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(71) **Demandeur/Applicant:**
SURFACE ONCOLOGY, LLC, US
(72) **Inventeurs/Inventors:**
O'NEILL, ALISON, US;
HARSHMAN, LAUREN, US;
HILL, JONATHAN, US;
CHUNG, JOU-KU, US;
WHITE, KERRY, US;
ROSS, ROBERT, US;
LEE, BENJAMIN, US
(74) **Agent:** GOWLING WLG (CANADA) LLP

(54) **Titre : ANTICORPS ANTI-IL-27 ET LEURS UTILISATIONS**
(54) **Title: ANTI-IL-27 ANTIBODIES AND USES THEREOF**

(57) **Abrégé/Abstract:**

The present disclosure relates to anti-IL-27 antibodies, and antigen-binding portions thereof. The disclosure also relates to methods for treating or ameliorating one or more symptoms of a disease, such as cancer, by administering the antibodies or antigen-binding portion thereof at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg.



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Abstract:

The present disclosure relates to anti-IL-27 antibodies, and antigen-binding portions thereof. The disclosure also relates to methods for treating or ameliorating one or more symptoms of a disease, such as cancer, by administering the antibodies or antigen-binding portion thereof at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg.

ANTI-IL-27 ANTIBODIES AND USES THEREOF**CROSS-REFERENCE TO RELATED APPLICATION**

[0001] This application claims priority to and benefit of U.S. Provisional Application Nos. US 63/185,989, filed on May 7, 2021; US 63/203,688, filed on July 28, 2021; and US 63/277,035, filed on November 8, 2021; each of which is hereby incorporated by reference herein in its entirety.

**REFERENCE TO SEQUENCE LISTING SUBMITTED
ELECTRONICALLY VIA EFS-WEB**

[0002] The content of the electronically submitted sequence listing (Name: 4416_013PC03_Seqlisting_ST25.txt; Size: 156,680 bytes; and Date of Creation: May 6, 2022) is herein incorporated by reference in its entirety.

FIELD

[0003] The present disclosure relates generally to compositions and methods for modulating IL-27 signaling. More particularly, the present disclosure relates to immunogenic compositions (e.g., antibodies, antibody fragments, and the like) that bind to IL-27 and modulate IL-27 signaling.

BACKGROUND

[0004] In recent years, an increasing body of evidence suggests that the immune system operates as a significant barrier to tumor formation and progression. The principle that naturally occurring T cells with anti-tumor potential or activity exist in a patient with cancer has rationalized the development of immunotherapeutic approaches in oncology. Immune cells, such as T cells, macrophages, and natural killer cells, can exhibit anti-tumor activity and effectively control the occurrence and growth of malignant tumors. Tumor-specific or -associated antigens can induce immune cells to recognize and eliminate malignancies (Chen & Mellman, (2013) *Immunity* 39(1):1-10). In spite of the existence of tumor-specific immune responses, malignant tumors often evade or avoid immune attack through a variety of immunomodulatory mechanisms resulting in the failure to control tumor occurrence and progression (Motz & Coukos, (2013) *Immunity* 39(1):61-730). Indeed, an emerging hallmark of cancer is the exploitation of these immunomodulatory mechanisms and the disablement of anti-tumor immune responses, resulting

in tumor evasion and escape from immunological killing (Hanahan and Weinberg (2011) *Cell* 144(5):646-674).

[0005] IL-27 is a heterodimeric cytokine, composed of two subunits (EBI3 and IL-27p28). IL-27 is structurally related to both the IL-12 and IL-6 cytokine families. IL-27 binds to and mediates signaling through a heterodimer receptor consisting of IL-27R α (WSX1) and gp130 chains, which mediate signaling predominantly through STAT1 and STAT3. Initial reports characterized IL-27 as an immune-enhancing cytokine that supports CD4⁺ T cell proliferation, T helper (Th)1 cell differentiation, and IFN- γ production, often acting in concert with IL-12. Subsequent studies have shown that IL-27 displays complex immunomodulatory functions, resulting in either proinflammatory or anti-inflammatory effects depending on the biological context and experimental models being used. IL-27 may drive the expression of different immune-regulatory molecules in human cancer cells, which may support local derangement of the immune response *in vivo* (Fabbi et al., (2017) *Mediators Inflamm* 3958069. Published online 2017 Feb 1. doi:10.1155/2017/3958069, and references contained therein).

[0006] Despite the significant advances being made in cancer treatment and management, there is still an ongoing need for new and effective therapies for treating and managing cancer.

SUMMARY OF THE DISCLOSURE

[0007] Some aspects of the present disclosure are directed to a method of stimulating an immune response in a subject, the method comprising administering to the subject an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof specifically binds to an epitope comprising one or more amino acids of (i) amino acids 37 to 56 corresponding to SEQ ID NO: 2 (IL-27p28), (ii) amino acids 142 to 164 corresponding to SEQ ID NO: 2 (IL-27p28), or (iii) both (i) and (ii); wherein the antibody or antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg.

[0008] Some aspects of the present disclosure are directed to a method of treating a cancer in a subject in need thereof comprising administering to the subject an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof specifically binds to an epitope comprising one or more amino acids of (i) amino acids 37 to 56 corresponding to SEQ ID NO: 2 (IL-27p28), (ii) amino acids 142 to 164 corresponding to SEQ ID NO: 2 (IL-27p28), or (iii) both (i) and (ii); wherein the antibody or

antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg.

[0009] In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg, at least about 0.006 mg/kg, at least about 0.009 mg/kg, at least about 0.03 mg/kg, at least about 0.06 mg/kg, at least about 0.09 mg/kg, at least about 0.3 mg/kg, at least about 0.6 mg/kg, at least about 0.9 mg/kg, at least about 1.0 mg/kg, at least about 2 mg/kg, at least about 3 mg/kg, at least about 4 mg/kg, at least about 5 mg/kg, at least about 6 mg/kg, at least about 7 mg/kg, at least about 8 mg/kg, at least about 9 mg/kg, at least about 10 mg/kg, at least about 11 mg/kg, at least about 12 mg/kg, at least about 13 mg/kg, at least about 14 mg/kg, at least about 15 mg/kg, at least about 16 mg/kg, at least about 17 mg/kg, at least about 18 mg/kg, at least about 19 mg/kg, or at least about 20 mg/kg.

[0010] In some aspects, the antibody or antigen binding portion thereof is administered once about every week, once about every two weeks, once about every three weeks, once about every four weeks, once about every 6 weeks, once about every 8 weeks, or once about every 12 weeks.

[0011] In some aspects, the antibody or antigen binding portion thereof is administered once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 0.3 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 1 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 3 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 6 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 10 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 13 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 16 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 20 mg/kg once about every four weeks.

[0012] In some aspects, the antibody or antigen binding portion thereof inhibits or reduces IL-27-dependent STAT1 and/or STAT3 phosphorylation in a cell in the subject. In some aspects, the antibody or antigen binding portion thereof inhibits or reduces inhibition of CD161 expression in a cell in the subject. In some aspects, the antibody or antigen binding portion thereof inhibits or

reduces PD-L1 expression in a cell in the subject. In some aspects, the antibody or antigen binding portion thereof induces or enhances PD-1 mediated secretion of one or more cytokines from a cell in the subject. In some aspects, the anti-IL-27 antibody alters the expression of TIM-3 in a cell. In some aspects, the cell is a tumor cell or an immune cell.

[0013] In some aspects, the epitope comprises one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, or Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope comprises Asp146, Arg149, and/or Phe153 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope further comprises His150 and/or Leu156 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope further comprises Gln37, Leu38, Glu42, Leu142, and/or Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope further comprises Glu46, Val49, Ser50, and/or Leu162 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope consists or consists essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope further comprises one or more amino acids of Leu53, Lys56, Asp143, Leu147, Arg152, Ala157, Gly159, Phe160, or Asn161 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope further comprises one or more amino acids of Leu53, Lys56, Asp143, Arg145, Leu147, Arg152, Ala157, Gly159, Phe160, Asn161, or Pro163 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope consists or consists essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope consists or consists essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164, of SEQ ID NO: 2 (IL-27p28).

[0014] In some aspects, the antibody or the antigen binding portion thereof comprise heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and light chain CDR3, wherein (i) light chain CDR1 consists of N-XXXXXXLFSSNXXKXYXX-C, light chain CDR3 consists of N-XXXASAXXX-C, heavy chain CDR2 consists of N-XXSSXSXYXXXXXXXXXX-C, and heavy chain CDR3 consists of N-XXXXGRTSYTATXHNXXXX-C, wherein X is any amino acids.

[0015] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 121 or 124. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 120 or 123. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 119 or 122. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 129 or 132. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR2 comprising the sequence set forth in SEQ ID NO: 128 or 131. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR1 comprising the sequence set forth in SEQ ID NO: 127 or 130.

[0016] In some aspects, the antibody or the antigen binding portion thereof comprises: (a) a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, and a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121; or (b) a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, and a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124.

[0017] In some aspects, the antibody or the antigen binding portion thereof comprises: (a) a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129; or (b) a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132.

[0018] In some aspects, the antibody or the antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129.

[0019] In some aspects, the antibody or the antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132.

[0020] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 125. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain variable region comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133.

[0021] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 135. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 139. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence

set forth in SEQ ID NO: 139 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137.

[0022] In some aspects, the cancer is selected from lung cancer (e.g., non-small cell lung cancer), sarcoma, testicular cancer, ovarian cancer, pancreas cancer, breast cancer (e.g., triple-negative breast cancer), melanoma, head and neck cancer (e.g., squamous head and neck cancer), colorectal cancer, bladder cancer, endometrial cancer, prostate cancer, thyroid cancer, hepatocellular carcinoma (HCC), gastric cancer, brain cancer, lymphoma (e.g., DL-BCL), leukemia (e.g., AML), renal cancer (e.g., renal cell carcinoma (RCC), e.g., clear cell RCC and/or non-clear cell RCC), and any combination thereof.

[0023] In some aspects, the method further comprises administering an additional therapeutic agent to the subject. In some aspects, the additional therapeutic agent is administered before the antibody or antigen-binding portion thereof, after the antibody or antigen-binding portion thereof, or concurrently with the antibody or antigen-binding portion thereof.

In some aspects, the additional therapeutic agent comprises a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, a cellular immunotherapy, a biologic agent, or a combination thereof. In some aspects, the additional therapeutic agent comprises a PD-1 antagonist, a PD-L1 inhibitor, a TIM-3 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, a CD112R inhibitor, a TAM inhibitor, a STING agonist, a 4-1BB agonist, or a combination thereof.

[0024] In some aspects, the additional therapeutic agent comprises a PD-1 antagonist. In some aspects, the PD-1 antagonist is selected from the group consisting of: PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224. In some aspects, the PD-L1 inhibitor is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559. In some aspects, the additional therapeutic agent is selected from the group consisting of Sunitinib (SUTENT[®]), Cabozantinib (CABOMETYX[®]), Axitinib (INLYTA[®]), Lenvatinib (LENVIMA[®]), Everolimus (AFINITOR[®]), Bevacizumab (AVASTIN[®]), epacadostat, NKTR-214 (CD-122-biased agonist), Tivozanib (FOTIVDA[®]), abexinostat, Ipilimumab (YERVOY[®]), tremelimumab, Pazopanib (VOTRIENT[®]), Sorafenib (NEXAVAR[®]), Temsirolimus (TORISEL[®]), Ramucirumab (CYRAMZA[®]), niraparib, savolitinib, vorolanib (X-82), Regorafenib (STIVARGO[®]), Donafenib (multikinase inhibitor), Camrelizumab (SHR-1210), pexastimogene devacirepvec (JX-594), Ramucirumab

(CYRAMZA[®]), apatinib (YN968D1), encapsulated doxorubicin (THERMODOX[®]), Tivantinib (ARQ197), ADI-PEG 20, binimetinib, apatinib mesylate, nintedanib, lirilumab, Nivolumab (OPDIVO[®]), Pembrolizumab (KEYTRUDA[®]), Atezolizumab (TECENTRIQ[®]), Avelumab (BAVENCIO[®]), Durvalumab (IMFIMZI[®]), Cemiplimab-rwlc (LIBTAYO[®]), tislelizumab, and spartalizumab. In some aspects, the additional therapeutic agent is a TIM-3 inhibitor. In some aspects, the TIM-3 inhibitor is MGB453 or TSR-022. In some aspects, the additional therapeutic agent is a LAG-3 inhibitor. In some aspects, the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, and TSR-033. In some aspects, the additional therapeutic agent is a TIGIT inhibitor. In some aspects, the additional therapeutic agent is a CD112R inhibitor. In some aspects, the additional therapeutic agent is a TAM (Axl, Mer, Tyro) inhibitor. In some aspects, the additional therapeutic agent is a 4-1BB agonist. In some aspects, the additional therapeutic agent is a Tyrosine Kinase Inhibitor (TKI).

[0025] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of one or more biomarkers selected from the group consisting of EBI3, IL-27, TNF α , MIP-1 α (CCL3), IFN γ , IL-10, IL-6, and any combination thereof; wherein the increased expression of the one or more biomarkers is relative to the expression of the one or more biomarker prior to the administration. In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of EBI3; wherein the increased expression EBI3 is relative to the expression EBI3 prior to the administration.

[0026] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of one or more biomarkers selected from the group consisting of Eotaxin-1 (CCL11), TARC (CCL17), VEGF-A, IL-7, IL-8, MCP-1, MCP-4, and any combination thereof; wherein the increased expression of the one or more biomarkers is relative to the expression of the one or more biomarker prior to the administration. In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of Eotaxin-1 (CCL11), wherein the increased expression of Eotaxin-1 (CCL11) is relative to the expression of Eotaxin-1 (CCL11) prior to the administration.

[0027] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits an increased circulating level of IFN γ , relative to the circulating level of IFN γ prior to the administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] **FIGs. 1A-1C** are schematics of a phase 1 dose-escalation study for an anti-IL-27 antibody. ccRCC = clear cell renal cell carcinoma; CR = complete response; HCC = hepatocellular carcinoma; N = number; PR = partial response; pts = patients, RP2D = recommended Phase 2 dose; 2L = second line. Dose level 1 = 0.003 mg/kg; Dose level 2 = 0.03 mg/kg; Dose level 3 = 0.1 mg/kg; Dose level 4 = 0.3 mg/kg; Dose level 5 = 1.0 mg/kg; Dose level 6 = 3.0 mg/kg; Dose level 7 = 10.0 mg/kg; Dose level 8 = 20.0 mg/kg (FIG. 1A).

[0029] **FIG. 2** is a Swimmer's plot showing the time on study and RECIST response grouped by starting dose.

[0030] **FIG. 3** is a waterfall plot illustrating the best percentage change in target lesions from baseline.

[0031] **FIG. 4** is a graphical representation of the pharmacokinetics of anti-IL-27 Ab1 administered at doses of 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg.

[0032] **FIGs. 5A-5B** are graphical representation of T cells gated using an anti-CD-3 antibody (**FIG. 5A**) and analyzed using an anti-pSTAT1 Y701 antibody, as compared to pre-dose (**FIG. 5B**). **FIGs. 5C-5D** are bar graphs illustrating pSTAT1 inhibition following administration of 0.1 mg/kg (**FIG. 5C**) or 1 mg/kg (**FIG. 5D**) anti-IL-27 Ab1 predose and up to cycle 2, day 1.

[0033] **FIGs. 6A-6F** are images of target lesions (target lesion 1, **FIGs. 6A-6C**; target lesion 2, **FIGs 6C-6F**; arrows) in a 64-year-old patient with squamous cell non-small cell lung cancer with metastases to the mediastinal nodes, lung, and pleura who was enrolled at 10 mg/kg. **FIGs. 6A and 6D** are images at baseline, **FIGs. 6B and 6E** are images at week 8, and **FIGs. 6C and 6F** are images at week 12.

[0034] **FIG. 7** is a Swimmer's plot depicting time on study and RECIST response grouped by starting dose of the 29 patients enrolled in a dose escalation study. The median time on study was 9 weeks (with a range of 1 to 71 weeks).

[0035] **FIGs. 8A-8B** show target lesion changes over time. **FIG. 8A** is a waterfall plot depicting the best percentage change in target lesions from baseline (n=27). **FIG. 8B** is a spider plot depicting the target lesion change from baseline over time.

[0036] **FIGs. 9A-9B** are graphical representations of anti-IL-27 Ab1 monotherapy dose escalation response. **FIG. 9A** is a waterfall plot depicting the best percentage change in sum of target lesions. **FIG. 9B** is a spider plot depicting the lesion change over time.

[0037] **FIGs. 10A-10B** are graphical representation of the anti-IL-27 Ab1 pharmacokinetic profile. **FIG. 10A** shows Cycle 1 anti-IL-27 Ab1 PK by dose regimen, irrespective of tumor type. **FIG. 10B** shows the PK of anti-IL-27 Ab1 when given once every four weeks as monotherapy in the dose escalation phase of the study (mixed solid tumors) and in the HCC and ccRCC expansions.

[0038] **FIGs. 11A-11B** are graphical representations of anti-IL-27 Ab1 ccRCC monotherapy dose escalation response. **FIG. 11A** is a waterfall plot depicting the best percentage change in sum of target lesions. **FIG. 11B** is a spider plot depicting the lesion change over time.

[0039] **FIGs. 12A-12B** are graphical representations of anti-IL-27 Ab1 HCC monotherapy response. **FIG. 12A** is a waterfall plot depicting the best percentage change in sum of target lesions. **FIG. 12B** is a spider plot depicting the lesion change over time.

[0040] **FIGs. 13A** is graphical representation of IL-27-dependent pSTAT1 inhibition in T cells from the blood of a patient following administration of 0.1 mg/kg, 1.0 mg/kg, and 3.0 mg/kg of an anti-IL-27 antibody (y-axis) and the corresponding serum levels of the anti-IL-27 antibody (x-axis) after anti-IL-27 antibody administration. The vertical dotted line represents the serum concentration of anti-IL-27 antibody that results in 90% inhibition (IC₉₀) of IL-27-dependent pSTAT1 inhibition (0.7 µg/ml). **FIGs. 13B-13D** show the pharmacokinetic analysis of anti-IL-27 antibody in the serum of subjects following repeated administration of 0.1 mg/kg (**FIG. 13B**), 1.0 mg/kg (**FIG. 13C**), and 3.0 mg/kg (**FIG. 13D**) of an anti-IL-27 antibody, once every 28 days. The serum level of anti-IL-27 antibody required to achieve the IC₉₀ for IL-27-dependent inhibition of pSTAT1 in T cells from the blood of a subject is indicated by the horizontal dotted line in **FIGs. 13B-13D**.

[0041] **FIG. 14A** is a graphical representation of Eotaxin-1 fold-change at C1D1 6-hour post dose time-point, relative to baseline, for patients exhibiting progressive disease (PD), stable disease (SD), or partial response (PR) following administration of varying doses of anti-IL-27 Ab1. **FIG. 14B** is a graphical representation of a longitudinal analysis of Eotaxin-1 fold-change over baseline across C1D1 (predose and 6 hours post dose), C1D8, C2D1 (predose and 6 hours post dose), and C3D1 timepoints. The data for the patient exhibiting a partial response is labelled as "PR." Each data set represents a single patient.

[0042] **FIG. 15** shows IL-27 fold-change levels over baseline at various visits, times, and dosage cohorts for anti-IL-27 Ab1 monotherapy patients.

[0043] **FIG. 16** shows circulating IFNγ fold-change levels over baseline at various visits and times for 10mg/kg anti-IL-27 Ab1 monotherapy patients.

[0044] **FIGs. 17A-17F** are graphical representations of fold-change expression relative to baseline of TARC (CCL17; **FIG. 17A**), VEGF-A (**FIG. 17B**), IL-7 (**FIG. 17C**), IL-8 (**FIG. 17D**), MCP-1 (**FIG. 17E**), and MCP-4 (**FIG. 17F**) in samples obtained from patients administered anti-IL-27 Ab1. **FIG. 17G** is a waterfall plot showing the percent change from baseline in target lesions for patients characterized in **FIGs. 17A-17F**. Data corresponding to a confirmed partial response (PR; 902-002) patient and a stable disease (SD; 901-008) patient exhibiting tumor reduction are labelled (**FIGs. 17A-17G**).

[0045] **FIGs. 18A-18B** are graphical representations of longitudinal analyses of IL-7, TARC (CCL17), and VEGF-A (**FIG. 18A**) and IL-8, MCP-1, and MCP-4 (**FIG. 18B**), as indicated, in samples obtained from patients administered anti-IL-27 Ab1. Data corresponding to a patient with a confirmed partial response (PR; 902-002) and a patient with stable disease (SD; 901-008) but exhibiting tumor reduction are labelled (**FIGs. 18A-18B**).

[0046] **FIG. 19** is a scatter plot illustrating IL-27-induced changes in gene expression from two individuals.

[0047] **FIGs. 20A-20C** are scatter plots illustrating changes in gene expression from two individuals following contact with IL-27 heterodimer (**FIG. 20A**), EBI3 alone (**FIG. 20B**), or IL-35 (**FIG. 20C**).

[0048] **FIGs. 21A-21B** are volcano plots representing a gene set enrichment analysis of the IL-27 gene signature from CD4⁺ T cells. **FIG. 21A** highlights (gray) enrichment of mRNA signatures associated with interferon signaling. **FIG. 21B** highlights (gray) hallmark IFN α signature genes.

[0049] **FIG. 22A-22H** are graphical representations of single cell RNA-sequencing analysis of PBMCs stimulated with anti-CD3 (0.25 μ g/ml) *in vitro* in the presence or absence of rhIL-27 (100 ng/ml). **FIG. 22A** shows the clustering of the various types of immune cells. **FIG. 22B** is a volcano plot illustrating IL-27-mediated gene expression changes identified in the total PBMC population, which included many interferon-stimulated genes. **FIGs. 22C-22H** are volcano plots illustrating the downregulation and upregulation of IL-27 signature genes in the immune cell subsets of NK cells (**FIG. 22C**), CD4⁺ T cells (**FIG. 22D**), B cells (**FIG. 22E**), monocytes (**FIG. 22F**), CD8⁺ T cells (**FIG. 22G**) and Treg cells (**FIG. 22H**).

[0050] **FIGs. 23A-23B** are bar graphs illustrating assessment of IL-17A (**FIG. 23A**) and IFN- γ (**FIG. 23B**) in cultured supernatants of pooled PBMCs activated in the presence of anti-CD3

(0.25 µg/ml) and anti-PD-1 (1 µg/ml) in the presence of various cytokines (100 ng/ml; x-axis) for 4 days.

[0051] **FIG. 24A** shows the clustering of the various types of immune cells based on single-cell RNA-seq analysis of IL27 expression. **FIG. 24B** is a scatter plot showing an MF2 macrophage gene signature associated with progressive disease contains several interferon-stimulated genes and is highly enriched in IL27-positive vs IL27-negative macrophages. **FIGs. 24C-24E** are graphical representations illustrating increased expression of IL27 in macrophages from patients with progressive disease (**FIG. 24C**); in macrophages from metastatic and primary tumors compared to normal tissue (**FIG. 24F**); and in macrophages from patients with Stage IV disease (**FIG. 24E**). **FIG. 24F** is a volcano plot illustrating the MF2 signature genes (gray) of IL-27 stimulated monocyte-derived macrophages *in vitro*. **FIGs. 24G-24H** are images of immunohistochemistry for IL-27 on tissue microarrays showing positive expression in macrophages in the TME of lung adenocarcinoma (AdenoCa; **FIG. 24G**) and squamous cell carcinoma (SCC; **FIG. 24H**).

[0052] **FIG. 25A** shows the clustering of the various types of cells in the tumor microenvironment based on single-cell RNA-seq analysis of IL27 expression. **FIG. 25B** is a violin plot of IL27RA expression in different cell populations compared to tumor cells. **FIG. 25C** is a violin plot of IL27RA expression in tumor cells from patients with progressive disease compared to tumor cells from patients with residual disease or who are treatment naïve.

[0053] **FIG. 26A** is a bar graph illustrating IL27RA mRNA transcript expression across the Cancer Cell Line Encyclopedia (CCLE) for various lung cancer cell lines including NCI-H2228. **FIGs. 26B-26C** are graphical representations illustrating pSTAT1 levels (**FIG. 26B**) and PDL1 expression (**FIG. 26C**) in NCI-H2228 lung cancer cells after IL-27 stimulation. **FIG. 26D** is a graphical representation of microarray profiling of NCI-H228 cells cultured in the presence or absence of IL-27 for 48 hrs. Several interferon-responsive genes are flagged (**FIG. 26D**).

DETAILED DESCRIPTION

[0054] Some aspects of the present disclosure are directed to methods of stimulating an immune response in a subject, the method comprising administering to the subject an antibody or an antigen binding portion thereof that antagonizes human IL-27, or an antigen binding portion thereof. Some aspects of the present disclosure are directed to methods of treating a cancer in a subject in need thereof comprising administering to the subject an antibody that antagonizes human IL-27, or an antigen binding portion thereof. In some aspects, the antibody or an antigen binding

portion thereof is administered at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg. In some aspects, the antibody or antigen binding portion thereof specifically binds to an epitope comprising one or more amino acids of (i) amino acids 37 to 56 corresponding to SEQ ID NO: 2 (IL-27p28), (ii) amino acids 142 to 164 corresponding to SEQ ID NO: 2 (IL-27p28), or (iii) both (i) and (ii).

I. Definitions

[0055] Terms used in the claims and specification are defined as set forth below unless otherwise specified.

[0056] It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise.

[0057] As used herein, "about" will be understood by persons of ordinary skill and will vary to some extent depending on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill given the context in which it is used, "about" will mean up to plus or minus 10% of the particular value.

[0058] As used herein, the term "agonist" refers to any molecule that partially or fully promotes, induces, increases, and/or activates a biological activity of a native polypeptide disclosed herein. Suitable agonist molecules specifically include agonist antibodies or antibody fragments, fragments or amino acid sequence variants of native polypeptides, peptides or proteins. In some aspects, activation in the presence of the agonist is observed in a dose-dependent manner. In some aspects, the measured signal (e.g., biological activity) is at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% higher than the signal measured with a negative control under comparable conditions. Also disclosed herein, are methods of identifying agonists suitable for use in the methods of the disclosure. For example, these methods include, but are not limited to, binding assays such as enzyme-linked immuno-absorbent assay (ELISA), FORTE BIO® systems, and radioimmunoassay (RIA). These assays determine the ability of an agonist to bind the polypeptide of interest (e.g., a receptor or ligand) and therefore indicate the ability of the agonist to promote, increase or activate the activity of the polypeptide. Efficacy of an agonist can also be determined using functional assays, such as the ability of an agonist to activate

or promote the function of the polypeptide. For example, a functional assay may comprise contacting a polypeptide with a candidate agonist molecule and measuring a detectable change in one or more biological activities normally associated with the polypeptide. The potency of an agonist is usually defined by its EC₅₀ value (concentration required to activate 50% of the agonist response). The lower the EC₅₀ value the greater the potency of the agonist and the lower the concentration that is required to activate the maximum biological response.

[0059] As used herein, the term "alanine scanning" refers to a technique used to determine the contribution of a specific wild-type residue to the stability or function(s) (e.g., binding affinity) of given protein or polypeptide. The technique involves the substitution of an alanine residue for a wild-type residue in a polypeptide, followed by an assessment of the stability or function(s) (e.g., binding affinity) of the alanine-substituted derivative or mutant polypeptide and comparison to the wild-type polypeptide. Techniques to substitute alanine for a wild-type residue in a polypeptide are known in the art.

[0060] The term "ameliorating" refers to any therapeutically beneficial result in the treatment of a disease state, e.g., cancer, including prophylaxis, lessening in the severity or progression, remission, or cure thereof.

[0061] As used herein, the term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., a carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that function in a manner similar to a naturally occurring amino acid.

[0062] Amino acids can be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, can be referred to by their commonly accepted single-letter codes.

[0063] As used herein, an "amino acid substitution" refers to the replacement of at least one existing amino acid residue in a predetermined amino acid sequence (an amino acid sequence of a starting polypeptide) with a second, different "replacement" amino acid residue. An "amino acid insertion" refers to the incorporation of at least one additional amino acid into a predetermined amino acid sequence. While the insertion will usually consist of the insertion of one or two amino acid residues, larger "peptide insertions," can also be made, e.g. insertion of about three to about five or even up to about ten, fifteen, or twenty amino acid residues. The inserted residue(s) may be naturally occurring or non- naturally occurring as disclosed above. An "amino acid deletion" refers to the removal of at least one amino acid residue from a predetermined amino acid sequence.

