects of h5D8 in the periphery and in the tumor and d) characterize impact of h5D8 treatment on exploratory biomarkers.

[00193] The study was designed as an open-label, Phase 1 study and enrolled advanced solid tumor patients. The study was and is being conducted in an accelerated-titration 3 + 3 design with flat dosing of h5D8 administered intravenously once Q3W (at dose cohorts of 75 mg, 225 mg, 750 mg, 1125 mg, and 1500 mg).

[00194] Anti-tumor response was designed to be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines. Assessments were designed to be performed at baseline and every 6 weeks for first 6 months and then every 12 weeks thereafter until confirmed progression of disease or patient withdrawal. Adverse events were designed to be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, and to be assessed continuously during the study and for 30 days after the last treatment.

[00195] 41 patients have been enrolled and dosed. Patient demographics are shown in **table 10**.

Table 10	Cohorts 1-5
Median Age (Range)	64.5 (36-78)
Gender, N (%)	
Male	20 (50%)
Female	20 (50%)
Race, N(%)	
Caucasian	33 (82.5%)
Black	4 (10%)
Asian	2 (5%)
Other	1 (2.5%)
Tumor type, N (%)	
Pancreatic	13 (31.7%)
Ovarian	5 (12.2%)
Colorectal	3 (7.3%)
Prostate	3 (7.3%)
Appendiceal	2 (4.9%)
Cholangiocarcinoma	3 (4.9%)
Nasopharyngeal	4 (4.9%)
NSCLC	5 (4.9%)
Rectal	6 (4.9%)
Squamous Cell	7 (4.9%)
Adenoid cystic carcinoma (ACC)	1 (2.4%)
Melanoma	1 (2.4%)
Mestatic mixoid liposarcoma	1 (2.4%)
Paraganglioma	1 (2.4%)
Uterine Cancer	1 (2.4%)

[00196] For the trial dose limiting toxicities (DLTs) were defined as: 1) those that were observed during 21 Days post Cycle 1, Day 1 as assessed by the Principal Investigator in agreement with the data review committee (DRC) as possibly related to h5D8; 2) any drug-related Grade ≥ 3 adverse event (AE). AEs with a clear-cut alternative explanation and pre-specified, self-limited Grade 3 AEs were deemed non-DLT, including: 1) fatigue, nausea, vomiting or diarrhea that resolves to Grade ≤2 within 72hrs with appropriate medical therapy; 2) transient (lasting ≤ 72 hrs) Grade 3 biochemical abnormalities that are considered clinically insignificant; 3) grade 3 neutropenia lasting ≤ 72 hrs; and 4) grade 3 thrombocytopenia without clinically significant bleeding. A drug-related AE of any grade that delays the start of Cycle 2, day 1 > 14 days may be considered a DLT by the DRC. The safety summary from Cohorts 1 to 5 to date is shown in **table 11**.

Table 11 Safety Summary

	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Cohort 5**	**Total**
Number of Subjects with Adverse Events (AEs)	2 (N = 2)	1 (N = 1)	10 (N = 10)	8 (N=10)	6 (N = 11)	27 (79.4%) (N = 34)
Number of Subjects with Grade ≥ 3 AEs	2 (10)	0	6 (11)	1 (1)	1 (1)	10 (23) (29.4%)
Number of Subjects with h5D8 Related AEs:	0	1 (2)	4 (8)	3 (9)	3 (5)	11 (24) (32.4%)
SAEs	8	0	8	0	2	18
h5D8 Related SAEs	0	0	0	0	0	0
Fatal AEs	1	0	1	0	0	2
Infusion Related AEs	0	1	1	0	0	2
DLTs during C1 (21d)	0	0	0	0	0	0
Delayed DLTs	0	0	0	0	0	0
AEs Causing h5D8 Interruption	0	0	1	1	0	2

AES Causing h5D8 Discontinuation	0	0	1	0	0	1
AES causing h5D8 Dose modification	0	0	0	0	0	0

[00197] There have been no dose-limiting toxicities or tolerability issues observed at any dose. Overall the data show that h58 is safe and well-tolerated at all doses tested.

Example 24-Case Studies of patients treated with h5D8

[00198] Subject 0106-002 is a 68 year old white female with Stage IV Pancreatic cancer heavily pre-treated with 4 lines of prior systemic anti-cancer therapy for metastatic disease. Subject was initially diagnosed with stage II/III moderate to poorly differentiated pancreatic ductal adenocarcinoma. Subject was treated with neoadjuvant FLOFIRINOX for about 167 days and achieved a partial response. Subject underwent "curative" laparascopic distal pancreatectomy and splenectomy followed by adjuvant Gemcitabine for about 7 months when Subject developed recurrent progressive disease in the pancreatic bed. Subject was treated with Gemcitabine and Abraxane for about 2 months with a best response of partial response followed by progressive disease in the pancreatic bed and peritoneal lymph nodes. Subject then received 5FU and Onivyde (liposomal irinotecan) for about 2 weeks which was discontinued for toxicity. For about 2 months, Subject was treated with an investigational Wnt Inhibitor (Samumed) and had progressive disease with malignant lymphadenopathy above and below the diaphragm. For about 4 months, Subject received a pyrimidine nucleoside metabolic inhibitor (Fujiflim) with best response being a partial response. Subject had confirmed radiologic progression as well as increasing CA19-9 and entered the h5D8 trial. The results of her prior treatments, prior to the h5D8 trial are summarized in **table 13**. (PR= partial response; PD= progressive disease; SD= stabile disease)

Table 12

Palliative Anti-cancer Therapy	**Duration of Therapy prior to PD**	**Best Response**	**CA19-9 at start of Treatment**	**CA19-9 at Best Response**	**CA19-9 at PD**
Gemcitabine/Abraxane	2 months	PR	63	UNK	97
Wnt Inhibitor	2 months	PD	1088	NA	4195
Pyrimidine Nucleoside Inhibitor	4 months	PR	4195	1249	1658

[00199] Subject received her first dose of h5D8 at 1125 mg and the most recent dose was Cycle 9 (C9) (1500 mg) about 165 days later. At baseline Subject had no clinically significant laboratory abnormalities; Eastern Cooperative Oncology Group ("ECOG") status = 1; an

elevated CA19-9 of 1658. Two lymph nodes (one chest and one abdominal) were identified as target lesions, and abdominal lymphadenopathy was identified as a non-target lesion. At cycle 3, day 1 ("C3D1"), her ECOG status improved to 0, the CA19-9 had fallen to 1069, and overall RECIST response was stable disease. Historically the CA19-9 has been a reliable predictive marker of disease. Per the physician, the use of oxycodone as needed for abdominal pain was no longer necessary. Subject received cycle 6 and about 2 weeks later, the patient's analgesic requirement increased and Subject was hospitalized remote from the site. Currently Subject is back to baseline requiring twice daily narcotic analgesia. Subject had repeat scans and showed stable disease. Her CA19-9 increased at cycle 5 but at cycle 9 returned to below baseline and below the initial decline at cycle 3. The results are shown in **table 13**. The Subject has experienced no adverse events from the treatment.

Table 13

Tumor Markers	**Baseline**	**C3**	**C5**	**C7**	**C9**
CA 19-9 (U/mL)	1658	1069	1224	1397	1045.8
RECIST Target Lesion	**Baseline**	**C3**	**C5**	**C7**	**C9**
Chest	15mm	17mm	14mm	14mm	13mm
Abdomen	19mm	19mm	20mm	18mm	15mm
Sum of LDs	34mm	36mm	34mm	32mm	28mm
Non-target Lesion					
Abdomen	Present	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD
New Lesion	NA	No	No	No	No
Overall Response	NA	Stable Disease	Stable Disease	Stable Disease	Stable Disease

[00200] Subject 0102-001 is a 78 year old white female with stage IV Uterine Leiomyosarcoma heavily pre-treated with 6 lines of systemic anti-cancer therapy. Subject was initially diagnosed with T1B uterine leiomyosarcoma and underwent curative TAH/BSO. Local recurrence occurred about 3 years after initial diagnosis, which was treated with surgical resection; chemoradiation was declined. Subject recurred again about 2 years later and was treated with 4 cycles of Gemcitabine and Docetaxel with a mixed response. Subject then received 3 cycles of Doxil, with a best response of progressive disease. This was followed by 2 months of Vinorelbine with a best response of PD. Trabectidin was administered for about 4 months with a mixed response and was discontinued due to toxicity. Subject was then treated with 4 months of DTIC with PD as best response. Subject received radiotherapy (XRT) to the dominant pelvic

masses for a total of 3750cGy in 10 fractions for about 22 days, and subsequently Votrient for about 1 month with PD as the best response. The results of her prior treatments are shown in **table 14**.

Table 14		
Palliative Anti-cancer Therapy	**Duration of Therapy prior to PD**	**Best Response**
Gemcitabine/Docetaxel	3 months	Mixed
Doxorubicin	2 months	PD
Vinorelbine	2 months	PD
Trabectidin	D/C for toxicity	Mixed
DTIC	4 months	PD
Votrient	2 months	PD

[00201] At baseline Subject had no clinically significant laboratories; ECOG =1, and an elevated CA-125 of 13. Subject received her first dose of h5D8 at 750mg and her CA-125 had decreased to 9 by C3. At the C5 assessment, her CA-125 was 8 and the overall RECIST response was stable disease.

[00202] From her baseline scan, one (1) lung lesion, 1 liver lesion, 2 rectus muscle lesions and 1 pelvic cul de sac lesion were identified as target lesions, and a peritoneal lesion was identified as a non-target lesion. At the C7 assessment, her CA-125 was 9 and Subject had an overall RECIST response of stable disease. C7 images of the 3 target lesions and the previous radiation therapy ports are shown in **Figs. 18A-C**. And the above results are shown in **table 15**.

Table 15					
Tumor Markers	**Baseline**	**C3**	**C5**	**C7**	**EOT**
CA-125 (U/mL)	13	9	8	9	10
RECIST Target Lesion	**Baseline**	**C3**	**C5**	**C7**	**EOT**
Lung	13.4mm	17.7mm	15.7mm	20.0mm	27.1mm
Liver	14.9mm	14.5mm	17.7mm	18.1mm	22.6mm
Rectus M #1	39.1mm	37.6mm	38.0mm	37.8mm	40.1mm
Rectus M#2	31.9mm	26.6mm	22.7mm	24.3mm	28.5mm
Cul de Sac	36.9mm	28.3mm	24.9mm	25.0mm	25.0mm
Sum of LDs	136.2mm	124.7mm	119mm	125.2mm	143.3mm
Non-target Lesion					
Peritoneal nodule	Present	Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD	NE
New Lesion	NA	No	No	No	No
Overall Response	NA	Stable Disease	Stable Disease	Stable Disease	Progressive Disease

[00203] Subject 0101-001 is a 50 year while female with stage IV KRAS + Colorectal Carcinoma receiving first-line systemic anti-cancer therapy for metastatic disease. Subject was initially diagnosed with Stage III moderately differentiated colorectal adenocarcinoma (T3N2M0). Subject underwent curative robotic low anterior resection followed by adjuvant 5FU and FOLFOX for about 7 months. Subject recurred with lung metastases about 2 years later and opted for expectant management and has received no palliative systemic therapy for her Stage IV disease. About 1 year after the recurrence, the lung metastases continued to progress. The Subject refused first line chemotherapy for mCRC and opted for the h5D8 clinical trial as her first line therapy.

[00204] Subject received her first dose of h5D8 at 225mg and her most recent dose was C6 (750mg) about 4 months later. At baseline, Subject had no clinically significant laboratory abnormalities; ECOG status = 0; an elevated tumor marker (CEA) of 11.8. Two (2) right lower lobe lung lesions were identified as target lesions, and 2 non-target lesions (ovary and bone) were identified. At the C3 assessment the response was stable disease and the CEA had risen to 11.8. At the C5 assessment Subject had stable disease followed by radiological progression after C6 treatment. The results are shown in **table 16**.

Table 16

Tumor Markers	**Baseline**	**C3**	**C5**	**EOT**
CEA	10.5	11.8	17.9	20.1
RECIST Target Lesion	**Baseline**	**C3**	**C5**	**EOT**
Lung #1	12.8mm	13.9mm	15.7mm	18.6mm
Lung #2	11.7mm	12.1mm	12.7mm	13.5mm
Sum of LDs	24.5mm	26mm	28.4mm	32.1mm
Non-target Lesion				
Bone	Present	Non-CR Non-PD	Non-CR Non-PD	Not reported
Ovary	Present	Non-CR Non-PD	Non-CR Non-PD	Not reported
New Lesion	NA	No	No	No
Overall Response	NA	Stable Disease	Stable Disease	Progressive Disease

[00205] Subject 0106-005 is a 75 year old white female with fallopian tube carcinoma. Subject underwent curative TAH BSO, LN dissection and debulking, followed by adjuvant Carboplatin and Taxol. Subject recurred about 5 years later with malignant adenopathy and received palliative radiotherapy (55cGy) to LNs at the aortic bifurcation. Subject had LN progression and received palliative radiotherapy (60cGy) to the periaortic LNs. Subject developed lung

metastases and was treated with an investigational BET inhibitor for about 1 month, which was discontinued due to toxicity followed by an investigational anti-PD-1 for about 4 months, with a best response of stable disease. Subject was then treated with an investigational TIGIT inhibitor for about 200 days, with a best response of stable disease. Following progression, Subject was treated with an investigational monoclonal antibody for about 4 months, with a best response of stable disease. Subject had confirmed progression and entered the h5D8 trial. The results of her prior treatments are shown in **table 17**.

Table 17		
Palliative Anti-cancer Therapy	**Duration of Therapy prior to PD**	**Best Response**
Anti-PDL-1	16 months	SD
TIGIT Inhibitor	7 months	SD
Pyrimidine Nucleoside Inhibitor	4 months	SD

[00206] Subject received her first dose of h5D8 at 750mg; at C4 2 months later, the dose of h5D8 cycle was increased to 1125mg. Her last dose (C6) was given about 44 days after this dose escalation. Subject had radiologic progression about 1 month after treatment and had her EOT visit. At baseline, Subject had no clinically significant laboratory abnormalities and an ECOG performance status = 1. Subject expressed no tumor markers in the blood. Two lung lesions (one in the right upper lobe and one at the left thoracic inlet) were chosen as target lesions, multiple pulmonary nodules were selected as non-target lesions. Subject experienced no treatment related adverse events. The results of these trials are shown in **table 18**.

Table 18				
Target Lesion	**Baseline**	**Cycle 3**	**Cycle 5**	**EOT**
RUL	20mm	20mm	22mm	28mm
Left Thoracic Inlet	36mm	40mm	41mm	44mm
Sum of LDs	56mm	60mm	63mm	72mm
Non-target Lesion				
Pulmonary nodules	Present	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD
New Lesion	NA	No	No	No
Overall Response	NA	Stable Disease	Stable Disease	Progressive Disease

[00207] Subject 0301-002 is a 66 year old white female diagnosed with ovarian cancer. Subject was treated with neo-adjuvant Carboplatin and Taxol followed by a curative hysterectomy, BSO and omentectomy about 4 months later and additional Carboplatin/Taxol for about an additional 3 months. Subject recurred in about 8 months and received palliative chemotherapy with Carboplatin/Taxol for about 6 months; the best response is not reported. Subject had radiologic progression about 3 months after this chemotherapy and was treated with Doxorubicin for about 7 months, with a best response of stable disease; Subject progressed again about 4 months later.

Subject then received single agent Taxol for about 3 months, with a best response of progressive disease. For about 6 months, Subject was treated with Gemcitabine and Carboplatin with a best response of stable disease. Subject demonstrated radiologic progression about 3 months after this treatment and entered the h5D8 trial. The results from her prior treatments are shown in **table 19**.

Table 19		
Palliative Anti-cancer Therapy	**Duration of Therapy prior to PD**	**Best Response**
Carboplatin/Taxol	9 months	UNKNOWN
Doxorubicin	11 months	SD
Taxol	2 – 3 months	PD
Carboplatin/Gemcitabine	5 months	NOT EVALUABLE

[00208] Subject received her first dose of h5D8 at 1500mg. Her most recent dose C7 was about 5 months later. At baseline, Subject had no clinically significant laboratory abnormalities and an ECOG performance status = 0. Her CA-125 was 412.3 at baseline. Three lesions (1 pancreatic implant, 1 soft tissue in the hypochondrium and 1 pleural nodules) were chosen as target lesions, and 3 non-target lesions were identified (liver, peritoneum and retroperitoneal lymph nodes). Subject experienced no treatment related adverse events. The results of her trial are shown in **table 20**.

Table 20				
Tumor Markers	**Baseline**	**Cycle 3**	**Cycle 5**	**Cycle 7**
CA 125	412.3	Not done	1071.7	1613.6
Target Lesion	**Baseline**	**Cycle 3**	**Cycle 5**	**Cycle 7**
Right pleural nodule	24mm	25mm	25mm	26mm
Hypochondrium ST mass	51mm	52mm	52mm	61mm
Pancreatic implant	32mm	30mm	32mm	57mm
Sum of LDs	107mm	107mm	109mm	144
Non-target Lesion				
Liver segment V	Present	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD
Peritoneal	Present	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD
Retroperitoneal LNs	Present	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD
New Lesion	NA	No	No	No
Overall Response	NA	Stable Disease	Stable Disease	Progressive Disease

[00209] Subject 0102-004 is a 65year old white female diagnosed with Head and Neck cancer. Subject underwent a curative total glossectomy followed by adjuvant radiotherapy (6000cGy) one month later. Subject recurred about 10 months later with lung metastases which were

irradiated (5000cGy) for about 1 week. There was progression of lung disease and new bone metastases in 8 months after irradiation and the Subject was treated with ipilimumab and nivolumab for about 1 year and 45 days, with a best response of stable disease. Subject had radiologic progression and entered the h5D8 trial. The results of her prior treatment are shown in **table 21**.

Table 21		
Palliative Anti-cancer Therapy	**Duration of Therapy prior to PD**	**Best Response**
Ipilimumab/Nivolumab	13 months	SD

[00210] Subject received her first dose of h5D8 at 1500mg, and the most recent C7 dosing about 155 days later. At baseline Subject had no clinically significant laboratory abnormalities and an ECOG performance status = 1. Subject expressed no peripheral tumor serum markers. Four lesions (2 lung and 2 pleural lesions) were chosen as target lesions, and two bone lesions were identified as non-target lesions. The results are shown in **table 22**.

Table 22				
Target Lesion	**Baseline**	**Cycle 3**	**Cycle 5**	**Cycle 7**
RLL	37mm	35.4mm	36.3mm	39.4mm
RUL	37.8mm	36.8mm	37.2mm	40.8mm
Pleura	13.3mm	13.6mm	13.9mm	14.3mm
Pleura	37.3mm	37.5mm	38.4	38.6mm
Sum of LDs	125.4mm	123.3mm	125.8	133.1
Non-target Lesion				
Bone	Present	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD
Bone	Present	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD
New Lesion	NA	No	No	No
Overall Response	NA	Stable Disease	Stable Disease	Stable Disease

[00211] Subject 0201-003 is a 57year old white male diagnosed with a myxoid liposarcoma. Subject was treated with neoadjuvant Adriamycin and Ifosfamide for about 4 months and neoadjuvant radiotherapy (5000cGy) to the right calf for about 35 days. Subject then underwent a curative wide resection of the right calf, dissection of the right posterior tibial nerve and popliteal, anterior and posterior tibial and peroneal vessels. Subject recurred with pleural disease and malignant lymphadenopathy in the chest. Subject was treated with Gemcitabine and Taxotere for about 41 days, the best response progressive disease. Subject was then treated with Dacarbazine for 4 months, with a best response of partial response. Subject had radiologic progression 22 days later and entered the h5D8 trial. The results of his prior treatments are shown in **table 23**.