[0064] As used herein, the term "amount" or "level" is used in the broadest sense and refers to a quantity, concentration or abundance of a substance (e.g., a metabolite, a small molecule, a protein, an mRNA, a marker). When referring to a metabolite or small molecule (e.g. a drug), the terms "amount", "level" and "concentration" are generally used interchangeably and generally refer to a detectable amount in a biological sample. "Elevated levels" or "increased levels" refers to an increase in the quantity, concentration or abundance of a substance within a sample relative to a control sample, such as from an individual or individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control. In some aspects, the elevated level of a substance (e.g., a drug) in a sample refers to an increase in the amount of the substance of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% relative to the amount of the substance in a control sample, as determined by techniques known in the art (e.g., HPLC). "Reduced levels" refers to a decrease in the quantity, concentration or abundance of a substance (e.g., a drug) in an individual relative to a control, such as from an individual or individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control. In some aspects, a reduced level is little or no detectable quantity, concentration or abundance. In some aspects, the reduced level of a substance (e.g., a drug) in a sample refers to a decrease in the amount of the substance of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% relative to the amount of the substance in a control sample, as determined by techniques known in the art (e.g., HPLC).

[0065] When referring to a protein, mRNA or a marker, such as those described herein, the terms "level of expression" or "expression level" in general are used interchangeably and generally refer to a detectable amount of a protein, mRNA, or marker in a biological sample. In some aspects,

a detectable amount or detectable level of a protein, mRNA or a marker is associated with a likelihood of a response to an agent, such as those described herein. "Expression" generally refers to the process by which information contained within a gene is converted into the structures (e.g., a protein marker, such as PD-L1) present and operating in the cell. Therefore, as used herein, "expression" may refer to transcription into a polynucleotide, translation into a polypeptide, or even polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide). Fragments of the transcribed polynucleotide, the translated polypeptide, or polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide) shall also be regarded as expressed whether they originate from a transcript generated by alternative splicing or a degraded transcript, or from a post-translational processing of the polypeptide, e.g., by proteolysis. "Expressed genes" include those that are transcribed into a polynucleotide as mRNA and then translated into a polypeptide, and also those that are transcribed into RNA but not translated into a polypeptide (for example, transfer and ribosomal RNAs). "Elevated expression," "elevated expression levels," or "elevated levels" refers to an increased expression or increased levels of a substance within a sample relative to a control sample, such as an individual or individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control. In some aspects, the elevated expression of a substance (e.g., a protein marker, such as PD-L1) in a sample refers to an increase in the amount of the substance of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% relative to the amount of the substance in a control sample, as determined by techniques known in the art (e.g., FACS). "Reduced expression," "reduced expression levels," or "reduced levels" refers to a decrease expression or decreased levels of a substance (e.g., a protein marker) in an individual relative to a control, such as an individual or individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control. In some aspects, reduced expression is little or no expression. In some aspects, the reduced expression of a substance (e.g., a protein marker) in a sample refers to a decrease in the amount of the substance of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% relative to the amount of the substance in a control sample, as determined by techniques known in the art (e.g., FACS).

[0066] As used herein, the term "angiogenesis" or "neovascularization" refers to the process by which new blood vessels develop from pre-existing vessels (Varner et al., (1999) *Angiogen.* 3:53-60; Mousa et al., (2000) *Angiogen. Stim. Inhib.* 35:42-44; Kim et al., (2000) *Amer.*

J. Path. 156:1345-1362; Kim et al., (2000) *J. Biol. Chem.* 275:33920-33928; Kumar et al. (2000) *Angiogenesis: From Molecular to Integrative Pharm.* 169-180). Endothelial cells from pre-existing blood vessels or from circulating endothelial stem cells (Takahashi et al., (1995) *Nat. Med.* 5:434-438; Isner et al., (1999) *J. Clin. Invest.* 103:1231-1236) become activated to migrate, proliferate, and differentiate into structures with lumens, forming new blood vessels, in response to growth factor or hormonal cues, or hypoxic or ischemic conditions. During ischemia, such as occurs in cancer, the need to increase oxygenation and delivery of nutrients apparently induces the secretion of angiogenic factors by the affected tissue; these factors stimulate new blood vessel formation. Several additional terms are related to angiogenesis.

[0067] The term “antagonist,” as used herein, refers to an inhibitor of a target molecule and may be used synonymously herein with the term “inhibitor.” As used herein, the term “antagonist” refers to any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native polypeptide disclosed herein. Suitable antagonist molecules specifically include antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native polypeptides, peptides or proteins. In some aspects, inhibition in the presence of the antagonist is observed in a dose-dependent manner. In some aspects, the measured signal (e.g., biological activity) is at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% lower than the signal measured with a negative control under comparable conditions. Also disclosed herein, are methods of identifying antagonists suitable for use in the methods of the disclosure. For example, these methods include, but are not limited to, binding assays such as enzyme-linked immuno-absorbent assay (ELISA), ForteBio® systems, radioimmunoassay (RIA), Meso Scale Discovery assay (e.g., Meso Scale Discovery Electrochemiluminescence (MSD-ECL), and bead-based Luminex® assay. These assays determine the ability of an antagonist to bind the polypeptide of interest (e.g., a receptor or ligand) and therefore indicate the ability of the antagonist to inhibit, neutralize or block the activity of the polypeptide. Efficacy of an antagonist can also be determined using functional assays, such as the ability of an antagonist to inhibit the function of the polypeptide or an agonist. For example, a functional assay may comprise contacting a polypeptide with a candidate antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the

polypeptide. The potency of an antagonist is usually defined by its IC₅₀ value (concentration required to inhibit 50% of the agonist response). The lower the IC₅₀ value the greater the potency of the antagonist and the lower the concentration that is required to inhibit the maximum biological response.

[0068] As used herein, the phrase "antibody that antagonizes human IL-27, or an antigen binding portion thereof" refers to an antibody that antagonizes at least one art-recognized activity of human IL-27 (e.g., IL-27 biological activity and/or downstream pathway(s) mediated by IL-27 signaling or other IL-27-mediated function), for example, relating to a decrease (or reduction) in human IL-27 activity that is at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more. Additional examples of IL-27 biological activities and/or downstream pathway(s) mediated by IL-27 signaling or other IL-27-mediated function are described in additional detail below and elsewhere herein.

[0069] As used herein, the term "anti-IL-27 antagonist antibody" (interchangeably termed "anti-IL-27 antibody") refers to an antibody that specifically binds to IL-27 and inhibits IL-27 biological activity and/or downstream pathway(s) mediated by IL-27 signaling or other IL-27-mediated function. An anti-IL-27 antagonist antibody encompasses antibodies that block, antagonize, suppress, inhibit or reduce an IL-27 biological activity (e.g., ligand binding, enzymatic activity), including downstream pathways mediated by IL-27 signaling or function, such as receptor binding and/or elicitation of a cellular response to IL-27 or its metabolites. In some aspects, an anti-IL-27 antagonist antibody provided by the disclosure binds to human IL-27 and prevents, blocks, or inhibits binding of human IL-27 to its cognate or normal receptor (e.g., IL-27 receptor), or one or more receptor subunits (e.g., gp130 and/or IL-27R α (also known as WSX1/TCCR)). In some aspects, the anti-IL-27 antagonist antibody prevents, blocks, or inhibits the binding of human IL-27 to the gp130. In some aspects, the anti-IL-27 antagonist antibody prevents, blocks, or inhibits the binding of human IL-27 to the IL-27R α . In some aspects, the anti-IL-27 antagonist antibody prevents, blocks, or inhibits the dimerization of IL-27 monomers. In some aspects, the anti-IL-27 antibody does not specifically bind to the EBI3 monomer. In some aspects, the anti-IL-27 antibody specifically binds to the IL-27p28 monomer. In some aspects, the anti-IL-27 antibody specifically binds to a non-contiguous epitope comprising P28, but does not bind to the EBI3 monomer. In some aspects, the anti-IL-27 antibody inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell. In some aspects, the anti-IL-27 antibody inhibits or reduces inhibition of CD161 expression in a cell (e.g., ameliorates or relieves IL-27 mediated

inhibition of CD161 expression in a cell). In some aspects, the anti-IL-27 antibody inhibits or reduces PD-L1 expression in a cell. In some aspects, the anti-IL-27 induces or enhances PD-1-mediated secretion of one or more cytokines from a cell. In some aspects, the anti-IL-27 antibody alters the expression of TIM-3 in a cell. In some aspects, an anti-IL-27 antagonist antibody binds to human IL-27 and stimulates or enhances an anti-tumor response. In some aspects, the anti-IL-27 antagonist antibody binds to human IL-27 with an affinity of 15nM or less. In some aspects, the anti-IL-27 antagonist antibody binds to human IL-27 and comprises a wild type or mutant IgG1 heavy chain constant region or a wild type or mutant IgG4 heavy chain constant region. Examples of anti-IL-27 antagonist antibodies are provided herein.

[0070] As used herein, the term "antibody" refers to a whole antibody comprising two light chain polypeptides and two heavy chain polypeptides. Whole antibodies include different antibody isotypes including IgM, IgG, IgA, IgD, and IgE antibodies. The term "antibody" includes a polyclonal antibody, a monoclonal antibody, a chimerized or chimeric antibody, a humanized antibody, a primatized antibody, a deimmunized antibody, and a fully human antibody. The antibody can be made in or derived from any of a variety of species, e.g., mammals such as humans, non-human primates (e.g., orangutan, baboons, or chimpanzees), horses, cattle, pigs, sheep, goats, dogs, cats, rabbits, guinea pigs, gerbils, hamsters, rats, and mice. The antibody can be a purified or a recombinant antibody. As used herein, the term "antibody fragment," "antigen-binding fragment," or similar terms refer to a fragment of an antibody that retains the ability to bind to a target antigen (e.g., IL-27) and inhibit the activity of the target antigen. Such fragments include, e.g., a single chain antibody, a single chain Fv fragment (scFv), an Fd fragment, an Fab fragment, an Fab' fragment, or an F(ab')₂ fragment. An scFv fragment is a single polypeptide chain that includes both the heavy and light chain variable regions of the antibody from which the scFv is derived. In addition, intrabodies, minibodies, triabodies, and diabodies are also included in the definition of antibody and are compatible for use in the methods described herein. See, e.g., Todorovska et al., (2001) *J. Immunol. Methods* 248(1):47-66; Hudson and Kortt, (1999) *J. Immunol. Methods* 231(1):177-189; Poljak, (1994) *Structure* 2(12):1121-1123; Rondon and Marasco, (1997) *Annu. Rev. Microbiol.* 51:257-283, the disclosures of each of which are incorporated herein by reference in their entirety.

[0071] As used herein, the term "antibody fragment" also includes, e.g., single domain antibodies such as camelized single domain antibodies. See, e.g., Muyldermans et al., (2001) *Trends Biochem. Sci.* 26:230-235; Nuttall et al., (2000) *Curr. Pharm. Biotech.* 1:253-263;

Reichmann et al., (1999) *J. Immunol. Meth.* 231:25-38; PCT application publication nos. WO 94/04678 and WO 94/25591; and U.S. patent no. 6,005,079, all of which are incorporated herein by reference in their entireties. In some aspects, the disclosure provides single domain antibodies comprising two VH domains with modifications such that single domain antibodies are formed.

[0072] In some aspects, an antigen-binding fragment includes the variable region of a heavy chain polypeptide and the variable region of a light chain polypeptide. In some aspects, an antigen-binding fragment described herein comprises the CDRs of the light chain and heavy chain polypeptide of an antibody.

[0073] The term "antigen presenting cell" or "APC" is a cell that displays foreign antigen complexed with MHC on its surface. T cells recognize this complex using T cell receptor (TCR). Examples of APCs include, but are not limited to, B cells, dendritic cells (DCs), peripheral blood mononuclear cells (PBMC), monocytes (such as THP-1), B lymphoblastoid cells (such as C1R.A2, 1518 B-LCL) and monocyte-derived dendritic cells (DCs). Some APCs internalize antigens either by phagocytosis or by receptor-mediated endocytosis.

[0074] The term "antigen presentation" refers to the process by which APCs capture antigens and enables their recognition by T cells, *e.g.*, as a component of an MHC-I and/or MHC-II conjugate.

[0075] As used herein, the term "apoptosis" refers to the process of programmed cell death that occurs in multicellular organisms (*e.g.* humans). The highly regulated biochemical and molecular events that result in apoptosis can lead to observable and characteristic morphological changes to a cell, including membrane blebbing, cell volume shrinkage, chromosomal DNA condensation and fragmentation, and mRNA decay. A common method to identify cells, including T cells, undergoing apoptosis is to expose cells to a fluorophore-conjugated protein (Annexin V). Annexin V is commonly used to detect apoptotic cells by its ability to bind to phosphatidylserine on the outer leaflet of the plasma membrane, which is an early indicator that the cell is undergoing the process of apoptosis.

[0076] As used herein, the term "B cell" (alternatively "B lymphocyte") refers to a type of white blood cell of the lymphocyte subtype. B cells function in the humoral immunity component of the adaptive immune system by secreting antibodies. B cells also present antigen and secrete cytokines. B cells, unlike the other two classes of lymphocytes, T cells and natural killer cells, express B cell receptors (BCRs) on their cell membrane. BCRs allow the B cell to bind to a specific antigen, against which it will initiate an antibody response.

[0077] As used herein, the term "binds to immobilized IL-27," refers to the ability of an antibody of the disclosure to bind to IL-27, for example, expressed on the surface of a cell or which is attached to a solid support.

[0078] As used herein, the term "bispecific" or "bifunctional antibody" refers to an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann, (1990) *Clin. Exp. Immunol.* 79:315-321; Kostelny et al., (1992) *J. Immunol.* 148:1547-1553.

[0079] Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chain/light chain pairs have different specificities (Milstein and Cuello, (1983) *Nature* 305:537-539). Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion of the heavy chain variable region is preferably with an immunoglobulin heavy-chain constant domain, including at least part of the hinge, CH2, and CH3 regions. For further details of illustrative currently known methods for generating bispecific antibodies see, e.g., Suresh et al., (1986) *Methods Enzymol.* 121:210; PCT Publication No. WO 96/27011; Brennan et al., (1985) *Science* 229:81; Shalaby et al., *J. Exp. Med.* (1992) 175:217-225; Kostelny et al., (1992) *J. Immunol.* 148(5):1547-1553; Hollinger et al., (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Gruber et al., (1994) *J. Immunol.* 152:5368; and Tutt et al., (1991) *J. Immunol.* 147:60. Bispecific antibodies also include cross-linked or heteroconjugate antibodies. Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Pat. No. 4,676,980, along with a number of cross-linking techniques.

[0080] Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. See, e.g., Kostelny et al. (1992) *J Immunol* 148(5):1547-1553. The leucine zipper peptides from the Fos and Jun proteins may be linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers may be reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al. (1993) *Proc Natl Acad Sci USA* 90:6444-6448 has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a

heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the VH and VL domains of one fragment are forced to pair with the complementary VL and VH domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (scFv) dimers has also been reported. See, e.g., Gruber et al. (1994) *J Immunol* 152:5368. Alternatively, the antibodies can be "linear antibodies" as described in, e.g., Zapata et al. (1995) *Protein Eng.* 8(10):1057-1062. Briefly, these antibodies comprise a pair of tandem Fd segments (VH-CH1-VH-CH1) which form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

[0081] Antibodies with more than two valencies (e.g., trispecific antibodies) are contemplated and described in, e.g., Tutt et al. (1991) *J Immunol* 147:60.

[0082] The disclosure also embraces variant forms of multi-specific antibodies such as the dual variable domain immunoglobulin (DVD-Ig) molecules described in Wu et al. (2007) *Nat Biotechnol* 25(11): 1290-1297. The DVD-Ig molecules are designed such that two different light chain variable domains (VL) from two different parent antibodies are linked in tandem directly or via a short linker by recombinant DNA techniques, followed by the light chain constant domain. Similarly, the heavy chain comprises two different heavy chain variable domains (VH) linked in tandem, followed by the constant domain CH1 and Fc region. Methods for making DVD-Ig molecules from two parent antibodies are further described in, e.g., PCT Publication Nos. WO 08/024188 and WO 07/024715. In some aspects, the bispecific antibody is a Fabs-in-Tandem immunoglobulin, in which the light chain variable region with a second specificity is fused to the heavy chain variable region of a whole antibody. Such antibodies are described in, e.g., International Patent Application Publication No. WO 2015/103072.

[0083] As used herein, "cancer antigen" or "tumor antigen" refers to (i) tumor- specific antigens, (ii) tumor- associated antigens, (iii) cells that express tumor- specific antigens, (iv) cells that express tumor- associated antigens, (v) embryonic antigens on tumors, (vi) autologous tumor cells, (vii) tumor- specific membrane antigens, (viii) tumor- associated membrane antigens, (ix) growth factor receptors, (x) growth factor ligands, and (xi) any other type of antigen or antigen-presenting cell or material that is associated with a cancer.

[0084] As used herein, the term "cancer-specific immune response" refers to the immune response induced by the presence of tumors, cancer cells, or cancer antigens. In certain aspects, the response includes the proliferation of cancer antigen specific lymphocytes. In certain aspects,

the response includes expression and upregulation of antibodies and T-cell receptors and the formation and release of lymphokines, chemokines, and cytokines. Both innate and acquired immune systems interact to initiate antigenic responses against the tumors, cancer cells, or cancer antigens. In certain aspects, the cancer-specific immune response is a T cell response.

[0085] The term "carcinoma" is art recognized and refers to malignancies of epithelial or endocrine tissues including respiratory system carcinomas, gastrointestinal system carcinomas, genitourinary system carcinomas, testicular carcinomas, breast carcinomas, prostatic carcinomas, endocrine system carcinomas, and melanomas. The anti-IL-27 antibodies described herein can be used to treat patients who have, who are suspected of having, or who may be at high risk for developing any type of cancer, including renal carcinoma or melanoma, or any viral disease. Exemplary carcinomas include those forming from tissue of the cervix, lung, prostate, breast, head and neck, colon and ovary. The term also includes carcinosarcomas, which include malignant tumors composed of carcinomatous and sarcomatous tissues. An "adenocarcinoma" refers to a carcinoma derived from glandular tissue or in which the tumor cells form recognizable glandular structures.

[0086] As used herein, the term "CD112R" refers to a member of poliovirus receptor-like proteins and is a co-inhibitory receptor for human T cells. CD112R is an inhibitory receptor primarily expressed by T cells and NK cells and competes for CD112 binding with the activating receptor CD226. The interaction of CD112 with CD112R is of higher affinity than with CD226 and thereby effectively regulates CD226 mediated cell activation. Anti-CD112R antagonists that block the interaction with CD112 limit inhibitory signaling directly downstream of CD112R while simultaneously promoting greater immune cell activation by increasing CD226 interactions with CD112. As used herein the term "CD112R inhibitor" refers to an agent that disrupts, blocks or inhibits the biological function or activity of CD112R.

[0087] As used herein, the term "CD137" (alternatively "4-1BB") refers to a member of the tumor necrosis factor (TNF) receptor superfamily. 4-1BB is a co-stimulatory immune checkpoint molecule, primarily for activated T cells. Crosslinking of CD137 enhances T cell proliferation, IL-2 secretion, survival and cytolytic activity. As used herein, the term "4-1BB agonist" refers to an agent that stimulates, induces or increases one or more function of 4-1BB. An exemplary 4-1BB agonist is Utomilumab (PF-05082566), a fully human IgG2 monoclonal antibody that targets this 4-1BB to stimulate T cells.

[0088] As used herein, the term "CD161" (alternatively known as Killer cell lectin-like receptor subfamily B, member 1 (KLRB1); NK1.1, or NKR-P1A) refers to a member of the C-type lectin superfamily. CD161 is a marker of T cells and CD161 expression has been associated with T cell infiltration into the tumor microenvironment for a number of different cancer types. CD161 is further described in Fergusson et al., (2014) Cell Reports 9(3):1075-1088, which is incorporated herein by reference in its entirety.

[0089] As used herein, the term "IL-27" or "interleukin 27" refers to the IL-27 cytokine. IL-27 is related to the IL-6/IL-12 cytokine families, and is a heterodimeric cytokine that comprises a first subunit known as Epstein-Barr Virus Induced Gene 3 (EBI3; also known as IL-27 subunit β and IL-27B) and a second subunit known as IL-27p28 (also known as IL30, IL-27 subunit α and IL-27A). IL-27 is predominantly synthesized by activated antigen-presenting cells including monocytes, endothelial cells and dendritic cells (Jankowski et al. (2010) Arch Immunol. Ther. Exp. 58:417-425, Diakowski et al. (2013) Adv. Clin. Exp. Med. (2013) 22(5): 683-691). Although IL-27 can have proinflammatory effects, many studies suggest an important role of IL-27 as an immunosuppressive agent (Shimizu et al. (2006) J. Immunol. 176:7317-7324, Hisada et al. (2004) Cancer Res. 64:1152-1156, Diakowski (2013) supra). Although it was initially described as a factor promoting the initiation of Th1 responses, IL-27 was later found to play a major T-cell suppressive function by limiting Th1 responses, inhibiting Th2 and Th17 cell differentiation, and regulating the development of Tr1 and other T regulatory cell populations (Dietrich et al. (2014) J. Immunol. 192:5382-5389). In addition to its role as an immunoregulator, IL-27 also regulates angiogenesis, hematopoiesis, and osteocalcogenesis (Id.).

[0090] IL-27 signals through a heterodimeric type I cytokine receptor (the IL-27 receptor or IL-27R) that comprises a first subunit known as WSX1 (also known as IL-27 receptor subunit α , IL-27RA, T-Cell Cytokine Receptor Type 1 (TCCR), and Cytokine Receptor-Like 1 (CRL1)) and a second subunit known as gp130 (also known as Interleukin-6 Signal Transducer (IL6ST), Interleukin-6 Receptor Subunit β (IL-6RB), and Oncostatin M Receptor). gp130 is also a receptor subunit for the IL-6 family cytokines (Liu et al. (2008) Scan. J. Immunol. 68:22-299, Diakowski (2013) supra). IL-27 signaling through IL-27R activates multiple signaling cascades, including the JAK-STAT and p38 MAPK pathways.

[0091] EBI3 is also believed to have biological functions independent of p28 or the IL-27 heterodimer. For example, EBI3 also interacts with p35 to form the heterodimeric cytokine IL-35 (Yoshida et al. (2015) Annu. Rev Immunol. 33:417-43) and has been shown to be selectively

overexpressed in certain cell types without a corresponding increase in p28 or IL-27 (Larousserie et al. (2005) Am. J. Pathol. 166(4):1217-28).

[0092] An amino acid sequence of an exemplary human EBI3 protein is provided in SEQ ID NO: 1 (NCBI Reference Sequence: NP_005746.2; N-mtpqlllalvfwascppcsgrkgppaaltprvqcrasrypiavdcswtlppapnstspvsfiatylrgmaarghswpcqqtpststtitdvqlfsmapyvlnvtavhpgwsssfvpfitehiikpdppegvrlsplaqrlqvqweppgswpfpeifslkywirykrqgaarfhrvgpieatsfilravrprraryyvqaaqldtdygelsdwsipatatmslgk-C). An amino acid sequence of an exemplary human p28 protein is provided in SEQ ID NO: 2 (NCBI Reference Sequence: NP_663634.2; N-mgqtagdlgwrlslrlllplllvqagvwgfrppgrpqslqlrreftvslhlarkllsevrqgahrfaeshlpgvnlyllplgeqlpdvsltfqawrrlsdperlcfstltpfhallggltqgrwnmermqwamrldlrldlqrhlrfqvlaagfnlpeeeeeeeeeeeerkglpgalg salqgpaqvswpqllstlyrllhslslsravrelllkskaghsvwplgfpplspqp-C). An amino acid sequence of an exemplary human WSX1 protein is provided in SEQ ID NO: 3 (NCBI Reference Sequence: NP_004834.1; N-mrggrgapfwlwpklallpllwvlfqrtrpqgsagplqcygvglgdlncsweplgdlgapsehlhqsqkyrsnktqtvaagrs wvaipreqltmsdkllvwgkagqplwppvfvnletqmkpnarlgpdvdfseddpleatvhwapptwpskhvlicqfhyrrcqa awtllepelktipltpeiqdlatgykvygrcrmekeedlwgewspilfsqtppsapkdvwvsgnlcgtpggeeplllwkagpcv qvsykvwfwvggrelspegitccslipsgaewarvsavnat swepltnslvclsdasaprsvavssiagstellvtwqpgpgepleh vvdwardgdpleklnwvrlppgnlsallpgnftvgvpyritvtavssaglasassvwgfreelaplvgpplwrlqdappgtpaiawgev prhqlrghlthyltcaqsgtspvcmmvsgntqsvtlpdlpwgpcelwvtastiagqgppgilrlhlpdntlrwkvlpgilflwglflgc glslatsgrcyhlrhkvlprwvwekvpdpansssgqphmeqvpeaqplgdlpileveemepppvmessqpaqatapl dsgyekhf lptpeelgllgpprpqvla-C). An amino acid sequence of an exemplary human gp130 protein is provided in SEQ ID NO: 4 (NCBI Reference Sequence: NP_002175.2; N-mtlqtwlqvalfiflttestgelldpcgyispepvqlhsnftavcvlkekcmdyfhvnanyivwktnhftipkeqytiinrtassvtftd iaslniqltcniltfggleqnvigitiisglppekpknlscivnegkkmrcewdggrethletnftlksewathkfadckakrdtpstctvd ystvyfvnievwveaenalgkvtshinfdpvykvkpnpphnlsvinseelssilklwtwnpsiksviilkyniqyrtkdastwsqippe dtastrssftvqdlkpfteyvfrircmkedgkgywsdwseasgityedrpskapsfwykidpshtqgyrtvqlvwkltppfeangkil dyevltlrwkshlqnytvnatkltnlndrylatltvrnlvgksdaavltipacdfqathpvmldlkafpkdnmlwvewtppresvkkyi lewcvlsdkapcitdwqqedgtvhrtylrgnlaeskyilitvtpvyadgpgspesikaylkqappskgptvrtkkvgkneavlewdql pvdvqngfimyrtifyrtiigmetavnvdssteytssltstlymvrmaaytdegkdgpeftftpkfaqgeieaivvpvciafltltlg vlfefnkrdlikkhiwpnvpdpkskhiaqwsphpprhfnfskdqmysdgnftdsvsveieandkkpfpedlksldlffkkekinteg hssgiggsscmsssrpsissdenessqntsstvqystvvhsgyrhqvpvsvqfsrsestqplldseerpedlqlvdhvdggdgilprqq

yfkqncsqhesspdishferskqvssvneedfvrlkqqisdhisqscgsgqmkmfqevsaadafgpgteggqverfctvgmeaatdeg
mpksylpqtvrqggypq-C).

[0093] As used herein the term "compete", when used in the context of antigen-binding proteins (e.g., immunoglobulins, antibodies, or antigen-binding fragments thereof) that compete for binding to the same epitope, refers to a interaction between antigen-binding proteins as determined by an assay (e.g., a competitive binding assay; a cross-blocking assay), wherein a test antigen-binding protein (e.g., a test antibody) inhibits (e.g., reduces or blocks) specific binding of a reference antigen-binding protein (e.g., a reference antibody) to a common antigen (e.g., IL-27 or a fragment thereof).

[0094] A polypeptide or amino acid sequence "derived from" a designated polypeptide or protein refers to the origin of the polypeptide. Preferably, the polypeptide or amino acid sequence which is derived from a particular sequence has an amino acid sequence that is essentially identical to that sequence or a portion thereof, wherein the portion consists of at least 10-20 amino acids, preferably at least 20-30 amino acids, more preferably at least 30-50 amino acids, or which is otherwise identifiable to one of ordinary skill in the art as having its origin in the sequence. Polypeptides derived from another peptide may have one or more mutations relative to the starting polypeptide, e.g., one or more amino acid residues which have been substituted with another amino acid residue or which has one or more amino acid residue insertions or deletions.

[0095] A polypeptide can comprise an amino acid sequence which is not naturally occurring. Such variants necessarily have less than 100% sequence identity or similarity with the starting molecule. In certain aspects, the variant will have an amino acid sequence from about 75% to less than 100% amino acid sequence identity or similarity with the amino acid sequence of the starting polypeptide, more preferably from about 80% to less than 100%, more preferably from about 85% to less than 100%, more preferably from about 90% to less than 100% (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%) and most preferably from about 95% to less than 100%, e.g., over the length of the variant molecule.

[0096] In certain aspects, the antibodies of the disclosure are encoded by a nucleotide sequence. Nucleotide sequences of the disclosure can be useful for a number of applications, including: cloning, gene therapy, protein expression and purification, mutation introduction, DNA vaccination of a host in need thereof, antibody generation for, e.g., passive immunization, PCR, primer and probe generation, and the like.

[0097] It will also be understood by one of ordinary skill in the art that the antibodies suitable for use in the methods disclosed herein may be altered such that they vary in sequence from the naturally occurring or native sequences from which they were derived, while retaining the desirable activity of the native sequences. For example, nucleotide or amino acid substitutions leading to conservative substitutions or changes at "non-essential" amino acid residues may be made. Mutations may be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis.

[0098] The antibodies suitable for use in the methods disclosed herein may comprise conservative amino acid substitutions at one or more amino acid residues, e.g., at essential or non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a nonessential amino acid residue in a binding polypeptide is preferably replaced with another amino acid residue from the same side chain family. In certain aspects, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members. Alternatively, in certain aspects, mutations may be introduced randomly along all or part of a coding sequence, such as by saturation mutagenesis, and the resultant mutants can be incorporated into binding polypeptides of the disclosure and screened for their ability to bind to the desired target.

[0099] As used herein, the term antigen "cross-presentation" refers to presentation of exogenous protein antigens to T cells via MHC class I and class II molecules on APCs.

[0100] As used herein, the term "cross-reacts" refers to the ability of an antibody of the disclosure to bind to IL-27 from a different species. For example, an antibody of the present disclosure which binds human IL-27 may also bind another species of IL-27. As used herein, cross-reactivity is measured by detecting a specific reactivity with purified antigen in binding assays (e.g., SPR, ELISA) or binding to, or otherwise functionally interacting with, cells physiologically expressing IL-27. Methods for determining cross-reactivity include standard binding assays as described herein, for example, by BiacoreTM surface plasmon resonance (SPR)

analysis using a Biacore™ 2000 SPR instrument (Biacore AB, Uppsala, Sweden), or flow cytometric techniques.

[0101] As used herein, the term "cytotoxic T lymphocyte (CTL) response" refers to an immune response induced by cytotoxic T cells. CTL responses are mediated primarily by CD8⁺ T cells.

[0102] As used herein, the term "dendritic cell" or "DC" refers to type of antigen-presenting cells that are bone marrow (BM)-derived leukocytes and are the most potent type of antigen-presenting cells. DCs capture and process antigens, converting proteins to peptides that are presented on major histocompatibility complex (MHC) molecules recognized by T cells. DCs are heterogeneous, e.g. myeloid and plasmacytoid DCs; although all DCs are capable of antigen uptake, processing and presentation to naive T cells, the DC subtypes have distinct markers and differ in location, migratory pathways, detailed immunological function and dependence on infections or inflammatory stimuli for their generation. During the development of an adaptive immune response, the phenotype and function of DCs play a role in initiating tolerance, memory, and polarized T-helper 1 (Th1), Th2 and Th17 differentiation.

[0103] As used herein, the term "dendritic cell activation" refers to the transition from immature to mature dendritic cell; and the activated dendritic cells encompass mature dendritic cells and dendritic cells in the process of the transition, wherein the expression of CD80 and CD86 that induce costimulatory signals are elevated by the activating stimuli. Mature human dendritic cells are cells that are positive for the expression of CD40, CD80, CD86, and HLA-class II (e.g., HLA-DR). An immature dendritic cell can be distinguished from a mature dendritic cell, for example, based on markers selected from the group consisting of CD80 and CD86. An immature dendritic cell is weakly positive and preferably negative for these markers, while a mature dendritic cell is positive. Discrimination of mature dendritic cells is routinely performed by those skilled in the art, and the respective markers described above and methods for measuring their expression are also well known to those skilled in the art.

[0104] As used herein, the term "EC₅₀" refers to the concentration of an antibody or an antigen-binding portion thereof, which induces a response, either in an *in vitro* or an *in vivo* assay, which is 50% of the maximal response, *i.e.*, halfway between the maximal response and the baseline.

[0105] As used herein, the term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term

"therapeutically effective dose" is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts effective for this use will depend upon the severity of the disorder being treated and the general state of the patient's own immune system.

[0106] As used herein, the term "epitope" or "antigenic determinant" refers to a site on an antigen to which an immunoglobulin or antibody specifically binds. The term "epitope mapping" refers to a process or method of identifying the binding site, or epitope, of an antibody, or antigen binding fragment thereof, on its target protein antigen. Epitope mapping methods and techniques are provided herein. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods for determining what epitopes are bound by a given antibody (*i.e.*, epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation assays, wherein overlapping or contiguous peptides from IL-27 are tested for reactivity with the given anti-IL-27 antibody. Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance (see, *e.g.*, *Epitope Mapping Protocols in Methods in Molecular Biology*, Vol. 66, G. E. Morris, Ed. (1996)).

[0107] Also encompassed by the present disclosure are antibodies that bind to an epitope on IL-27 which comprises all or a portion of an epitope recognized by the particular antibodies described herein (*e.g.*, the same or an overlapping region or a region between or spanning the region).

[0108] Also encompassed by the present disclosure are antibodies that bind the same epitope and/or antibodies that compete for binding to human IL-27 with the antibodies described herein. Antibodies that recognize the same epitope or compete for binding can be identified using routine techniques. Such techniques include, for example, an immunoassay, which shows the ability of one antibody to block the binding of another antibody to a target antigen, *i.e.*, a competitive binding assay. Competitive binding is determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as IL-27. Numerous types of competitive binding assays are known, for example: solid phase

direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli *et al.*, *Methods in Enzymology* 9:242 (1983)); solid phase direct biotin-avidin EIA (see Kirkland *et al.*, *J. Immunol.* 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press (1988)); solid phase direct label RIA using I-125 label (see Morel *et al.*, *Mol. Immunol.* 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung *et al.*, *Virology* 176:546 (1990)); and direct labeled RIA. (Moldenhauer *et al.*, *Scand. J. Immunol.* 32:77 (1990)). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70% 70-75% or more.

[0109] Other techniques include, for example, epitope mapping methods, such as, x-ray analyses of crystals of antigen:antibody complexes which provides atomic resolution of the epitope and mass spectrometry combined with hydrogen/deuterium (H/D) exchange which studies the conformation and dynamics of antigen:antibody interactions. Other methods monitor the binding of the antibody to antigen fragments or mutated variations of the antigen where loss of binding due to a modification of an amino acid residue within the antigen sequence is often considered an indication of an epitope component. In addition, computational combinatorial methods for epitope mapping can also be used. These methods rely on the ability of the antibody of interest to affinity isolate specific short peptides from combinatorial phage display peptide libraries. The peptides are then regarded as leads for the definition of the epitope corresponding to the antibody used to screen the peptide library. For epitope mapping, computational algorithms have also been developed which have been shown to map conformational discontinuous epitopes.

[0110] As used herein, the term "Fc-mediated effector functions" or "Fc effector functions" refer to the biological activities of an antibody other than the antibody's primary function and purpose. For example, the effector functions of a therapeutic agnostic antibody are the biological activities other than the activation of the target protein or pathway. Examples of antibody effect functions include C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell

surface receptors (e.g., B cell receptor); lack of activation of platelets that express Fc receptor; and B cell activation. Many effector functions begin with Fc binding to an Fc γ receptor. In some aspects, the tumor antigen-targeting antibody has effector function, e.g., ADCC activity. In some aspects, a tumor antigen-targeting antibody described herein comprises a variant constant region having increased effector function (e.g. increased ability to mediate ADCC) relative to the unmodified form of the constant region.

[0111] As used herein, the term "Fc receptor" refers to a polypeptide found on the surface of immune effector cells, which is bound by the Fc region of an antibody. In some aspects, the Fc receptor is an Fc γ receptor. There are three subclasses of Fc γ receptors, Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIII (CD16). All four IgG isotypes (IgG1, IgG2, IgG3 and IgG4) bind and activate Fc receptors Fc γ RI, Fc γ RIIA and Fc γ RIIIA. Fc γ RIIB is an inhibitory receptor, and therefore antibody binding to this receptor does not activate complement and cellular responses. Fc γ RI is a high affinity receptor that binds to IgG in monomeric form, whereas Fc γ RIIA and Fc γ RIIIA are low affinity receptors that bind IgG only in multimeric form and have slightly lower affinity. The binding of an antibody to an Fc receptor and/or C1q is governed by specific residues or domains within the Fc regions. Binding also depends on residues located within the hinge region and within the CH2 portion of the antibody. In some aspects, the agonistic and/or therapeutic activity of the antibodies described herein is dependent on binding of the Fc region to the Fc receptor (e.g., Fc γ R). In some aspects, the agonistic and/or therapeutic activity of the antibodies described herein is enhanced by binding of the Fc region to the Fc receptor (e.g., Fc γ R).

[0112] A list of certain Fc receptor sequences employed in the instant disclosure is set forth as Table 1B below.

[0113] As used herein, the term "glycosylation pattern" is defined as the pattern of carbohydrate units that are covalently attached to a protein, more specifically to an immunoglobulin protein. A glycosylation pattern of a heterologous antibody can be characterized as being substantially similar to glycosylation patterns which occur naturally on antibodies produced by the species of the nonhuman transgenic animal, when one of ordinary skill in the art would recognize the glycosylation pattern of the heterologous antibody as being more similar to said pattern of glycosylation in the species of the nonhuman transgenic animal than to the species from which the CH genes of the transgene were derived.

[0114] As used herein, the term "human antibody" includes antibodies having variable and constant regions (if present) of human germline immunoglobulin sequences. Human antibodies of

the disclosure can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*) (See, *e.g.*, Lonberg et al., (1994) *Nature* 368(6474): 856-859; Lonberg, (1994) *Handbook of Experimental Pharmacology* 113:49-101; Lonberg & Huszar, (1995) *Intern. Rev. Immunol.* 13:65-93, and Harding & Lonberg, (1995) *Ann. N.Y. Acad. Sci.* 764:536-546). However, the term "human antibody" does not include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences (*i.e.* humanized antibodies).

[0115] As used herein, the term a "heterologous antibody" is defined in relation to the transgenic non-human organism producing such an antibody. This term refers to an antibody having an amino acid sequence or an encoding nucleic acid sequence corresponding to that found in an organism not consisting of the transgenic non-human animal, and generally from a species other than that of the transgenic non-human animal.

[0116] The terms "inducing an immune response" and "enhancing an immune response" are used interchangeably and refer to the stimulation of an immune response (*i.e.*, either passive or adaptive) to a particular antigen. The terms "induce" as used with respect to inducing CDC or ADCC refer to the stimulation of particular direct cell killing mechanisms.

[0117] As used herein, the term "immunogenic cell death" (alternatively known as "immunogenic apoptosis" refers to a cell death modality associated with the activation of one or more signaling pathways that induces the pre-mortem expression and emission of damaged-associated molecular pattern (DAMPs) molecules (*e.g.*, adenosine triphosphate, ATP) from the tumor cell, resulting in the increase of immunogenicity of the tumor cell and the death of the tumor cell in an immunogenic manner (*e.g.*, by phagocytosis). As used herein, the term "immunogenic cell death-inducing agent" refers to a chemical, biological, or pharmacological agent that induces an immunogenic cell death process, pathway, or modality.

[0118] As used herein, the terms "inhibits", "reduces" or "blocks" (*e.g.*, referring to inhibition or reduction of human IL-27-mediated phosphorylation of STAT1 and/or STAT3 in a cell) are used interchangeably and encompass both partial and complete inhibition/blocking. The inhibition/blocking of IL-27 reduces or alters the normal level or type of activity that occurs without inhibition or blocking. Inhibition and blocking are also intended to include any measurable decrease in the binding affinity of IL-27 when in contact with an anti-IL-27 antibody as compared to IL-27 not in contact with an anti-IL-27 antibody, *e.g.*, inhibits binding of IL-27 by at least about

10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%.

[0119] As used herein, the terms "inhibits angiogenesis," "diminishes angiogenesis," and "reduces angiogenesis" refer to reducing the level of angiogenesis in a tissue to a quantity which is at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or less than the quantity in a corresponding control tissue, and most preferably is at the same level which is observed in a control tissue.

[0120] As used herein, the term "inhibits growth" (e.g., referring to cells) is intended to include any measurable decrease in the growth of a cell, e.g., the inhibition of growth of a cell by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, or 100%.

[0121] As used herein, a subject "in need of prevention," "in need of treatment," or "in need thereof," refers to one, who by the judgment of an appropriate medical practitioner (e.g., a doctor, a nurse, or a nurse practitioner in the case of humans; a veterinarian in the case of non-human mammals), would reasonably benefit from a given treatment (such as treatment with a composition comprising an anti-IL-27 antibody).

[0122] The term "*in vivo*" refers to processes that occur in a living organism.

[0123] As used herein, the term "isolated antibody" is intended to refer to an antibody which is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds to human IL-27 is substantially free of antibodies that specifically bind antigens other than IL-27). An isolated antibody that specifically binds to an epitope may, however, have cross-reactivity to other IL-27 proteins from different species. However, the antibody continues to display specific binding to human IL-27 in a specific binding assay as described herein. In addition, an isolated antibody is typically substantially free of other cellular material and/or chemicals. In some aspects, a combination of "isolated" antibodies having different IL-27 specificities is combined in a well-defined composition.

[0124] As used herein, the term "isolated nucleic acid molecule" refers to nucleic acids encoding antibodies or antibody portions (e.g., V_H , V_L , CDR3) that bind to IL-27, is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the antibody or antibody portion are free of other nucleotide sequences encoding antibodies or antibody portions that bind antigens other than IL-27, which other sequences may naturally flank the nucleic acid in human genomic DNA. For example, a sequence selected from a sequence set forth in Table 1A

corresponds to the nucleotide sequences comprising the heavy chain (V_H) and light chain (V_L) variable regions of anti-IL-27 antibody monoclonal antibodies described herein.

[0125] As used herein, "isotype" refers to the antibody class (*e.g.*, IgM or IgG1) that is encoded by heavy chain constant region genes. In some aspects, a human monoclonal antibody of the disclosure is of the IgG1 isotype. In some aspects, a human monoclonal antibody of the disclosure is of the IgG2 isotype. In some aspects, a human monoclonal antibody of the disclosure is of the IgG3 isotype. In some aspects, a human monoclonal antibody of the disclosure is of the IgG4 isotype. As is apparent to a skilled artisan, identification of antibody isotypes (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgM, IgA1 IgA2, IgD, and IgE) is routine in the art and commonly involves a combination of sequence alignments with known antibodies, published Fc variant sequences and conserved sequences.

[0126] As used herein, the term "isotype switching" refers to the phenomenon by which the class, or isotype, of an antibody changes from one Ig class to one of the other Ig classes.

[0127] As used herein the term "KD" or " K_D " refers to the equilibrium dissociation constant of a binding reaction between an antibody and an antigen. The value of K_D is a numeric representation of the ratio of the antibody off-rate constant (k_d) to the antibody on-rate constant (k_a). The value of K_D is inversely related to the binding affinity of an antibody to an antigen. The smaller the K_D value the greater the affinity of the antibody for its antigen. Affinity is the strength of binding of a single molecule to its ligand and is typically measured and reported by the equilibrium dissociation constant (K_D), which is used to evaluate and rank order strengths of bimolecular interactions.

[0128] As used herein, the term " k_d " or " k_d " (alternatively " k_{off} " or " k_{off} ") is intended to refer to the off-rate constant for the dissociation of an antibody from an antibody/antigen complex. The value of k_d is a numeric representation of the fraction of complexes that decay or dissociate per second, and is expressed in units sec^{-1} .

[0129] As used herein, the term " k_a " or " k_a " (alternatively " k_{on} " or " k_{on} ") is intended to refer to the on-rate constant for the association of an antibody with an antigen. The value of k_a is a numeric representation of the number of antibody/antigen complexes formed per second in a 1 molar (1M) solution of antibody and antigen, and is expressed in units $\text{M}^{-1}\text{sec}^{-1}$.

[0130] As used herein, the term "leukocyte" refers to a type of white blood cell involved in defending the body against infective organisms and foreign substances. Leukocytes are produced in the bone marrow. There are 5 main types of white blood cells, subdivided between 2 main

groups: polymorphonuclear leukocytes (neutrophils, eosinophils, basophils) and mononuclear leukocytes (monocytes and lymphocytes).

[0131] As used herein, the term "lymphocytes" refers to a type of leukocyte or white blood cell that is involved in the immune defenses of the body. There are two main types of lymphocytes: B-cells and T-cells.

[0132] As used herein, the terms "linked," "fused", or "fusion", are used interchangeably. These terms refer to the joining together of two more elements or components or domains, by whatever means including chemical conjugation or recombinant means. Methods of chemical conjugation (e.g., using heterobifunctional crosslinking agents) are known in the art.

[0133] As used herein, "local administration" or "local delivery," refers to delivery that does not rely upon transport of the composition or agent to its intended target tissue or site via the vascular system. For example, the composition may be delivered by injection or implantation of the composition or agent or by injection or implantation of a device containing the composition or agent. Following local administration in the vicinity of a target tissue or site, the composition or agent, or one or more components thereof, may diffuse to the intended target tissue or site.

[0134] As used herein, "MHC molecules" refers to two types of molecules, MHC class I and MHC class II. MHC class I molecules present antigen to specific CD8⁺ T cells and MHC class II molecules present antigen to specific CD4⁺ T cells. Antigens delivered exogenously to APCs are processed primarily for association with MHC class II. In contrast, antigens delivered endogenously to APCs are processed primarily for association with MHC class I.

[0135] As used herein, the term "monoclonal antibody" refers to an antibody which displays a single binding specificity and affinity for a particular epitope. Accordingly, the term "human monoclonal antibody" refers to an antibody which displays a single binding specificity and which has variable and optional constant regions derived from human germline immunoglobulin sequences. In some aspects, human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[0136] As used herein, the term "monocyte" refers to a type of leukocyte and can differentiate into macrophages and dendritic cells to effect an immune response.

[0137] As used herein, the term "natural killer (NK) cell" refers to a type of cytotoxic lymphocyte. These are large, usually granular, non-T, non-B lymphocytes, which kill certain tumor

cells and play an important role in innate immunity to viruses and other intracellular pathogens, as well as in antibody-dependent cell-mediated cytotoxicity (ADCC).

[0138] As used herein, the term "naturally occurring" as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally occurring.

[0139] As used herein, the term "nonswitched isotype" refers to the isotypic class of heavy chain that is produced when no isotype switching has taken place; the CH gene encoding the nonswitched isotype is typically the first CH gene immediately downstream from the functionally rearranged VDJ gene. Isotype switching has been classified as classical or non-classical isotype switching. Classical isotype switching occurs by recombination events which involve at least one switch sequence region in the transgene. Non-classical isotype switching may occur by, for example, homologous recombination between human σ_{μ} and human Σ_{μ} (δ -associated deletion). Alternative non-classical switching mechanisms, such as intertransgene and/or interchromosomal recombination, among others, may occur and effectuate isotype switching.

[0140] As used herein, the term "nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double- stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences and as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions can be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081, 1991; Ohtsuka et al., Biol. Chem. 260:2605-2608, 1985; and Cassol et al, 1992; Rossolini et al, Mol. Cell. Probes 8:91-98, 1994). For arginine and leucine, modifications at the second base can also be conservative. The term nucleic acid is used interchangeably with gene, cDNA, and mRNA encoded by a gene.

[0141] Polynucleotides used herein can be composed of any polyribonucleotide or polydeoxyribonucleotide, which can be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double- stranded regions, single- and double- stranded RNA, and RNA that

is mixture of single- and double- stranded regions, hybrid molecules comprising DNA and RNA that can be single- stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide can also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

[0142] A nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For instance, a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. With respect to transcription regulatory sequences, operably linked means that the DNA sequences being linked are contiguous and, where necessary to join two protein coding regions, contiguous and in reading frame. For switch sequences, operably linked indicates that the sequences are capable of effecting switch recombination.

[0143] As used herein, "parenteral administration," "administered parenterally," and other grammatically equivalent phrases, refer to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intranasal, intraocular, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural, intracerebral, intracranial, intracarotid and intrasternal injection and infusion.

[0144] As used herein, the term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

[0145] As used herein, the term "PD-1 antagonist" refers to any chemical compound or biological molecule that inhibits the PD-1 signaling pathway or that otherwise inhibits PD-1 function in a cell (e.g. an immune cell). In some aspects, a PD-1 antagonist blocks binding of PD-L1 to PD-1 and/or PD-L2 to PD-1. In some aspects, the PD-1 antagonist specifically binds PD-1. In some aspects, the PD-1 antagonist specifically binds PD-L1.

[0146] The term "percent identity," in the context of two or more nucleic acid or polypeptide sequences, refer to two or more sequences or subsequences that have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned

for maximum correspondence, as measured using one of the sequence comparison algorithms described below (e.g., BLASTP and BLASTN or other algorithms available to persons of skill) or by visual inspection. Depending on the application, the "percent identity" can exist over a region of the sequence being compared, e.g., over a functional domain, or, alternatively, exist over the full length of the two sequences to be compared. For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0147] Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by visual inspection (see generally Ausubel et al., *infra*).

[0148] One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al., *J. Mol. Biol.* 215:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information website.

[0149] As generally used herein, "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues, organs, and/or bodily fluids of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

[0150] As used herein, a "pharmaceutically acceptable carrier" refers to, and includes, any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. The compositions can include a pharmaceutically acceptable salt, e.g., an acid addition salt or a base addition salt (see, e.g., Berge et al. (1977) *J Pharm Sci* 66:1-19).

[0151] As used herein, the terms "polypeptide," "peptide", and "protein" are used interchangeably to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

[0152] As used herein, the term "preventing" when used in relation to a condition, refers to administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition.

[0153] As used herein, the term "purified" or "isolated" as applied to any of the proteins (antibodies or fragments) described herein refers to a polypeptide that has been separated or purified from components (e.g., proteins or other naturally occurring biological or organic molecules) which naturally accompany it, e.g., other proteins, lipids, and nucleic acid in a prokaryote expressing the proteins. Typically, a polypeptide is purified when it constitutes at least 60 (e.g., at least 65, 70, 75, 80, 85, 90, 92, 95, 97, or 99) %, by weight, of the total protein in a sample.

[0154] As used herein, the term "Programmed Cell Death Protein 1" or "PD-1" refers to the Programmed Cell Death Protein 1 polypeptide, an immune-inhibitory receptor belonging to the CD28 family and is encoded by the *PDCDI* gene in humans. Alternative names or synonyms for PD-1 include: PDCD1, PD1, CD279 and SLEB2. PD-1 is expressed predominantly on previously activated T cells, B cells, and myeloid cells *in vivo*, and binds to two ligands, PD-L1 and PD-L2. The term "PD-1" as used herein includes human PD-1 (hPD-1), variants, isoforms, and species homologs of hPD-1, and analogs having at least one common epitope with hPD-1. The complete hPD-1 sequence can be found under GenBank Accession No. AAC51773.

[0155] As used herein, the term "Programmed Death Ligand-1" or "PD-L1" is one of two cell surface glycoprotein ligands for PD-1 (the other being PD-L2) that downregulates T cell activation and cytokine secretion upon binding to PD-1. Alternative names and synonyms for PD-L1 include: PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H. The term "PD-L1" as used herein includes human PD-L1 (hPD-L1), variants, isoforms, and species homologs of hPD-L1, and analogs having at least one common epitope with hPD-L1. The complete hPD-L1 sequence can be found under GenBank Accession No. Q9NZQ7.

[0156] PD-1 is known as an immune-inhibitory protein that negatively regulates TCR signals (Ishida, Y. et al. (1992) EMBO J. 11:3887-3895; Blank, C. et al. (Epub 2006 Dec. 29)

Immunol. Immunother. 56(5):739-745). The interaction between PD-1 and PD-L1 can act as an immune checkpoint, which can lead to a decrease in T-cell receptor mediated proliferation (Dong et al. (2003) J. Mol. Med. 81:281-7; Blank et al. (2005) Cancer Immunol. Immunother. 54:307-314; Konishi et al. (2004) Clin. Cancer Res. 10:5094-100). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1 or PD-L2; the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai et al. (2002) Proc. Nat'l. Acad. Sci. USA 99:12293-7; Brown et al. (2003) J. Immunol. 170:1257-66).

[0157] For several cancers, tumor survival and proliferation is sustained by tumor-mediated immune checkpoint modulation. This modulation can result in the disruption of anti-cancer immune system functions. For example, recent studies have indicated that the expression of immune checkpoint receptors ligands, such as PD-L1 or PD-L2, by tumor cells can downregulate immune system activity in the tumor microenvironment and promote cancer immune evasion, particularly by suppressing T cells. PD-L1 is abundantly expressed by a variety of human cancers (Dong et al., (2002) Nat Med 8:787-789). The receptor for PD-L1, PD-1, is expressed on lymphocytes (e.g., activated T cells) and is normally involved in down-regulating the immune system and promoting self-tolerance, particularly by suppressing T cells. However, when PD-1 receptors expressed on T cells bind to cognate PD-L1 ligands on tumor cells, the resulting T cell suppression contributes to an impaired immune response against the tumor (e.g., a decrease in tumor infiltrating lymphocytes or the establishment of immune evasion by cancer cells).

[0158] In large sample sets of e.g. ovarian, renal, colorectal, pancreatic, liver cancers and melanoma, it was shown that PD-L1 expression correlated with poor prognosis and reduced overall survival irrespective of subsequent treatment (see e.g., Dong et al., (2002) Nat Med 8(8):793-800; Yang et al., (2008) Invest Ophthalmol Vis Sci 49(6):2518-2525; Ghebeh et al., (2006) Neoplasia 8:190-198; Hamanishi et al., (2007) Proc Nat Acad Sci USA 104:3360-3365; Thompson et al., (2006) Clin Genitourin Cancer 5:206-211; Nomi et al., (2005) Clin Cancer Res 11:2947-2953; Inman et al., (2007) Cancer 109:1499-1505; Shimauchi et al., (2007) Int J Cancer 121:2585-2590; Gao et al., (2009) Clin Cancer Res 15:971-979; Nakanishi et al., (2007) Cancer Immunol Immunother 56:1173-1182; Hino et al., (2010) Cancer 116(7):1757-1766). Similarly, PD-1 expression on tumor lymphocytes was found to mark dysfunctional T cells in breast cancer (Kitano et al., (2017) ESMO Open 2(2):e000150) and melanoma (Kleffel et al., (2015) Cell 162(6):1242-1256). PD-1 antagonists, such as those that affect the function of the PD-1/PD-L1/PD-L2 signaling axis and/or disrupt the interaction between PD-1 and PD-L1 and/or PD-L2, for example, have been

developed and represent a novel class of anti-tumor inhibitors that function via modulation of immune cell-tumor cell interaction.

[0159] As used herein, the term "rearranged" refers to a configuration of a heavy chain or light chain immunoglobulin locus wherein a V segment is positioned immediately adjacent to a D- J or J segment in a conformation encoding essentially a complete V_H or V_L domain, respectively. A rearranged immunoglobulin gene locus can be identified by comparison to germline DNA; a rearranged locus will have at least one recombined heptamer/nonamer homology element.

[0160] As used herein, the term "recombinant host cell" (or simply "host cell") is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

[0161] As used herein, the term "recombinant human antibody" includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art (see, *e.g.*, Lonberg (2005) Nature Biotech. 23(9):1117-1125), the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (*i.e.*, isotype switch). Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen

may not have sequence identity with the original nucleic acid molecules, but instead will be substantially identical or similar (*i.e.*, have at least 80% identity).

[0162] As used herein, the term "reference antibody" (used interchangeably with "reference mAb") or "reference antigen-binding protein" refers to an antibody, or an antigen-binding fragment thereof, that binds to a specific epitope on IL-27 and is used to establish a relationship between itself and one or more distinct antibodies, wherein the relationship is the binding of the reference antibody and the one or more distinct antibodies to the same epitope on IL-27. As used herein, the term connotes an anti-IL-27 antibody that is useful in a test or assay, such as those described herein, (*e.g.*, a competitive binding assay), as a competitor, wherein the assay is useful for the discovery, identification or development, of one or more distinct antibodies that bind to the same epitope.

[0163] As used herein, the terms "specific binding," "selective binding," "selectively binds," and "specifically binds," refer to antibody binding to an epitope on a predetermined antigen. Typically, the antibody binds with an equilibrium dissociation constant (K_D) of approximately less than 10^{-6} M, such as approximately less than 10^{-7} , 10^{-8} M, 10^{-9} M or 10^{-10} M or even lower when determined by surface plasmon resonance (SPR) technology in a BIACORE 2000 instrument using recombinant human IL-27 as the analyte and the antibody as the ligand and binds to the predetermined antigen with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (*e.g.*, BSA, casein) other than the predetermined antigen or a closely-related antigen. In certain aspects, an antibody that specifically binds to IL-27 binds with an equilibrium dissociation constant (K_D) of approximately less than 100 nM (10^{-7} M), optionally approximately less than 50 nM (5×10^{-8} M), optionally approximately less than 15 nM (1.5×10^{-8} M), optionally approximately less than 10 nM (10^{-8} M), optionally approximately less than 5 nM (5×10^{-9} M), optionally approximately less than 1 nM (10^{-9} M), optionally approximately less than 0.1 nM (10^{-10} M), optionally approximately less than 0.01 nM (10^{-11} M), or even lower, when determined by surface plasmon resonance (SPR) technology in a BIACORE 2000 instrument using recombinant human IL-27 as the analyte and the antibody as the ligand, where binding to the predetermined antigen occurs with an affinity that is at least two-fold greater than the antibody's affinity for binding to a non-specific antigen (*e.g.*, BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

[0164] As used herein, the term "STAT1 phosphorylation" refers to the phosphorylation of the Signal Transducer and Activator of Transcription 1 (STAT1) polypeptide, a transcription factor encoded by the *STAT1* gene in humans. STAT molecules are phosphorylated by receptor associated kinases, that cause activation and dimerization by forming homo- or heterodimers which translocate to the nucleus to work as transcription factors. STAT1 can be activated (i.e., phosphorylated) in response to signaling via several ligands, including IL-27. IL-27 signaling through the IL-27R results in phosphorylation of STAT1 (pSTAT1). STAT1 has a key role in gene expression involved in survival of the cell, viability or pathogen response. Methods to determine STAT1 phosphorylation as a result of IL-27 signaling include, but are not limited to, flow cytometric analysis of cells labeled with antibodies that specifically recognize phosphorylated STAT1 (see e.g., Tochizawa et al., (2006) J Immunol Methods 313(1-2):29-37).