Table 23		
Palliative Anti-cancer Therapy	**Duration of Therapy prior to PD**	**Best Response**
Gemcitabine/Taxotere	1 month	PD

DTIC	4 months	PR

[00212] Subject received his first dose of h5D8 1125 mg, and his most recent dose (C6) (1500mg) about 136 days later. At baseline, Subject had no clinically significant laboratory abnormalities, and his ECOG performance status was 1. Subject has no peripheral tumor markers. Two pleural masses were selected as target lesions, and three non-target lesions were selected (1 pleural mass and 2 LNS). The results are shown in **table 24**. Subject has experienced no treatment related adverse events.

Table 24			
Target Lesion	**Baseline**	**Cycle 3**	**Cycle 5**
Right inferior pleural mass	110mm	106mm	103mm
Right superior pleural mass	56mm	61mm	64mm
Sum of LDs	166mm	167mm	167mm
Non-target Lesion			
Right pleural mass	Present	Non-CR Non-PD	Non-CR Non-PD
R epiphrenic LN	Present	Non-CR Non-PD	Non-CR Non-PD
R paratracheal LN	Present	Non-CR Non-PD	Non-CR Non-PD
New Lesion	NA	No	No
Overall Response	NA	Stable Disease	Stable Disease

Example 25-Biomarkers indicating positive response to h5D8 treatment

[00213] Subject 0201-003 is a 57year old white male diagnosed with a myeloid liposarcoma. The results from his current treatment regime are shown in **table 23**. Subject's h5D8 C5 assessment at 12 weeks showed no increases by RECIST criteria of his bulky lung metastatic target lesion (167mm). *See* **table 24**. Subject is on the treatment regime (+14 weeks) and the best response recorded has been "stable disease." A biopsy was collected from a metastatic lung site to determine biomarkers for h5D8 treatment. At the time the biopsy was taken, Subject showed evidence of saturated LIF stabilization. LIF stabilization of Subject 0201-003 is shown in **Fig. 19.**

[00214] Biomarkers for anti-tumor immunity were observed in the "on-treatment" biopsy relative to pre-h5D8 treatment. The results are shown in **Figs. 20A-C**. The results show an increase in CD8 positive T cell infiltration and also an increase in tumor-associated macrophage ("TAM") populations. *See* **Fig. 20A**. The TAMs showed an immunostimulatory phenotype (MHCII+). *See* **Fig. 20B**. A decrease in pSTAT3+ nuclei was also observed. *See* **Fig. 20C.**

[00215] Subject 0301-003 is a 47 year old female with stage IV retroperitoneal paraganglioma. The results of her treatments prior to h5D8 treatment are shown in **table 25**.

Table 25		
Palliative Anti-cancer Therapy	**Duration of Therapy prior to PD**	**Best Response**
Cyclophosphamide/Vincristine/Dacarbazine	2 years	PR
Selective RET Inhibitor	5 months	SD
Octreotide	4 months	SD

Her h5D8 C3 assessment at 6 weeks showed stable CEA levels (0.5 ng/ml) and"stable disease" by RECIST criteria of the lung and liver metastatic target lesions. Patient remains on the treatment regime (+11 weeks) and the best response recorded has been "stable disease." A biopsy was collected from a metastatic liver site to determine biomarkers for h5D8 treatment. LIF stabilization data not processed at this time.

Biomarkers for anti-tumor immunity were observed in the "on-treatment" biopsy relative to pre-h5D8 treatment. The results are shown in **Figs. 21A-C**. The results showed an increase in CD8 positive T cell infiltration. *See* **Fig. 21A**, and reduced TAM polarization towards suppressive phenotypes (CD163+; CD206+). *See* **Fig. 21B**. A decrease in pSTAT+ nuclei was also observed. *See* **Fig. 21C**.

Subject 0301-004 is a 74 year old male with stage IV pancreatic adenocarcinoma. Subject had two treatments prior to h5D8 treatment. The results of his prior treatment are shown in **table 26**.

Table 26		
Palliative Anti-cancer Therapy	**Duration of Therapy prior to PD**	**Best Response**
Gemcitabine-NAB Paclitaxel	3 months	PR
FOLFOX	2 months	PD

[00216] Subject 0301-004 had very aggressive cancer, essentially rapidly failing the two first line treatment therapies given at the time of tumor occurrence, including immediate progressive disease state on FOLFOX. Subject is on the h5D8 treatment regime (6 weeks). A biopsy was collected from a metastatic liver site. LIF stabilization data not processed at this time.

[00217] Biomarkers for anti-tumor immunity were observed in the "on-treatment" biopsy relative to pre-h5D8 treatment. The results are shown in **Fig. 22**. Immunohistochemistry resulted in the Subject being characterized as LIF^{low}. Despite rapid disease progression on highly aggressive chemotherapy regime, expansion of CD8+ T-cell populations were observed in the tumor microenvironment. *See* **Fig. 22**. Modest effects on macrophage populations were observed (data not shown). And no difference in pSTAT3+ nuclei was observed (data not shown).

[00218] Subject 0201-004 is a 66 year old male diagnosed with stage IV melanoma. Subject was administered one treatment prior to the h5D8 trial. The best response was not evaluable and the results are not shown (Nivolumab; 4 months). The failed Nivolumab treatment indicated profound tumor immune suppression. Subject is on the treatment regime (6 weeks) and the best

response recorded has been "progressive disease." A biopsy was collected from a metastatic skin site. At the time the biopsy was collected, a generally higher level of LIF was observed in the Subject via stabilization assay with no evidence of saturation of LIF stabilization. The results of the LIF stabilization assay are shown in **Fig. 23**.

[00219] Biomarkers for anti-tumor immunity were observed in the "on-treatment" biopsy relative to pre-h5D8 treatment. The results are shown in **Fig. 24**. Immunohistochemistry resulted in the Subject being characterized as LIF^{high}. The macrophage analysis was limited to the tumor microenvironment (TME) and showed little change in T-cell activity (data not shown).An increased macrophage phenotype polarization was observed in MHCII+. *See* **Fig. 24**. Preliminary results of manual pathology indicate that pSTAT3+ nuclei are decreased in on-treatment sample.

[00220] Subject 0301-002 is a 66 year old white female diagnosed with ovarian cancer. The results from her current treatment regime are shown in **table 19**. Subject's h5D8 C5 assessment at 12 weeks showed an increase in CA19-9 (412 to 1072 U/ml) but her target lesions showed no significant increases by RECIST criteria (107 to 109 mm). *See* **table 20**. Subject is on the treatment regime (+16 weeks) and the best response recorded has been "stable disease." A biopsy was collected from a metastatic lymph node site to determine biomarkers for h5D8 treatment. At the time the biopsy was taken, the Subject showed evidence of saturated LIF stabilization. LIF stabilization of Subject 0201-003 is shown in **Fig. 25.**

[00221] Biomarkers for anti-tumor immunity were observed in the "on-treatment" biopsy relative to pre-h5D8 treatment. No observable changes in tumor immunology biomarkers (data not shown). Immunohistochemistry resulted in Subject being characterized as LIF^{low}.

[00222] A summary of the above results of assays to determine biomarkers for effective h5D8 treatment is shown in **table 27**. Multiple parameters demonstrate h5D8 treatment's effects on increased anti-tumor immunology, TAM modulation, and LIF signaling. (NC= no change; NE= no effect).

Table 27

Tumor Type	**Biopsy site**	**Dose (mg)**	**Status**	**CD8 Infiltration**	**TAM skewing**	**pSTAT3**
Paraganglioma	Liver	1125	+11 weeks	+	- in M2	-
Myxoid liposarcoma	Lung	1125	+14 weeks	++	++ in M1	NC
Pancreatic	Liver	1125	6 weeks	+	NC	NC
Melanoma	Skin	1125	6 weeks	-	+/-	-

Ovarian	Lymph-node	1500	+16 weeks	-	NE	NE

Example 26-PK/PD of h5D8 in subjects administered hD5

[00223] To determine pharmacokinetics of the h5D8 antibody in humans the level of h5D8 was measured in the serum of treated patients from the trial. Briefly, the quantification of h5D8 antibody in human serum samples was performed by a sandwich immunoassay. The h5D8 antibody in patient serum samples was captured on rhuLIF (recombinant human LIF) coated MSD plates and detected with a sulfo-labeled anti-human IgG (sulfo-anti-h5d8-Fab2-IgG) antibody. The sulfo signal was measured by the MSD reader S600 and quantified using an h5D8 standard curve. The results as shown in **Fig. 26** revealed that h5D8 exhibited standard pharmacokinetics with an estimated half-life of about 17 days. Further, the results show h5D8 exhibits linear PK over a dosage range of 750 – 1500 mg q3weekly and saturation of target-mediated drug disposition occurs at above 225 mg.

[00224] To determine if the target LIF was engaged by the h5D8 antibody a capture ELISA assay was used to determine total LIF levels after treatment. The half-life of LIF is relatively short in the plasma, and increases upon binding by h5D8 leading to increased plasma LIF levels. Thus, an increase of LIF levels in the periphery indicates target engagement. **Figs. 27A-B** show a time-course of total LIF levels in multiple patients after receiving i.v. administration of h5D8. Overall the data shows target saturation after three cycles of drug administration at non-saturating dose levels (cohorts 2-3). *See* **Fig. 27B**.

[00225] Total LIF levels in patient serum samples were quantified by sandwich immunoassay. Briefly, MSD plates were spot coated with the anti-LIF A4 capture antibody (rabbit monoclonal). After incubation with patient serum samples the bound LIF/h5D8 complex was detected by the Sulfo-tagged anti-LIF antibody 7C3 PB001. Sulfo signals were measured by the MSD reader S600 and patient serum LIF/h5D8 levels were quantified using the rhLIF/h5D8 standard curve.

[00226] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[00227] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be

incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

SEQUENCES

SEQ ID NO	Sequence
1	GFTFSHAWMH
2	GFTFSHAW
3	HAWMH
4	QIKAKSDDYATYYAESVKG
5	IKAKSDDYAT
6	TCWEWDLDF
7	WEWDLDF
8	TSWEWDLDF
9	RSSQSLLDSDGHTYLN
10	QSLLDSDGHTY
11	SVSNLES
12	SVS
13	MQATHAPPYT
14	EVQLVESGGGLVKPGGSLKLSCAAS
15	QVQLQESGGGLVKPGGSLRLSCAAS
16	EVQLVESGGGVVQPGRSLRLSCAAS
17	EVQLMESGGGLVKPGGSLRLSCATS
18	WVRQAPGKGLEWVA
19	WVRQAPGKGLEWVG
20	RFTISRDDSKNTLYLQMNSLKTEDTAVYYC
21	RFSISRDNAKNSLYLQMNSLRVEDTVVYYC
22	RFTISRDDSKSTLFLQMNNLKTEDTAVYYC
23	WGQGTLVTVSS
24	WGQGTMVTVSS
25	WGQGTTVTVSS
26	DVVMTQSPLSLPVTLGQPASISC
27	DIVMTQTPLSSPVTLGQPASISC
28	DIVMTQTPLSLSVTPGQPASISC
29	DVVMTQSPLSQPVTLGQPASISC
30	WFQQRPGQSPRRLIY
31	WLQQRPGQPPRLLIY
32	WLLQKPGQPPQLLIY
33	WLQQRPGQSPRRLIY
34	GVPDRFSGSGSGTDFTLKISRVEAEDVGLYYC
35	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC
36	GVPNRFSGSGSGTDFTLKISRVEAEDVGLYYC
37	GVPDRFNGSGSGTDFTLSISRVEAEDVGVYYC
38	FGQGTKLEIK
39	FGGGTKVEIK
40	FGQGTKVEIK
41	EVQLVESGGGLVKPGGSLKLSCAASGFTFSHAWMHWVRQAPGKGLEWVAQIKAKSDDYATYYAESVKGRFTISRD DSKNTLYLQMNSLKTEDTAVYYCTCWEWDLDFWGQGTLVTVSS

42	QVQLQESGGGLVKPGGSLRLSCAASGFTFSHAWMHWVRQAPGKGLEWVGQIKAKSDDYATYYAESVKGRFTISR DDSKNTLYLQMNSLKTEDTAVYYCTCWEWDLDFWGQGTMVTVSS
43	EVQLVESGGGVVQPGRSLRLSCAASGFTFSHAWMHWVRQAPGKGLEWVAQIKAKSDDYATYYAESVKGRFSISR DNAKNSLYLQMNSLRVEDTVVYYCTCWEWDLDFWGQGTTVTVSS
44	EVQLMESGGGLVKPGGSLRLSCATSGFTFSHAWMHWVRQAPGKGLEWVGQIKAKSDDYATYYAESVKGRFTISR DDSKSTLFLQMNNLKTEDTAVYYCTCWEWDLDFWGQGTLVTVSS
45	DVVMTQSPLSLPVTLGQPASISCRSSQSLLDSDGHTYLNWFQQRPGQSPRRLIYSVSNLESGVPDRFSGSGSG TDFTLKISRVEAEDVGLYYCMQATHAPPYTFGQGTKLEIK
46	DIVMTQTPLSSPVTLGQPASISCRSSQSLLDSDGHTYLNWLQQRPGQPPRLLIYSVSNLESGVPDRFSGSGAGTDFTL KISRVEAEDVGVYYCMQATHAPPYTFGQGTKLEIK
47	DIVMTQTPLSLSVTPGQPASISCRSSQSLLDSDGHTYLNWLLQKPGQPPQLLIYSVSNLESGVPNRFSGSGSGTDFTL KISRVEAEDVGLYYCMQATHAPPYTFGGGTKVEIK
48	DVVMTQSPLSQPVTLGQPASISCRSSQSLLDSDGHTYLNWLQQRPGQSPRRLIYSVSNLESGVPDRFNGSGSGTDF TLSISRVEAEDVGVYYCMQATHAPPYTFGQGTKVEIK
49	MGWTLVFLFLLSVTAGVHSEVQLVESGGGLVKPGGSLKLSCAASGFTFSHAWMHWVRQAPGKGLEWVAQIKAK SDDYATYYAESVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTCWEWDLDFWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
50	MGWTLVFLFLLSVTAGVHSQVQLQESGGGLVKPGGSLRLSCAASGFTFSHAWMHWVRQAPGKGLEWVGQIKAK SDDYATYYAESVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTCWEWDLDFWGQGTMVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
51	MGWTLVFLFLLSVTAGVHSEVQLVESGGGVVQPGRSLRLSCAASGFTFSHAWMHWVRQAPGKGLEWVAQIKAK SDDYATYYAESVKGRFSISRDNAKNSLYLQMNSLRVEDTVVYYCTCWEWDLDFWGQGTTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
52	MGWTLVFLFLLSVTAGVHSEVQLMESGGGLVKPGGSLRLSCATSGFTFSHAWMHWVRQAPGKGLEWVGQIKAK SDDYATYYAESVKGRFTISRDDSKSTLFLQMNNLKTEDTAVYYCTCWEWDLDFWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
53	MVSSAQFLGLLLLCFQGTRCDVVMTQSPLSLPVTLGQPASISCRSSQSLLDSDGHTYLNWFQQRPGQSPRRLIYSVS NLESGVPDRFSGSGSGTDFTLKISRVEAEDVGLYYCMQATHAPPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
54	MVSSAQFLGLLLLCFQGTRCDIVMTQTPLSSPVTLGQPASISCRSSQSLLDSDGHTYLNWLQQRPGQPPRLLIYSVS NLESGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQATHAPPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
55	MVSSAQFLGLLLLCFQGTRCDIVMTQTPLSLSVTPGQPASISCRSSQSLLDSDGHTYLNWLLQKPGQPPQLLIYSVSN LESGVPNRFSGSGSGTDFTLKISRVEAEDVGLYYCMQATHAPPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
56	MVSSAQFLGLLLLCFQGTRCDVVMTQSPLSQPVTLGQPASISCRSSQSLLDSDGHTYLNWLQQRPGQSPRRLIYSVS NLESGVPDRFSGSGSGTDFTLSISRVEAEDVGVYYCMQATHAPPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC

57	EVQLVESGGGLVKPGGSLKLSCAASGFTFSHAWMHWVRQAPGKGLEWVAQIKAKSDDYATYYAESVKGRFTISRD DSKNTLYLQMNSLKTEDTAVYYCTCWEWDLDFWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
58	QVQLQESGGGLVKPGGSLRLSCAASGFTFSHAWMHWVRQAPGKGLEWVGQIKAKSDDYATYYAESVKGRFTISR DDSKNTLYLQMNSLKTEDTAVYYCTCWEWDLDFWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
59	EVQLVESGGGVVQPGRSLRLSCAASGFTFSHAWMHWVRQAPGKGLEWVAQIKAKSDDYATYYAESVKGRFSISR DNAKNSLYLQMNSLRVEDTVVYYCTCWEWDLDFWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
60	EVQLMESGGGLVKPGGSLRLSCATSGFTFSHAWMHWVRQAPGKGLEWVGQIKAKSDDYATYYAESVKGRFTISR DDSKSTLFLQMNNLKTEDTAVYYCTCWEWDLDFWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
61	DVVMTQSPLSLPVTLGQPASISCRSSQSLLDSDGHTYLNWFQQRPGQSPRRLIYSVSNLESGVPDRFSGSGSGTDFT LKISRVEAEDVGLYYCMQATHAPPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
62	DIVMTQTPLSSPVTLGQPASISCRSSQSLLDSDGHTYLNWLQQRPGQPPRLLIYSVSNLESGVPDRFSGSGAGTDFTL KISRVEAEDVGVYYCMQATHAPPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
63	DIVMTQTPLSLSVTPGQPASISCRSSQSLLDSDGHTYLNWLLQKPGQPPQLLIYSVSNLESGVPNRFSGSGSGTDFTL KISRVEAEDVGLYYCMQATHAPPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
64	DVVMTQSPLSQPVTLGQPASISCRSSQSLLDSDGHTYLNWLQQRPGQSPRRLIYSVSNLESGVPDRFSGSGSGTDFT LSISRVEAEDVGVYYCMQATHAPPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
65	**BLANK**
66	QVQLQESGGGLVKPGGSLRLSCAASGFTFSHAWMHWVRQAPGKGLEWVGQIKAKSDDYATYYAESVKGRFTISR DDSKNTLYLQMNSLKTEDTAVYYCT**S**WEWDLDFWGQGTMVTVSS
67	QVQLQESGGGLVKPGGSLRLSCAASGFTFSHAWMHWVRQAPGKGLEWVGQIKAKSDDYATYYAESVKGRFTISR DDSKNTLYLQMNSLKTEDTAVYYCT**S**WEWDLDFWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
68	SPLPITPVNATCAIRHPCHNNLMNQIRSQLAQLNGSANALFILYYTAQGEPFPNNLDKLCGPNVTDFPPFHANGTEK AKLVELYRIVVYLGTSLGNITRDQKILNPSALSLHSKLNATADILRGLLSNVLCRLCSKYHVGHVDVTYGPDTSGKDVF QKKKLGCQLLGKYKQIIAVLAQAF

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating an individual with cancer comprising administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising:

a) an immunoglobulin heavy chain complementarity determining region 1 (VH-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 1-3;

b) an immunoglobulin heavy chain complementarity determining region 2 (VH-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 4 or 5;

c) an immunoglobulin heavy chain complementarity determining region 3 (VH-CDR3) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 6-8;

d) an immunoglobulin light chain complementarity determining region 1 (VL-CDR1) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 9 or 10;

e) an immunoglobulin light chain complementarity determining region 2 (VL-CDR2) comprising an amino acid sequence set forth in any one of SEQ ID NOs: 11or 12; and

f) an immunoglobulin light chain complementarity determining region 3 (VL-CDR3) comprising an amino acid sequence set forth in SEQ ID NO: 13;

wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

2. The method of claim 1, wherein the recombinant antibody binds to glycosylated LIF.

3. The method of claim 1 or 2, wherein the recombinant antibody is humanized.

4. The method of any one of claims 1 to 3, wherein the recombinant antibody is deimmunized.

5. The method of any one of claims 1 to 4, wherein the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains.

6. The method of claim 5, wherein the recombinant antibody is an IgG antibody.

7. The method of any one of claims 1 to 4, wherein the recombinant antibody is a Fab, $F(ab)_2$, single-domain antibody, a single chain variable fragment (scFv), or a nanobody.

8. The method of any one of claims 1 to 7, wherein the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 200 picomolar.

9. The method of any one of claims 1 to 7, wherein the recombinant antibody specifically binds LIF with a dissociation constant (K_D) of less than about 100 picomolar.

10. The method of any one of claims 1 to 9, wherein the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 1 (GFTFSHAWMH), wherein the VH-CDR2 comprises

an amino acid sequence set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), wherein the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 6 (TCWEWDLDF), wherein the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), wherein the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 11 (SVSNLES), and wherein the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT).

11. The method of any one of claims 1 to 9, wherein the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 2 (GFTFSHAW), wherein the VH-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 5 (IKAKSDDYAT), wherein the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 6 (TCWEWDLDF), wherein the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 10 (QSLLDSDGHTYLN), wherein the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 12 (SVS), and wherein the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT).

12. The method of any one of claims 1 to 9, wherein the VH-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 3 (HAWMH), wherein the VH-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 4 (QIKAKSDDYATYYAESVKG), wherein the VH-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 7 (WEWDLDF), wherein the VL-CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 9 (RSSQSLLDSDGHTYLN), wherein the VL-CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 11 (SVSNLES), and wherein the VL-CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 13 (MQATHAPPYT).

13. The method of any one of claims 1 to 12, wherein the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer.

14. The method of claim 13, wherein the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma.

15. The method of any one of claims 1 to 14, wherein the recombinant antibody is administered as a component of a pharmaceutical formulation, the pharmaceutical formulation comprising the recombinant antibody and a pharmaceutically acceptable excipient, carrier, or diluent.

16. The method of claim 15, wherein the pharmaceutical formulation has a pH of about 6.0.

17. The method of claim 15, wherein the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL.

18. The method of any one of claims 1 to 17, wherein the recombinant antibody is administered intravenously.

19. The method of any one of claims 1 to 18, wherein the recombinant antibody is administered about once a week.

20. The method of any one of claims 1 to 18, wherein the recombinant antibody is administered about once every two weeks.

21. The method of any one of claims 1 to 18, wherein the recombinant antibody is administered about once every three weeks.

22. The method of any one of claims 1 to 21, wherein the recombinant antibody is administered at a dose of about 750 milligrams.

23. The method of any one of claims 1 to 21, wherein the recombinant antibody is administered at a dose of about 1125 milligrams.

24. The method of any one of claims 1 to 21, wherein the recombinant antibody is administered at a dose of about 1500 milligrams.

25. The method of any one of claims 1 to 21, wherein the recombinant antibody is administered at a dose of about 2000 milligrams.

26. A method of treating an individual with cancer comprising administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising:

a) an immunoglobulin heavy chain variable region (VH) sequence with an amino acid sequence at least about 90% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 41, 42, 44, or 66; and

b) an immunoglobulin light chain variable region (VL) sequence with an amino acid sequence at least about 90% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 45-48;

wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

27. The method of claim 26, wherein the VH sequence is at least about 90% identical to the amino acid sequence set forth in SEQ ID NO: 42; and the VL sequence is at least about 90% identical to the amino acid sequence set forth in SEQ ID NO: 46.

28. The method of claim 26, wherein the VH sequence is identical to the amino acid sequence set forth in SEQ ID NO: 42; and the VL sequence is identical to the amino acid sequence set forth in SEQ ID NO: 46.

29. The method of any one of claims 26 to 28, wherein the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains.

30. The method of claim 29, wherein the recombinant antibody is an IgG antibody.

31. The method of any one of claims 26 to 30, wherein the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer.

32. The method of claim 31, wherein the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma.

33. The method of any one of claims 26 to 32, wherein the recombinant antibody is administered as a component of a pharmaceutical formulation, the pharmaceutical formulation comprising the recombinant antibody and further comprising a pharmaceutically acceptable a pharmaceutically acceptable excipient, carrier, or diluent.

34. The method of claim 33, wherein the pharmaceutical formulation has a pH of about 6.0.

35. The method of claim 33, wherein the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL.

36. The method of any one of claims 26 to 35, wherein the recombinant antibody is administered intravenously.

37. The method of any one of claims 26 to 36, wherein the recombinant antibody is administered about once a week.

38. The method of any one of claims 26 to 36, wherein the recombinant antibody is administered about once every two weeks.

39. The method of any one of claims 26 to 36, wherein the recombinant antibody is administered about once every three weeks.

40. The method of any one of claims 26 to 39, wherein the recombinant antibody is administered at a dose of about 750 milligrams.

41. The method of any one of claims 26 to 39, wherein the recombinant antibody is administered at a dose of about 1125 milligrams.

42. The method of any one of claims 26 to 39, wherein the recombinant antibody is administered at a dose of about 1500 milligrams.

43. The method of any one of claims 26 to 39, wherein the recombinant antibody is administered at a dose of about 2000 milligrams.

44. A method of treating an individual with cancer comprising administering to the individual a recombinant antibody that specifically binds Leukemia Inhibitory Factor (LIF) comprising:

a) an immunoglobulin heavy chain sequence with an amino acid sequence at least about 90% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 57-60 or 67; and

b) an immunoglobulin light chain sequence with an amino acid sequence at least about 90% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 61-64;

wherein the recombinant antibody is administered to the individual at a dose from about 75 to about 2000 milligrams.

45. The method of claim 44, wherein the immunoglobulin heavy chain sequence is at least about 90% identical to the amino acid sequence set forth in SEQ ID NO: 58; and the immunoglobulin light chain sequence is at least about 90% identical to the amino acid sequence set forth in SEQ ID NO: 62.

46. The method of claim 44, wherein the immunoglobulin heavy chain sequence is identical to the amino acid sequence set forth in SEQ ID NO: 58; and the immunoglobulin light chain sequence is identical to the amino acid sequence set forth in SEQ ID NO: 62.

47. The method of any one of claims 44 to 46, wherein the recombinant antibody comprises two immunoglobulin heavy chains and two immunoglobulin light chains.

48. The method of any one of claims 44 to 47, wherein the cancer comprises an advanced solid tumor, glioblastoma, stomach cancer, skin cancer, prostate cancer, pancreatic cancer, breast cancer, testicular cancer, thyroid cancer, head and neck cancer, liver cancer, kidney cancer, esophageal cancer, ovarian cancer, colon cancer, lung cancer, lymphoma, or soft tissue cancer.

49. The method of claim 48, wherein the cancer comprises non-small cell lung cancer, epithelial ovarian carcinoma, or pancreatic adenocarcinoma.

50. The method of any one of claims 44 to 49, wherein the recombinant antibody is administered as a component of a pharmaceutical formulation, the pharmaceutical formulation comprising the recombinant antibody and a pharmaceutically acceptable excipient, carrier, or diluent.

51. The method of claim 50, wherein the pharmaceutical formulation has a pH of about 6.0.

52. The method of claim 50, wherein the pharmaceutical formulation comprises about 25mM histidine, about 6% sucrose, and about 0.01% polysorbate 80, wherein the recombinant antibody is included at a concentration of about 20 mg/mL.

53. The method of any one of claims 44 to 52, wherein the recombinant antibody is administered intravenously.

54. The method of any one of claims 44 to 53, wherein the recombinant antibody is administered about once a week.

55. The method of any one of claims 44 to 53, wherein the recombinant antibody is administered about once every two weeks.

56. The method of any one of claims 44 to 53, wherein the recombinant antibody is administered about once every three weeks.

57. The method of any one of claims 44 to 56, wherein the recombinant antibody is administered at a dose of about 750 milligrams.

58. The method of any one of claims 44 to 56, wherein the recombinant antibody is administered at a dose of about 1125 milligrams.

59. The method of any one of claims 44 to 56, wherein the recombinant antibody is administered at a dose of about 1500 milligrams.

60. The method of any one of claims 44 to 56, wherein the recombinant antibody is administered at a dose of about 2000 milligrams.

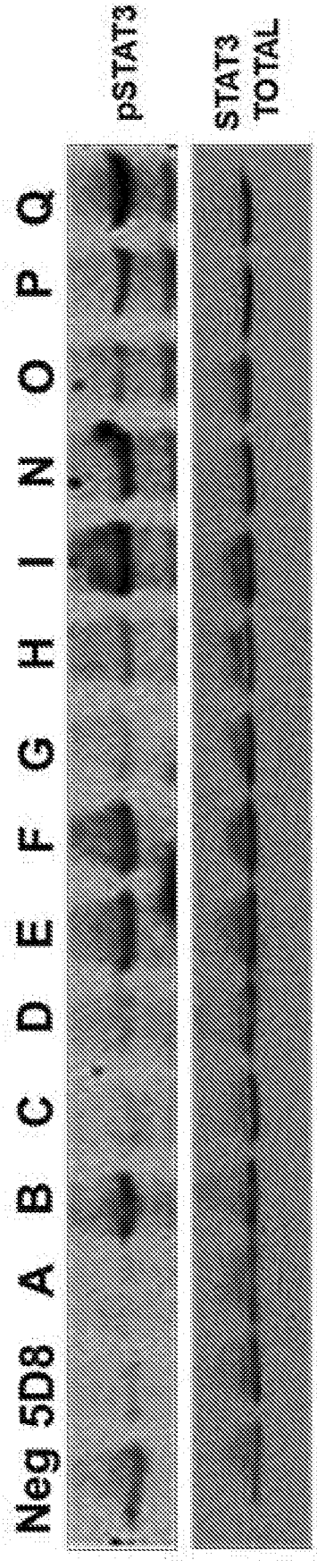

Fig. 1

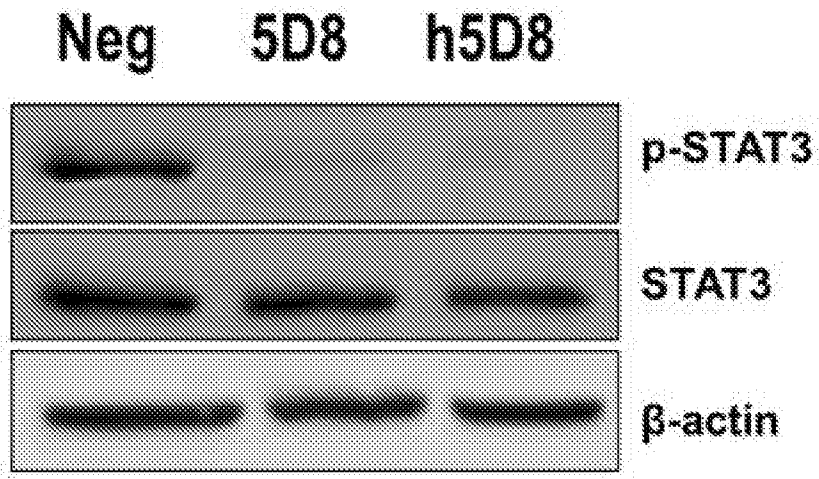
Neg
5D8
h5D8
p-STAT3
STAT3
β-actin

Fig. 2A

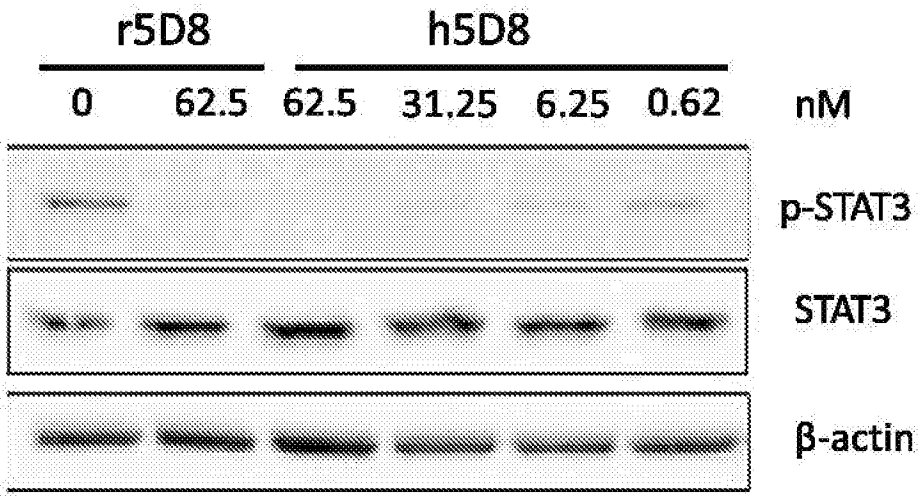
r5D8
h5D8
0
62.5
62.5
31.25
6.25
0.62
nM
p-STAT3
STAT3
β-actin

Fig. 2B

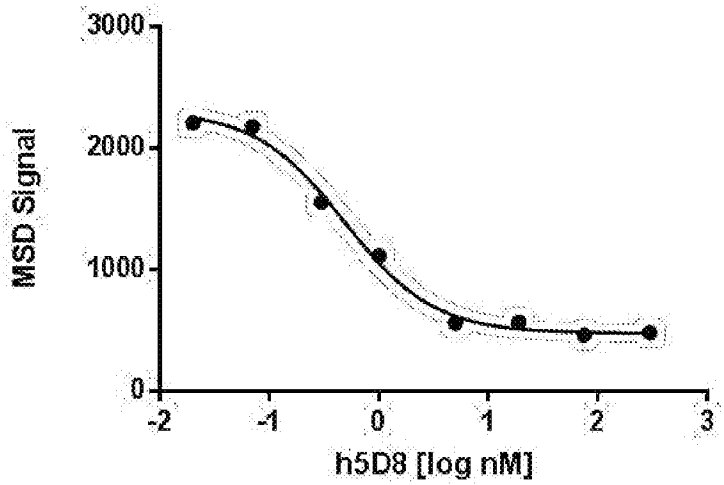
MSD Signal
3000
2000
1000
0
-2
-1
0
1
2
3
h5D8 [log nM]

Fig. 3A

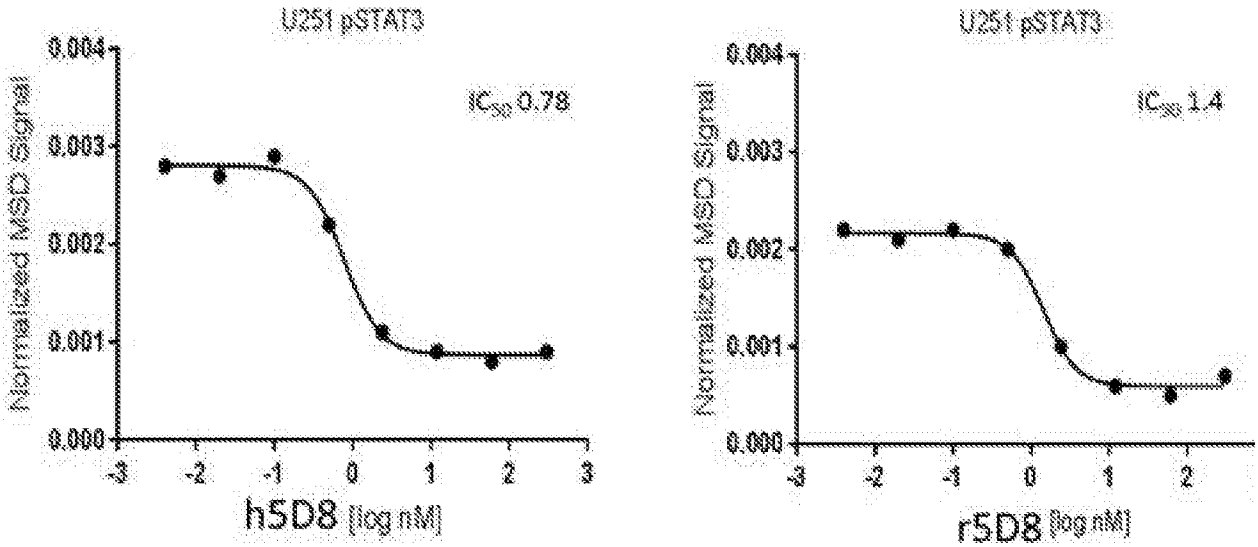
U251 pSTAT3
IC50 0.78
Normalized MSD Signal
0.004
0.003
0.002
0.001
0.000
-3
-2
-1
0
1
2
3
h5D8 [log nM]
U251 pSTAT3
IC50 1.4
Normalized MSD Signal
0.004
0.003
0.002
0.001
0.000
-3
-2
-1
0
1
2
r5D8 [log nM]