[0165] As used herein, the term "STAT3 phosphorylation" refers to the phosphorylation of the Signal Transducer and Activator of Transcription 3 (STAT3) polypeptide, a transcription factor encoded by the *STAT3* gene in humans. STAT3 mediates the expression of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis. Methods to determine STAT3 phosphorylation as a result of IL-27 signaling include, but are not limited to, analysis of cells or cell extracts labeled with antibodies that specifically recognize phosphorylated STAT3 (see e.g., Fursov et al., (2011) Assay Drug Dev Technol 9(4):420-429).

[0166] As used herein, the term "switch sequence" refers to those DNA sequences responsible for switch recombination. A "switch donor" sequence, typically a μ switch region, will be 5' (i.e., upstream) of the construct region to be deleted during the switch recombination. The "switch acceptor" region will be between the construct region to be deleted and the replacement constant region (e.g., γ , ϵ , etc.). As there is no specific site where recombination always occurs, the final gene sequence will typically not be predictable from the construct.

[0167] As used herein, the term "subject" includes any human or non-human animal. For example, the methods and compositions of the present disclosure can be used to treat a subject with an immune disorder. The term "non-human animal" includes all vertebrates, e.g., mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, etc.

[0168] For nucleic acids, the term "substantial homology" indicates that two nucleic acids, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least about 80% of the nucleotides, usually at

least about 90% to 95%, and more preferably at least about 98% to 99.5% of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to the complement of the strand.

[0169] The percent identity between two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % homology = # of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

[0170] The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between two nucleotide or amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0171] The nucleic acid and protein sequences of the present disclosure can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the disclosure. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the protein molecules of the disclosure. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.

[0172] The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, *e.g.*, other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. *See*, F. Ausubel, *et al.*, ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

[0173] The nucleic acid compositions of the present disclosure, while often in a native sequence (except for modified restriction sites and the like), from either cDNA, genomic or mixtures thereof may be mutated, in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, may affect amino acid sequence as desired. In particular, DNA sequences substantially homologous to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

[0174] As used herein, the term "STING" (alternatively TMEM173) refers to the Stimulator of Interferon Genes, a protein that functions both as a direct cytosolic DNA sensor and as an adaptor protein. In humans, STING is encoded by the *TMEM173* gene. STING plays an important role in innate immunity. STING induces type I interferon production when cells are infected with intracellular pathogens, such as viruses, mycobacteria and intracellular parasites. Type I interferon, mediated by STING, protects infected cells and nearby cells from local infection by binding to the same cell that secretes it and nearby cells. An exemplary amino acid sequence for STING is provided by the NCBI Genbank database under the accession number NP_001288667.

[0175] The term "T cell" refers to a type of white blood cell that can be distinguished from other white blood cells by the presence of a T cell receptor on the cell surface. There are several subsets of T cells, including, but not limited to, T helper cells (a.k.a. T_H cells or CD4⁺ T cells) and subtypes, including T_H1, T_H2, T_H3, T_H17, T_H9, and T_{FH} cells, cytotoxic T cells (a.k.a T_C cells, CD8⁺ T cells, cytotoxic T lymphocytes, T-killer cells, killer T cells), memory T cells and subtypes, including central memory T cells (T_{CM} cells), effector memory T cells (T_{EM} and T_{EMRA} cells), and resident memory T cells (T_{RM} cells), regulatory T cells (a.k.a. T_{reg} cells or suppressor T cells) and subtypes, including CD4⁺ FOXP3⁺ T_{reg} cells, CD4⁺FOXP3⁻ T_{reg} cells, Tr1 cells, Th3 cells, and T_{reg}17 cells, natural killer T cells (a.k.a. NKT cells), mucosal associated invariant T cells (MAITs),

and gamma delta T cells ($\gamma\delta$ T cells), including $V\gamma 9/V\delta 2$ T cells. Any one or more of the aforementioned or unmentioned T cells may be the target cell type for a method of use of the disclosure.

[0176] As used herein, the term "T cell-mediated response" refers to any response mediated by T cells, including, but not limited to, effector T cells (e.g., $CD8^+$ cells) and helper T cells (e.g., $CD4^+$ cells). T cell mediated responses include, for example, T cell cytotoxicity and proliferation.

[0177] As used herein, the terms "therapeutically effective amount" or "therapeutically effective dose," or similar terms used herein are intended to mean an amount of an agent (e.g., an anti-IL-27 antibody or an antigen-binding fragment thereof) that will elicit the desired biological or medical response (e.g., an improvement in one or more symptoms of a cancer).

[0178] As used herein, the term "TAM receptor" refers to the TAM receptor protein tyrosine kinases (TYRO3, AXL and MER). TAM receptors are involved in the regulation of immune system homeostasis. In a cancer setting, TAM receptors have a dual regulatory role, controlling the initiation and progression of tumor development and, at the same time, the associated anti-tumor responses of diverse immune cells. Further description of TAM receptors is found in Paolino and Penninger (2016) *Cancers* 8(97): doi:10.3390/cancers8100097). As used herein, the term "TAM receptor inhibitor" or "TAM inhibitor" refers to an agent that inhibits, blocks or reduces the function or activity of a TAM receptor.

[0179] As used herein, the term "TIGIT" or "T-cell immunoreceptor with Ig and ITIM domains" refers to any native TIGIT from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. TIGIT is also known in the art as DKFZp667A205, FLJ39873, V-set and immunoglobulin domain-containing protein 9, V-set and transmembrane domain-containing protein 3, VSIG9, VSTM3, and WUCAM. The term also encompasses naturally occurring variants of TIGIT, e.g., splice variants or allelic variants. The amino acid sequence of an exemplary human TIGIT may be found under UniProt Accession Number Q495A1.

[0180] The terms "treat," "treating," and "treatment," as used herein, refer to therapeutic or preventative measures described herein. The methods of "treatment" employ administration to a subject, in need of such treatment, a human antibody of the present disclosure, for example, a subject in need of an enhanced immune response against a particular antigen or a subject who ultimately may acquire such a disorder, in order to prevent, cure, delay, reduce the severity of, or

ameliorate one or more symptoms of the disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

[0181] As used herein, the term "tumor microenvironment" (alternatively "cancer microenvironment"; abbreviated TME) refers to the cellular environment or milieu in which the tumor or neoplasm exists, including surrounding blood vessels as well as non-cancerous cells including, but not limited to, immune cells, fibroblasts, bone marrow-derived inflammatory cells, and lymphocytes. Signaling molecules and the extracellular matrix also comprise the TME. The tumor and the surrounding microenvironment are closely related and interact constantly. Tumors can influence the microenvironment by releasing extracellular signals, promoting tumor angiogenesis and inducing peripheral immune tolerance, while the immune cells in the microenvironment can affect the growth and evolution of tumor cells.

[0182] As used herein, the term "unrearranged" or "germline configuration" refers to the configuration wherein the V segment is not recombined so as to be immediately adjacent to a D or J segment.

[0183] As used herein, the term "vector" is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the present disclosure is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[0184] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure

pertains. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the presently disclosed methods and compositions. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

II. Methods of the Disclosure

[0185] Some aspects of the present disclosure are directed to methods of stimulating an immune response in a subject, the method comprising administering to the subject an antibody or an antigen binding portion thereof that antagonizes human IL-27, or an antigen binding portion thereof. Some aspects of the present disclosure are directed to methods of treating a cancer in a subject in need thereof comprising administering to the subject an antibody that antagonizes human IL-27, or an antigen binding portion thereof. Some aspects of the present disclosure are directed to methods of inhibiting or reducing STAT1 and/or STAT3 phosphorylation in a cell, the method comprising contacting the cell with an isolated antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell. Some aspects of the present disclosure are directed to methods of inhibiting or reducing inhibition of CD161 expression in a cell, the method comprising contacting the cell with an isolated antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or reduces inhibition of CD161 expression in a cell. Some aspects of the present disclosure are directed to methods of inhibiting or reducing PD-L1 expression in a cell, the method comprising contacting the cell with an isolated antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or reduces PD-L1 expression in a cell. Some aspects of the present disclosure are directed to methods of altering TIM-3 expression in a cell, the method comprising contacting the cell with an isolated antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, alters TIM-3 expression. Some aspects of the present disclosure are directed to methods of inducing or enhancing secretion of one or more cytokines from a cell, the method comprising contacting the cell with the isolated antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, induces or enhances PD-1 mediated secretion of one or more cytokines from a cell.

[0186] In some aspects, the antibody or an antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg. In some aspects, the antibody or

antigen binding portion thereof specifically binds to an epitope comprising one or more amino acids of (i) amino acids 37 to 56 corresponding to SEQ ID NO: 2 (IL-27p28), (ii) amino acids 142 to 164 corresponding to SEQ ID NO: 2 (IL-27p28), or (iii) both (i) and (ii). In some aspects, the antibody or an antigen binding portion thereof is administered at a dose that is sufficient to maintain IC90 of pSTAT1 inhibition level, i.e., above about 0.7 ug/mL for the duration of the treatment, e.g., 28 days, 56 days, or 84 days.

[0187] In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.006 mg/kg to at least about 20 mg/kg, at least about 0.009 mg/kg to at least about 20 mg/kg, at least about 0.01 mg/kg to at least about 20 mg/kg, at least about 0.03 mg/kg to at least about 20 mg/kg, at least about 0.06 mg/kg to at least about 20 mg/kg, at least about 0.09 mg/kg to at least about 20 mg/kg, at least about 0.1 mg/kg to at least about 20 mg/kg, at least about 0.3 mg/kg to at least about 20 mg/kg, at least about 0.6 mg/kg to at least about 20 mg/kg, at least about 0.9 mg/kg to at least about 20 mg/kg, at least about 1 mg/kg to at least about 20 mg/kg, at least about 1 mg/kg to at least about 20 mg/kg, at least about 3 mg/kg to at least about 20 mg/kg, at least about 6 mg/kg to at least about 20 mg/kg, at least about 10 mg/kg to at least about 20 mg/kg, at least about 13 mg/kg to at least about 20 mg/kg, at least about 13 mg/kg to at least about 18 mg/kg, at least about 13 mg/kg to at least about 16 mg/kg, at least about 16 mg/kg to at least about 20 mg/kg, at least about 16 mg/kg to at least about 18 mg/kg, at least about 3 mg/kg to at least about 18 mg/kg, at least about 6 mg/kg to at least about 15 mg/kg, at least about 13 mg/kg to at least about 18 mg/kg, or at least about 10 mg/kg to at least about 15 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.006 mg/kg to at least about 10 mg/kg, at least about 0.009 mg/kg to at least about 10 mg/kg, at least about 0.01 mg/kg to at least about 10 mg/kg, at least about 0.03 mg/kg to at least about 10 mg/kg, at least about 0.06 mg/kg to at least about 10 mg/kg, at least about 0.09 mg/kg to at least about 10 mg/kg, at least about 0.1 mg/kg to at least about 10 mg/kg, at least about 0.3 mg/kg to at least about 10 mg/kg, at least about 0.6 mg/kg to at least about 10 mg/kg, at least about 0.9 mg/kg to at least about 10 mg/kg, at least about 1 mg/kg to at least about 10 mg/kg, at least about 1 mg/kg to at least about 9 mg/kg, at least about 3 mg/kg to at least about 9 mg/kg, at least about 1 mg/kg to at least about 6 mg/kg, at least about 3 mg/kg to at least about 6 mg/kg, or at least about 1 mg/kg to at least about 3 mg/kg.

[0188] In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg, at least about 0.006 mg/kg, at least about 0.009 mg/kg, at

least about 0.01 mg/kg, at least about 0.03 mg/kg, at least about 0.06 mg/kg, at least about 0.09 mg/kg, at least about 0.1 mg/kg, at least about 0.3 mg/kg, at least about 0.6 mg/kg, at least about 0.9 mg/kg, at least about 1.0 mg/kg, at least about 2 mg/kg, at least about 3 mg/kg, at least about 4 mg/kg, at least about 5 mg/kg, at least about 6 mg/kg, at least about 7 mg/kg, at least about 8 mg/kg, at least about 9, or at least about 10 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 11 mg/kg, at least about 12 mg/kg, at least about 13 mg/kg, at least about 14 mg/kg, at least about 15 mg/kg, at least about 16 mg/kg, at least about 17 mg/kg, at least about 18 mg/kg, at least about 19, or at least about 20 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.006 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.009 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.01 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.03 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.06 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.09 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.1 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.3 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.6 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 0.9 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 1.0 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 2 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 3 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 4 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 5 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 6 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 7 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 8 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about

9. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 10 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 11 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 12 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 13 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 14 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 15 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 16 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 17 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 18 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 19 mg/kg. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of at least about 20 mg/kg.

[0189] In some aspects, the antibody or antigen binding portion thereof is administered once about every week, once about every two weeks, once about every three weeks, once about every four weeks, once about every 6 weeks, once about every 8 weeks, or once about every 12 weeks. In some aspects, the antibody or antigen binding portion thereof is administered once about every four weeks.

[0190] In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 0.3 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 1 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 2 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 3 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 4 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 5 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 6 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 7 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 8 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered

at a dose of about 9 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 10 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 11 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 12 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 13 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 14 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 15 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 16 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 17 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 18 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 19 mg/kg once about every week. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 20 mg/kg once about every week.

[0191] In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 0.3 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 1 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 2 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 3 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 4 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 5 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 6 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 7 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 8 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 9 mg/kg once about every two weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 10 mg/kg once about every two weeks. In some aspects, the

administered at a dose of about 12 mg/kg once about every three weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 13 mg/kg once about every three weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 14 mg/kg once about every three weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 15 mg/kg once about every three weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 16 mg/kg once about every three weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 17 mg/kg once about every three weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 18 mg/kg once about every three weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 19 mg/kg once about every three weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 20 mg/kg once about every three weeks.

[0193] In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 0.3 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 1 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 2 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 3 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 4 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 5 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 6 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 7 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 8 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 9 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 10 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 11 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 12 mg/kg once about every four weeks. In some aspects, the antibody or antigen

binding portion thereof is administered at a dose of about 13 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 14 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 15 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 16 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 17 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 18 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 19 mg/kg once about every four weeks. In some aspects, the antibody or antigen binding portion thereof is administered at a dose of about 20 mg/kg once about every four weeks.

[0194] Certain aspects of the present disclosure are directed to methods of treating a cancer in a subject in need thereof. In some aspects, the cancer is selected from Kaposi's sarcoma, leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblasts promyelocyte myelomonocytic monocytic erythroleukemia, chronic leukemia, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, mantle cell lymphoma, primary central nervous system lymphoma, Burkitt's lymphoma and marginal zone B cell lymphoma, Polycythemia vera Lymphoma, Hodgkin's disease, non-Hodgkin's disease, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, solid tumors, sarcomas, and carcinomas, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, osteosarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon sarcoma, colorectal carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, retinoblastoma, nasopharyngeal carcinoma, esophageal carcinoma, basal cell carcinoma, biliary tract cancer,

bladder cancer, bone cancer, brain and central nervous system (CNS) cancer, cervical cancer, choriocarcinoma, colorectal cancers, connective tissue cancer, cancer of the digestive system, endometrial cancer, esophageal cancer, eye cancer, head and neck cancer, gastric cancer, intraepithelial neoplasm, kidney cancer, larynx cancer, liver cancer, lung cancer (small cell, large cell), melanoma, neuroblastoma; oral cavity cancer (for example lip, tongue, mouth and pharynx), ovarian cancer, retinoblastoma, rhabdomyosarcoma, rectal cancer; cancer of the respiratory system, sarcoma, skin cancer, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, cancer of the urinary system, and any combination thereof. In some aspects, the cancer is chosen from lung cancer (e.g., non-small cell lung cancer), sarcoma, testicular cancer, ovarian cancer, pancreas cancer, breast cancer (e.g., triple-negative breast cancer), melanoma, head and neck cancer (e.g., squamous head and neck cancer), colorectal cancer, bladder cancer, endometrial cancer, prostate cancer, thyroid cancer, hepatocellular carcinoma, gastric cancer, brain cancer, lymphoma (e.g., DL-BCL), leukemia (e.g., AML) or renal cancer (e.g., renal cell carcinoma, e.g., clear cell RCC and/or non-clear cell RCC). In some aspects, the methods can be performed in conjunction with other therapies for cancer. For example, the composition can be administered to a subject at the same time, prior to, or after, radiation, surgery, targeted or cytotoxic chemotherapy, chemoradiotherapy, hormone therapy, immunotherapy, gene therapy, cell transplant therapy, precision medicine, genome editing therapy, or other pharmacotherapy.

[0195] In some aspects, the compositions disclosed herein are administered to a subject, e.g., a human subject, using a variety of methods that depend, in part, on the route of administration. The route can be, e.g., intravenous injection or infusion (IV), subcutaneous injection (SC), intraperitoneal (IP) injection, intramuscular injection (IM), or intrathecal injection (IT). The injection can be in a bolus or a continuous infusion.

[0196] Administration can be achieved by, e.g., local infusion, injection, or by means of an implant. The implant can be of a porous, non-porous, or gelatinous material, including membranes, such as silastic membranes, or fibers. The implant can be configured for sustained or periodic release of the composition to the subject. See, e.g., U.S. Patent Application Publication No. 20080241223; U.S. Patent Nos. 5,501,856; 4,863,457; and 3,710,795; EP488401; and EP 430539, the disclosures of each of which are incorporated herein by reference in their entirety. The composition can be delivered to the subject by way of an implantable device based on, e.g., diffusive, erodible, or convective systems, e.g., osmotic pumps, biodegradable implants,

electrodifusion systems, electroosmosis systems, vapor pressure pumps, electrolytic pumps, effervescent pumps, piezoelectric pumps, erosion-based systems, or electromechanical systems.

[0197] In some aspects, an anti-IL-27 antibody or antigen-binding fragment thereof is therapeutically delivered to a subject by way of local administration.

[0198] In certain aspects, the route of administration is in accord with known methods, e.g. orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, subcutaneously, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain aspects, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device. In certain aspects, individual elements of the combination therapy may be administered by different routes.

[0199] In certain aspects, the composition can be administered locally via implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In certain aspects, where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion, timed-release bolus, or continuous administration. In certain aspects, it can be desirable to use a pharmaceutical composition comprising an anti-IL-27 antibody in an ex vivo manner. In such instances, cells, tissues and/or organs that have been removed from the patient are exposed to a pharmaceutical composition comprising an anti-IL-27 antibody after which the cells, tissues and/or organs are subsequently implanted back into the patient.

[0200] In certain aspects, an anti-IL-27 antibody can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptides. In certain aspects, such cells can be animal or human cells, and can be autologous, heterologous, or xenogeneic. In certain aspects, the cells can be immortalized. In certain aspects, in order to decrease the chance of an immunological response, the cells can be encapsulated to avoid infiltration of surrounding tissues. In certain aspects, the encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

[0201] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of one or more biomarkers selected from the group consisting of Eotaxin-1 (CCL11), TARC (CCL17), VEGF-A, IL-7, IL-8, MCP-1, MCP-4,

and any combination thereof; wherein the increased expression of the one or more biomarkers is relative to the expression of the one or more biomarker prior to the administration. In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of Eotaxin-1 (CCL11), wherein the increased expression of Eotaxin-1 (CCL11) is relative to the expression of Eotaxin-1 (CCL11) prior to the administration.

[0202] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of TARC (CCL17), wherein the increased expression of TARC (CCL17) is relative to the expression of TARC (CCL17) prior to the administration.

[0203] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of VEGF-A, wherein the increased expression of VEGF-A is relative to the expression of VEGF-A prior to the administration.

[0204] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of IL-7, wherein the increased expression of IL-7 is relative to the expression of IL-7 prior to the administration.

[0205] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of IL-8, wherein the increased expression of IL-8 is relative to the expression of IL-8 prior to the administration.

[0206] In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of MCP-1, wherein the increased expression of MCP-1 is relative to the expression of MCP-1 prior to the administration.

In some aspects, following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of MCP-4, wherein the increased expression of MCP-4 is relative to the expression of MCP-4 prior to the administration.

A. Anti-IL-27 Antibodies and Antigen-Binding Portions Thereof

[0207] Certain aspects of the present disclosure are directed to methods of administering antibodies, and antigen binding portions thereof, that specifically bind to IL-27p28 and antagonize IL-27, in particular human IL-27.

[0208] In some aspects, the antibody or antigen binding portion thereof inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell in the subject. In some aspects, the antibody or antigen binding portion thereof inhibits or reduces pSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling). In some aspects, the antibody or antigen binding portion thereof inhibits or

reduces pSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) by at least about 25%, at least about 50%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, relative to pSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (*e.g.*, an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) by at least about 90% relative to PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (*e.g.*, an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) by at least about 91% relative to PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (*e.g.*, an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) by at least about 92% relative to PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (*e.g.*, an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) by at least about 93% relative to PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (*e.g.*, an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) by at least about 94% relative to PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (*e.g.*, an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) by at least about 95% relative to PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (*e.g.*, an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) by at least about 96% relative to PSTAT1 signaling (*e.g.*, IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (*e.g.*, an anti-IL-27 antibody disclosed herein). In some aspects,

the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (e.g., IL-27 mediated pSTAT1 signaling) by at least about 97% relative to PSTAT1 signaling (e.g., IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (e.g., an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (e.g., IL-27 mediated pSTAT1 signaling) by at least about 98% relative to PSTAT1 signaling (e.g., IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (e.g., an anti-IL-27 antibody disclosed herein). In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PSTAT1 signaling (e.g., IL-27 mediated pSTAT1 signaling) by at least about 99% relative to PSTAT1 signaling (e.g., IL-27 mediated pSTAT1 signaling) prior to administration of the antibody or antigen binding portion thereof (e.g., an anti-IL-27 antibody disclosed herein).

[0209] In some aspects, the antibody or antigen binding portion thereof inhibits or reduces inhibition of CD161 expression in a cell in the subject. In some aspects, the antibody or antigen binding portion thereof inhibits or reduces PD-L1 expression in a cell in the subject. In some aspects, the antibody or antigen binding portion thereof induces or enhances PD-1 mediated secretion of one or more cytokines from a cell in the subject. In some aspects, the antibody or antigen binding portion thereof alters TIM-3 expression in a cell in the subject. In some aspects, the cell is a tumor cell or an immune cell.

[0210] Accordingly, in one aspect, the disclosure provides an isolated antibody that specifically binds to and antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof specifically binds to the epitopes disclosed herein and exhibits at least one or more of the following properties: (i) binds to human IL-27 with an equilibrium dissociation constant (K_D) of 15 nM or less; (ii) blocks binding of IL-27 to IL-27 receptor; (iii) inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell; (iv) inhibits or reduces IL-27 mediated inhibition of CD161 expression in a cell; (v) inhibits or reduces IL-27 mediated PD-L1 expression in a cell; (vi) induces or enhances PD-1 mediated secretion of one or more cytokines from a cell; (vii) alters TIM-3 expression in a cell; and (viii) a combination of (i)-(vii).

[0211] In some aspects, the antibody or antigen binding portion thereof specifically binds to an epitope comprising one or more amino acids of (i) amino acids 37 to 56 corresponding to SEQ ID NO: 2 (IL-27p28), (ii) amino acids 142 to 164 corresponding to SEQ ID NO: 2 (IL-27p28), or (iii) both (i) and (ii). In some aspects, an isolated antibody of the disclosure that antagonizes

human IL-27, or an antigen binding portion thereof, specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, or Glu164 of SEQ ID NO: 2 (IL-27p28).

[0212] Some aspects of the present disclosure are directed to a method of treating a cancer in a subject in need thereof comprising administering to the subject an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof specifically binds to an epitope comprising one or more amino acids of (i) amino acids 37 to 56 corresponding to SEQ ID NO: 2 (IL-27p28), (ii) amino acids 142 to 164 corresponding to SEQ ID NO: 2 (IL-27p28), or (iii) both (i) and (ii); wherein the antibody or antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg to at least about 10 mg/kg; wherein the antibody or the antigen binding portion thereof comprises a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 121 or 124. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 121. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 124. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 120 or 123. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 120. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 123. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 119 or 122. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 119. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 122. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 129 or 132. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 129. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 132. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR2 comprising the sequence set forth in SEQ

ID NO: 128 or 131. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR2 comprising the sequence set forth in SEQ ID NO: 128. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR2 comprising the sequence set forth in SEQ ID NO: 131. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR1 comprising the sequence set forth in SEQ ID NO: 127 or 130. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR1 comprising the sequence set forth in SEQ ID NO: 127. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain CDR1 comprising the sequence set forth in SEQ ID NO: 130.

[0213] In some aspects, the antibody or the antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, and a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121. In some aspects, the antibody or the antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, and a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124.

[0214] In some aspects, the antibody or the antigen binding portion thereof comprises: a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129. In some aspects, the antibody or the antigen binding portion thereof comprises: a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132.

[0215] In some aspects, the antibody or the antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129. In some aspects, the method comprises

administering a dose of at least about 0.003 mg/kg to at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129. In some aspects, the method comprises administering a dose of at least about 1 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129. In some aspects, the method comprises administering a dose of at least about 3 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129. In some aspects, the method comprises administering a dose of at least about 6 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129. In some aspects,

the method comprises administering a dose of at least about 10 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129. In some aspects, the method comprises administering a dose of at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129.

[0216] In some aspects, the antibody or the antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132. In some aspects, the method comprises administering a dose of at least about 0.003 mg/kg to at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132. In some aspects, the method comprises administering a dose of at least about 0.003 mg/kg to at least about 20 mg/kg

of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132. In some aspects, the method comprises administering a dose of at least about 1 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132. In some aspects, the method comprises administering a dose of at least about 3 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132. In some aspects, the method comprises administering a dose of at least about 6 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132. In some aspects, the method comprises administering a dose of at least about 10 mg/kg of an antibody that

antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132. In some aspects, the method comprises administering a dose of at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132.

[0217] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 125. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125.

[0218] In some aspects, the antibody or the antigen binding portion thereof comprises a light chain variable region comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133.

[0219] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the method comprises administering a dose of at least about 0.003 mg/kg to at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof,

wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the method comprises administering a dose of at least about 1 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the method comprises administering a dose of at least about 3 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the method comprises administering a dose of at least about 6 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the method comprises administering a dose of at least about 10 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133. In some aspects, the method comprises administering a dose of at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133.

[0220] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 135. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 135.

[0221] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 139. In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 139.

[0222] In some aspects, the antibody or the antigen binding portion thereof comprises a light chain comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the antibody or the antigen binding portion thereof comprises a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137.

[0223] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 0.003 mg/kg to at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 1 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 3 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 6 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain

variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 10 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137.

[0224] In some aspects, the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 139 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 0.003 mg/kg to at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 1 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 3 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 6 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 10 mg/kg of an antibody that

antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137. In some aspects, the method comprises administering a dose of at least about 20 mg/kg of an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 139 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 137.

[0225] In some aspects, the antibody or antigen-binding portion thereof comprises an amino acid sequence set forth in Table 1A.