Fig. 3B

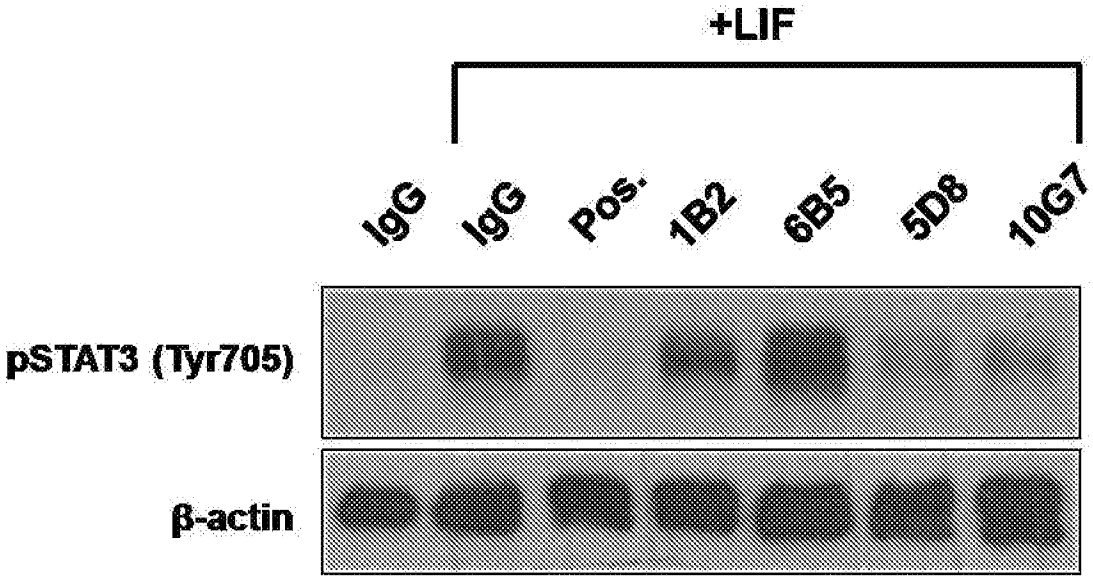

Fig. 4

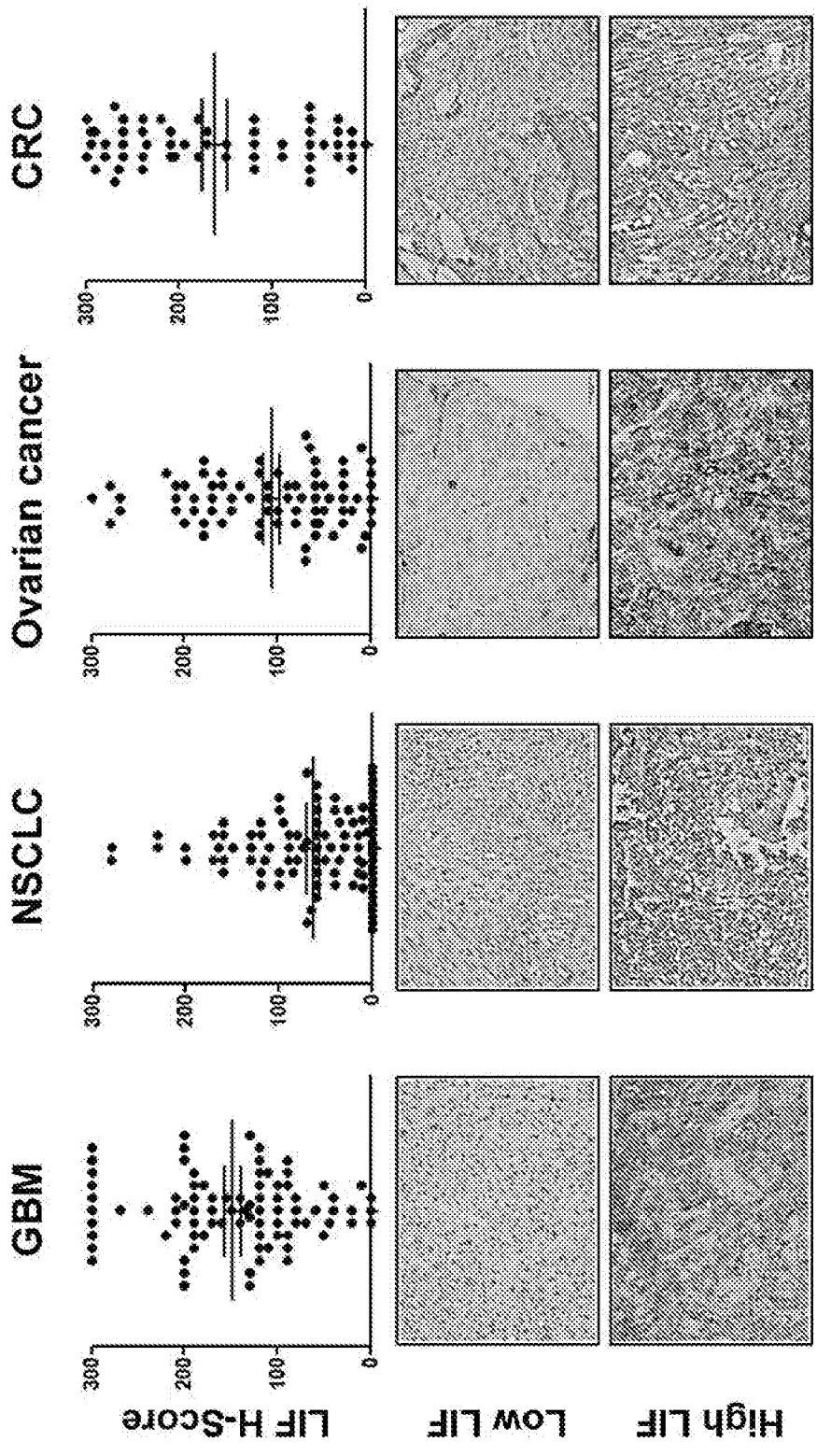
GBM
NSCLC
Ovarian cancer
CRC
LIF H-Score
300
200
100
0
Low LIF
High LIF

Fig. 5

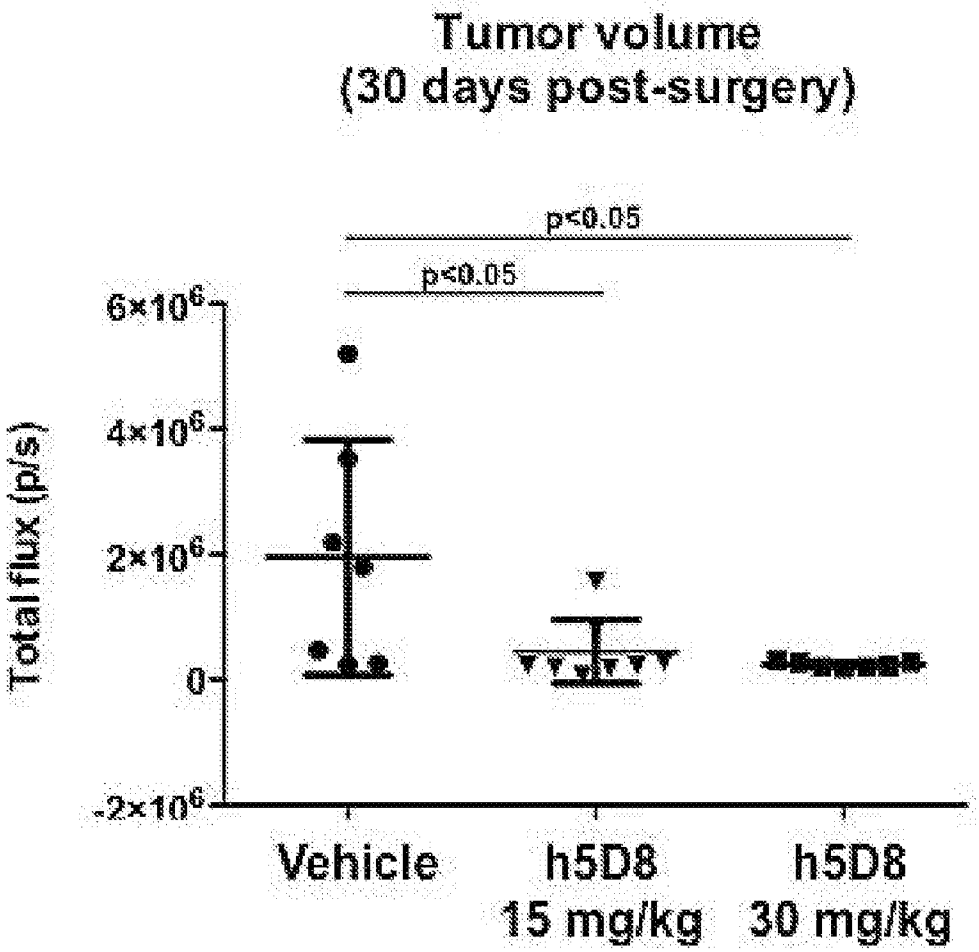
Tumor volume
(30 days post-surgery)
p<0.05
p<0.05
6×10^6
4×10^6
2×10^6
0
-2×10^6
Total flux (p/s)
Vehicle
h5D8
15 mg/kg
h5D8
30 mg/kg

Fig. 6

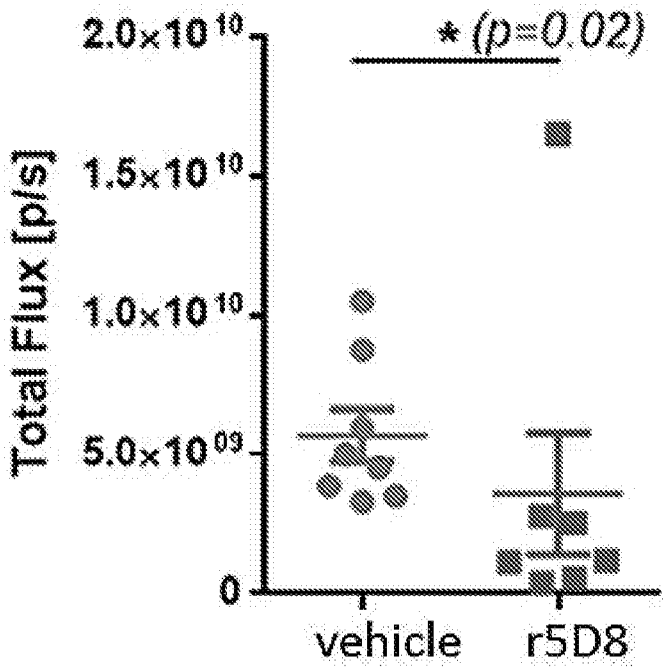
2.0×10 10
1.5×10 10
1.0×10 10
5.0×10 09
0
Total Flux [p/s]
* (p=0.02)
vehicle
r5D8

Fig. 7A

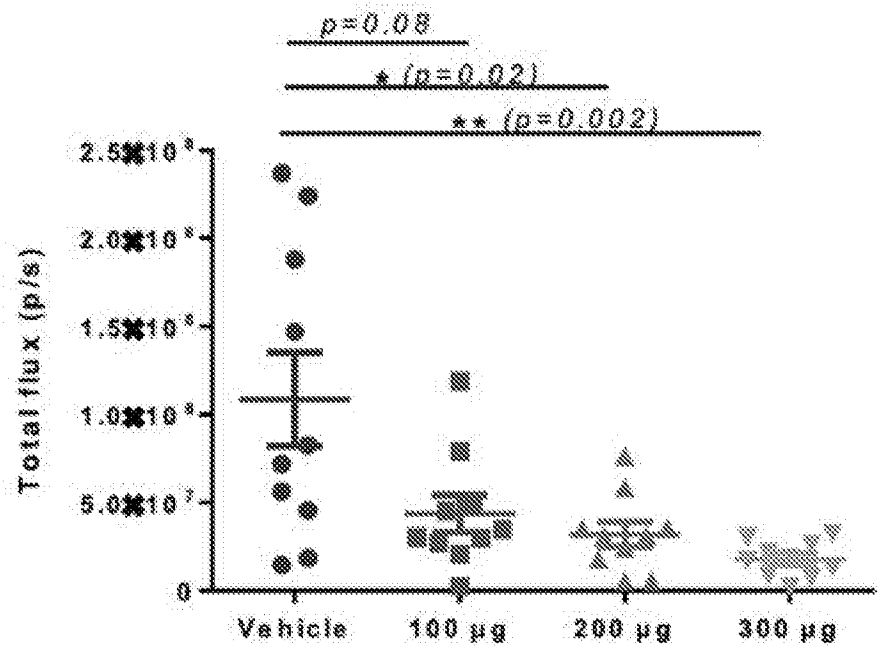
p=0.08
* (p=0.02)
** (p=0.002)
Total flux (p/s)
Vehicle
100 µg
200 µg
300 µg

Fig. 7B

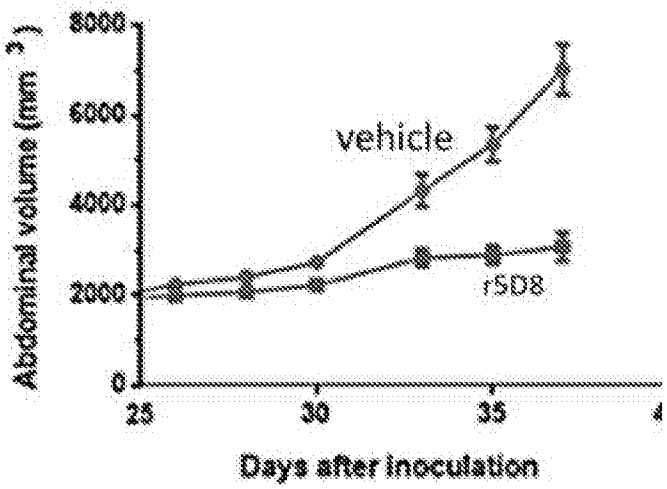

Fig. 8A

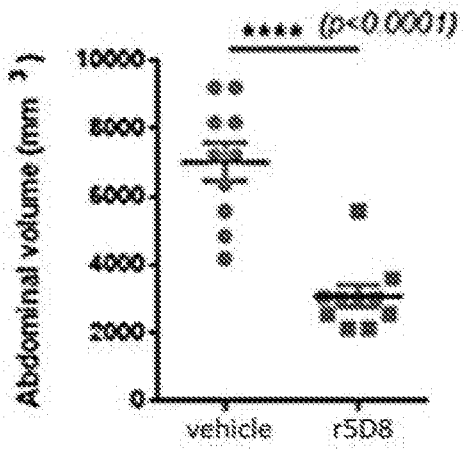

Fig. 8B

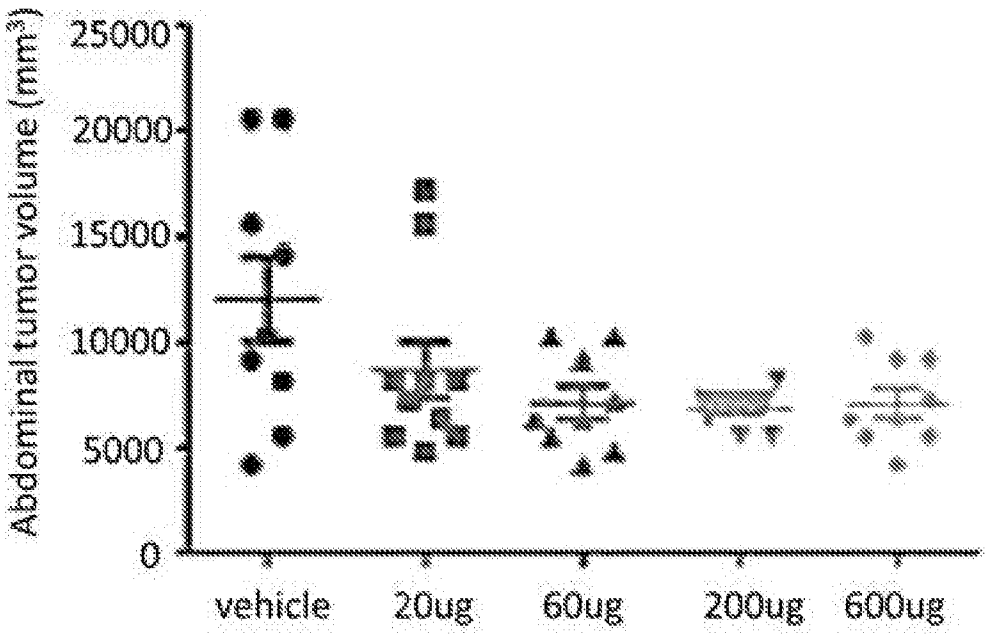

Fig. 8C

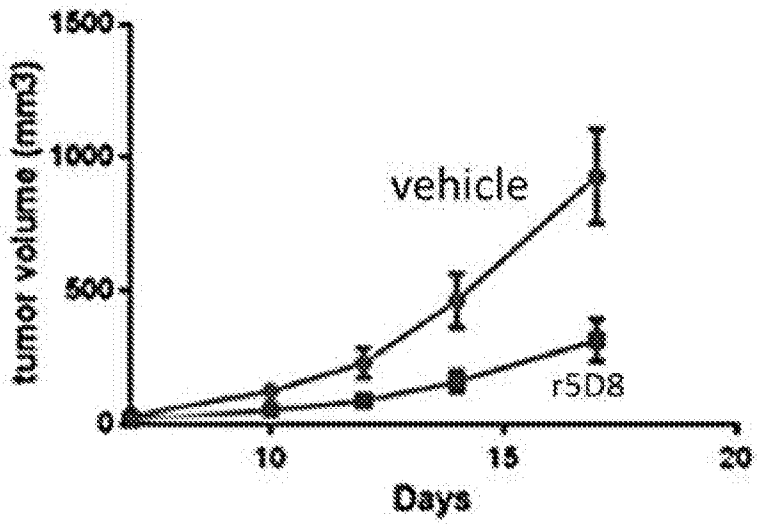
1500
1000
500
0
tumor volume (mm3)
vehicle
r5D8
10
15
20
Days

Fig. 9A

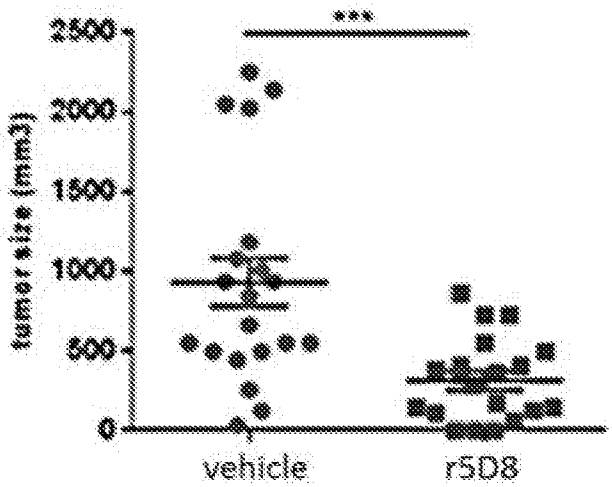
***
2500
2000
1500
1000
500
0
tumor size (mm3)
vehicle
r5D8

Fig. 9B

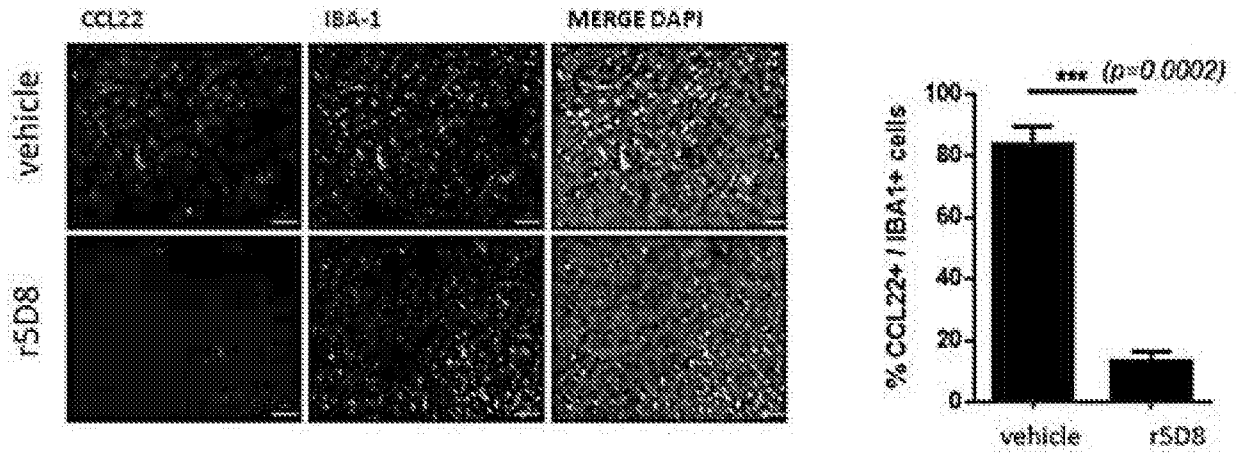
CCL22
IBA-1
MERGE DAPI
vehicle
rSD8
*** (p=0.0002)
% CCL22+ / IBA1+ cells
100
80
60
40
20
0
vehicle
rSD8