Table 1A: Anti-IL-27 Antibodies

SEQ ID NO	Description	Sequence
		anti-IL-27 Ab2-A
9	HCDR1 (IMGT)	GFTFSSYS
10	HCDR2 (IMGT)	ISSSSSYI
11	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
12	HCDR1 (NT)	FTFSSYSMN
13	HCDR2 (NT)	SISSSSSYIYYADSVKG
14	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
15	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSS
16	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACACCTTCA GTAGCTATAGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGAAGAAG GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCA
17	LCDR1 (IMGT)	QSVLFSSNNKNY
18	LCDR2 (IMGT)	WAS
19	LCDR3 (IMGT)	QQHASAPPT

20	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
21	LCDR2 (NT)	WASTRES
22	LCDR3 (NT)	QQHASAPPT
23	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISLQAED VAVYYCQQHASAPPTFGGGTKVEIK
24	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGAGCAGCAGCCAGTGCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
25	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKG LEWVSSISSSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDWPWGQTLTVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEHA LHNHYTQKSLSLSPGK
26	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGCTATAGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGAAGAAG GTCTTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTCTGGGCGGCCCCGAGCGTGT TTCTGTTTCCGCCGAAACCGAAAGATAACCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAAGAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG

		CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT GACCAAAAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACTATAAAACCACCCCGCCGGTGCTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAAGTACCCTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCAGAAAAGCCTGAGCCTGAGCCCGG CAAA
27	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
28	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGAGCAGCACGCCAGTGCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTCTCTCCACCCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCCTGCTGAACAACTTCTACCC TCGCGAGGCCAAAGTGAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCAGGAATCCGTACCCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCTCCACCCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGACGCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCTTCAACCGGGGCGAGTGC
		anti-IL-27 Ab2-B
29	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG
30	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACACCTCA GTAGCTATAGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCTTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC

		TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTTGGAACTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGAATCTAAGTACGGCCCTCCCTGCCCTTCTCTG CCCTGCCCTGAGTTCTTGGCGGACCTTCCGTGTTCTGTTC CTCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAA TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		anti-IL-27 Ab3-A
31	HCDR1 (IMGT)	GFTFRSYG
32	HCDR2 (IMGT)	ISSSSSYI
33	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
34	HCDR1 (NT)	FTFRSYGMN
35	HCDR2 (NT)	SISSSSSYIYYADSVKG
36	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
37	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSS
38	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCC GGAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCAACCGTCTCTCTCA
39	LCDR1 (IMGT)	QSVLFSSNNKNY
40	LCDR2 (IMGT)	WAS

41	LCDR3 (IMGT)	QQHASAPPT
42	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
43	LCDR2 (NT)	WASTRES
44	LCDR3 (NT)	QQHASAPPT
45	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIK
46	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGACGAGCACGCCAGTGCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
47	Heavy Chain	EVOLVESGGGLVLPKGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDWPWGQGLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKHTCTPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHEA LHNHYTQKSLSLSPGK
48	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCC GGAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGCGGTGTACTACTGCGCCAGAGATGGTGAAGAAG GTCCTACACCGCCACAGCCCAATTTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAGGCCCCG AGCGTGTTCGCTGGCGCCGAGCAGCAAAAGCACCAGCGGCGG CACCAGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGGCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTCTGGGCGGCCCCGAGCGTGT TTCTGTTTCGCGCGAAACCGAAAGATACCCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT

		GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT GACCAAAAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACCTATAAAACCACCCCGCCGGTGCTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
49	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISLQAED VAVYQCQHASAPPTFGGGTKVEIKRTVAAPSVFI FPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
50	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTCAAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGAGCAGCACGCCAGTGCCCCCTCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCCGTGTTTCACTCTCCCAACCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTCTGTGTGCTGCTGAACAACTTCTACCC TCGCGAGGCCAAAGTGCAAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCAGGAATCCGTCACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCTCCACCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		anti-IL-27 Ab3-B
51	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHLEAHN HYTQKSLSLSLG
52	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCC GGAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGAAGAAC

		GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTTGGAACTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGAATCTAAGTACGGCCCTCCCTGCCCTTCCTG CCCTGCCCTGAGTTCCTGGGCGGACCTTCCGTGTTCTGTTC CTCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		anti-IL-27 Ab4-A
53	HCDR1 (IMGT)	GFTFSR TG
54	IICDR2 (IMGT)	ISSSSSYI
55	HCDR3 (IMGT)	ARDGGRTSYTATAHNW FDP
56	HCDR1 (NT)	FTFSRTGMN
57	HCDR2 (NT)	SISSSSSYIYYADSVKG
58	HCDR3 (NT)	ARDGGRTSYTATAHNW FDP
59	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRTGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNW FDPWGQGLTVTVSS
60	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGACTGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAATGGGTCTCATCCATTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCA
61	LCDR1 (IMGT)	QSVLFSSNNKNY

62	LCDR2 (IMGT)	WAS
63	LCDR3 (IMGT)	QQHASAPPT
64	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
65	LCDR2 (NT)	WASTRES
66	LCDR3 (NT)	QQHASAPPT
67	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIK
68	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT TATTTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTGAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGTCAGCAGCACGCCAGTGCCCTCCTAC TTTTGGCGGAGGGACCAAGTTGAGATCAAA
69	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFTRTGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDWPWGQGLVTVSSASTKGP SVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMSHEA LHNHYTQKSLSLSPGK
70	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGACTGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAATGGGTCTCATCCATTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAGAAGAC GTCTTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCAACGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTCGCGCTGGCGCCGAGCAGCAAAAGCACCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGT TTCTGTTTCCGCCGAAACCGAAAGATACCCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC

		ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGTTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT GACCAAAAACAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACTATAAAACCACCCCGCCGGTGCTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAAGTACCGTGGAATAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
71	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSDTFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFIFFPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYKHKVYACEVTHQGLSSPVTKSFNRGEC
72	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT'TT TATT'CAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATT'TACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATT'CAGTGGCAGCGGGTCTG GGACAGATTT'CACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGT'CAGCAGCACGCCAGTGGCCCTCCTAC 'T'T'T'GGCGGAGGGACCAAGG'T'T'GAGAT'CAAACG'T'ACGG'T'GGCCG CTCCCTCCGTGTT'CATCTTCCACCCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCCTGCTGAACAACCTTCTACCC TCGCGAGGGCAAAGT'GCAGTGGAAAGTGGACAACGCCCTGCAGT' CCGGCAACTCCCAGGAATCCGT'CACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCTCCACCCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		anti-IL-27 Ab4-B
73	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRTGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTIVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN HYTQKSLSLSLG
74	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGACTGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAATGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA

		ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCAACGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTTGGAACCTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACGTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCTTG CCCTGCCCTGAGTTCCTGGGCGGACCTTCCGTGTTCTGTTC CTCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCTCCCCTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		anti-IL-27 Ab5-A
75	HCDR1 (IMGT)	GFTF'SRYG
76	HCDR2 (IMGT)	ISSSSAYI
77	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
78	HCDR1 (NT)	FTFSRYGMN
79	HCDR2 (NT)	SISSSSAYILYADSVKG
80	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
81	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYGMNWVRQAPGKG LEWVSSISSSSAYILYADSVKGRFTISRDNKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSS
82	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTGCTTACATACT GTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCAACGTCTCCTCA

83	LCDR1 (IMGT)	QSVLFSSNNKNY
84	LCDR2 (IMGT)	WAS
85	LCDR3 (IMGT)	QQHASAPPT
86	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
87	LCDR2 (NT)	WASTRES
88	LCDR3 (NT)	QQHASAPPT
89	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTITSSLOAED VAVYYCQQHASAPPTFGGGTKVEIK
90	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTTCAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGTCAGCAGCACGCCAGTGGCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAA
91	Heavy Chain	EVQLVESGGGLVLPKGGSLRLSCAASGFTFSRYGMNWVRQAPGKG LEWVSSISSSSAYILYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEA LHNHYTQKSLSLSPGK
92	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACACCTTCA GTAGGTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTGCTTACATACT GTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCTTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAGCACCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCAGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGCGCCGGAAGTCTGGGCGGCCCCGAGCGTGT TTCTGTTTCCGCCGAAACCGAAAGATACCCTGATGATTAGCCGC

		ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT GACCAAAAACAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACTATAAAACCACCCCGCCGGTGCTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAACCTGACCGTGGAATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
93	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
94	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTAGTGCGAGCGGGTCTG GGACAGATTTTACATCTCACCATCAGCAGCCTGCAGGCCTGAAGA GTGGCAGTTTATTACTGTGAGCAGCACGCCAGTGCCCTCCTAC TTTTGGCGGAGGGACCAAGTTGAGATCAAACGTACGGTGGCCG CTCCTCCGTGTTTATCTTCCCACCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCCTGCTGAACAACCTTCTACCC TCGCGAGGCCAAAGTGCAAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCCAGGAATCCGTACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCTTCCACCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		anti-IL-27 Ab5-B
95	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYGMNWVRQAPGKG LEWVSSISSSSAYILYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN HYTQKSLSLSLG
96	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG

		CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTGCTTACATACT GTACGCAGACTCAGTGAAGGGCCGATTACCATTCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCAACGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTTGGAACCTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCCTG CCCTGCCCTGAGTTCCCTGGGCGGACCTTCCGTGTTCCCTGTTCC CTCCAAGGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		anti-IL-27 Ab6-A
97	HCDR1 (IMGT)	GFTFASYG
98	HCDR2 (IMGT)	ISSSSSYI
99	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
100	HCDR1 (NT)	F'TFASYGMN
101	HCDR2 (NT)	SISSSSSYIYYADSVKG
102	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
103	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFASYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSS
104	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCG CTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTTCTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATTCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC

		GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGGTCACCGTCTCCTCA
105	LCDR1 (IMGT)	QSVLFSSNNKNY
106	LCDR2 (IMGT)	WAS
107	LCDR3 (IMGT)	QQHASAPPT
108	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
109	LCDR2 (NT)	WASTRES
110	LCDR3 (NT)	QQHASAPPT
111	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAE VAVYYCQQHASAPPTFGGGTKVEIK
112	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTTCAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGACGACGACGCCAGTGCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
113	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFASYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDWPWGQGLTVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHEA LHNHYTQKSLSLSPGK
114	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCG CTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTTCTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACACGCGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTTGACCGTTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGT CATACCTTTCCGGCGGTGCTGCAGAGCAGCGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG

		CCCGCCGTGCCCCGGCGCCGGAAGTCTGGGCGGCCCCGAGCGTGT TTCTGTTTTCGCGCGAAACCGAAAGATACCTGTATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCTGCCGCCGAGCCGCGATGAACT GACCAAAAACAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACTATAAAACCAACCCCGCCGGTGTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAAGTACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
115	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISLQAE VAVYYCQHASAPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
116	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT TATTTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCCTCCTAAGCTGCTCACTTACCTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTGAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGAGCAGCACGCCAGTGCCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTATCTTCCACCCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCTGCTGAACAACCTCTACCC TCGCGAGGCCAAAGTGCAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCAGGAATCCGTACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCTCTCCACCCCTGACCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		anti-IL-27 Ab6-B
117	Heavy Chain	EVQLVESGGGLVKGPGSLRLSCAASGFTFASYGMNWVRQAPGKG LEWVSSISSSSSYIYADSVKGRFTISRDNKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDWPWGQGLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG

118	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCG CTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTTCTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAAGTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTTGAACTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACGTGGACCACAAGCCCTCCAACACCAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCTG CCCTGCCCTTGAGTTCCTGGGCGGACCTTCCGTGTTCTGTTCC CTCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		anti-IL-27 Abl-A
119	HCDR1 (IMGT)	GFTRSYG
120	HCDR2 (IMGT)	ISSSGSYI
121	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
122	HCDR1 (NT)	FTFRSYGMN
123	HCDR2 (NT)	GISSSGSYIYYADSVKG
124	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
125	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSGISSSGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPPWGQGLTVTVSS
126	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCC GTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCAGGTATTAGTAGTAGTGGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA

		ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCAACCGTCTCCTCA
127	LCDR1 (IMGT)	QSVLFSSNNKNY
128	LCDR2 (IMGT)	WAS
129	LCDR3 (IMGT)	QQHASAPPT
130	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
131	LCDR2 (NT)	WASTRES
132	LCDR3 (NT)	QQHASAPPT
133	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLA WYQQKPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLT ISSIQAEDVAVYYCQQHASAPPTFGGGTKVEIK
134	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT TTTATTTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTTCAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGACGACGACGCCAGTGGCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
135	Heavy Chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSGISSGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRSTSYTATAHNWFDWPWGQGLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKHTHTCPPCPAPELGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEA LHNHYTQKSLSLSPGK
136	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCC GTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCAGGTATTAGTAGTAGTGGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCAACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTCTTCCGCTGGCGCCGAGCAGCAAAGCACCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA

		CCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGT TTCTGTTTTCCGCCGAAACCGAAAGATAACCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAAGCTGCTGACCGTGTGTCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCAGGTGTATACCTGCCGCCGAGCCGCGATGAACT GACCAAAAACAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACTATAAAACCAACCCCGCCGGTGTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGG CAAA
137	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDFRSGSGSGTDFTLTISSLQAE VAVYYCQHASAPPTFGGGTKVEIKRTVAAPSVFIFFPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
138	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGT TATTTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTGAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGAGCAGCACGCCAGTGCCCTCCTAC TTTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTCTCTCCACCCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCCTGCTGAACAACTTCTACCC TCGCGAGGCCAAAGTGCAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCAGGAATCCGTACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCTCCACCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		anti-IL-27 Ab1-B
139	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSGISSGSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN

		YKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG
140	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCC GTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCAGGTATTAGTAGTAGTGGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGAAGAAC GTCCTACACCGCCACAGCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTTGGAACTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACGTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCCTG CCCTGCCCCCTGAGTTCCCTGGGCGGACCTTCCGTGTTCTGTTC CTCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
141	FLAG	DYKDDDDK
142	6-HIS	HHHHHH
143	HA	YPYDVPDYA

[0226] In some aspects, the antibody, or antigen binding portion thereof, comprises an Fc sequence set forth in Table 1B. In some aspects, the antibody, or antigen binding portion thereof, comprises a heavy chain, wherein the heavy chain comprises an Fc region having an amino acid at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the sequence set forth in SEQ ID NO: 5, 6, 7, or 8. In some aspects, the antibody, or antigen binding portion thereof, comprises a heavy chain, wherein the heavy chain comprises an Fc region comprising the amino acid sequence set forth in SEQ ID NO:

5. In some aspects, the antibody, or antigen binding portion thereof, comprises a heavy chain, wherein the heavy chain comprises an Fc region comprising the amino acid sequence set forth in SEQ ID NO: 6. In some aspects, the antibody, or antigen binding portion thereof, comprises a heavy chain, wherein the heavy chain comprises an Fc region comprising the amino acid sequence set forth in SEQ ID NO: 7. In some aspects, the antibody, or antigen binding portion thereof, comprises a heavy chain, wherein the heavy chain comprises an Fc region comprising the amino acid sequence set forth in SEQ ID NO: 8.

Table 1B: Fc Sequences (=CH₂+CH₃)

Name	Alias	Amino Acid Sequence
Human IgG1	1.0	EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT V LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 5)
Human IgG4	4.0	ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT V LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNV FSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 6)
Human IgG4 (S228P)	4.1	ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT V LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNV FSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 7)
Human IgG4 (S228P / L235E)	4.2	ESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT V LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNV FSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 8)

[0227] In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Asp146 and Arg149 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Asp146 and Phe153 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Arg149 and Phe153 of SEQ ID NO: 2 (IL-27p28). In some aspects,

an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Asp146, Arg149, and/or Phe153 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Asp146, Arg149, and Phe153 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope comprises Asp146, Arg149, His150, and Phe153 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope comprises Asp146, Arg149, Phe153, and Leu156 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope comprises Asp146, Arg149, His150, Phe153, and Leu156 of SEQ ID NO: 2 (IL-27p28).

[0228] In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising at least one, at least two, at least three, at least four, at least five, or at least six amino acids of IL-27p28 selected from Leu142, Asp146, Arg149, His150, Phe153, Leu156, and Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Leu142, Asp146, Arg149, His150, Phe153, Leu156, and Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, the epitope comprises Gln37, Leu38, Glu42, Asp146, Arg149, His150, Phe153, and Leu156 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Gln37, Leu38, Glu42, Leu142, Asp146, Arg149, His150, Phe153, Leu156, and Glu164 of SEQ ID NO: 2 (IL-27p28).

[0229] In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising at least one, at least two, at least three, at least four, at least five, or at least six, at least seven, at least eight, or at least nine amino acids of IL-27p28 selected from Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, and Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, and Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising at least one, at least two, at least three, at least four, at least five, or at least six, at least seven, at least eight, or at least nine amino acids of IL-27p28 selected from Gln37, Leu38, Glu42, Glu46, Val49, Ser50,

Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28). In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28).

[0230] In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope consisting of or consisting essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28).

[0231] In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28) and at least one residues selected from the group consisting of: Leu53, Lys56, Asp143, Leu147, Arg152, Ala157, Gly159, Phe160, or Asn161 of SEQ ID NO: 2 (IL-27p28).

[0232] In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope comprising Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28) and at least one residues selected from the group consisting of: Leu53, Lys56, Asp143, Arg145, Leu147, Arg152, Ala157, Gly159, Phe160, Asn161, or Pro163 of SEQ ID NO: 2 (IL-27p28).

[0233] In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope consisting or consisting essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28).

[0234] In some aspects, an antibody, or antigen binding portion thereof, of the present disclosure specifically binds to an epitope consisting or consisting essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28).

[0235] In some aspects, the disclosure provides an isolated antibody that specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153,

Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28) and antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof exhibits at least one or more of the following properties: (i) binds to human IL-27 with an equilibrium dissociation constant (K_D) of 15 nM or less; (ii) blocks binding of IL-27 to IL-27 receptor; (iii) inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell; (iv) inhibits or reduces inhibition of CD161 expression in a cell; (v) inhibits or reduces PD-L1 expression in a cell; (vi) induces or enhances PD-1 mediated secretion of one or more cytokines from a cell; (vii) alters TIM-3 expression in a cell; and (viii) a combination of (i)-(vii).

[0236] In some aspects, the isolated antibody, or antigen binding portion thereof, binds to an epitope of one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (human IL-27p28) with an equilibrium dissociation constant (K_D) of 15 nM or less.

[0237] In some aspects, the isolated antibody, or antigen binding portion thereof, binds to recombinant human IL-27p28. In some aspects, the isolated antibody, or antigen binding portion thereof, binds to murine IL-27p28.

[0238] In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and STAT3 phosphorylation in a cell. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%, relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 50%, relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 60%,

relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 70%, relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 75%, relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 80%, relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 85%, relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 90%, relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT1 phosphorylation in a cell by at least about 95%, relative to the STAT1 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, eliminates STAT1 phosphorylation in the cell.

[0239] In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 50%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion

thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 60%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 70%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 75%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 80%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 85%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 90%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces STAT3 phosphorylation in a cell by at least about 95%, relative to the STAT3 phosphorylation in the cell prior to contacting the cell with the antibody, or antigen binding portion thereof. In some aspects, the isolated antibody, or antigen binding portion thereof, eliminates STAT3 phosphorylation in the cell.

[0240] In some aspects, the cell is an immune cell. In some aspects, the cell is a cancer cell.

[0241] In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces inhibition of CD161 expression in a cell (e.g. ameliorates or relieves the inhibition of CD161 expression in a cell). In some aspects, the cell is an immune cell.

[0242] In some aspects, the isolated antibody, or antigen binding portion thereof, inhibits or reduces PD-L1 expression in a cell. In some aspects, PD-L1 expression is inhibited or reduced. In some aspects, TIM-3 expression is altered. In some aspects, both PD-L1 expression and TIM-3 expression is altered. In some aspects, the cell is an immune cell. In some aspects, the antibodies are monoclonal antibodies.

[0243] In some aspects, the isolated antibody, or antigen binding portion thereof, induces or enhances the PD-1-mediated secretion of one or more cytokines from a cell. In some aspects, the one or more cytokines is TNF α . In some aspects, the one or more cytokine is IL-6. In some aspects, the one or more cytokine is TNF α and IL-6. In some aspects, the cell is an immune cell.

[0244] In some aspects, the isolated antibody, or antigen binding portion thereof, is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, an IgD, and an IgE antibody. In some aspects, the antibody is an IgG1 antibody or an IgG4 antibody. In some aspects, the antibody comprises a wild type IgG1 heavy chain constant region. In some aspects, the antibody comprises a wild type IgG4 heavy chain constant region. In some aspects, the antibody comprises an Fc domain comprising at least one mutation. In some aspects, the antibody comprises a mutant IgG1 heavy chain constant region. In some aspects, the antibody comprises a mutant IgG4 heavy chain constant region. In some aspects, the mutant IgG4 heavy chain constant region comprises any one of the substitutions S228P, L235E, L235A, or a combination thereof, according to EU numbering.

[0245] In some aspects, the disclosure provides an isolated antibody, or antigen binding portion thereof, that binds to substantially the same epitope on IL-27 as the antibody, or antigen binding portion thereof, according to any one of the aforementioned aspects.

[0246] In some aspects, the disclosure provides an isolated antibody, or antigen binding portion thereof, that binds to at least one of the amino acid residues selected from the group consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28) bound by the antibody, or antigen binding portion thereof, according to any one of the aforementioned aspects.

[0247] In some aspects, the disclosure provides an isolated antibody, or antigen binding portion thereof, wherein a mutation of the epitope (Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28)) bound by the antibody or antigen binding portion thereof inhibits, reduces, or blocks binding to both the antibody or antigen binding portion thereof and to the antibody or antigen binding portion thereof according to any one of the aforementioned aspects.

[0248] In some aspects, the antibody, or antigen binding portion thereof, comprises heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and

light chain CDR3, wherein light chain CDR1 consists of N-XXXXXXLFSSNXKXYXX-C. In some aspects, the antibody, or antigen binding portion thereof, comprises heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and light chain CDR3, wherein light chain CDR3 consists of N-XXXASAXXX-C. In some aspects, the antibody, or antigen binding portion thereof, comprises heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and light chain CDR3, wherein heavy chain CDR2 consists of N-XXSSXSXYXXXXXXXXX-C. In some aspects, the antibody, or antigen binding portion thereof, comprises heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and light chain CDR3, wherein heavy chain CDR3 consists of N-XXXXGRTSYTATXHNXXXX-C, wherein X is any amino acids.

[0249] In some aspects, the antibody, or antigen binding portion thereof, comprises heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and light chain CDR3, wherein light chain CDR1 consists of N-XXXXXXLFSSNXKXYXX-C and light chain CDR3 consists of N-XXXASAXXX-C. In some aspects, the antibody, or antigen binding portion thereof, comprises heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and light chain CDR3, wherein heavy chain CDR2 consists of N-XXSSXSXYXXXXXXXXX-C and heavy chain CDR3 consists of N-XXXXGRTSYTATXHNXXXX-C, wherein X is any amino acids.

[0250] In some aspects, the antibody, or antigen binding portion thereof, comprises heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and light chain CDR3, wherein light chain CDR1 consists of N-XXXXXXLFSSNXKXYXX-C, light chain CDR3 consists of N-XXXASAXXX-C, heavy chain CDR2 consists of N-XXSSXSXYXXXXXXXXX-C, and heavy chain CDR3 consists of N-XXXXGRTSYTATXHNXXXX-C, wherein X is any amino acids.

[0251] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 9, 10 and 11, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 17, 18 and 19, respectively;

(ii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 31, 32 and 33, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 39, 40 and 41, respectively;

(iii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 53, 54 and 55, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 61, 62 and 63, respectively;

(iv) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 75, 76 and 77, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 83, 84 and 85, respectively;

(v) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 97, 98 and 99, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 105, 106 and 107, respectively; or

(vi) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 119, 120 and 121, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 127, 128 and 129, respectively.

[0252] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 9, 10 and 11, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 17, 18 and 19, respectively;

(ii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 31, 32 and 33, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 39, 40 and 41, respectively;

(iii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 53, 54 and 55, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 61, 62 and 63, respectively;

(iv) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 75, 76 and 77, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 83, 84 and 85, respectively;

(v) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 97, 98 and 99, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 105, 106 and 107, respectively; or

(vi) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 119, 120 and 121, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 127, 128 and 129, respectively.

[0253] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 9, 10 and 11, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 17, 18 and 19, respectively;

(ii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 31, 32 and 33, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 39, 40 and 41, respectively;

(iii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 53, 54 and 55, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 61, 62 and 63, respectively;

(iv) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 75, 76 and 77, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 83, 84 and 85, respectively;

(v) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 97, 98 and 99, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 105, 106 and 107, respectively; or

(vi) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 119, 120 and 121, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 127, 128 and 129, respectively.

[0254] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 12, 13 and 14, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 20, 21 and 22, respectively;

(ii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 34, 35 and 36, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 42, 43 and 44, respectively;

(iii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 56, 57 and 58, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 64, 65 and 66, respectively;

(iv) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 78, 79 and 80, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 86, 88 and 89, respectively;

(v) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 100, 101 and 102, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 108, 109 and 110, respectively; or

(vi) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 122, 123 and 124, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 130, 131 and 132, respectively.

[0255] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 12, 13 and 14, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 20, 21 and 22, respectively;

(ii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 34, 35 and 36, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 42, 43 and 44, respectively;

(iii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 56, 57 and 58, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 64, 65 and 66, respectively;

(iv) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 78, 79 and 80, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 86, 88 and 89, respectively;

(v) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 100, 101 and 102, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 108, 109 and 110, respectively; or

(vi) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 122, 123 and 124, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 130, 131 and 132, respectively.

[0256] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 12, 13 and 14, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 20, 21 and 22, respectively;

(ii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 34, 35 and 36, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 42, 43 and 44, respectively;

(iii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 56, 57 and 58, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 64, 65 and 66, respectively;

(iv) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 78, 79 and 80, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 86, 88 and 89, respectively;

(v) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 100, 101 and 102, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 108, 109 and 110, respectively; or

(vi) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 122, 123 and 124, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 130, 131 and 132, respectively.

[0257] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain CDR1, a heavy chain CDR2, a heavy chain CDR3, a light chain CDR1, a light chain CDR2, and a light chain CDR3 and wherein the heavy chain CDR1 does not consist of N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 144) and/or the heavy chain CDR2 does not consist of N-ISSS[S/G][S/A]YI-C (SEQ ID NO: 146).

[0258] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain CDR1, a heavy chain CDR2, a heavy chain CDR3, a light chain CDR1, a light chain CDR2, and a light chain CDR3 and wherein the heavy chain CDR1 does not consist of N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 144) and/or the heavy chain CDR2 does not consist of N-ISSS[S/G][S/A]YI-C (SEQ ID NO: 146).

[0259] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147,

Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain CDR1, a heavy chain CDR2, a heavy chain CDR3, a light chain CDR1, a light chain CDR2, and a light chain CDR3 and wherein the heavy chain CDR1 does not consist of N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 144) and/or the heavy chain CDR2 does not consist of N-ISSS[S/G][S/A]YI-C (SEQ ID NO: 146).

[0260] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain CDR1, a heavy chain CDR2, a heavy chain CDR3, a light chain CDR1, a light chain CDR2, and a light chain CDR3 and wherein the heavy chain CDR1 does not comprise N-FTF[S/A/R][S/R][T/Y][G/S]MN-C (SEQ ID NO: 148) and/or the heavy chain CDR2 does not comprise N-[G/S]ISSS[S/G][S/A]YI[L/Y]YADSVKG-C (SEQ ID NO: 149).

[0261] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain CDR1, a heavy chain CDR2, a heavy chain CDR3, a light chain CDR1, a light chain CDR2, and a light chain CDR3 and wherein the heavy chain CDR1 does not comprise N-FTF[S/A/R][S/R][T/Y][G/S]MN-C (SEQ ID NO: 148) and/or the heavy chain CDR2 does not comprise N-[G/S]ISSS[S/G][S/A]YI[L/Y]YADSVKG-C (SEQ ID NO: 149).

[0262] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain CDR1, a heavy chain CDR2, a heavy chain CDR3, a light chain CDR1, a light chain CDR2, and a light chain CDR3 and wherein the heavy chain CDR1 does not comprise N-FTF[S/A/R][S/R][T/Y][G/S]MN-C (SEQ ID NO: 148) and/or the heavy chain CDR2 does not comprise N-[G/S]ISSS[S/G][S/A]YI[L/Y]YADSVKG-C (SEQ ID NO: 149).

[0263] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise:

(i) heavy chain CDR1 consisting of N-GFTFXXXX-C (SEQ ID NO: 145), heavy chain CDR2 consisting of N-ISSSXXYI-C (SEQ ID NO: 147), and heavy chain CDR3 sequence set forth in SEQ ID NO: 121; and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 127, 128 and 129, respectively; or

(ii) heavy chain CDR1 consisting of N-FTFXXXXMN-C (SEQ ID NO: 150), heavy chain CDR2 consisting of N-XISSSXXYIXYADSVKG-C (SEQ ID NO: 151), and heavy chain CDR3 sequence set forth in SEQ ID NO: 124; and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 130, 131 and 132, respectively.

[0264] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise:

(i) heavy chain CDR1 consisting of N-GFTFXXXX-C (SEQ ID NO: 145), heavy chain CDR2 consisting of N-ISSSXXYI-C (SEQ ID NO: 147), and heavy chain CDR3 sequence set forth in SEQ ID NO: 121; and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 127, 128 and 129, respectively; or

(ii) heavy chain CDR1 consisting of N-FTFXXXXMN-C (SEQ ID NO: 150), heavy chain CDR2 consisting of N-XISSSXXYIXYADSVKG-C (SEQ ID NO: 151), and heavy chain CDR3 sequence set forth in SEQ ID NO: 124; and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 130, 131 and 132, respectively.

[0265] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163,

and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise:

(i) heavy chain CDR1 consisting of N-GFTFXXXX-C (SEQ ID NO: 145), heavy chain CDR2 consisting of N-ISSSXXYI-C (SEQ ID NO: 147), and heavy chain CDR3 sequence set forth in SEQ ID NO: 121; and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 127, 128 and 129, respectively; or

(ii) heavy chain CDR1 consisting of N-FTFXXXXMN-C (SEQ ID NO: 150), heavy chain CDR2 consisting of N-XISSSXXYIXYADSVKG-C (SEQ ID NO: 151), and heavy chain CDR3 sequence set forth in SEQ ID NO: 124; and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 130, 131 and 132, respectively.

[0266] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise: heavy chain CDR1 consisting of N-GFTFXXXX-C (SEQ ID NO: 145), heavy chain CDR2 consisting of N-IXXXXXXXXXX-C (SEQ ID NO: 152), and heavy chain CDR3 sequence consisting of N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 153); and light chain CDR1 consisting of N-QS[X]_{n=1-3}SS[X]_{n=0-4}Y-C (SEQ ID NO: 154), light chain CDR2 consisting of N-XXS-C (SEQ ID NO: 155), and light chain CDR3 sequence consisting of N-QQXXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 156), respectively.

[0267] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise: heavy chain CDR1 consisting of N-GFTFXXXX-C (SEQ ID NO: 145), heavy chain CDR2 consisting of N-IXXXXXXXXXX-C (SEQ ID NO: 152), and heavy chain CDR3 sequence consisting of N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 153); and light chain CDR1 consisting of N-QS[X]_{n=1-3}SS[X]_{n=0-4}Y-C (SEQ ID NO: 154), light chain CDR2 consisting of N-XXS-C (SEQ ID NO: 155), and light chain CDR3 sequence consisting of N-QQXXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 156), respectively.

[0268] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that specifically binds to an epitope comprising or consisting of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof does not comprise heavy chain CDR1 consisting of N-GFTFXXXX-C (SEQ ID NO: 145), heavy chain CDR2 consisting of N-IXXXXXXXXX-C (SEQ ID NO: 152), and heavy chain CDR3 sequence consisting of N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 153); and light chain CDR1 consisting of N-QS[X]_{n=1-3}SS[X]_{n=0-4}Y-C (SEQ ID NO: 154), light chain CDR2 consisting of N-XXS-C (SEQ ID NO: 155), and light chain CDR3 sequence consisting of N-QQXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 156), respectively.

[0269] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region does not comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 37, 59, 81, 103, and 125; and wherein the light chain variable region does not comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 45, 67, 89, 111, and 133.

[0270] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region and the light chain variable region are not amino acid sequences selected from the group consisting of:

- (i) SEQ ID NO: 15 and 65, respectively;
- (ii) SEQ ID NO: 37 and 45, respectively;
- (iii) SEQ ID NO: 59 and 67, respectively;

- (iv) SEQ ID NO: 81 and 89, respectively;
- (v) SEQ ID NO: 103 and 111, respectively; and
- (vi) SEQ ID NO: 125 and 133, respectively.

[0271] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region does not comprise an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 37, 59, 81, 103, and 125; and wherein the light chain variable region does not comprise an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 45, 67, 89, 111, and 133.

[0272] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region and the light chain variable region do not comprise amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:

- (i) SEQ ID NO: 15 and 65, respectively;
- (ii) SEQ ID NO: 37 and 45, respectively;
- (iii) SEQ ID NO: 59 and 67, respectively;
- (iv) SEQ ID NO: 81 and 89, respectively;
- (v) SEQ ID NO: 103 and 111, respectively; and
- (vi) SEQ ID NO: 125 and 133, respectively.

[0273] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142,

Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain does not comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 25,47, 69, 91, 113, and 135; and wherein the light chain does not comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 20, 42, 71, 93, and 1115.

[0274] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain, wherein the heavy chain does not comprise an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 25,47, 69, 91, 113, and 135; and wherein the light chain does not comprise an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 20, 42, 71, 93, and 115.

[0275] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain does not comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 51, 73, 95, 117, and 139; and wherein the light chain does not comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 71, 49, 71, 93, 115, and 137.

[0276] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain, wherein the heavy chain

does not comprise an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 51, 73, 95, 117, and 139; and wherein the light chain does not comprise an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 71, 49, 71, 93, 115, and 137.

[0277] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, and wherein the heavy chain and the light chain do not comprise amino acid sequences selected from the group consisting of:

- (i) SEQ ID NO: 25 and 27, respectively;
- (ii) SEQ ID NO: 47 and 49, respectively;
- (iii) SEQ ID NO: 69 and 71, respectively;
- (iv) SEQ ID NO: 91 and 93, respectively;
- (v) SEQ ID NO: 113 and 115, respectively; and
- (vi) SEQ ID NO: 135 and 137, respectively.

[0278] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain and wherein the heavy chain and the light chain do not comprise amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:

- (i) SEQ ID NO: 25 and 27, respectively;
- (ii) SEQ ID NO: 47 and 49, respectively;
- (iii) SEQ ID NO: 69 and 71, respectively;
- (iv) SEQ ID NO: 91 and 93, respectively;
- (v) SEQ ID NO: 113 and 115, respectively; and

(vi) SEQ ID NO: 135 and 137, respectively.

[0279] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL-27p28), wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain and wherein the heavy chain and the light chain do not comprise amino acid sequences selected from the group consisting of:

- (i) SEQ ID NO: 29 and 27, respectively;
- (ii) SEQ ID NO: 51 and 49, respectively;
- (iii) SEQ ID NO: 73 and 72, respectively;
- (iv) SEQ ID NO: 95 and 93, respectively;
- (v) SEQ ID NO: 117 and 115, respectively; and
- (vi) SEQ ID NO: 139 and 137, respectively.

[0280] In some aspects, the present disclosure provides an isolated antibody or antigen binding portion thereof that antagonizes IL-27 and specifically binds to an epitope comprising one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164 of SEQ ID NO: 2 (IL27-p28), wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain and wherein the heavy chain and the light chain do not comprise amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of: (i) SEQ ID NO: 29 and 27, respectively; (ii) SEQ ID NO: 51 and 49, respectively; (iii) SEQ ID NO: 73 and 72, respectively; (iv) SEQ ID NO: 95 and 93, respectively; (v) SEQ ID NO: 117 and 115, respectively; and (vi) SEQ ID NO: 139 and 137, respectively.

B. Pharmaceutical Compositions and Formulations

[0281] In some aspects, the antibody, or antigen-binding portion thereof, useful in the methods and compositions disclosed herein is present in a pharmaceutical composition. As such, some aspects of the present disclosure are directed to a pharmaceutical composition comprising an anti-IL-27 antibody with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[0282] In certain aspects, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In certain aspects, the formulation material(s) are for s.c. and/or I.V. administration. In certain aspects, the pharmaceutical composition comprises formulation materials for modifying, maintaining or preserving, for example, the pH, osmolality, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In certain aspects, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen- sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta- cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company (1995). In certain aspects, the formulation comprises PBS; 20 mM NaOAC, pH 5.2, 50 mM NaCl; and/or 10 mM NAOAC, pH 5.2, 9% Sucrose. In certain aspects, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, Remington's Pharmaceutical Sciences, *supra*. In certain aspects, such compositions influence the physical state, stability, rate of *in vivo* release and/or rate of *in vivo* clearance of the anti-IL-27 antibody.

[0283] In certain aspects, the primary vehicle or carrier in a pharmaceutical composition is either aqueous or non-aqueous in nature. For example, in certain aspects, a suitable vehicle or carrier is water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. In certain aspects, the saline comprises isotonic phosphate-buffered saline. In certain aspects, neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In certain aspects, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5. In some aspects, the pharmaceutical composition further comprises sorbitol or a suitable substitute therefore. In certain aspects, a composition comprising an anti-IL-27 antibody is prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (Remington's Pharmaceutical Sciences, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, in certain aspects, a composition comprising an anti-IL-27 antibody is formulated as a lyophilizate using appropriate excipients such as sucrose.

[0284] In certain aspects, the pharmaceutical composition is selected for parenteral delivery. In certain aspects, the composition is selected for inhalation or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the ability of one skilled in the art.

[0285] In certain aspects, the formulation components are present in concentrations that are acceptable to the site of administration. In certain aspects, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0286] In certain aspects, when parenteral administration is contemplated, a therapeutic composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising an anti-IL-27 antibody, in a pharmaceutically acceptable vehicle. In certain aspects, a vehicle for parenteral injection is sterile distilled water in which an anti-IL-27 antibody is formulated as a sterile, isotonic solution, and properly preserved. In certain aspects, the preparation involves the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that can provide for the controlled or sustained release of the product which can then be delivered via a depot injection. In certain aspects, hyaluronic acid is also used. Hyaluronic acid, when present, can have the effect of promoting sustained duration in the circulation. In certain aspects, implantable drug delivery devices are used to introduce the desired molecule.

[0287] In certain aspects, a pharmaceutical composition is formulated for inhalation. In certain aspects, an anti-IL-27 antibody is formulated as a dry powder for inhalation. In certain aspects, an inhalation solution comprising an anti-IL-27 antibody is formulated with a propellant for aerosol delivery. In certain aspects, solutions are nebulized. Pulmonary administration is further described in PCT application No. PCT/US94/001875, which describes pulmonary delivery of chemically modified proteins.

[0288] In certain aspects, the pharmaceutical composition disclosed herein is formulated for oral administration. In some aspects, the pharmaceutical composition is administered orally. In certain aspects, an anti-IL-27 antibody that is administered in this fashion is formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In certain aspects, a capsule is designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. In certain aspects, at least one additional agent is included to facilitate absorption of an anti-IL-27 antibody. In certain aspects, diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders are also employed.

[0289] In certain aspects, a pharmaceutical composition involves an effective quantity of an anti-IL-27 antibody in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. In certain aspects, by dissolving the tablets in sterile water, or another appropriate vehicle, solutions are prepared in unit-dose form. In certain aspects, suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[0290] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving an anti-IL-27 antibody in sustained- or controlled-delivery formulations. In certain aspects, techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See for example, PCT Application No. PCT/US93/00829 which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. In certain aspects, sustained-release preparations can include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides (U.S.

Pat. No. 3,773,919 and EP 058,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., Biopolymers, 22:547-556 (1983)), poly (2-hydroxyethyl-methacrylate) (Langer et al., J. Biomed. Mater. Res., 15: 167-277 (1981) and Langer, Chem. Tech., 12:98- 105 (1982)), ethylene vinyl acetate (Langer et al., supra) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). In certain aspects, sustained release compositions can also include liposomes, which can be prepared by any of several methods known in the art. See, e.g., Eppstein et al, Proc. Natl. Acad. Sci. USA, 82:3688-3692 (1985); EP 036,676; EP 088,046 and EP 143,949.

[0291] The pharmaceutical composition to be used for *in vivo* administration typically is sterile. In certain aspects, this is accomplished by filtration through sterile filtration membranes. In certain aspects, where the composition is lyophilized, sterilization using this method is conducted either prior to or following lyophilization and reconstitution. In certain aspects, the composition for parenteral administration is stored in lyophilized form or in a solution. In certain aspects, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0292] In certain aspects, once the pharmaceutical composition has been formulated, it is stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. In certain aspects, such formulations are stored either in a ready-to-use form or in a form (e.g., lyophilized) that is reconstituted prior to administration.

In certain aspects, kits are provided for producing a single-dose administration unit. In certain aspects, the kit comprises both a first container having a dried protein and a second container having an aqueous formulation. In certain aspects, kits comprising single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes) are included.

C. Combination Therapy

[0293] In some aspects, an anti-IL-27 antibody, or antigen binding portion thereof, provided by the disclosure, can be combined with one or more additional therapeutics or treatments, e.g., another therapeutic or treatment for a cancer. For example, the anti-IL-27 antibody, or antigen binding portion thereof, can be administered to a subject (e.g., a human patient) in combination with one or more additional therapeutics, wherein the combination provides a therapeutic benefit to a subject who has, or is at risk of developing, cancer.

[0294] In some aspects, an anti-IL-27 antibody, or antigen binding portion thereof, and the one or more additional therapeutics are administered at the same time (e.g., simultaneously). In

other aspects, the anti-IL-27 antibody, or antigen binding portion thereof, is administered first in time and the one or more additional therapeutics are administered second in time (e.g., sequentially). In some aspects, the one or more additional therapeutics are administered first in time and the anti-IL-27 antibody is administered second in time.

[0295] An anti-IL-27 antibody or an antigen-binding fragment thereof described herein can replace or augment a previously or currently administered therapy. For example, upon treating with an anti-IL-27 antibody or antigen-binding fragment thereof, administration of the one or more additional therapeutics can cease or diminish, e.g., be administered at lower levels. In some aspects, administration of the previous therapy can be maintained. In some aspects, a previous therapy will be maintained until the level of the anti-IL-27 antibody reaches a level sufficient to provide a therapeutic effect.

[0296] In some aspects, the disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of an isolated antibody, or antigen binding portion thereof, that specifically binds to and antagonizes IL-27, provided by the disclosure, in combination with one or more additional therapeutic agents or procedure, wherein the second therapeutic agent or procedure is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, a biologic agent, or a combination thereof.

[0297] In some aspects, the one or more additional therapeutic agents is a PD-1 antagonist, a TIM-3 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, a CD112R inhibitor, a TAM inhibitor, a STING agonist, a 4-1BB agonist, or a combination thereof. In some aspects, the one or more additional therapeutic agents is a CD39 antagonist, a CD73 antagonist, a CCR8 antagonist, or a combination thereof. In some aspects, the anti-CD73 is any anti-CD73 antibody disclosed in, e.g., U.S. Publication No. 2019/0031766 A1, which is incorporated by reference herein in its entirety. In some aspects, the anti-CD39 is any anti-CD39 antibody disclosed in, e.g., Int'l Publication No. WO 2019/178269 A2, which is incorporated by reference herein in its entirety.

[0298] In some aspects, the one or more additional therapeutic agents is a PD-1 antagonist. In some aspects, the PD-1 antagonist is selected from the group consisting of: PDR001, nivolumab, pembrolizumab, pidilizumab, tislelizumab, zimberelimuab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224. In certain aspects, the one or more additional therapeutic agents is a

PD-L1 inhibitor. In some aspects, the PD-L1 inhibitor is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559. In some aspects, the disclosure provides a method of enhancing one or more activities of an anti-PD-1 antibody (e.g., enhances PD-1-mediated cytokine secretion; enhances anti-PD-1 mediated TNF α secretion; enhances anti-PD-1 mediated IL-6 secretion from a cell exposed to anti-PD-1 antibodies), the method comprising exposing a cell to an antibody, or antigen binding portion thereof, provided by the disclosure, concurrently with or sequentially to an anti-PD-1 antibody, thereby to enhance one or more activities of the anti-PD1 antibody.

[0299] In some aspects, the one or more additional therapeutic agents is Sunitinib (Sutent[®]), Cabozantinib (CABOMETYX[®]), Axitinib (INLYTA[®]), Lenvatinib (LENVIMA[®]), Everolimus (AFINITOR[®]), Bevacizumab (AVASTIN[®]), epacadostat, NKTR-214 (CD-122-biased agonist), tivozanib (FOTIVDA[®]), abexinostat, Ipilimumab (YERVOY[®]), tremelimumab, Pazopanib (VOTRIENT[®]), Sorafenib (NEXAVAR[®]), Temsirolimus (TORISEL[®]), Ramucirumab (CYRAMZA[®]), niraparib, savolitinib, vorolanib (X-82), Regorafenib (STIVARGO[®]), Donafenib (multikinase inhibitor), Camrelizumab (SHR-1210), pexastimogene devacirepvec (JX-594), Ramucirumab (CYRAMZA[®]), apatinib (YN968D1), encapsulated doxorubicin (THERMODOX[®]), Tivantinib (ARQ197), ADI-PEG 20, binimetinib, apatinib mesylate, nintedanib, lirilumab, Nivolumab (OPDIVO[®]), Pembrolizumab (KEYTRUDA[®]), Atezolizumab (TECENTRIQ[®]), Avelumab (BAVENCIO[®]), Durvalumab (IMFIMZI[®]), Cemiplimab-rwlc (LIBTAYO[®]), tislelizumab, and/or spartalizumab.

[0300] In some aspects, the one or more additional therapeutic agents is a TIM-3 inhibitor, optionally wherein the TIM-3 inhibitor is MGB453 or TSR-022.

[0301] In some aspects, the one or more additional therapeutic agents is a LAG-3 inhibitor, optionally wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, and TSR-033.

[0302] In some aspects, the one or more additional therapeutic agents is a TIGIT inhibitor. In some aspects, the one or more additional therapeutic agents is a CD112R inhibitor. In some aspects, the one or more additional therapeutic agents is a TAM (Axl, Mer, Tyro) inhibitor. In some aspects, the one or more additional therapeutic agents is a STING agonist. In some aspects, the one or more additional therapeutic agents is a 4-1BB agonist.

[0303] In some aspects, the one or more additional therapeutic agents is a tyrosine kinase inhibitor, an agent targeting the adenosine axis (for example a CD39 antagonist, a CD73 antagonist

or a A2AR, A2BR or dual A2AR/A2BR antagonist), a CCR8 antagonist, a CTLA4 antagonist, a VEG-F inhibitor or a combination thereof.

1. *Combination with Chemotherapeutic Agents*

[0304] In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and a chemotherapeutic agent. Chemotherapeutic agents suitable for combination and/or co-administration with compositions of the present disclosure include, for example: taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxyanthracindione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Further agents include, for example, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioTEPA, chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II)(DDP), procarbazine, altretamine, cisplatin, carboplatin, oxaliplatin, nedaplatin, satraplatin, or triplatin tetranitrate), anthracycline (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine) and temozolomide.

2. *Combination with PD-1/PD-L1 Antagonists*

[0305] In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and one or more PD-1 antagonist. In some aspects, the one or more PD-1 antagonist specifically binds to human PD-1 or PD-L1 and inhibits PD-1/PD-L1 biological activity and/or downstream pathway(s) and/or cellular processes mediated by human PD-1/PD-L1 signaling or other human PD-1/PD-L1-mediated functions.

[0306] Accordingly, provided herein are PD-1 antagonists that directly or allosterically block, antagonize, suppress, inhibit or reduce PD-1/PD-L1 biological activity, including downstream pathways and/or cellular processes mediated by PD-1/PD-L1 signaling, such as receptor binding and/or elicitation of a cellular response to PD-1/PD-L1. Also provided herein are

PD-1 antagonists that reduce the quantity or amount of human PD-1 or PD-L1 produced by a cell or subject.

[0307] In some aspects, the disclosure provides a PD-1 antagonist that binds human PD-1 and prevents, inhibits or reduces PD-L1 binding to PD-1. In some aspects, the PD-1 antagonist binds to the mRNA encoding PD-1 or PD-L1 and prevents translation. In some aspects, the PD-1 antagonist binds to the mRNA encoding PD-1 or PD-L1 and causes degradation and/or turnover.

[0308] In some aspects, the PD-1 antagonist inhibits PD-1 signaling or function. In some aspects, the PD-1 antagonist blocks binding of PD-1 to PD-L1, PD-L2, or to both PD-L1 and PD-L2. In some aspects, the PD-1 antagonist blocks binding of PD-1 to PD-L1. In some aspects, the PD-1 antagonist blocks binding of PD-1 to PD-L2. In some aspects, the PD-1 antagonist blocks the binding of PD-1 to PD-L1 and PD-L2. In some aspects, the PD-1 antagonist specifically binds PD-1. In some aspects, the PD-1 antagonist specifically binds PD-L1. In some aspects, the PD-1 antagonist specifically binds PD-L2.

[0309] In some aspects, the PD-1 antagonist inhibits the binding of PD-1 to its cognate ligand. In some aspects, the PD-1 antagonist inhibits the binding of PD-1 to PD-L1, PD-1 to PD-L2, or PD-1 to both PD-L1 and PD-L2. In some aspects, the PD-1 antagonist does not inhibit the binding of PD-1 to its cognate ligand.

[0310] In some aspects, the PD-1 antagonist is an isolated antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1. In some aspects, the PD-1 antagonist is an antibody or antigen binding fragment thereof that specifically binds to human PD-1. In some aspects, the PD-1 antagonist is an antibody or antigen binding fragment thereof that specifically binds to human PD-L1. In some aspects, the PD-1 antagonist is an antibody or antigen binding fragment that binds to human PD-L1 and inhibits the binding of PD-L1 to PD-1. In some aspects, the PD-1 antagonist is an antibody or antigen binding fragment that binds to human PD-1 and inhibits the binding of PD-L1 to PD-1.

[0311] Several immune checkpoint antagonists that inhibit or disrupt the interaction between PD-1 and either one or both of its ligands PD-L1 and PD-L2 are in clinical development or are currently available to clinicians for treating cancer.

[0312] Examples of anti-human PD-1 antibodies, or antigen binding fragments thereof, that may comprise the PD-1 antagonist in any of the compositions, methods, and uses provided by the disclosure include, but are not limited to: KEYTRUDA[®] (pembrolizumab, MK-3475, h409A11; see US8952136, US8354509, US8900587, and EP2170959, all of which are included herein by

reference in their entirety; Merck), OPDIVO® (nivolumab, BMS-936558, MDX-1106, ONO-4538; see US7595048, US8728474, US9073994, US9067999, EP1537878, US8008449, US8779105, and EP2161336, all of which are included herein by reference in their entirety; Bristol Myers Squibb), MEDI0680 (AMP-514), BGB-A317 and BGB-108 (BeiGene), 244C8 and 388D4 (see WO2016106159, which is incorporated herein by reference in its entirety; Enumeral Biomedical), PDR001 (Novartis), and REGN2810 (Regeneron). Accordingly, in some aspects the PD-1 antagonist is pembrolizumab. In some aspects, the PD-1 antagonist is nivolumab. In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and pembrolizumab. In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and nivolumab.

[0313] Examples of anti-human PD-L1 antibodies, or antigen binding fragments thereof, that may comprise the PD-1 antagonist in any of the compositions, methods, and uses provided by the disclosure include, but are not limited to: BAVENCIO® (avelumab, MSB0010718C, see WO2013/79174, which is incorporated herein by reference in its entirety; Merck/Pfizer), IMFINZI® (durvalumab, MEDI4736), TECENTRIQ® (atezolizumab, MPDL3280A, RG7446; see WO2010/077634, which is incorporated herein by reference in its entirety; Roche), MDX-1105 (BMS-936559, 12A4; see US7943743 and WO2013/173223, both of which are incorporated herein by reference in their entirety; Medarex/BMS), and FAZ053 (Novartis). Accordingly, in some aspects the PD-1 antagonist is avelumab. In some aspects, the PD-1 antagonist is durvalumab. In some aspects, the PD-1 antagonist is atezolizumab.

[0314] In some aspects, the PD-1 antagonist is an immunoadhesin that specifically bind to human PD-1 or human PD-L1, e.g., a fusion protein containing the extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region such as an Fc region of an immunoglobulin molecule. Examples of immunoadhesion molecules that specifically bind to PD-1 are described in WO2010/027827 and WO2011/066342, both of which are incorporated herein by reference in their entirety. In some aspects, the PD-1 antagonist is AMP-224 (also known as B7-DCIg), which is a PD-L2-FC fusion protein that specifically binds to human PD-1.

[0315] It will be understood by one of ordinary skill that any PD-1 antagonist which binds to PD-1 or PD-L1 and disrupts the PD-1/PD-L1 signaling pathway, is suitable for compositions, methods, and uses disclosed herein.

[0316] In some aspects, the PD-1/PD-L1 antagonist is a small molecule, a nucleic acid, a peptide, a peptide mimetic, a protein, a carbohydrate, a carbohydrate derivative, or a glycopolymer. Exemplary small molecule PD-1 inhibitors are described in Zhan et al., (2016) Drug Discov Today 21(6):1027-1036.

3. *Combinations with TIM-3 Inhibitors*

[0317] In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and a TIM-3 inhibitor. The TIM-3 inhibitor may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or an oligopeptide. In some aspects, the TIM-3 inhibitor is chosen from MGB453 (Novartis), TSR-022 (Tesaro), or LY3321367 (Eli Lilly). In some aspects, the anti-IL-27 antibody, or antigen binding portion thereof, is administered in combination with MGB453. In some aspects, the anti-IL-27 antibody, or antigen binding portion thereof, is administered in combination with TSR-022.

4. *Combinations with LAG-3 Inhibitors*

[0318] In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and a LAG-3 inhibitor. In some aspects, the LAG-3 inhibitor is an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, an oligopeptide, or any combination thereof. In some aspects, the LAG-3 inhibitor is chosen from LAG525 (Novartis), BMS-986016 (Bristol-Myers Squibb), TSR-033 (Tesaro), MK-4280 (Merck & Co), or REGN3767 (Regeneron).

5. *Other Combinations*

[0319] In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and a TIGIT inhibitor. In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and a kinase inhibitor (e.g., a tyrosine kinase inhibitor (TKI)). In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and a CD112R inhibitor. In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and a TAM receptor inhibitor. In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-

binding portion thereof that specifically binds to IL-27 and a STING agonist and/or a 4-1BB agonist. In some aspects, an anti-IL-27 antibody, or antigen binding portion thereof, provided by the disclosure is combined (e.g., administered in combination) with a tyrosine kinase inhibitor, an agent targeting the adenosine axis (for example a CD39 antagonist, a CD73 antagonist or a A2AR, A2BR or dual A2AR/A2BR antagonist), a CCR8 antagonist, a CTLA4 antagonist, a VEGF inhibitor or a combination thereof.

[0320] In some aspects, the methods disclosed herein comprise administering an antibody or an antigen-binding portion thereof that specifically binds to IL-27 and a cell therapy. In some aspects, the cell therapy comprises a modified immune cell therapy. In some aspects, the cell therapy comprises a chimeric antigen receptor (CAR) modified immune cell therapy, e.g., CAR T therapy. In some aspects, the cell therapy comprises an engineered T cell receptor (TCR) immune cell therapy. In some aspects, the cell therapy comprises an allogeneic tumor infiltrating lymphocyte (TIL) therapy.

III. Methods for Producing Anti-IL-27 Antibodies and Antigen-binding Fragments Thereof

[0321] The disclosure also features methods for producing any of the anti-IL-27 antibodies or antigen-binding fragments thereof described herein. In some aspects, methods for preparing an antibody described herein can include immunizing a subject (e.g., a non-human mammal) with an appropriate immunogen. Suitable immunogens for generating any of the antibodies described herein are set forth herein. For example, to generate an antibody that binds to IL-27p28, a skilled artisan can immunize a suitable subject (e.g., a non-human mammal such as a rat, a mouse, a gerbil, a hamster, a dog, a cat, a pig, a goat, a horse, or a non-human primate) with IL-27. In some aspects, a full-length human IL-27p28 monomer polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 is used as the immunogen.

[0322] A suitable subject (e.g., a non-human mammal) can be immunized with the appropriate antigen along with subsequent booster immunizations a number of times sufficient to elicit the production of an antibody by the mammal. The immunogen can be administered to a subject (e.g., a non-human mammal) with an adjuvant. Adjuvants useful in producing an antibody in a subject include, but are not limited to, protein adjuvants; bacterial adjuvants, e.g., whole bacteria (BCG, *Corynebacterium parvum* or *Salmonella minnesota*) and bacterial components including cell wall skeleton, trehalose dimycolate, monophosphoryl lipid A, methanol extractable residue (MER) of tubercle *bacillus*, complete or incomplete Freund's adjuvant; viral adjuvants;

chemical adjuvants, e.g., aluminum hydroxide, and iodoacetate and cholesteryl hemisuccinate. Other adjuvants that can be used in the methods for inducing an immune response include, e.g., cholera toxin and parapoxvirus proteins. See also Bieg et al. (1999) *Autoimmunity* 31(1):15-24. See also, e.g., Lodmell et al. (2000) *Vaccine* 18:1059-1066; Johnson et al. (1999) *J Med Chem* 42:4640-4649; Baldridge et al. (1999) *Methods* 19:103-107; and Gupta et al. (1995) *Vaccine* 13(14): 1263-1276.

[0323] In some aspects, the methods include preparing a hybridoma cell line that secretes a monoclonal antibody that binds to the immunogen. For example, a suitable mammal such as a laboratory mouse is immunized with an IL-27 polypeptide as described above. Antibody-producing cells (e.g., B cells of the spleen) of the immunized mammal can be isolated two to four days after at least one booster immunization of the immunogen and then grown briefly in culture before fusion with cells of a suitable myeloma cell line. The cells can be fused in the presence of a fusion promoter such as, e.g., vaccinia virus or polyethylene glycol. The hybrid cells obtained in the fusion are cloned, and cell clones secreting the desired antibodies are selected. For example, spleen cells of Balb/c mice immunized with a suitable immunogen can be fused with cells of the myeloma cell line PAI or the myeloma cell line Sp2/0-Ag 14. After the fusion, the cells are expanded in suitable culture medium, which is supplemented with a selection medium, for example HAT medium, at regular intervals in order to prevent normal myeloma cells from overgrowing the desired hybridoma cells. The obtained hybrid cells are then screened for secretion of the desired antibodies, e.g., an antibody that binds to human IL-27 and In some aspects, a skilled artisan can identify an anti-IL-27 antibody from a non-immune biased library as described in, e.g., U.S. patent no. 6,300,064 (to Knappik et al.; Morphosys AG) and Schoonbroodt et al. (2005) *Nucleic Acids Res* 33(9):e81.