Fig. 10A

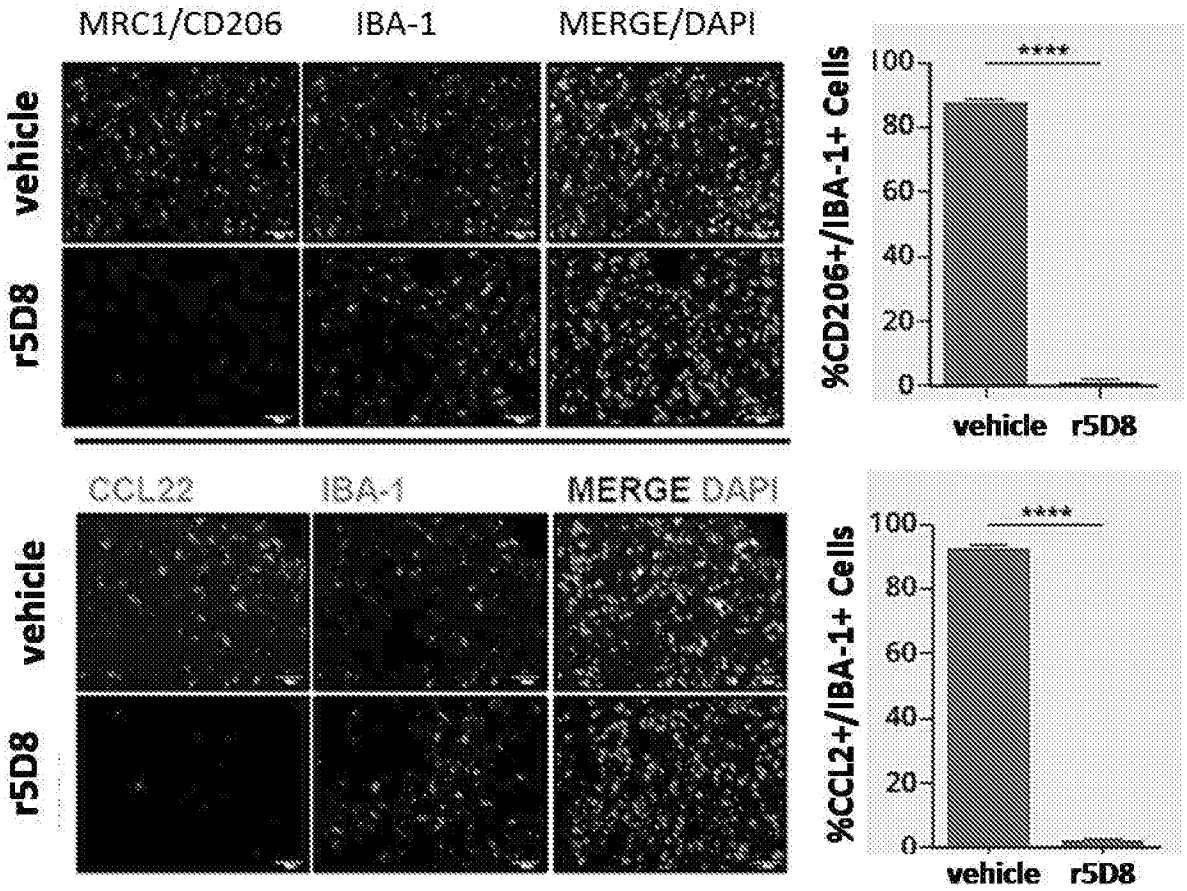
MRC1/CD206
IBA-1
MERGE/DAPI
vehicle
r5D8
%CD206+/IBA-1+ Cells
****
100
80
60
40
20
0
vehicle
r5D8
CCL22
IBA-1
MERGE DAPI
vehicle
r5D8
%CCL2+/IBA-1+ Cells
****
100
80
60
40
20
0
vehicle
r5D8

Fig. 10B

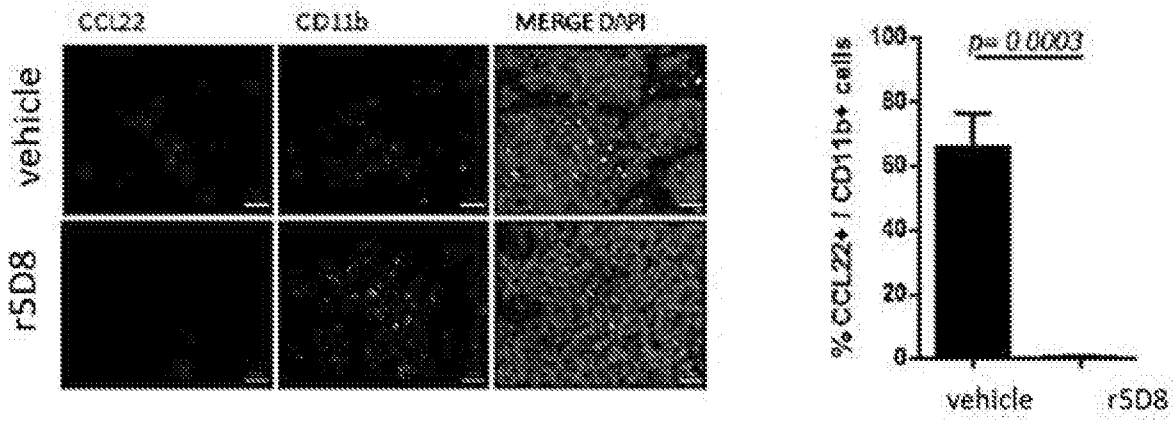

Fig. 10C

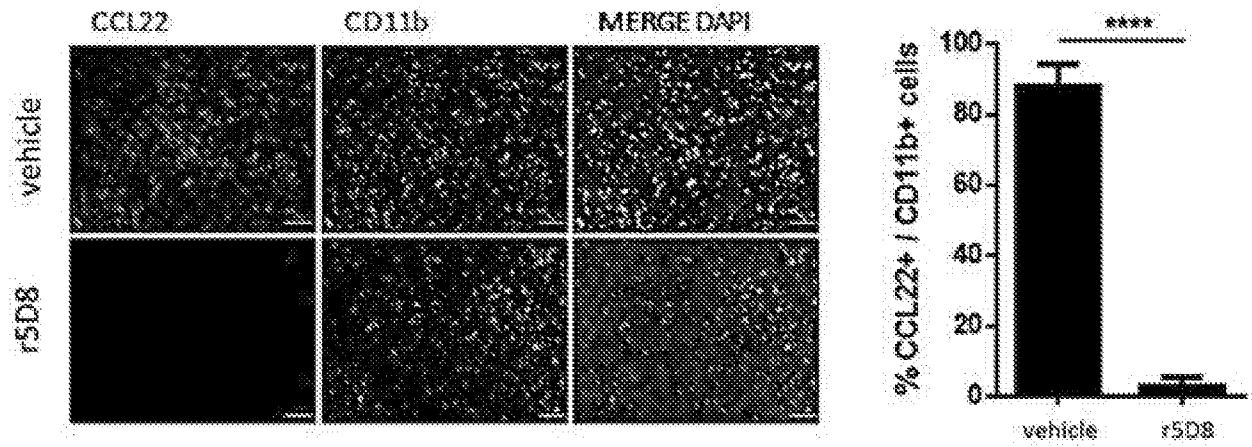

Fig. 10D

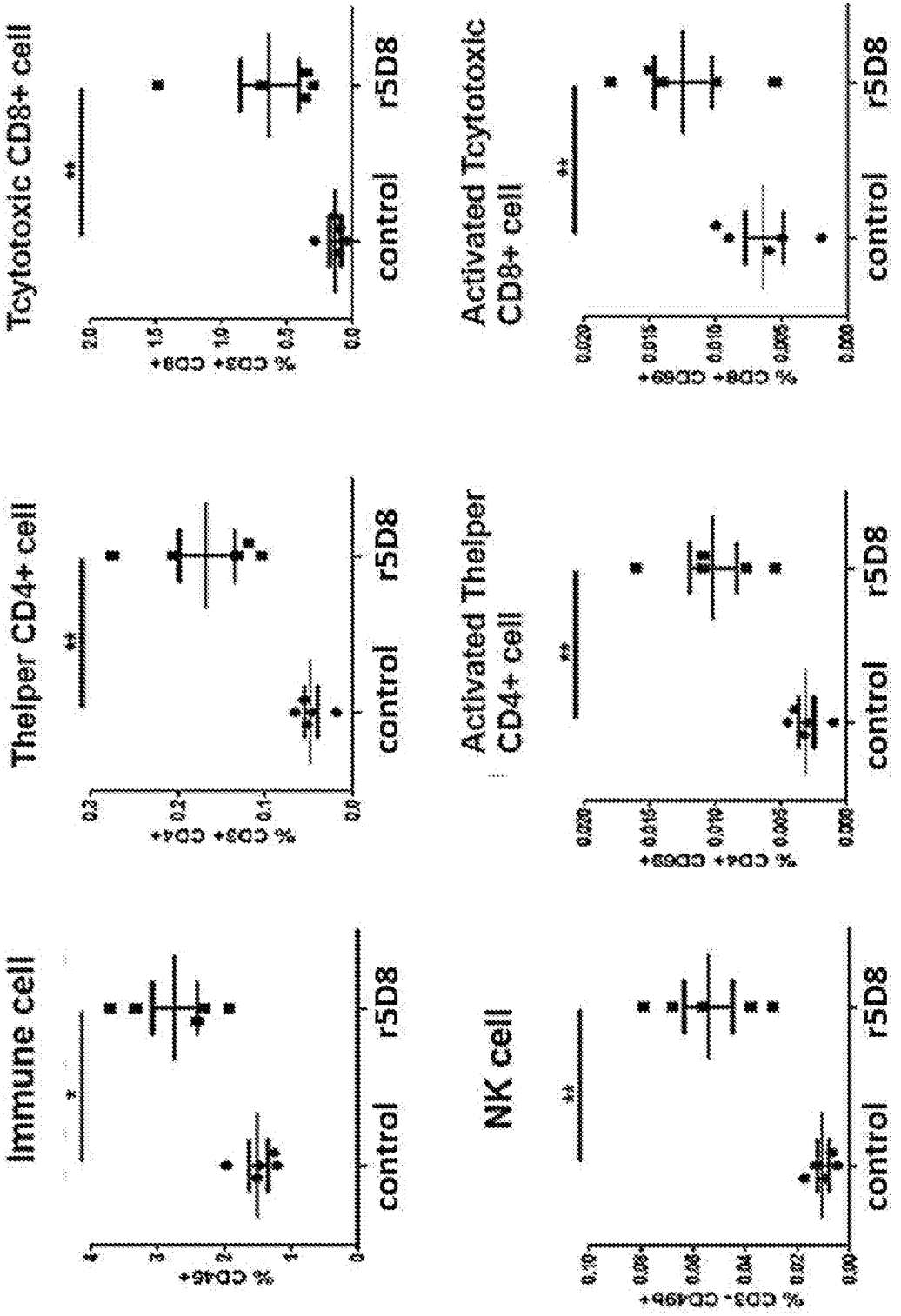
Tcytotoxic CD8+ cell
Thelper CD4+ cell
Activated Tcytotoxic CD8+ cell
Activated Thelper CD4+ cell
NK cell
Immune cell
control
r5D8

Fig. 11A

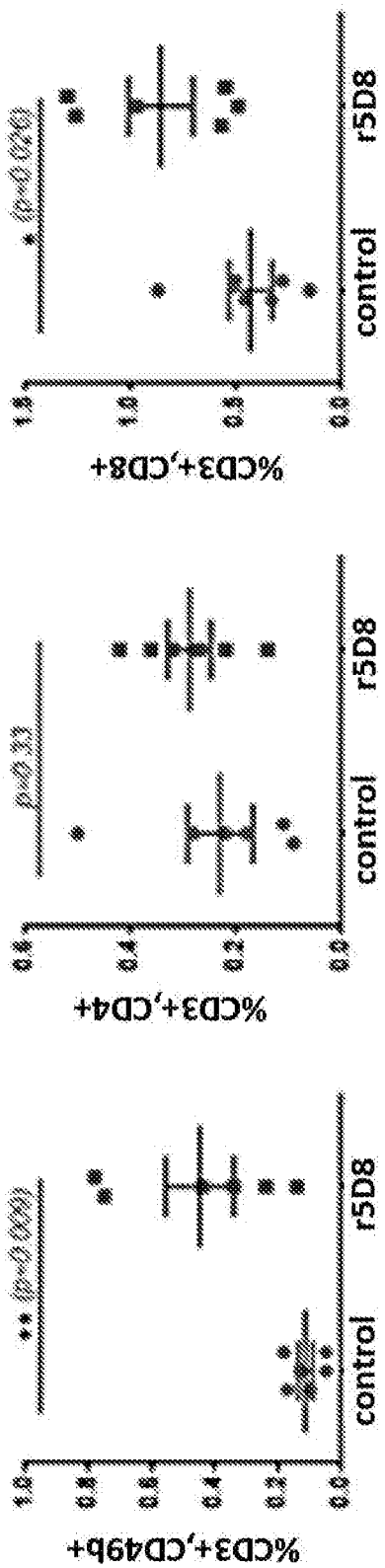
%CD3+,CD8+
1.5
1.0
0.5
0.0
* (p=0.0)
control
r5D8
%CD3+,CD4+
0.6
0.4
0.2
0.0
p=0.33
control
r5D8
%CD3+,CD49b+
1.0
0.8
0.6
0.4
0.2
0.0
** (p=0.0)
control
r5D8

Fig. 11B

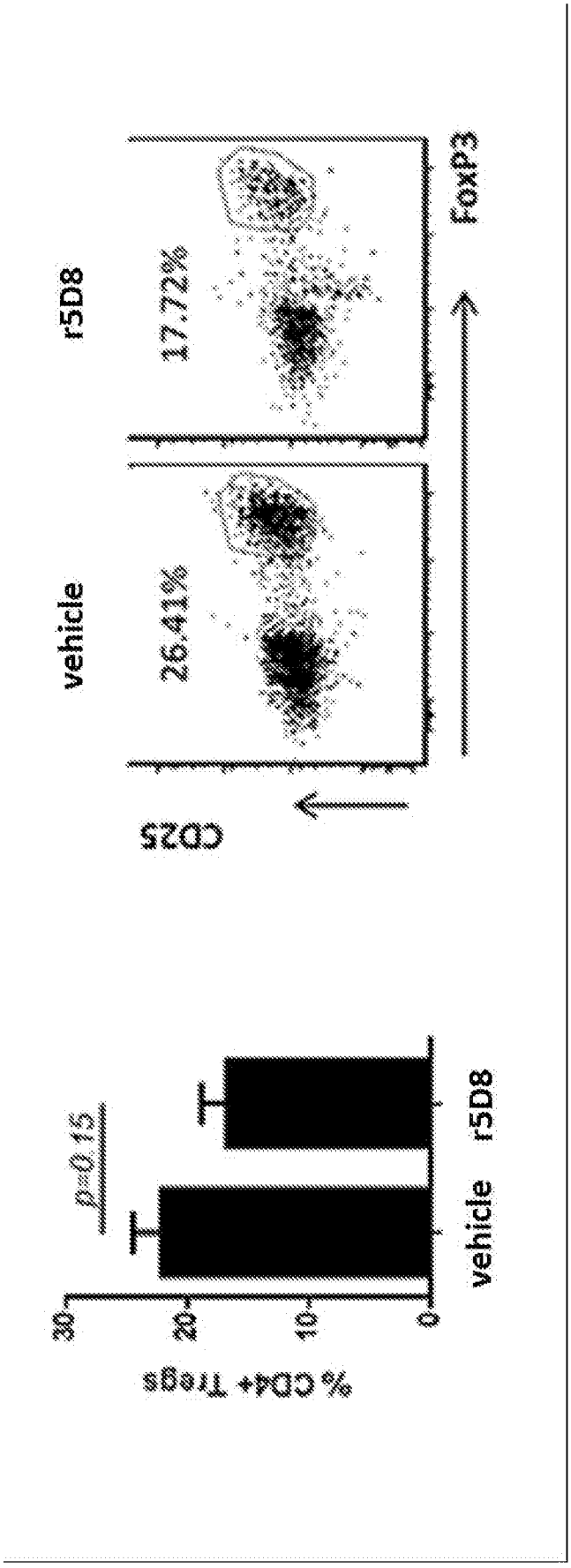
vehicle
r5D8
26.41%
17.72%
CD25
FoxP3
p=0.15
% CD4+ Tregs
30
20
10
0
vehicle
r5D8

Fig. 11C

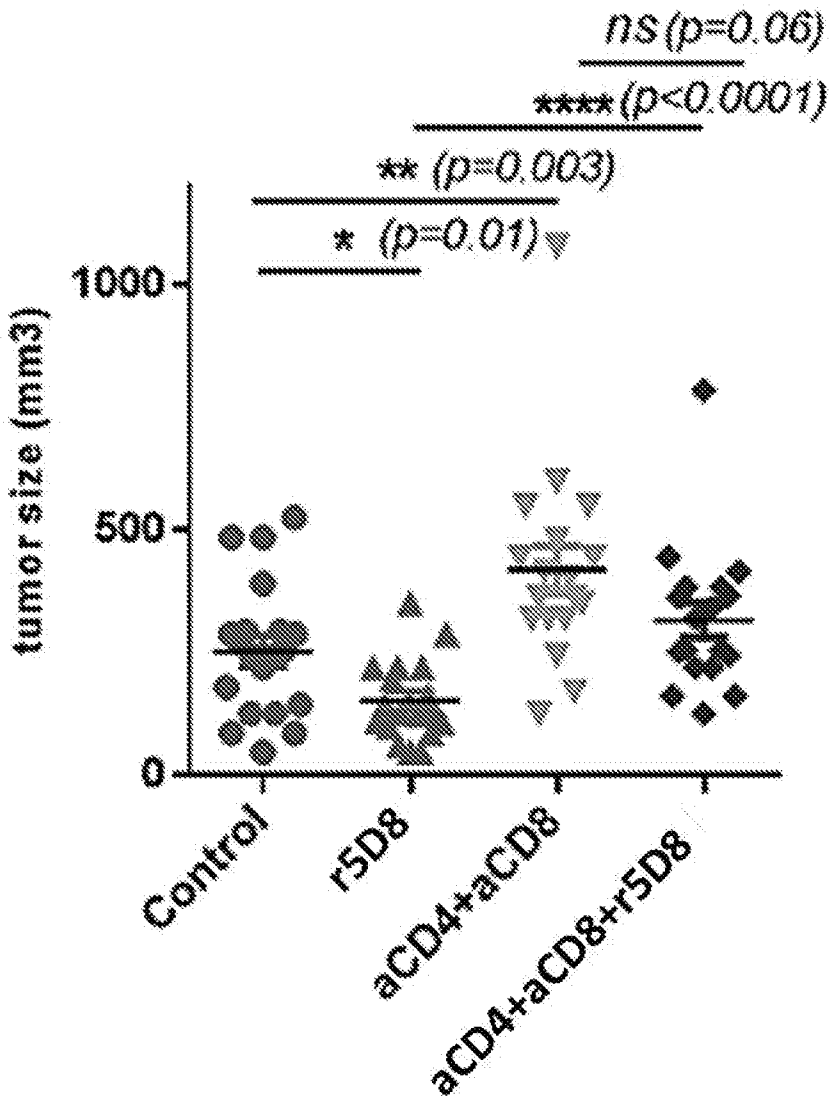
ns (p=0.06)
**** (p<0.0001)
** (p=0.003)
* (p=0.01)
tumor size (mm3)
1000
500
0
Control
r5D8
aCD4+aCD8
aCD4+aCD8+r5D8

Fig. 12

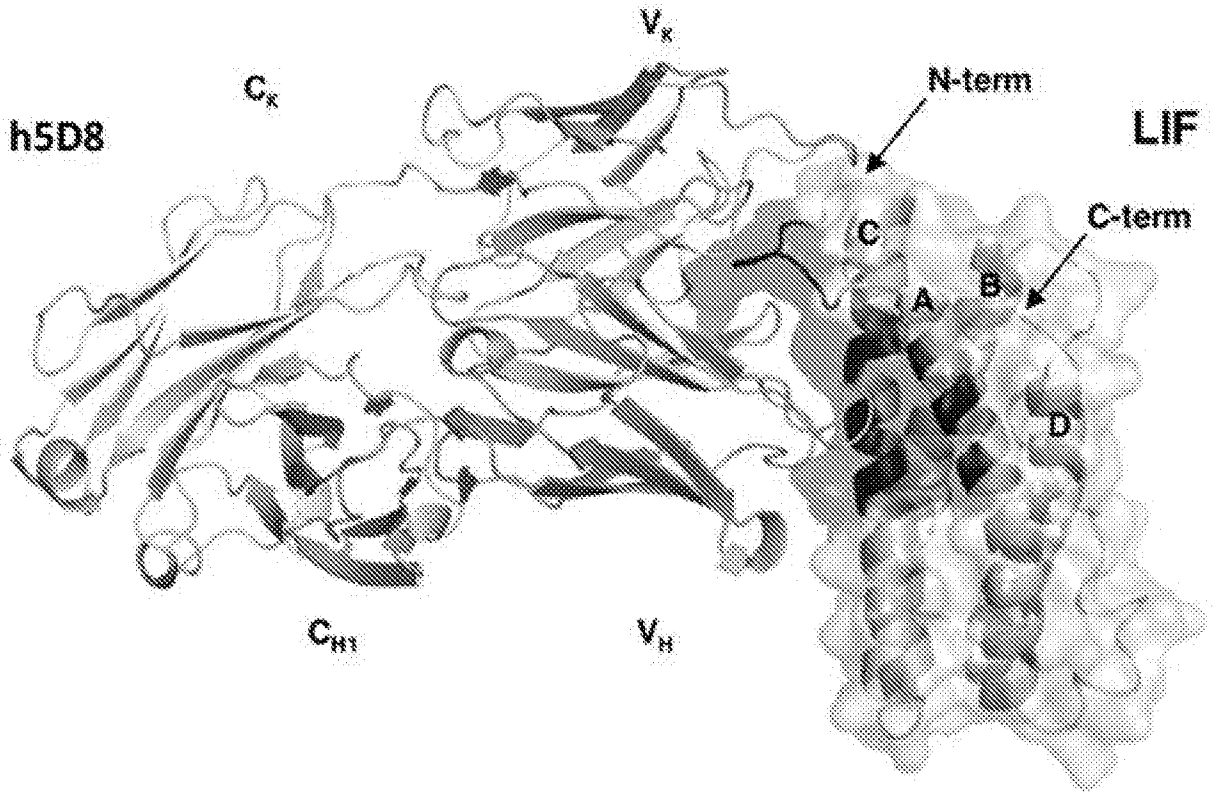

Fig. 13A

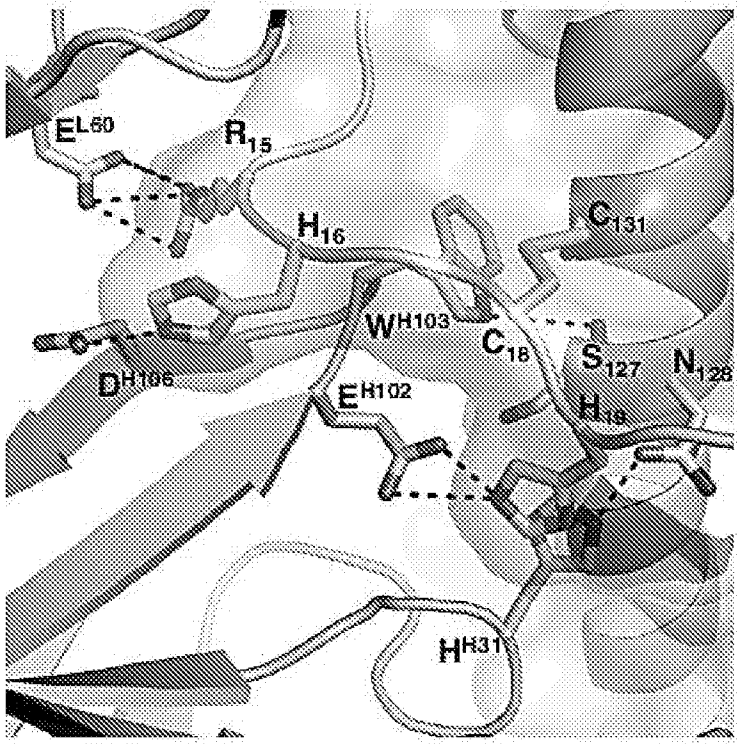

Fig. 13B

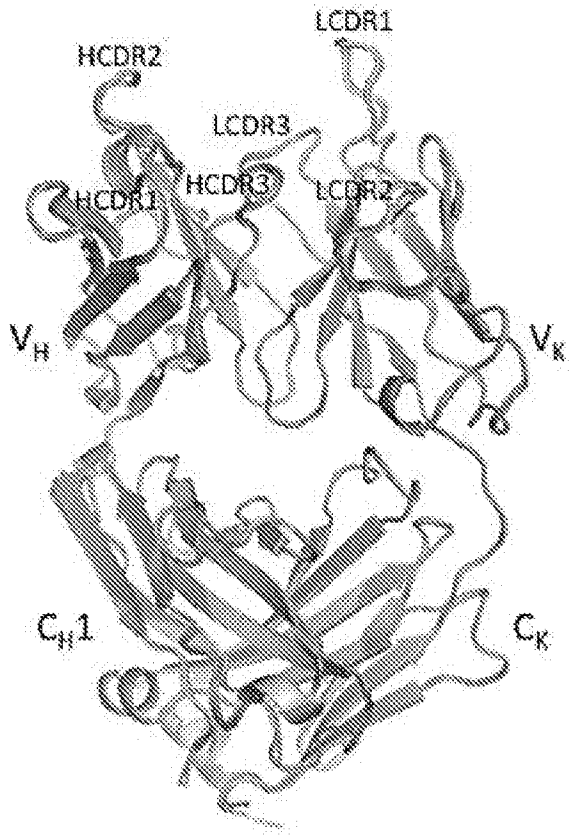

Fig. 14A

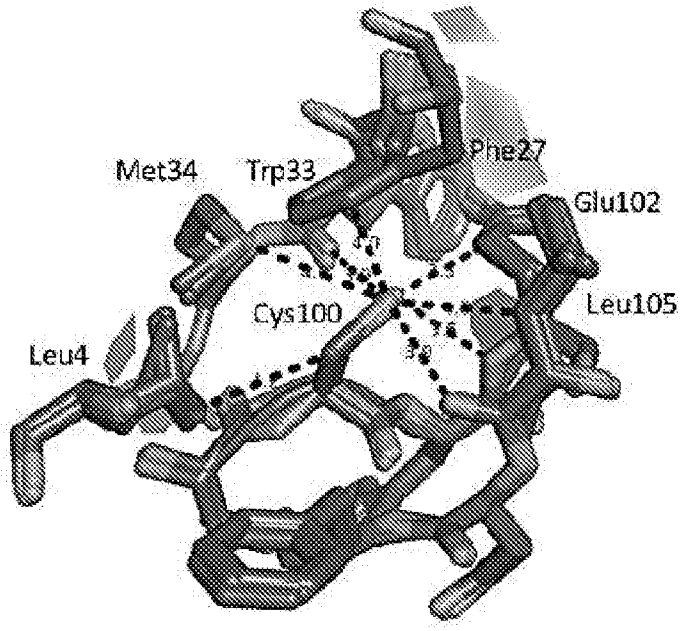

Fig. 14B

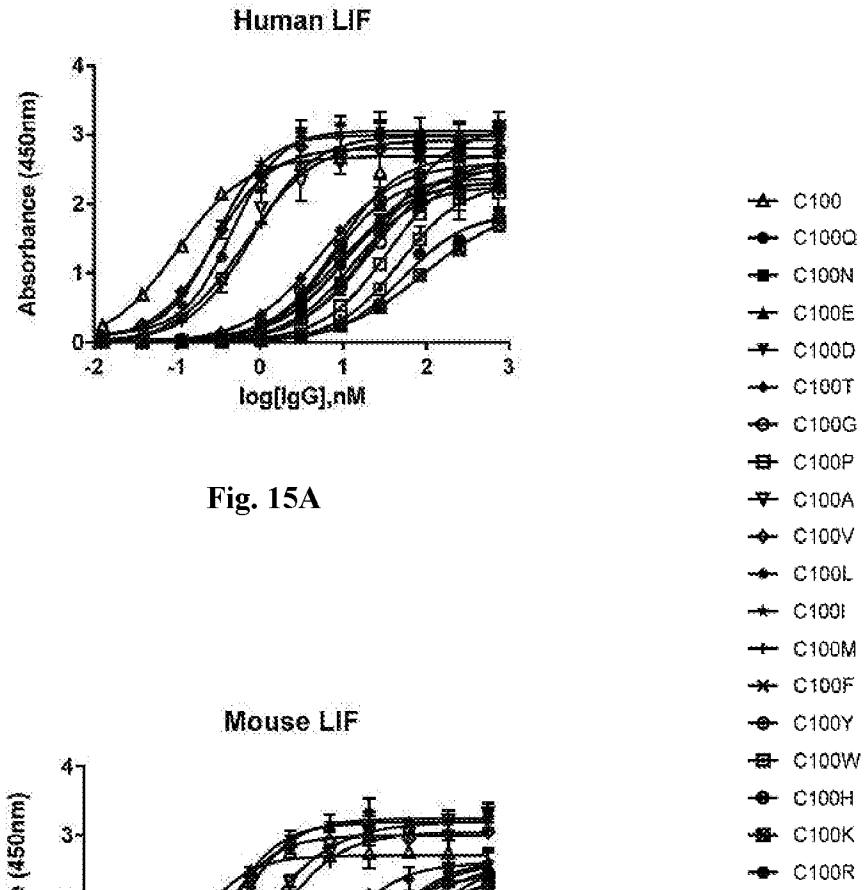

Fig. 15A

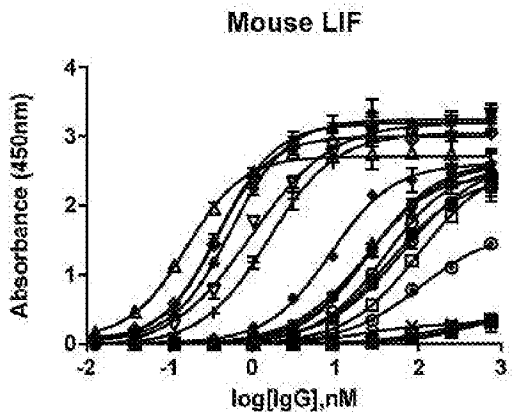

Fig. 15B

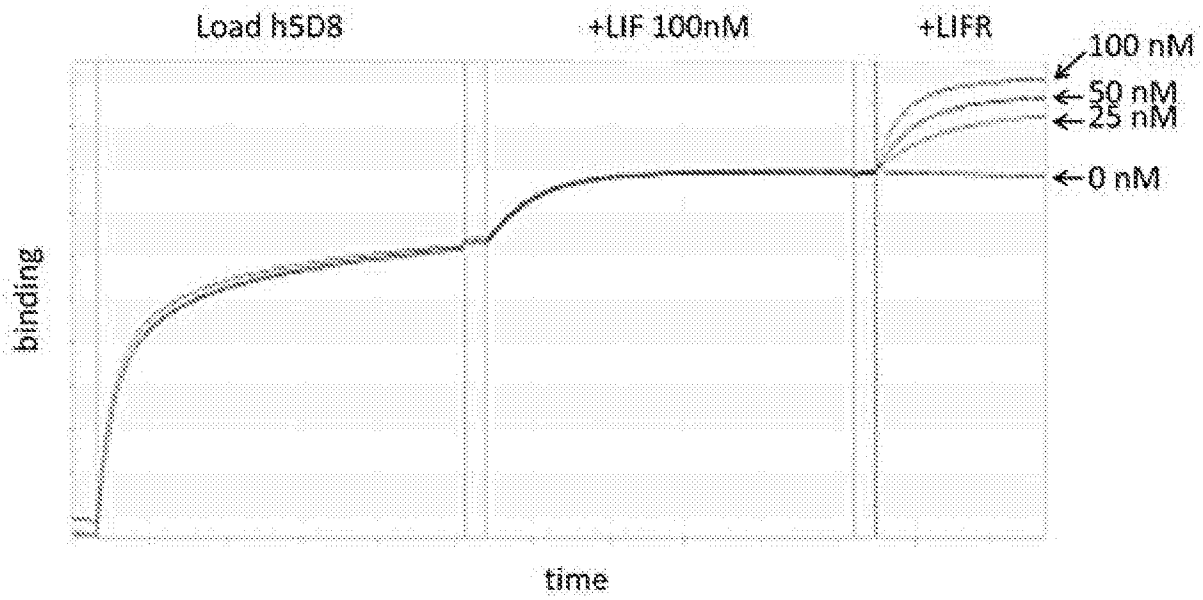

Fig. 16A

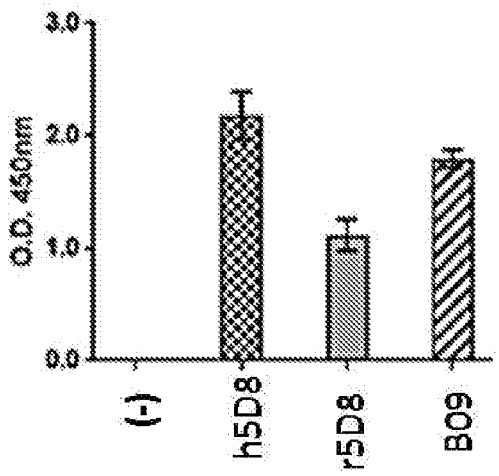

Fig. 16B

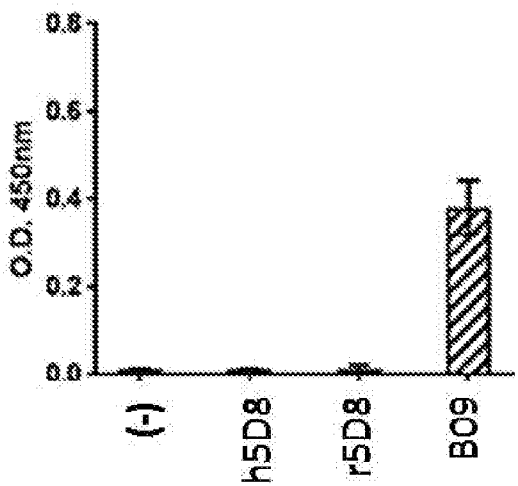

Fig. 16C

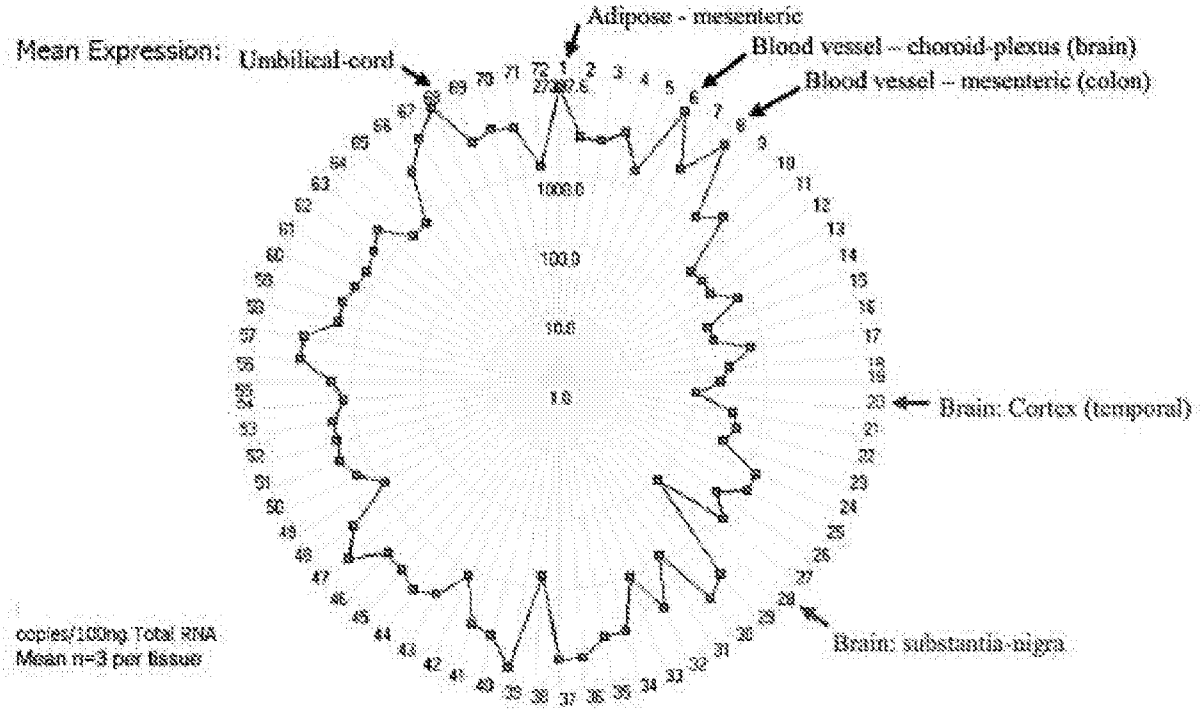
Mean Expression:
Adipose - mesenteric
Blood vessel – choroid-plexus (brain)
Blood vessel – mesenteric (colon)
Umbilical-cord
Brain: Cortex (temporal)
Brain: substantia-nigra
1000.0
100.0
10.0
1.0
copies/100ng Total RNA
Mean n=3 per tissue

Fig. 17A

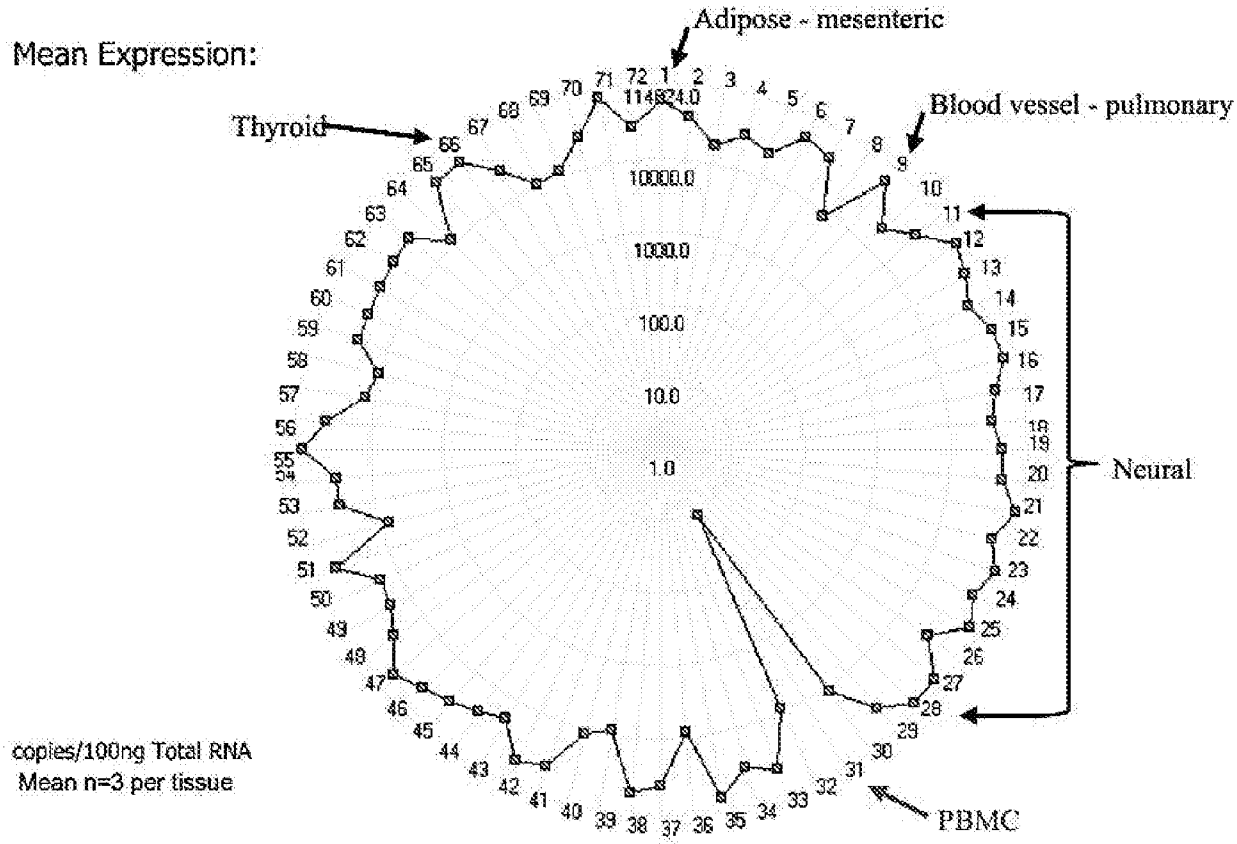
Mean Expression:
Adipose - mesenteric
Blood vessel - pulmonary
Thyroid
Neural
PBMC
10000.0
1000.0
100.0
10.0
1.0
copies/100ng Total RNA
Mean n=3 per tissue