[0324] In some aspects, the methods described herein can involve, or be used in conjunction with, e.g., phage display technologies, bacterial display, yeast surface display, eukaryotic viral display, mammalian cell display, and cell-free (e.g., ribosomal display) antibody screening techniques (see, e.g., Etz et al. (2001) *J Bacteriol* 183:6924-6935; Cornelis (2000) *Curr Opin Biotechnol* 11:450-454; Klemm et al. (2000) *Microbiology* 146:3025-3032; Kieke et al. (1997) *Protein Eng* 10:1303-1310; Yeung et al. (2002) *Biotechnol Prog* 18:212-220; Boder et al. (2000) *Methods Enzymology* 328:430-444; Grabherr et al. (2001) *Comb Chem High Throughput Screen* 4:185-192; Michael et al. (1995) *Gene Ther* 2:660-668; Pereboev et al. (2001) *J Virol*

75:7107-7113; Schaffitzel et al. (1999) *J Immunol Methods* 231:119-135; and Hanes et al. (2000) *Nat Biotechnol* 18:1287-1292).

[0325] Methods for identifying antibodies using various phage display methods are known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. Such phage can be utilized to display antigen-binding domains of antibodies, such as Fab, Fv, or disulfide-bond stabilized Fv antibody fragments, expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage used in these methods are typically filamentous phage such as fd and M13. The antigen binding domains are expressed as a recombinantly fused protein to any of the phage coat proteins pIII, pVIII, or pIX. See, e.g., Shi et al. (2010) *JMB* 397:385-396. Examples of phage display methods that can be used to make the immunoglobulins, or fragments thereof, described herein include those disclosed in Brinkman et al. (1995) *J Immunol Methods* 182:41-50; Ames et al. (1995) *J Immunol Methods* 184:177-186; Kettleborough et al. (1994) *Eur J Immunol* 24:952-958; Persic et al. (1997) *Gene* 187:9-18; Burton et al. (1994) *Advances in Immunology* 57:191-280; and PCT publication nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/11236, WO 95/15982, and WO 95/20401. Suitable methods are also described in, e.g., U.S. patent nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108.

[0326] In some aspects, the phage display antibody libraries can be generated using mRNA collected from B cells from the immunized mammals. For example, a splenic cell sample comprising B cells can be isolated from mice immunized with IL-27 polypeptide as described above. mRNA can be isolated from the cells and converted to cDNA using standard molecular biology techniques. See, e.g., Sambrook et al. (1989) "Molecular Cloning: A Laboratory Manual, 2nd Edition," Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Harlow and Lane (1988), *supra*; Benny K. C. Lo (2004), *supra*; and Borrebaek (1995), *supra*. The cDNA coding for the variable regions of the heavy chain and light chain polypeptides of immunoglobulins are used to construct the phage display library. Methods for generating such a library are described in, e.g., Merz et al. (1995) *J Neurosci Methods* 62(1-2):213-9; Di Niro et al. (2005) *Biochem J* 388(Pt 3):889-894; and Engberg et al. (1995) *Methods Mol Biol* 51:355-376.

[0327] In some aspects, a combination of selection and screening can be employed to identify an antibody of interest from, e.g., a population of hybridoma-derived antibodies or a phage display antibody library. Suitable methods are known in the art and are described in, e.g.,

Hoogenboom (1997) *Trends in Biotechnology* 15:62-70; Brinkman et al. (1995), *supra*; Ames et al. (1995), *supra*; Kettleborough et al. (1994), *supra*; Persic et al. (1997), *supra*; and Burton et al. (1994), *supra*. For example, a plurality of phagemid vectors, each encoding a fusion protein of a bacteriophage coat protein (e.g., pIII, pVIII, or pIX of M13 phage) and a different antigen-combining region are produced using standard molecular biology techniques and then introduced into a population of bacteria (e.g., *E. coli*). Expression of the bacteriophage in bacteria can, in some aspects, require use of a helper phage. In some aspects, no helper phage is required (see, e.g., Chasteen et al., (2006) *Nucleic Acids Res* 34(21):e145). Phage produced from the bacteria are recovered and then contacted to, e.g., a target antigen bound to a solid support (immobilized). Phage may also be contacted to antigen in solution, and the complex is subsequently bound to a solid support.

[0328] A subpopulation of antibodies screened using the above methods can be characterized for their specificity and binding affinity for a particular antigen (e.g., human IL-27p28) using any immunological or biochemical based method known in the art. For example, specific binding of an antibody to IL-27p28, may be determined for example using immunological or biochemical based methods such as, but not limited to, an ELISA assay, SPR assays, immunoprecipitation assay, affinity chromatography, and equilibrium dialysis as described above. Immunoassays which can be used to analyze immuno-specific binding and cross-reactivity of the antibodies include, but are not limited to, competitive and non-competitive assay systems using techniques such as Western blots, RIA, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays. Such assays are routine and well known in the art.

[0329] In aspects where the selected CDR amino acid sequences are short sequences (e.g., fewer than 10-15 amino acids in length), nucleic acids encoding the CDRs can be chemically synthesized as described in, e.g., Shiraishi et al. (2007) *Nucleic Acids Symposium Series* 51(1):129-130 and U.S. Patent No. 6,995,259. For a given nucleic acid sequence encoding an acceptor antibody, the region of the nucleic acid sequence encoding the CDRs can be replaced with the chemically synthesized nucleic acids using standard molecular biology techniques. The 5' and 3' ends of the chemically synthesized nucleic acids can be synthesized to comprise sticky end restriction enzyme sites for use in cloning the nucleic acids into the nucleic acid encoding the variable region of the donor antibody.

[0330] In some aspects, the anti-IL-27 antibodies described herein comprise an altered heavy chain constant region that has reduced (or no) effector function relative to its corresponding unaltered constant region. Effector functions involving the constant region of the anti-IL-27 antibody may be modulated by altering properties of the constant or Fc region. Altered effector functions include, for example, a modulation in one or more of the following activities: antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), apoptosis, binding to one or more Fc-receptors, and pro-inflammatory responses. Modulation refers to an increase, decrease, or elimination of an effector function activity exhibited by a subject antibody containing an altered constant region as compared to the activity of the unaltered form of the constant region. In particular aspects, modulation includes situations in which an activity is abolished or completely absent.

[0331] In one aspect, the anti-IL-27 antibodies described herein comprise an IgG4 heavy chain constant region. In one aspect, the IgG4 heavy chain constant region is a wild type IgG4 heavy chain constant region. In another aspect, the IgG4 constant region comprises a mutation, e.g., one or both of S228P and L235E or L235A, e.g., according to EU numbering (Kabat, E.A., et al., supra). In one aspect, the anti-IL-27 antibodies described herein comprise an IgG1 constant region. In one aspect, the IgG1 heavy chain constant region is a wild type IgG1 heavy chain constant region. In another aspect, the IgG1 heavy chain constant region comprises a mutation.

[0332] An altered constant region with altered FcR binding affinity and/or ADCC activity and/or altered CDC activity is a polypeptide which has either an enhanced or diminished FcR binding activity and/or ADCC activity and/or CDC activity compared to the unaltered form of the constant region. An altered constant region which displays increased binding to an FcR binds at least one FcR with greater affinity than the unaltered polypeptide. An altered constant region which displays decreased binding to an FcR binds at least one FcR with lower affinity than the unaltered form of the constant region. Such variants which display decreased binding to an FcR may possess little or no appreciable binding to an FcR, e.g., 0 to 50% (e.g., less than 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1%) of the binding to the FcR as compared to the level of binding of a native sequence immunoglobulin constant or Fc region to the FcR. Similarly, an altered constant region that displays modulated ADCC and/or CDC activity may exhibit either increased or reduced ADCC and/or CDC activity compared to the unaltered constant region. For example, in some aspects, the anti-IL-27 antibody comprising an altered

constant region can exhibit approximately 0 to 50% (e.g., less than 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1%) of the ADCC and/or CDC activity of the unaltered form of the constant region. An anti-IL-27 antibody described herein comprising an altered constant region displaying reduced ADCC and/or CDC may exhibit reduced or no ADCC and/or CDC activity.

[0333] In some aspects, an anti-IL-27 antibody described herein exhibits reduced or no effector function. In some aspects, an anti-IL-27 antibody comprises a hybrid constant region, or a portion thereof, such as a G2/G4 hybrid constant region (see e.g., Burton et al. (1992) *Adv Immun* 51:1-18; Canfield et al. (1991) *J Exp Med* 173:1483-1491; and Mueller et al. (1997) *Mol Immunol* 34(6):441-452). See above.

[0334] In some aspects, an anti-IL-27 antibody may contain an altered constant region exhibiting enhanced or reduced complement dependent cytotoxicity (CDC). Modulated CDC activity may be achieved by introducing one or more amino acid substitutions, insertions, or deletions in an Fc region of the antibody. See, e.g., U.S. patent no. 6,194,551. Alternatively, or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved or reduced internalization capability and/or increased or decreased complement-mediated cell killing. See, e.g., Caron et al. (1992) *J Exp Med* 176:1191-1195 and Shopes (1992) *Immunol* 148:2918-2922; PCT publication nos. WO 99/51642 and WO 94/29351; Duncan and Winter (1988) *Nature* 322:738-40; and U.S. Patent Nos. 5,648,260 and 5,624,821.

A. Recombinant Antibody Expression and Purification

[0335] The antibodies or antigen-binding fragments thereof described herein can be produced using a variety of techniques known in the art of molecular biology and protein chemistry. For example, a nucleic acid encoding one or both of the heavy and light chain polypeptides of an antibody can be inserted into an expression vector that contains transcriptional and translational regulatory sequences, which include, e.g., promoter sequences, ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, transcription terminator signals, polyadenylation signals, and enhancer or activator sequences. The regulatory sequences include a promoter and transcriptional start and stop sequences. In addition, the expression vector can include more than one replication system such that it can be maintained in

two different organisms, for example in mammalian or insect cells for expression and in a prokaryotic host for cloning and amplification.

[0336] Several possible vector systems are available for the expression of cloned heavy chain and light chain polypeptides from nucleic acids in mammalian cells. One class of vectors relies upon the integration of the desired gene sequences into the host cell genome. Cells which have stably integrated DNA can be selected by simultaneously introducing drug resistance genes such as *E. coli* gpt (Mulligan and Berg (1981) *Proc Natl Acad Sci USA* 78:2072) or *Tn5* neo (Southern and Berg (1982) *Mol Appl Genet* 1:327). The selectable marker gene can be either linked to the DNA gene sequences to be expressed or introduced into the same cell by co-transfection (Wigler et al. (1979) *Cell* 16:77). A second class of vectors utilizes DNA elements which confer autonomously replicating capabilities to an extrachromosomal plasmid. These vectors can be derived from animal viruses, such as bovine papillomavirus (Sarver et al. (1982) *Proc Natl Acad Sci USA*, 79:7147), cytomegalovirus, polyoma virus (Deans et al. (1984) *Proc Natl Acad Sci USA* 81:1292), or SV40 virus (Lusky and Botchan (1981) *Nature* 293:79).

[0337] The expression vectors can be introduced into cells in a manner suitable for subsequent expression of the nucleic acid. The method of introduction is largely dictated by the targeted cell type, discussed below. Exemplary methods include CaPO₄ precipitation, liposome fusion, cationic liposomes, electroporation, viral infection, dextran-mediated transfection, polybrene-mediated transfection, protoplast fusion, and direct microinjection.

[0338] Appropriate host cells for the expression of antibodies or antigen-binding fragments thereof include yeast, bacteria, insect, plant, and mammalian cells. Of particular interest are bacteria such as *E. coli*, fungi such as *Saccharomyces cerevisiae* and *Pichia pastoris*, insect cells such as SF9, mammalian cell lines (e.g., human cell lines), as well as primary cell lines.

[0339] In some aspects, an antibody or fragment thereof can be expressed in, and purified from, transgenic animals (e.g., transgenic mammals). For example, an antibody can be produced in transgenic non-human mammals (e.g., rodents) and isolated from milk as described in, e.g., Houdebine (2002) *Curr Opin Biotechnol* 13(6):625-629; van Kuik-Romeijn et al. (2000) *Transgenic Res* 9(2):155-159; and Pollock et al. (1999) *J Immunol Methods* 231(1-2):147-157.

[0340] The antibodies and fragments thereof can be produced from the cells by culturing a host cell transformed with the expression vector containing nucleic acid encoding the antibodies or fragments, under conditions, and for an amount of time, sufficient to allow expression of the proteins. Such conditions for protein expression will vary with the choice of the expression vector

and the host cell and will be easily ascertained by one skilled in the art through routine experimentation. For example, antibodies expressed in *E. coli* can be refolded from inclusion bodies (see, e.g., Hou et al. (1998) *Cytokine* 10:319-30). Bacterial expression systems and methods for their use are well known in the art (see Current Protocols in Molecular Biology, Wiley & Sons, and Molecular Cloning--A Laboratory Manual --3rd Ed., Cold Spring Harbor Laboratory Press, New York (2001)). The choice of codons, suitable expression vectors and suitable host cells will vary depending on a number of factors and may be easily optimized as needed. An antibody (or fragment thereof) described herein can be expressed in mammalian cells or in other expression systems including but not limited to yeast, baculovirus, and *in vitro* expression systems (see, e.g., Kaszubska et al. (2000) *Protein Expression and Purification* 18:213-220).

[0341] Following expression, the antibodies and fragments thereof can be isolated. An antibody or fragment thereof can be isolated or purified in a variety of ways known to those skilled in the art depending on what other components are present in the sample. Standard purification methods include electrophoretic, molecular, immunological, and chromatographic techniques, including ion exchange, hydrophobic, affinity, and reverse-phase HPLC chromatography. For example, an antibody can be purified using a standard anti-antibody column (e.g., a protein-A or protein-G column). Ultrafiltration and diafiltration techniques, in conjunction with protein concentration, are also useful. See, e.g., Scopes (1994) "Protein Purification, 3rd edition," Springer-Verlag, New York City, New York. The degree of purification necessary will vary depending on the desired use. In some instances, no purification of the expressed antibody or fragments thereof will be necessary.

[0342] Methods for determining the yield or purity of a purified antibody or fragment thereof are known in the art and include, e.g., Bradford assay, UV spectroscopy, Biuret protein assay, Lowry protein assay, amido black protein assay, high pressure liquid chromatography (HPLC), mass spectrometry (MS), and gel electrophoretic methods (e.g., using a protein stain such as Coomassie Blue or colloidal silver stain).

B. Modification of the Antibodies or Antigen-Binding Fragments Thereof

[0343] The antibodies or antigen-binding fragments thereof can be modified following their expression and purification. The modifications can be covalent or non-covalent modifications. Such modifications can be introduced into the antibodies or fragments by, e.g., reacting targeted amino acid residues of the polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues. Suitable sites for modification

can be chosen using any of a variety of criteria including, e.g., structural analysis or amino acid sequence analysis of the antibodies or fragments.

[0344] In some aspects, the antibodies or antigen-binding fragments thereof can be conjugated to a heterologous moiety. The heterologous moiety can be, e.g., a heterologous polypeptide, a therapeutic agent (e.g., a toxin or a drug), or a detectable label such as, but not limited to, a radioactive label, an enzymatic label, a fluorescent label, a heavy metal label, a luminescent label, or an affinity tag such as biotin or streptavidin. Suitable heterologous polypeptides include, e.g., an antigenic tag (FLAG (DYKDDDDK (SEQ ID NO: 141)), polyhistidine (6-His; HHHHHH (SEQ ID NO: 142), hemagglutinin (HA; YPYDVPDYA (SEQ ID NO: 143)), glutathione-S-transferase (GST), or maltose-binding protein (MBP)) for use in purifying the antibodies or fragments. Heterologous polypeptides also include polypeptides (e.g., enzymes) that are useful as diagnostic or detectable markers, for example, luciferase, a fluorescent protein (e.g., green fluorescent protein (GFP)), or chloramphenicol acetyl transferase (CAT). Suitable radioactive labels include, e.g., ^{32}P , ^{33}P , ^{14}C , ^{125}I , ^{131}I , ^{35}S , and ^3H . Suitable fluorescent labels include, without limitation, fluorescein, fluorescein isothiocyanate (FITC), green fluorescent protein (GFP), DyLight™ 488, phycoerythrin (PE), propidium iodide (PI), PerCP, PE-Alexa Fluor® 700, Cy5, allophycocyanin, and Cy7. Luminescent labels include, e.g., any of a variety of luminescent lanthanide (e.g., europium or terbium) chelates. For example, suitable europium chelates include the europium chelate of diethylene triamine pentaacetic acid (DTPA) or tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). Enzymatic labels include, e.g., alkaline phosphatase, CAT, luciferase, and horseradish peroxidase.

[0345] Two proteins (e.g., an antibody and a heterologous moiety) can be cross-linked using any of a number of known chemical cross linkers. Examples of such cross linkers are those which link two amino acid residues via a linkage that includes a "hindered" disulfide bond. In these linkages, a disulfide bond within the cross-linking unit is protected (by hindering groups on either side of the disulfide bond) from reduction by the action, for example, of reduced glutathione or the enzyme disulfide reductase. One suitable reagent, 4-succinimidylloxycarbonyl- α -methyl- α -(2-pyridyldithio) toluene (SMPT), forms such a linkage between two proteins utilizing a terminal lysine on one of the proteins and a terminal cysteine on the other. Heterobifunctional reagents that cross-link by a different coupling moiety on each protein can also be used. Other useful cross-linkers include, without limitation, reagents which link two amino groups (e.g., N-5-azido-2-nitrobenzoyloxysuccinimide), two sulfhydryl groups (e.g., 1,4-bis-maleimidobutane), an amino

group and a sulfhydryl group (e.g., m-maleimidobenzoyl-N-hydroxysuccinimide ester), an amino group and a carboxyl group (e.g., 4-[p-azidosalicylamido]butylamine), and an amino group and a guanidinium group that is present in the side chain of arginine (e.g., p-azidophenyl glyoxal monohydrate).

[0346] In some aspects, a radioactive label can be directly conjugated to the amino acid backbone of the antibody. Alternatively, the radioactive label can be included as part of a larger molecule (e.g., ^{125}I in meta- ^{125}I iodophenyl-N-hydroxysuccinimide (^{125}I mIPNHS) which binds to free amino groups to form meta-iodophenyl (mIP) derivatives of relevant proteins (see, e.g., Rogers et al. (1997) *J Nucl Med* **38**:1221-1229) or chelate (e.g., to DOTA or DTPA) which is in turn bound to the protein backbone. Methods of conjugating the radioactive labels or larger molecules/chelates containing them to the antibodies or antigen-binding fragments described herein are known in the art. Such methods involve incubating the proteins with the radioactive label under conditions (e.g., pH, salt concentration, and/or temperature) that facilitate binding of the radioactive label or chelate to the protein (see, e.g., U.S. Patent No. 6,001,329).

[0347] Methods for conjugating a fluorescent label (sometimes referred to as a "fluorophore") to a protein (e.g., an antibody) are known in the art of protein chemistry. For example, fluorophores can be conjugated to free amino groups (e.g., of lysines) or sulfhydryl groups (e.g., cysteines) of proteins using succinimidyl (NHS) ester or tetrafluorophenyl (TFP) ester moieties attached to the fluorophores. In some aspects, the fluorophores can be conjugated to a heterobifunctional cross-linker moiety such as sulfo-SMCC. Suitable conjugation methods involve incubating an antibody protein, or fragment thereof, with the fluorophore under conditions that facilitate binding of the fluorophore to the protein. See, e.g., Welch and Redvanly (2003) "Handbook of Radiopharmaceuticals: Radiochemistry and Applications," John Wiley and Sons (ISBN 0471495603).

[0348] In some aspects, the antibodies or fragments can be modified, e.g., with a moiety that improves the stabilization and/or retention of the antibodies in circulation, e.g., in blood, serum, or other tissues. For example, the antibody or fragment can be PEGylated as described in, e.g., Lee et al. (1999) *Bioconjug Chem* **10**(6): 973-8; Kinstler et al. (2002) *Advanced Drug Deliveries Reviews* **54**:477-485; and Roberts et al. (2002) *Advanced Drug Delivery Reviews* **54**:459-476 or HESylated (Fresenius Kabi, Germany; see, e.g., Pavisić et al. (2010) *Int J Pharm* **387**(1-2):110-119). The stabilization moiety can improve the stability, or retention of, the antibody (or fragment) by at least 1.5 (e.g., at least 2, 5, 10, 15, 20, 25, 30, 40, or 50 or more) fold.

[0349] In some aspects, the antibodies or antigen-binding fragments thereof described herein can be glycosylated. In some aspects, an antibody or antigen-binding fragment thereof described herein can be subjected to enzymatic or chemical treatment, or produced from a cell, such that the antibody or fragment has reduced or absent glycosylation. Methods for producing antibodies with reduced glycosylation are known in the art and described in, e.g., U.S. patent no. 6,933,368; Wright et al. (1991) *EMBO J* 10(10):2717-2723; and Co et al. (1993) *Mol Immunol* 30:1361.

Applications

[0350] The compositions described herein can be used in a number of diagnostic and therapeutic applications. For example, detectably labeled antigen-binding molecules can be used in assays to detect the presence or amount of the target antigens in a sample (e.g., a biological sample). The compositions can be used in *in vitro* assays for studying inhibition of target antigen function. In some aspects, e.g., in which the compositions bind to and inhibit a complement protein, the compositions can be used as positive controls in assays designed to identify additional novel compounds that inhibit complement activity or otherwise are useful for treating a complement-associated disorder. For example, a IL-27-inhibiting composition can be used as a positive control in an assay to identify additional compounds (e.g., small molecules, aptamers, or antibodies) that reduce or abrogate IL-27 production. The compositions can also be used in therapeutic methods as elaborated on below.

[0351] In some aspects, the disclosure provides a method of detecting IL-27 in a biological sample or in a subject, comprising (i) contacting the sample or the subject (and optionally, a reference sample or subject) with any antibody described herein under conditions that allow interaction of the antibody molecule and IL-27 to occur, and (ii) detecting formation of a complex between the antibody molecule and the sample or the subject (and optionally, the reference sample or subject).

Kits

[0352] A kit can include an anti-IL-27 antibody as disclosed herein, and instructions for use. The kits may comprise, in a suitable container, an anti-IL-27 antibody, one or more controls, and various buffers, reagents, enzymes and other standard ingredients well known in the art. In some aspects, the disclosure provides a kit comprising an anti-IL-27 antibody or antigen-binding portion as disclosed herein, and instructions for use in stimulating an immune response in a subject,

or treating cancer in a subject, optionally with instructions for use in combination with one or more additional therapeutic agents or procedure as disclosed herein.

[0353] The container can include at least one vial, well, test tube, flask, bottle, syringe, or other container means, into which an anti-IL-27 antibody may be placed, and in some instances, suitably aliquoted. Where an additional component is provided, the kit can contain additional containers into which this component may be placed. The kits can also include a means for containing an anti-IL-27 antibody and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained. Containers and/or kits can include labeling with instructions for use and/or warnings.

EXAMPLES

[0354] While the present disclosure has been described with reference to the specific aspects thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the disclosure. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present disclosure. All such modifications are intended to be within the scope of the disclosure.

Example 1: CDR Sequence Alignments

[0355] A number of sub-selections of anti-IL-27 antibodies of the instant disclosure share sequence homology across their CDR regions, providing a diversity of variant CDR sequences that have been validated as retaining functionality. It is expressly contemplated herein that the following consensus CDR sequences are fully supported by – and are therefore within the scope of – the instant disclosure.

[0356] For anti-IL-27 Ab1, anti-IL-27 Ab3, anti-IL-27 Ab4, anti-IL-27 Ab5, anti-IL-27 Ab6, and anti-IL-27 Ab7 antibodies, alignments of the CDR sequences of each of these anti-IL-27 antibodies revealed extensive homology, punctuated by variable residues. In particular, heavy chain CDR1 alignments revealed the following variable residues:

HCDR1 (IMGT)

CLUSTAL O(1.2.4) multiple sequence alignment

1	GFTFRSYG	8	(SEQ ID NO: 119)
5	GFTFRSYG	8	(SEQ ID NO: 31)

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4      GFTFASYG      8      (SEQ ID NO: 97)
2      GFTFSRTG      8      (SEQ ID NO: 53)
3      GFTFSRYG      8      (SEQ ID NO: 75)
6      GFTFSSYS      8      (SEQ ID NO: 9)
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[0357] A consensus heavy chain CDR1 (IMGT) sequence for these homologous antibodies is therefore N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 144) and, accordingly, more generally contemplated herein as a consensus heavy chain CDR1 (IMGT) sequence is N-GFTFXXXX-C (SEQ ID NO: 145), where X is any amino acid residue.

[0358] Alignment of the anti-IL-27 Ab1, anti-IL-27 Ab3, anti-IL-27 Ab4, anti-IL-27 Ab5, anti-IL-27 Ab6, and anti-IL-27 Ab7 antibody heavy chain CDR2 (IMGT) sequences revealed the following:

HCDR2 (IMGT)

CLUSTAL O(1.2.4) multiple sequence alignment

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10     ISSSGSYI      8      (SEQ ID NO: 120)
11     ISSSSSYI      8      (SEQ ID NO: 98)
7      ISSSSSYI      8      (SEQ ID NO: 32)
9      ISSSSSYI      8      (SEQ ID NO: 54)
8      ISSSSAYI      8      (SEQ ID NO: 76)
12     ISSSSSYI      8      (SEQ ID NO: 10)
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[0359] A consensus heavy chain CDR2 (IMGT) sequence for these homologous antibodies is therefore N-ISSSS[S/G][S/A]YI-C (SEQ ID NO: 146) and, accordingly, more generally contemplated herein as a consensus heavy chain CDR2 (IMGT) sequence is N-ISSSXXYI-C (SEQ ID NO: 147), where X is any amino acid residue.

[0360] Alignments of the human CDR1 (NT) and human CDR2 (NT) sequences also revealed the following:

HCDR1 (NT)

CLUSTAL O(1.2.4) multiple sequence alignment

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13     FTFRSYGMN     9      (SEQ ID NO: 34)
16     FTFRSYGMN     9      (SEQ ID NO: 122)
17     FTFASYGMN     9      (SEQ ID NO: 100)
14     FTFSRTGMN     9      (SEQ ID NO: 56)
15     FTFSRYGMN     9      (SEQ ID NO: 78)
18     FTFSSYSMN     9      (SEQ ID NO: 12)
      ***      ***

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HCDR2 (NT)

CLUSTAL O(1.2.4) multiple sequence alignment

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23      GISSSGSYIYYADSVKG 17      (SEQ ID NO: 123)
19      SSSSSSYIYYADSVKG 17      (SEQ ID NO: 35)
20      SSSSSSYIYYADSVKG 17      (SEQ ID NO: 57)
22      SSSSSSYIYYADSVKG 17      (SEQ ID NO: 101)
21      SSSSSAYILYADSVKG 17      (SEQ ID NO: 79)
24      SSSSSSYIYYADSVKG 17      (SEQ ID NO: 13)
      .****.:**  ****

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[0361] Consensus heavy chain CDR1 (NT) and CDR2 (NT) sequences for these homologous antibodies are therefore N-FTF[S/A/R][S/R][T/Y][G/S]MN-C (SEQ ID NO: 148) and N-[G/S]ISS[S/G][S/A]YI[L/Y]YADSVKG-C (SEQ ID NO: 149), respectively. In view of these consensus sequences, more generally contemplated herein are consensus heavy chain CDR1 (NT) and CDR2 (NT) sequences N-FTFXXXMN-C (SEQ ID NO: 150) and N-XISSXXYIXYADSVKG-C (SEQ ID NO: 151), respectively, where X is any amino acid residue.

[0362] Heavy chain CDR3 (IMGT or NT) and light chain CDRs CDR1 (IMGT or NT), CDR2 (IMGT or NT) and CDR3 (IMGT or NT) were fully conserved between anti-IL-27 Ab1, anti-IL-27 Ab3, anti-IL-27 Ab4, anti-IL-27 Ab5, anti-IL-27 Ab6, and anti-IL-27 Ab7.

Example 2: In vivo Administration of Anti-IL-27 Antibodies

[0363] A Phase 1, open-label, FIH, monotherapy dose-escalation, safety, and expansion study is ongoing to analyze the effects of in vivo administration of anti-IL-27 antibodies disclosed herein in the treatment of solid tumors. Part A consists of the anti-IL-27 monotherapy dose-escalation portion of the study and will enroll approximately 42 patients with advanced solid tumors. This dose escalation part will employ an Accelerated Phase (single patient) for Dose Levels 1-3, followed by a Standard Phase (3+3) for Dose Levels 4-8.