Fig. 17B

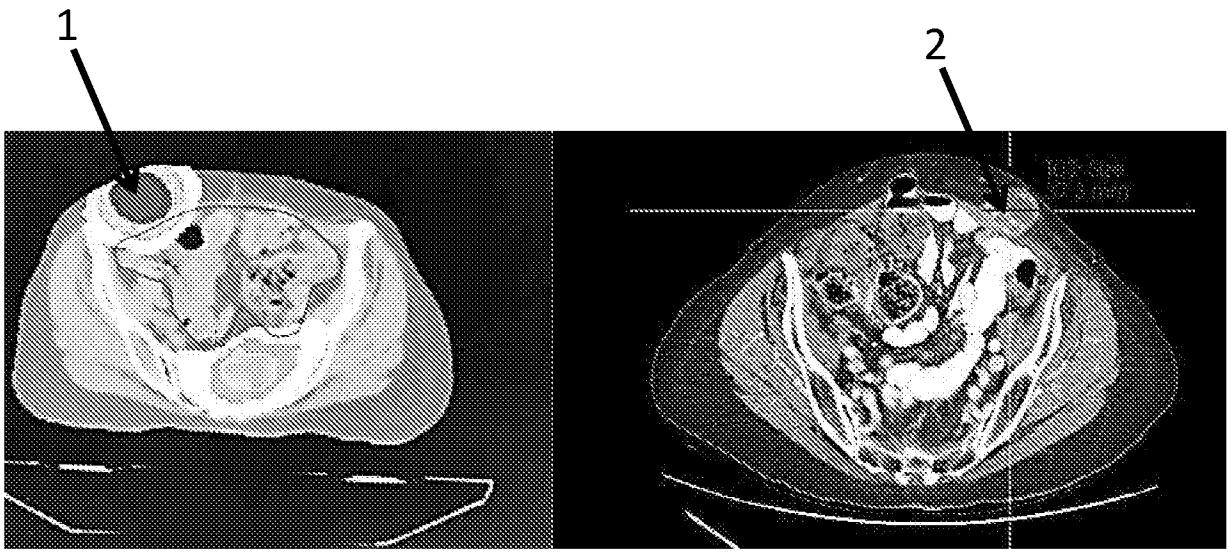

Fig. 18A

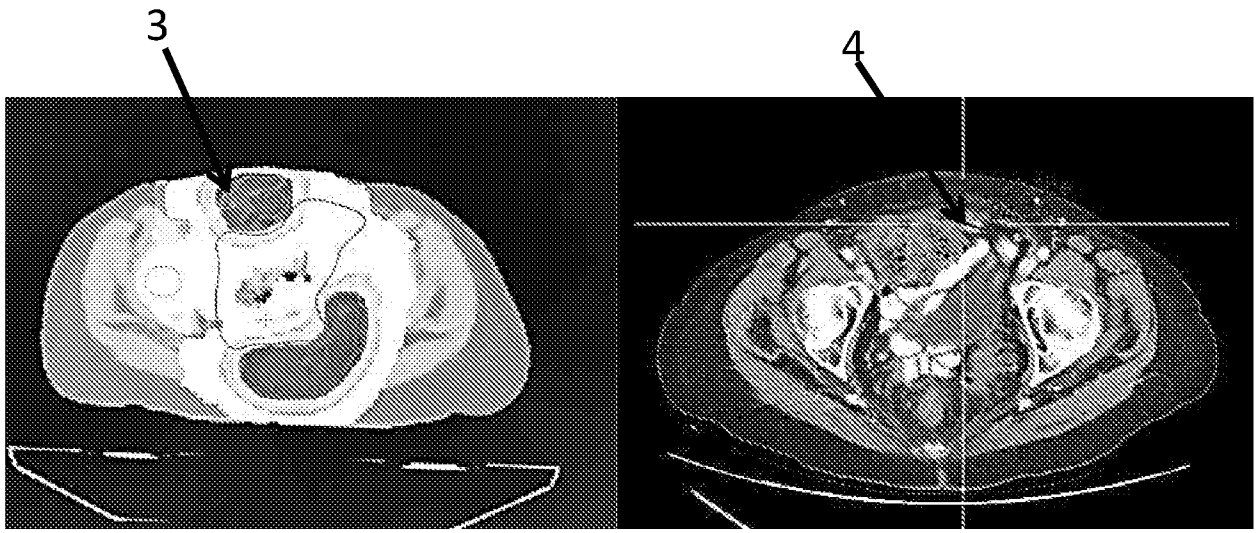

Fig. 18B

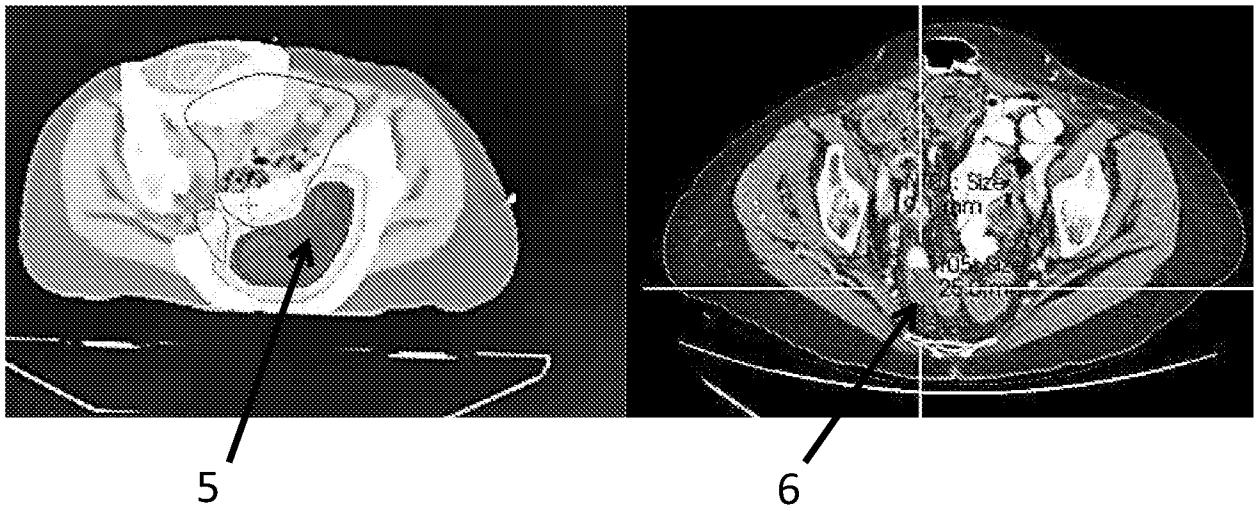

Fig. 18C

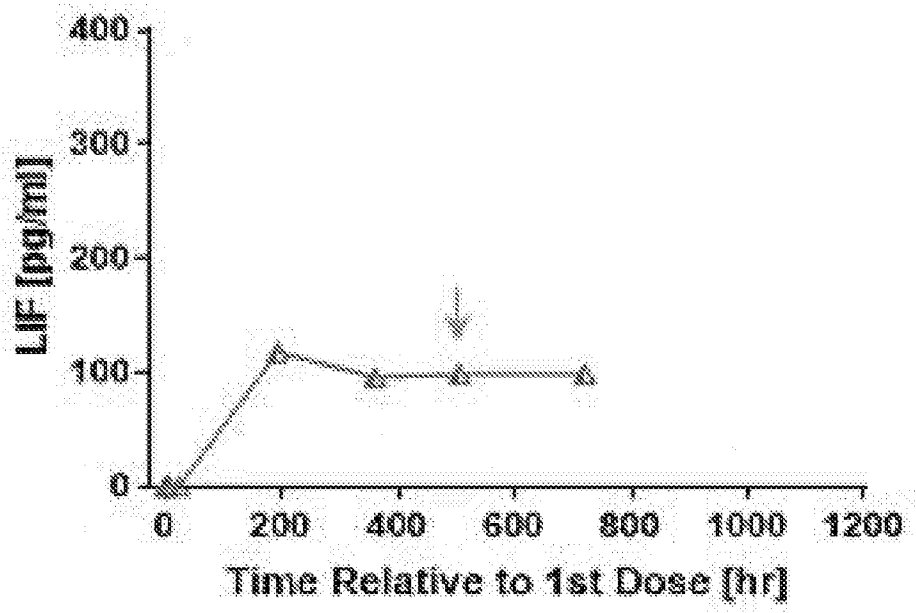

Fig. 19

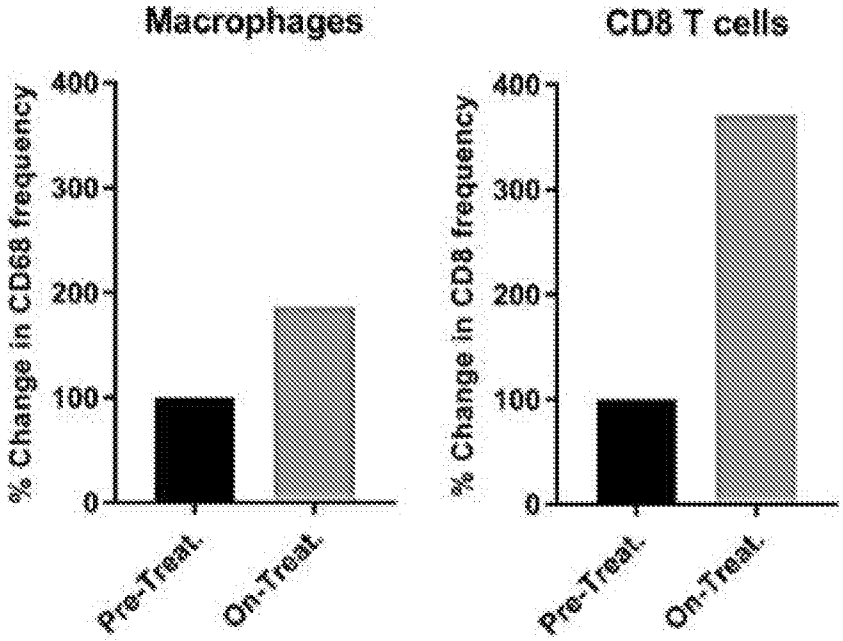

Fig. 20A

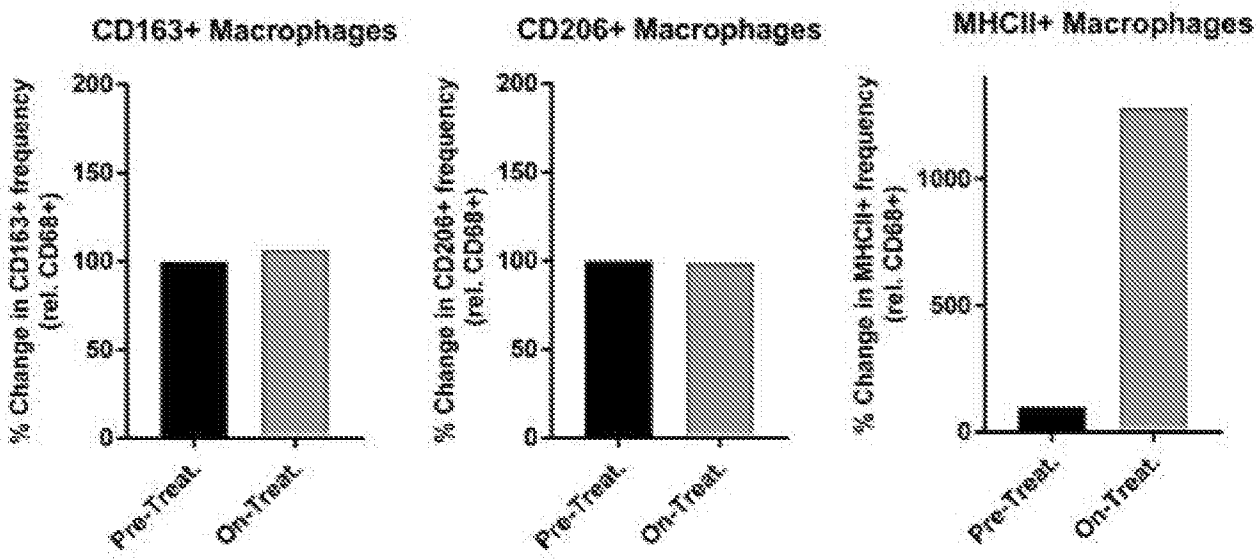

Fig. 20B

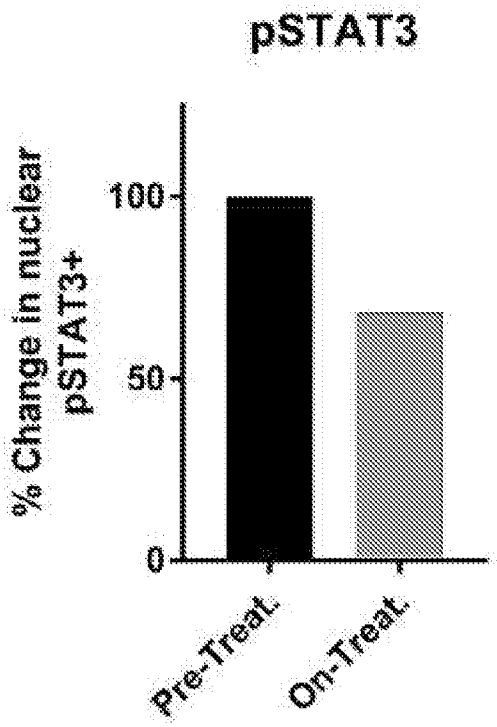

Fig. 20C

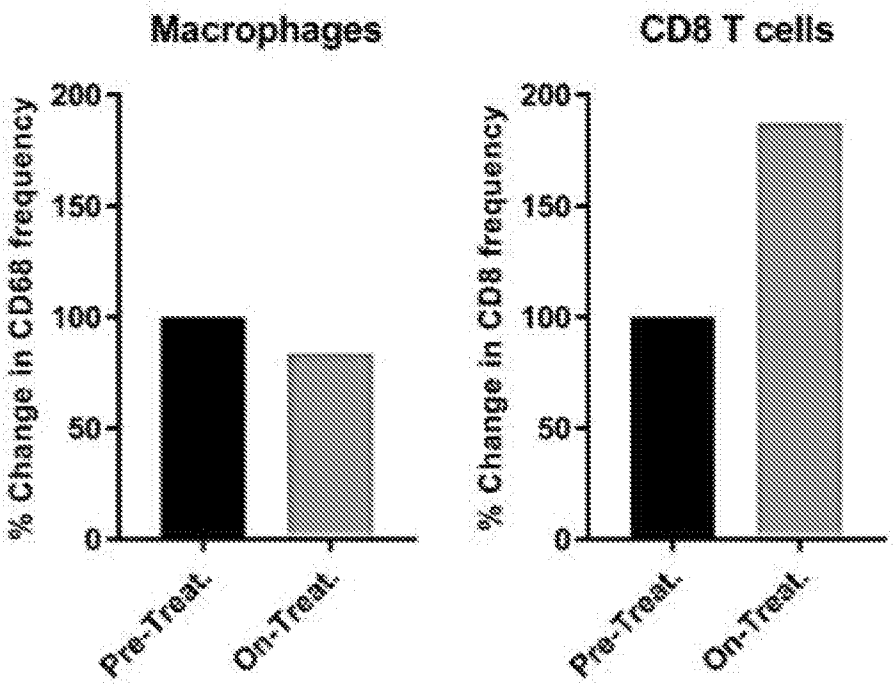

Fig. 21A

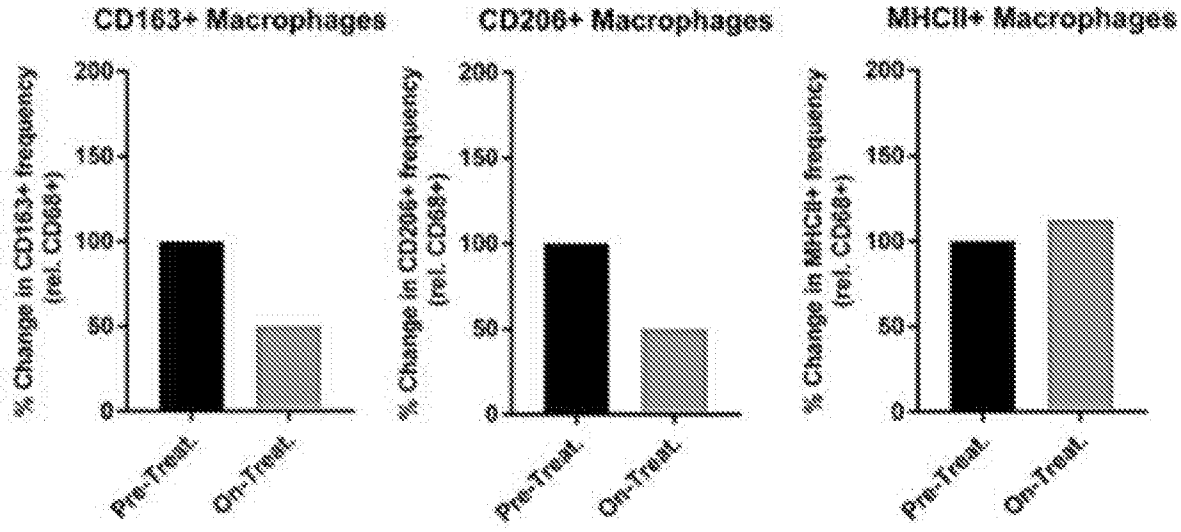

Fig. 21B

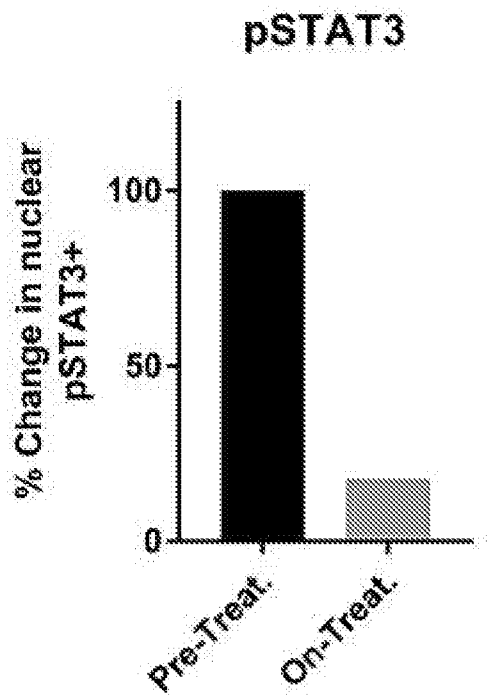

Fig. 21C

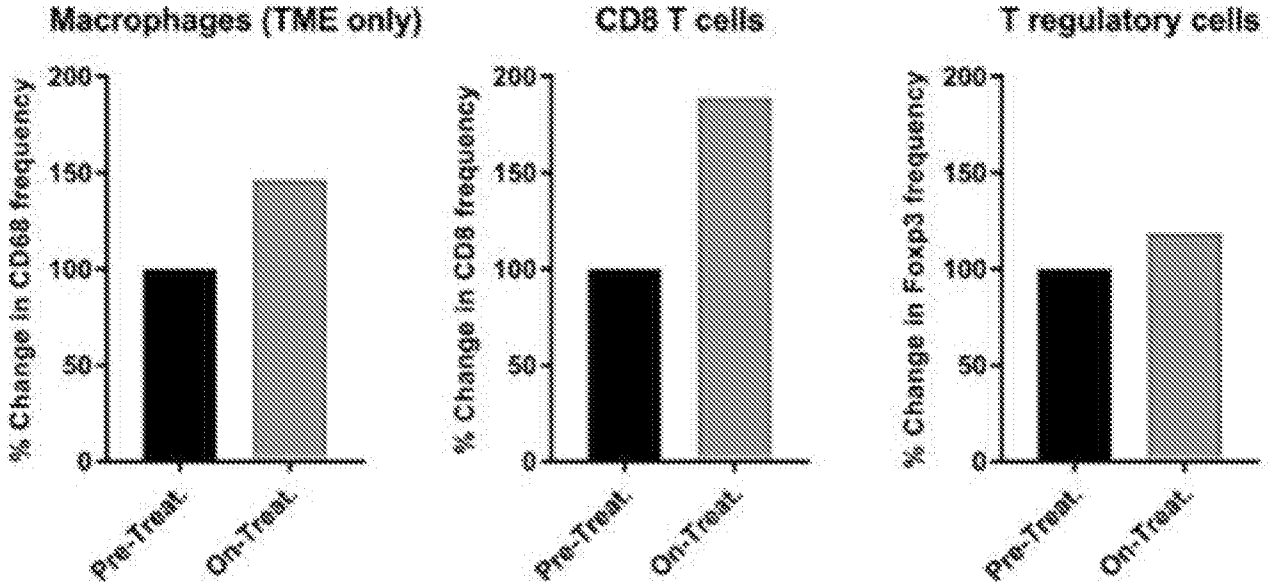
Macrophages (TME only)
CD8 T cells
T regulatory cells
% Change in CD68 frequency
% Change in CD8 frequency
% Change in Foxp3 frequency
200
150
100
50
0
Pre-Treat.
On-Treat.

Fig. 22

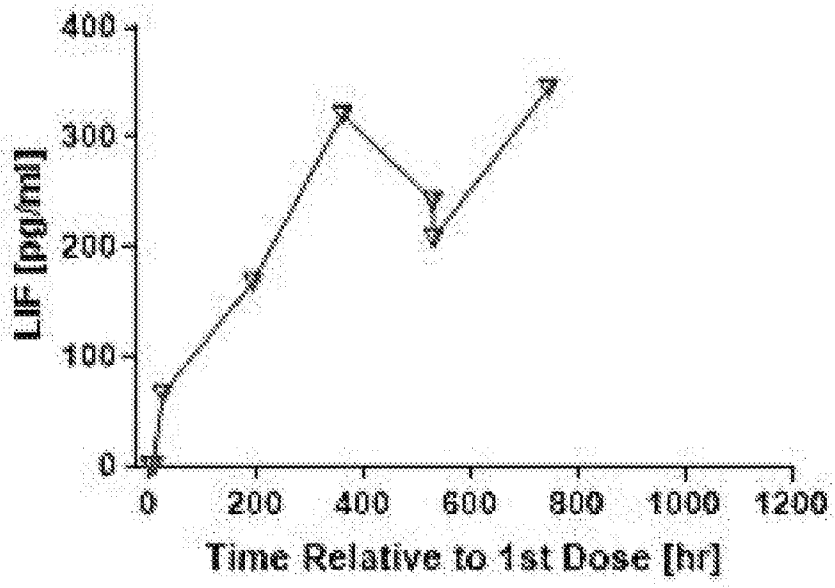
LIF [pg/ml]
400
300
200
100
0
0
200
400
600
800
1000
1200
Time Relative to 1st Dose [hr]

Fig. 23

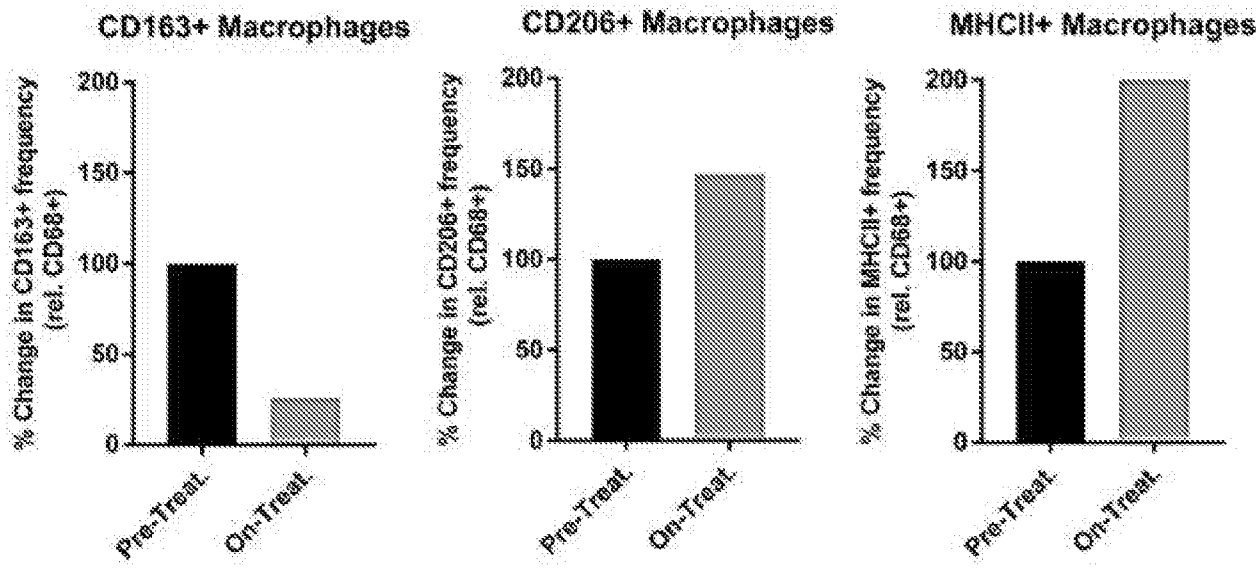
CD163+ Macrophages
CD206+ Macrophages
MHCII+ Macrophages
% Change in CD163+ frequency (rel. CD68+)
% Change in CD206+ frequency (rel. CD68+)
% Change in MHCII+ frequency (rel. CD68+)
200
150
100
50
0
Pre-Treat.
On-Treat.

Fig. 24

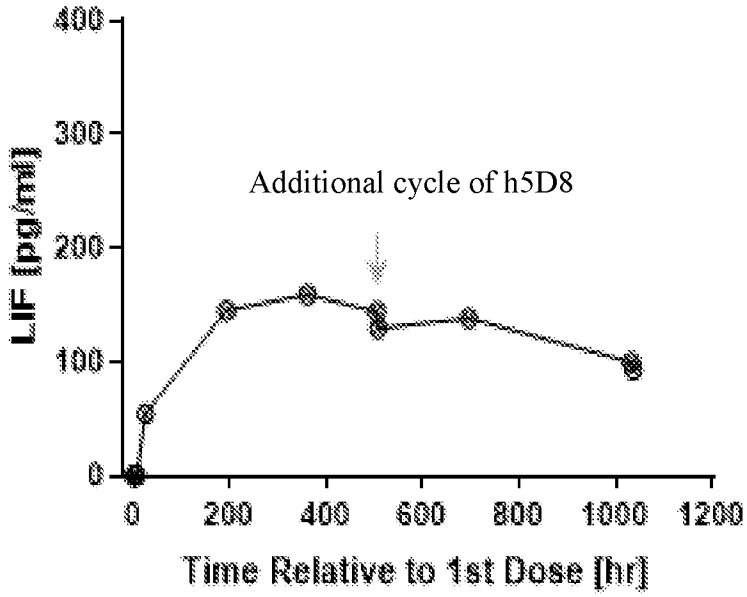
LIF [pg/ml]
400
300
200
100
0
Additional cycle of h5D8
0
200
400
600
800
1000
1200
Time Relative to 1st Dose [hr]

Fig. 25

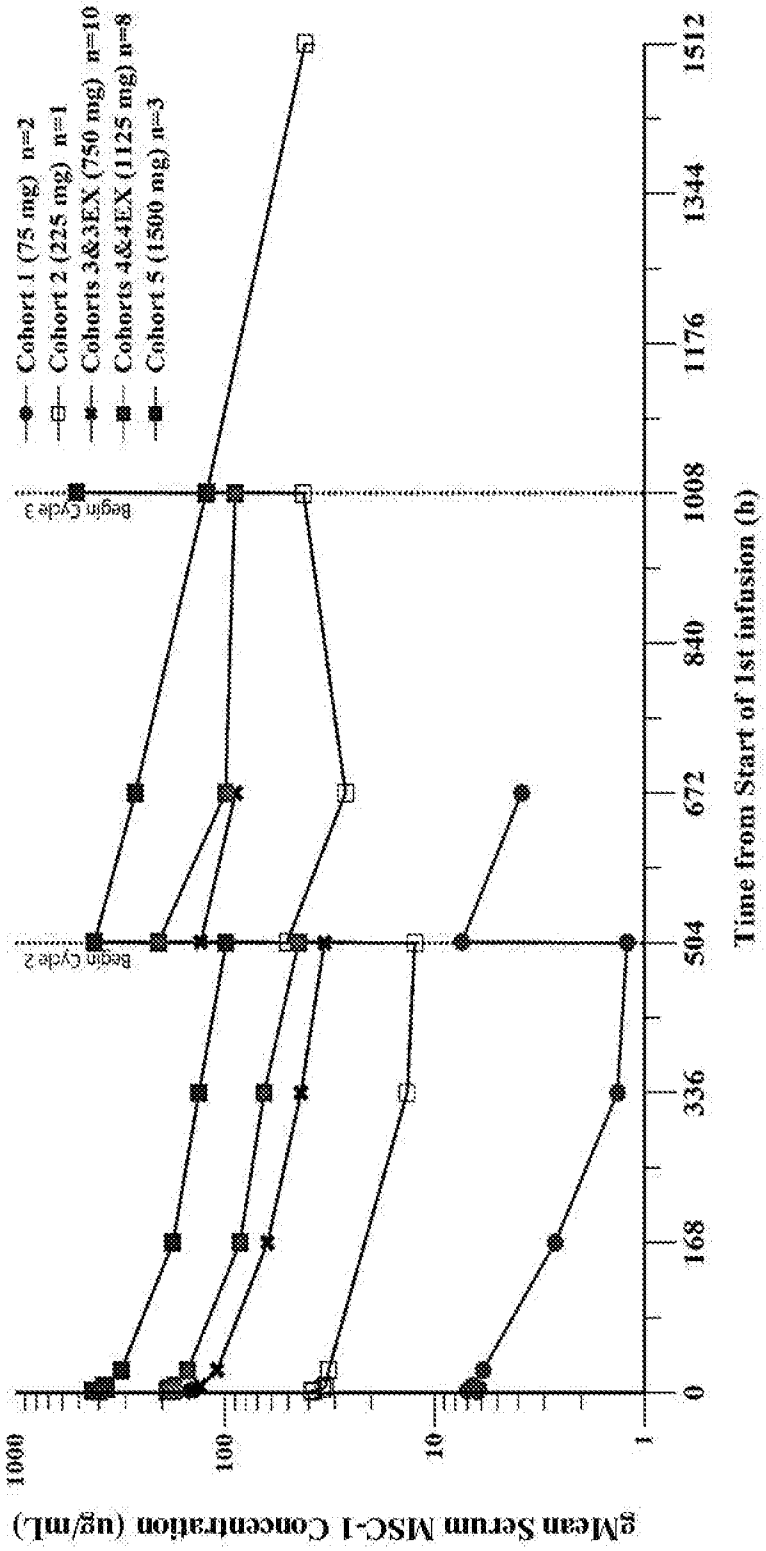
Cohort 1 (75 mg) n=2
Cohort 2 (225 mg) n=1
Cohorts 3&3EX (750 mg) n=10
Cohorts 4&4EX (1125 mg) n=8
Cohort 5 (1500 mg) n=3
Begin Cycle 3
Begin Cycle 2
gMean Serum MSC-1 Concentration (ug/mL)
1000
100
10
1
0
168
336
504
672
840
1008
1176
1344
1512
Time from Start of 1st infusion (h)

Fig. 26

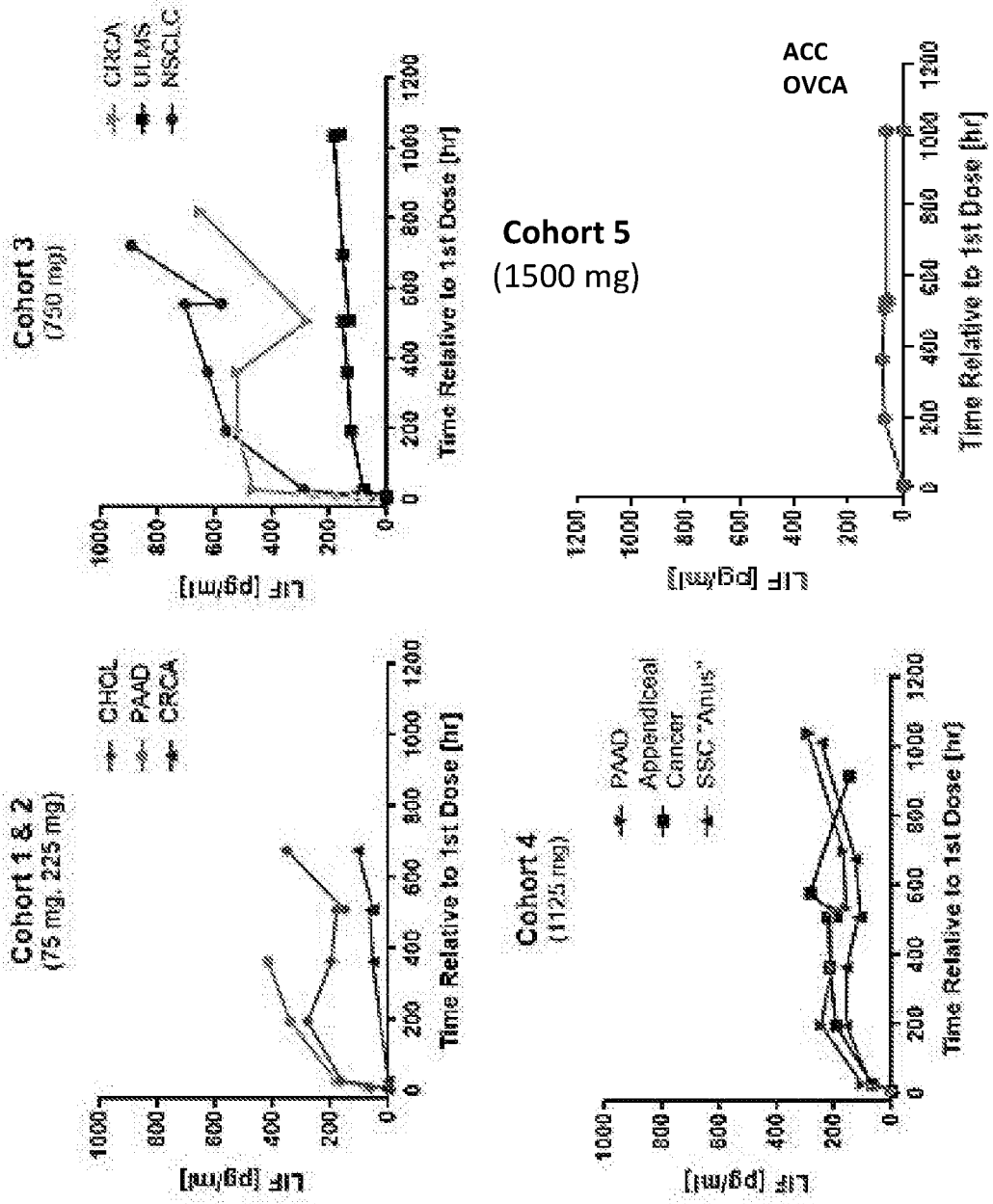
Cohort 1 & 2
(75 mg, 225 mg)
CHOL
PAAD
CRCA
LIF [pg/ml]
Time Relative to 1st Dose [hr]
Cohort 3
(750 mg)
CRCA
UMS
NSCLC
LIF [pg/ml]
Time Relative to 1st Dose [hr]
Cohort 4
(1125 mg)
PAAD
Appendiceal Cancer
SSC "Anus"
LIF [pg/ml]
Time Relative to 1st Dose [hr]
Cohort 5
(1500 mg)
ACC
OVCA
LIF [pg/ml]
Time Relative to 1st Dose [hr]

Fig. 27A

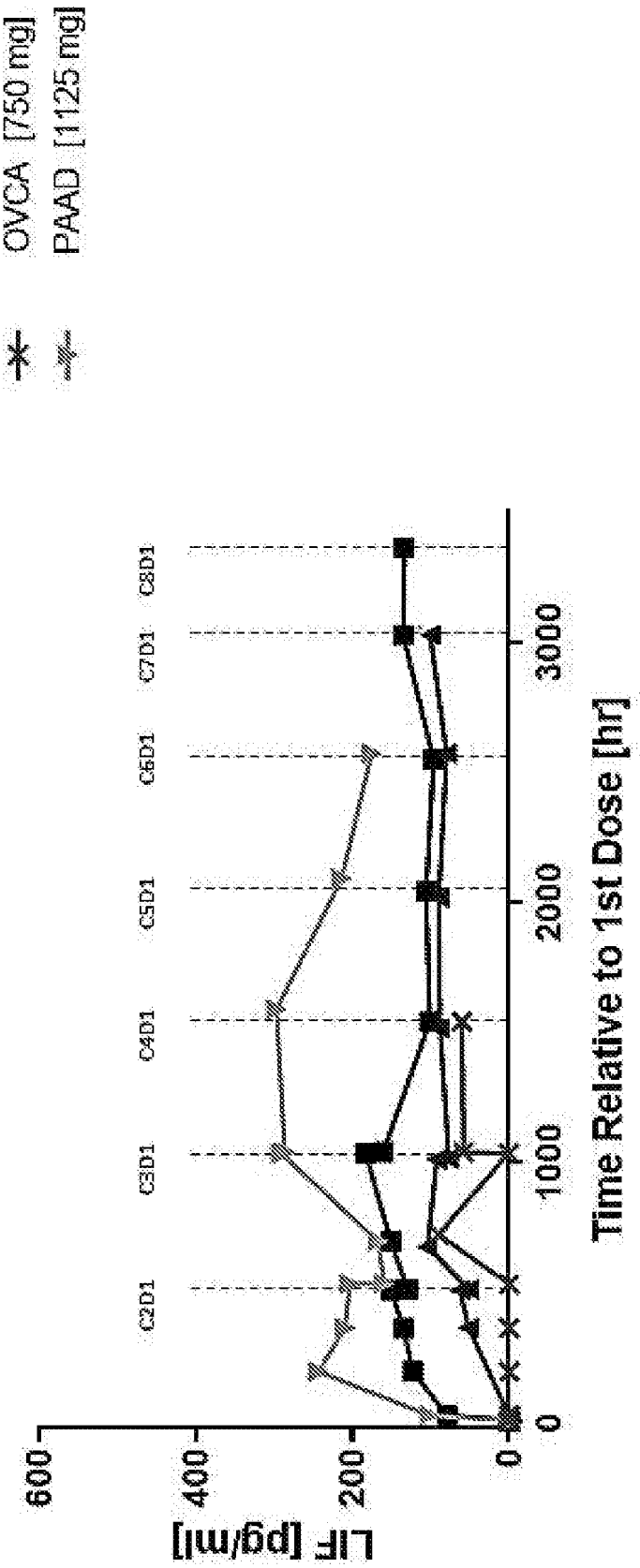
Total LIF
(Multi-dosed Patients)
* EOT
CRCA [225 mg]
ULMS [750 mg]
OVCA [750 mg]
PAAD [1125 mg]
C2D1
C3D1
C4D1
C5D1
C6D1
C7D1
C8D1
LIF [pg/ml]
600
400
200
0
0
1000
2000
3000
Time Relative to 1st Dose [hr]

Fig. 27B