[0364] Part B will enroll patients with advanced or metastatic ccRCC (any clear cell component in the histologic definition) or HCC into indication-specific monotherapy expansion cohorts, to further examine the safety, efficacy, tolerability, PK, and pharmacodynamics of the anti-IL-27 antibody as a monotherapy using a 2-stage design. Stage 1 of each expansion cohort will enroll approximately 17 patients. If ≥ 1 of the 17 patients in Stage 1 has a confirmed radiographic response (complete response [CR] or partial response [PR]), then approximately 23 additional patients will be enrolled in Stage 2. Approximately 12 patients (out of approximately 40

patients) in each of the indication-specific cohorts will be required to have a soft tissue metastasis or primary tumor that is accessible for biopsy. The total number of patients enrolled in Part B will be approximately 80 (approximately 40 in each expansion cohort).

[0365] The study design is presented in FIG. 1.

[0366] The starting dose of the anti-IL-27 antibody monotherapy will be 0.003 mg/kg given IV q4 week. Subsequent anti-IL-27 antibody dose levels may be modified and additional dose levels and/or schedules may be investigated based on the recommendation of the Safety Review Committee (SRC).

Table 2: Proposed dose levels for monotherapy dose escalation.

Dose level	Anti-IL-27 dose	Number of patients
1 (starting dose)	0.003 mg/kg	N = 1-6
2	0.03 mg/kg	N = 1-6
3	0.1 mg/kg	N = 1-6
4	0.3 mg/kg	N = 3-6
5	1.0 mg/kg	N = 3-6
6	3.0 mg/kg	N = 3-6
7	10.0 mg/kg	N = 3-6
8	20.0 mg/kg	N = 3-6

Note: Escalation of dose levels may continue after completion of Dose Level 8 at the recommendation of the Safety Review Committee (SRC) at no more than 50% dose increases.

[0367] Monotherapy dose escalation will begin with an Accelerated Phase, whereby 1 patient each will be enrolled in Dose Levels 1-3 and DLTs and AEs will be monitored during the first cycle of study treatment (a cycle is defined as 4 weeks [28 days] from Day 1). Had a patient in the Accelerated Phase experienced a DLT or any $\geq$ Grade 2 treatment-related adverse event during the first cycle, dose escalation would have converted to Standard Phase at that dose level. Had any dose level in the Accelerated Phase been converted to the Standard Phase, all subsequent dose levels would have been evaluated in Standard Phase for the remainder of dose escalation. As no DLTs were observed at Dose Levels 1-3, no conversion from Accelerated Phase to Standard Phase was required.

[0368] If ≥ 2 DLTs occur at Dose Level 1 (0.003 mg/kg), a Dose Level -1 may be considered. The dose for this level will be discussed with the SRC.

[0369] Assuming no conversion to Standard Phase during Accelerated Phase (Dose Levels 1, 2, and 3), dose escalation will transition to a traditional 3+3 design at Dose Level 4 (0.3 mg/kg), whereby 3 patients will be treated at a dose level and monitored for DLTs during the first cycle of study drug. If a DLT occurs in the first 3 patients, an additional 3 patients will be treated at that

same dose level. If no DLTs occur in these additional 3 patients (ie, < 2 DLTs per 6 patients), dose escalation may proceed to the next dose level.

[0370] In the Standard Phase of monotherapy dose escalation, once a dose level is cleared and enrollment in the next dose level has begun, up to 3 patients may be enrolled and treated in parallel in the previously cleared dose level at the Sponsor's discretion. For these patients, preference will be given to patients with ccRCC, HCC, and/or patients who agree to tumor biopsies.

[0371] Dose escalation will continue in monotherapy until 1 of the following occurs: (i) determination of a RP2D for each dosing schedule investigated; and (ii) recommendation by the SRC to halt dose escalation based on comprehensive review of all applicable data.

[0372] A RP2D will be determined by the SRC for the anti-IL-27 antibody monotherapy. A minimum of 6 patients must be treated at a particular dose level and schedule for it to be considered the RP2D. The RP2D will be based upon cumulative safety, PK, and pharmacodynamic data. If 2 or more patients at a dose level experience a DLT (out of 6 in total enrolled), this dose level is above the RP2D. The SRC may recommend investigating intermediate doses or alternative schedules to optimize RP2D determination.

[0373] The anti-IL-27 antibody will be administered as monotherapy in a q4 week schedule; 1 cycle of treatment will include 1 dose of the anti-IL-27 antibody. The SRC will monitor the safety, PK, and pharmacodynamics of the anti-IL-27 antibody during the study, and may recommend altering the dosing paradigm (e.g., dose level and/or schedule).

[0374] If not initiated on treatment at the RP2D, patients may have their dose escalated to a higher dose or change to a different dosing schedule if they have received their current dose level for at least 3 cycles, if no toxicities > Grade 1 on their current dose level are reported, and if they have not had a dose reduction. If any treatment-related $\geq$ Grade 3 toxicity occurs at any level, no inpatient dose escalation will be allowed at that level for any patient. Patients may only have their dose escalated or moved to an alternative dosing schedule at a dose level that has already been evaluated and is at or below the RP2D for the anti-IL-27 antibody monotherapy. There is no limit to how many dose levels a patient can be escalated (if below RP2D) as long as they meet the above criteria. Toxicities that occur during the first cycle of a higher dose for such a patient would not be considered DLTs.

[0375] Dose-limiting toxicities will be evaluated during the first treatment cycle (28 days) using NCI-CTCAE version 5.0 or higher and defined for Part A and Part C of the study. Patients must have received at least 50% of the prescribed dose of the anti-IL-27 antibody and have not

discontinued study therapy in the first 28 days (Cycle 1) for reasons other than drug-related adverse events to be evaluable for DLTs. Patients unevaluable for DLTs will be replaced.

[0376] Toxicities (regardless of Grade) considered clearly related to disease progression, intercurrent illness, or concomitant medications are not considered DLTs. Grade 3 or Grade 4 non-hematologic laboratory abnormalities without clinical sequelae, resolving within 72 hours, and not requiring treatment, are not considered DLTs.

[0377] Toxicities that occur after the Cycle 1 DLT review period that have significant clinical impact will be considered by the SRC in the evaluation of dose selection. Patients who experience a DLT may have the opportunity to continue treatment at a lower dose.

[0378] The occurrence of any certain toxicities during Cycle 1 will be considered a DLT, if assessed by the Investigator to be possibly, probably, or definitely related to study treatment.

[0379] Part B: Anti-IL-27 Antibody Monotherapy Expansion

[0380] The Part B monotherapy expansion cohorts will evaluate the safety, efficacy, tolerability, PK, and pharmacodynamics of the anti-IL-27 antibody monotherapy at the RP2D in patients with ccRCC (any clear cell component in the histologic definition), HCC and non-small cell lung cancer (NSCLC) in indication-specific cohorts using a 2-stage design. Stage 1 of each expansion cohort will enroll approximately 17 patients. If ≥ 1 of the 17 patients in Stage 1 has a confirmed radiographic response (CR or PR), then approximately 23 additional patients will be enrolled in Stage 2. Approximately 12 patients (out of approximately 40 patients) in each of the indication-specific cohorts will be required to have a soft tissue metastasis or primary tumor that is accessible for biopsy. The total number of patients enrolled in Part B will be approximately 120 (approximately 40 in each expansion cohort).

[0381] Inclusion Criteria

[0382] All patients must meet the following criteria for inclusion:

1. Patients must be ≥ 18 years of age.
2. Locally advanced or metastatic (Stage IV) solid tumor that has progressed during or after standard therapy, and for whom no available therapies are appropriate (based on the judgment of the Investigator).
3. Patients in Part B with advanced or metastatic ccRCC, HCC or NSCLC must have at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
4. Patients with HCC in Part B must have at least 1 measurable target lesion according to modified RECIST (mRECIST) meeting the following criteria. Lesion(s) should be suitable for repeat measurement.

- Hepatic target lesion(s) should be at least ≥ 1.0 cm (for typical, ie, arterial enhancing lesions, this should be of the viable tumor, whereas for atypical lesions, the longest diameter should be used).
 - Nonhepatic target lesion(s) can include the following:
 - Lymph node (LN) lesion measuring ≥ 1.5 cm in the short axis, unless it is a porta hepatis LN, which should be at least ≥ 2.0 cm in the short axis.
 - Non-nodal lesion measuring ≥ 1.0 cm in the longest diameter. Bone lesions are not eligible.
 - Lesions previously treated with radiation or other forms of locoregional therapy must show radiographic evidence of disease progression to be used as a target lesion.
5. Patients with HCC must have unresectable disease, Barcelona Clinic Liver Cancer¹ Stage B (not eligible for transcatheter arterial chemoembolization) or Stage C.
 6. For patients in Part B with ccRCC, demonstrated progressive disease (PD) during or after the most recent treatment regimen. Prior treatment history must include progression during or after treatment with regimen(s) that have included a vascular endothelial growth factor (VEGF)-targeted agent and a programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor. Patients who did not progress on but discontinued the VEGF-targeted agent for toxicity or intolerability are permitted.
 7. For patients in Part B with HCC, demonstrated PD during or after the most recent treatment regimen. Prior treatment history must include progression during or after treatment with a VEGF-targeted agent. Patients who did not progress on but discontinued the VEGF-targeted agent for toxicity or intolerability are permitted.
 8. For Part B patients in the tumor biopsy subsets only, must have tumor tissue that is accessible for pretreatment and on-treatment tumor biopsy in the opinion of the Investigator and be willing to undergo pretreatment and on-treatment biopsies per protocol.
 9. Washout period from the last dose of previous anticancer therapy (chemotherapy, biologic, or other investigational agent) to the initiation of study drug must be > 5 times the half-life of the agent or > 21 days (whichever is shorter).
 - Note: The washout period for palliative radiotherapy to non-central nervous system disease is 7 days.
 10. Resolution of non-immune related AEs secondary to prior anticancer therapy (excluding alopecia and peripheral neuropathy) to $\leq$ Grade 1 per NCI-CTCAE version 5.0 or higher, and complete resolution of immune-related AEs secondary to prior checkpoint inhibitor therapy.
 - Note: Patients with other clinically stable or \ nonsignificant AEs related to prior therapy may be enrolled pending discussion with the Sponsor (e.g., controlled thyroid disorders, vitiligo, asymptomatic elevated amylase/lipase, type 1 diabetes on insulin, $\leq$ Grade 2 controlled rash, $\leq$ Grade 2 electrolyte abnormalities on a stable dose of supplementation).
 11. Serum creatinine clearance ≥ 30 mL/min per Cockcroft-Gault formula or serum creatinine $\leq 2.0 \times$ the upper limit of normal (ULN).

12. Total bilirubin $\leq 1.5 \times \text{ULN}$ ($\leq 3 \times \text{ULN}$ if elevated because of Gilbert's syndrome, and $\leq 2 \times \text{ULN}$ for patients with HCC or patients with known liver metastases).
13. Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) $< 2.5 \times \text{ULN}$ ($< 5 \times \text{ULN}$ if liver metastasis or for patients with HCC).
14. For patients with HCC, Child-Pugh class A or B7 with a serum albumin $\geq 2.8 \text{ g/dL}$ ($\geq 28 \text{ g/L}$).
15. Adequate hematologic function, defined as absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/\text{L}$, hemoglobin $\geq 9.0 \text{ g/dL}$, and platelet count $\geq 100 \times 10^9/\text{L}$. For patients with HCC, platelet count $\geq 75 \times 10^9/\text{L}$ without transfusion.
16. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
17. Ejection fraction $\geq 50\%$, as measured by echocardiogram or multigated acquisition scan at Screening.
18. For women of childbearing potential (WCBP): negative serum β human chorionic gonadotropin pregnancy test within 1 week before first treatment (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months for women > 55 years of age).
19. Willingness of male and female patients who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study treatment period, including 75 days after the last dose of SRF388; male patients must refrain from donating sperm during this period. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception. Azoospermic male patients and WCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, female patients must still undergo pregnancy testing as described in this section.
20. Ability to adhere to the study visit schedule and all protocol requirements.
21. Signed and dated institutional review board /independent ethics committee-approved informed consent form before any screening procedures are performed.
22. Patients with NSCLC must have histologically confirmed locally advanced and/or metastatic Stage IV NSCLC.
23. Patients with NSCLC must have demonstrated PD during or after the most recent treatment regimen. Prior treatment history must include progression during or after treatment with (1) anti-PD-(L)1 if disease has no driver alterations and (2) a targeted therapy if the patient has disease with driver alterations. Patients who did not progress on but discontinued the targeted agent for toxicity or intolerability are permitted.

Note: Patients with driver alterations are not required to have had prior anti-PD-(L)1 therapy.

[0383] Exclusion Criteria

[0384] Patients are to be excluded from the study if they meet any of the following criteria:

1. Previously received an anti-IL-27 antibody or anti-IL-27 targeted therapy.
2. For patients in Part B with renal cell carcinoma (RCC), non-clear cell RCC histology.
3. For patients in Part B, received > 4 prior systemic regimens for Stage IV disease.
4. For patients with HCC, known fibrolamellar or mixed hepatocellular cholangiocarcinoma.
5. For patients with HCC, moderate or severe ascites.
6. Receiving chronic anti-coagulation therapy (eg, warfarin, enoxaparin) that cannot be safely discontinued temporarily for the required biopsies (only if in the applicable tumor biopsy subset).
7. History of Grade 4 allergic or anaphylactic reaction to any monoclonal antibody therapy, or any excipient in the study drugs.
8. Major surgery within 4 weeks prior to Screening.
9. Symptomatic or untreated brain metastases (including leptomeningeal metastases). Patients previously treated for brain metastases must be ≥ 28 days from completion of radiation treatment with follow-up imaging showing no progression.
10. Primary central nervous system malignancy.
11. Prior autologous stem cell transplant ≤ 3 months before the first dose of SRF388.
12. Prior allogeneic hematopoietic cell transplant within 6 months of the first dose of SRF388 or with a history of or current clinical Graft-Versus-Host Disease.
13. Known infection with HIV.
14. Known infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). The following exceptions are permitted:
 - Patients with HCC: controlled active HBV or fully treated HCV infection is permitted. Antiviral therapy as per local standard of care should be continued.
 - For patients with HCC with active HBV, controlled disease is considered HBV DNA < 500 IU/mL during the Screening Period with willingness to continue antiviral treatment during length of study. The patient must be on anti-HBV treatment (per local standard of care; eg, entecavir) for a minimum of 14 days prior to study entry.
 - For patients with HCC with HCV, only cured disease or HCV considered fully treated and no longer requiring antiviral therapy for control is permitted.
 - No co-infection with HCV and HBV is allowed. Co-infection is defined as HCV RNA positive and hepatitis B surface antigen (HBsAg) positive. However, a patient who is HCV Ab+, hepatitis B core antibody (HBcAb) + but negative HBsAg is not considered co-infected and is permitted.
 - Patients with any solid tumor who have a history of cured HCV are permitted.
15. Active autoimmune disease requiring steroids or immunosuppressive (eg, cyclosporine) therapy or medical conditions requiring chronic steroid (ie, > 10 mg/day prednisone or equivalent) or immunosuppressive therapy.

- Note: Topical, intranasal, or inhaled corticosteroids are permitted. Physiologic replacement for patients with thyroid, adrenal, or pituitary insufficiency (eg, thyroxine, physiologic corticosteroids [≤ 10 mg/day of prednisone or its equivalent], or insulin) is allowed. Patients with a history of autoimmune disease may be eligible following discussion with the Medical Monitor.
16. Ongoing uncontrolled systemic bacterial, fungal, or viral infections at Screening.
 - Note: Oral antibiotics for a controlled infection are permitted. Patients on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met.
 17. Administration of a live attenuated vaccine within 6 weeks before the first dose of study drug.
 18. Baseline QT interval corrected (QTc) with Fridericia's method (QTcF) > 480 ms.
 - Note: If 1 elevated QTc reading, the screening requirement can be met with the average of triplicate ECGs. Criterion does not apply to patients with a right or left bundle branch block.
 19. Female patients who are pregnant or breastfeeding.
 20. Another malignancy, other than those with negligible risk of death, including but not limited to non-melanoma skin cancer, low risk localized or cured prostate cancer, ductal carcinoma in situ, or carcinoma in situ of the cervix, within 2 years before Screening.
 21. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within 6 months before Screening.
 22. Unstable or severe uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition including pneumonitis and/or interstitial lung disease, uncontrolled diabetes, symptomatic fistula) or any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the risk to the patient associated with his or her participation in the study.
 23. For patients with NSCLC, any component of small cell histology.

[0385] Biomarker Assessments

[0386] Samples will be collected for biomarker analysis to investigate the biological effects of anti-IL-27 at the molecular and cellular level, as well as to evaluate how changes in the markers and immune cell populations may relate to exposure and clinical outcomes. The goal of the biomarker assessments is to provide supportive data for the clinical trial. There may be circumstances when a decision is made to stop a collection, not perform, or discontinue an analysis due to either practical or strategic reasons (eg, inadequate sample number, sample quality issues precluding analysis, etc). Therefore, sample collection and/or analysis may be omitted at the discretion of the Sponsor.

[0387] Additional biomarker samples may be requested (when feasible) at the time of any unusual safety event (ie, an AE different in type and severity from that which is expected in the setting of anti-IL-27 use), or if a sample is found to be compromised.

[0388] The following biomarker samples may be analyzed: blood (whole blood and PBMCs) for immunophenotyping and immune monitoring (to monitor the effects of treatment on various peripheral blood immune cell populations; subsets may include, but are not limited to, monocytes, neutrophils, myeloid-derived suppressor cells, and T/NK/myeloid-cell populations); blood serum for cytokine/chemokine/soluble factors (for profiling of potential predictive and pharmacodynamic biomarkers of response and/or resistance to anti-IL-27; serum levels of soluble factors associated with cancer and immunological function will be assessed. Examples include but are not limited to: EBI3, IL-27, TNF α , MIP-1 α (CCL3), IFN γ , IL-10, and IL-6.

Example 3: In vivo Administration of Anti-IL-27 Antibodies

[0389] Patients with advanced solid tumors refractory to standard therapy were enrolled in an ongoing phase 1 dose-escalation study (accelerated single patient followed by standard 3+3) to establish the preliminary safety of anti-IL-27 Ab1 monotherapy and to identify a dose suitable for expansion (NCT04374877). The anti-IL-27 antibody was administered intravenously every 4 weeks on day one of each four-week cycle (FIG. 1). Anti-IL-27 Ab1 monotherapy expansions (Part B) are enrolling patients with advanced ccRCC, HCC and NSCLC in Simon 2-stage designs, and anti-IL-27 Ab1 will be explored in combination with pembrolizumab (Part C) in patients with advanced ccRCC and HCC (FIGs. 1A-1C).

[0390] In Part A, the dose escalation component, the primary end points were rate of dose limiting toxicities (DLTs), safety, and tolerability with overarching objective of RP2D determination. Key secondary end points included objective response rate (ORR) based on investigator review per RECIST v1.1 and iRECIST (if HCC, by mRECIST), pharmacokinetics, pharmacodynamic assessments (phosphorylated signal transducer and activator of transcription-1 (pSTAT1) levels in immune cell subsets), and serum concentrations of EBI3. Exploratory analyses planned to identify potential biomarkers of response and resistance. The safety analysis set included all patients who received any amount of study medication. The response evaluable analysis set included all patients with measurable disease at baseline who received at least one dose of anti-IL-27 Ab1 and had one post-baseline response assessment or who discontinued study treatment within 6 weeks ($\pm$ 2 weeks) of first dose. For the primary pharmacodynamic marker, fresh whole blood samples were analyzed by flow cytometry to monitor inhibition of pSTAT1.

[0391] Preliminary Study Results

[0392] In Part A, dose escalation, of the study, twenty-one (21) patients have received the anti-IL-27 antibody at doses ranging from 0.003 to 10 mg/kg. Median age was 66 years, 67% were female, and ECOG PS was 0/1 (29%/71%) (Table 3). Median number of prior therapies was 2 (range 1–9), and 81% were anti-PD-L1 experienced (n=17). The only treatment-related adverse events observed across dose levels were low-grade fatigue (n=1, 8%), nausea (n=1, 8%) and excess salivation (n=1, 8%). No dose-limiting toxicities (DLTs) or $\geq$ Grade 3 related toxicity have occurred, including through the first 4 patients at the 10 mg/kg dose level. There have been 6 reproted related TEAEs, which were all low grade, including fatigue (n=2), nausea (n=1), excess salivation (n=1), cough (n=1), and hyperthyroidism (n=1).

Table 3: Part A, Dose Escalation Demographics and Baseline Characteristics (All patients, N = 21)

Median age, years (range)	66 (46, 83)
Sex, n (%)	
Male	7 (33%)
Female	14 (67%)
Ecog PS at baseline, n (%)	
0	6 (29%)
1	15 (71%)
Median time since initial diagnosis, months (range), n=20	46 (6, 234)
Number of prior systemic therapies, n (%)	
1	3 (14%)
2	4 (19%)
3	2 (10%)
≥ 4	12 (57%)
Prior aPD-1/aPD-L1, n (%)	
Yes	17 (81%)
No	4 (19%)

[0393] Mean time on study is 8 weeks (range 1-50), as measured by the days from the first dose to the last visit, including safety follow-up visits (FIG. 2). Five patients were escalated to higher doses on study, as depicted by changing of the lane color at the time of dose increase. Disease assessment was performed at week 8 and then every 12 weeks thereafter. Of the 18 evaluable patients, approximately 40% experienced clinical benefit in the form of disease stabilization or partial response, with 50% of disease stabilization persisting beyond 16 weeks. One patient (6%) exhibited a partial response, 7 patients (39%) exhibited stable disease, and 10 patients (55%) exhibited progressive disease, as measured by RECISTv1.1 (FIG. 3). One patient with RCC who received prior anti-PD-1 has prolonged stable disease for > 9 months. In particular, one patient

with NSCLC treated at 10 mg/kg experienced a rapid partial response evident at the first response assessment at 8 weeks, which was confirmed at 12 weeks.

[0394] A preliminary PK analysis of patient samples who were administered 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg doses of anti-IL-27 antibody in Part A of the study was performed. Anti-IL-27 antibody PK are linear and dose proportional with estimated $T_{1/2}$ being 11.7 (7.1-18.8) days (FIG. 4). There is evidence of accumulation and steady state reached by Cycle 3. There is no evidence of anti-drug antibody development to date.

[0395] Based on non-clinical efficacy models, goal serum trough drug concentrations are greater than 20x the IC_{90} for pSTAT1 signaling inhibition. Inhibition of downstream pSTAT1 signaling in whole blood served as a primary PD marker and we observed that complete pSTAT1 inhibition was maintained through trough at 0.3 mg/kg and above (FIGs. 5A-5D). Maximal inhibition of the IL-27 signaling pathway as measured by >90% pSTAT1 inhibition in whole blood was achieved starting at 0.3 mg/kg and above. Given combined evidence in the Hepa 1-6 mouse model of near-complete pathway inhibition and preclinical human equivalent dose modeling projecting biologically active doses, additional slots were opened for RCC and HCC starting at 1 mg/kg.

[0396] One particular patient is a 64-year-old man with squamous cell NSCLC with metastases to the mediastinal nodes, lung, pleura and adrenal gland, who is receiving anti-IL-27 antibody Ab1 at 10 mg/kg intravenously once every four weeks. The patient was previously treated with adjuvant gemcitabine/cisplatin, first line carboplatin/nab-paclitaxel/pembrolizumab (with a PD-L1 expression 10%), and second line docetaxel, with no response to any therapy and progressively symptomatic prior to anti-IL-27 antibody Ab1 initiation. This patient is experiencing a partial response with 42% tumor shrinkage after 2 cycles of anti-IL-27 antibody Ab1 administration in both mediastinal node target lesions as shown by the arrows with significant improvement in his dyspnea (FIGs. 6A-6F). This partial response was confirmed as a 66% decrease in target lesions after 3 cycles (FIGs. 6A-6F).

[0397] Anti-IL-27 Ab1 is well-tolerated at all tested doses to date in patients with advanced solid tumors. Preliminary results of IL-27 pathway blockade with a first-in-class therapeutic study of anti-IL-27 Ab1 shows evidence of single-agent activity even in heavily pre-treated patients, including a confirmed partial response in a patient with squamous cell NSCLC whose disease was resistant to three prior regimens including chemotherapy and PD-1 blockade, and multiple patients have experienced disease stabilization. PK are linear and dose-proportional with maximal target inhibition of downstream IL-27-mediated pSTAT1 maintained throughout the dosing interval.

Preliminary results of IL-27 pathway blockade with a first-in-class immunotherapy support further evaluation of anti-IL-27 Ab1 as monotherapy and in combination with standard and investigational regimens in both immune checkpoint naïve and experienced patients with the initial focus planned in HCC, RCC, and NSCLC.

[0398] Updated Preliminary Study Results

[0399] In Part A, twenty-nine (29) patients have received the anti-IL-27 antibody at doses ranging from 0.003 to 20 mg/kg. Median age was 64 years, 62% were female, and ECOG PS was 0/1 (24%/76%) (Table 4). 62% of patients had received 3 or more lines off prior therapy, and 79% were anti-PD-(L)1 experienced (n=23). The only treatment-related adverse events observed across dose levels at $\geq 10\%$ was low-grade fatigue (n=3). No dose-limiting toxicities (DLTs), $\geq$ Grade 3 related toxicity have occurred at any dose level. There have been 6 reported related TEAEs, which were all low grade, including fatigue (n=3), nausea (n=2), excess salivation (n=1), cough (n=1), and hyperthyroidism (n=1).

Table 4: Part A, Dose Escalation Demographics and Baseline Characteristics (All patients, N = 29)

Median age, years (range)	64 (46, 83)
Sex, n (%)	
Male	11 (38%)
Female	18 (62%)
ECOG PS at baseline, n (%)	
0	7 (24%)
1	22 (76%)
Median time since initial diagnosis, months (range)	43 (6, 234)
Number of prior systemic therapies, n (%)	
1	7 (24%)
2	4 (14%)
3-4	7 (24%)
≥ 5	11 (38%)
Prior aPD-1/aPD-L1, n (%)	
Yes	23 (79%)
No	6 (21%)

[0400] Mean time on study for Part A is 9 weeks (range 1-71), as measured by the days from the first dose to the last visit, including safety follow-up visits (FIG. 7). Six patients were escalated to higher doses on study, as depicted by changing of the lane color at the time of dose increase. Disease assessment was performed at week 8 and then every 12 weeks thereafter. Of the 27 evaluable patients, approximately 40% experienced clinical benefit in the form of disease stabilization or partial response, with 28% of disease stabilization persisting beyond 16 weeks. One patient (3.7%) exhibited a confirmed partial response, 10 patients (37%) exhibited stable disease, and 16 patients (59%) exhibited progressive disease, as measured by RECISTv1.1 (FIGs. 8A-8B).

Three patients with RCC, cecal adenocarcinoma, and appendiceal adenocarcinoma who received prior anti-PD-1 had prolonged stable disease at 9 months or beyond. One patient with NSCLC whose disease was primarily refractory to 3 prior therapies including platinum and taxane chemotherapies and PD-1 blockade was treated at 10 mg/kg and experienced a rapid partial response evident at the first response assessment at 8 weeks, which was confirmed at 12 weeks.

[0401] A review of the subset of ccRCC patients enrolled in Part A of the study was performed. Of the 29 patients in Part A, 7 were ccRCC patients. The majority were men (71%) and of intermediate risk (80%). This subset of patients was heavily pretreated with 29% having 3-4 prior lines of therapy and 43% having 5 or more prior lines. All had received prior PD-1 pathway blockade. Of these 7 patients, 43% (n=3) experienced disease stabilization for ≥ 20 weeks (range: 20-32) (FIGs. 9A-9B).

[0402] A subsequent PK analysis of patient samples who were administered 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg and 20 mg/kg doses of anti-IL-27 antibody in Part A of the study was performed, confirming that anti-IL-27 antibody PK are linear and dose proportional from 0.03 to 20 mg/kg. The terminal elimination half-life was estimated to be approximately 10 days, ranging from 6 to 13 days. Steady state was attained by Cycle 4, with an Accumulation Index of 1.2. Exposures (C_{max} and AUC) in patients with ccRCC or HCC treated with 10 mg/kg anti-IL27 antibody as monotherapy were similar to those observed in the 10 mg/kg dose escalation cohort (FIGs. 10A-10B). Pre-existing low-titer anti-drug antibodies (ADA) were identified in the Cycle 1 pre-dose samples of 7 out of 63 patients; none were significantly boosted (increase in titer of >4-fold) post-treatment. Two out of 65 patients developed ADA after initiation of treatment.

[0403] The confirmed partial response in a 64-year NSCLC patient receiving anti-IL-27 antibody Ab1 at 10 mg/kg intravenously once every four weeks deepened to a 74% decrease in target lesions at cycle 6 response assessment.

[0404] The Part B Simon 2 Stage studies are ongoing with the primary endpoint of objective response. No concerning new safety signals have been identified thus far.

[0405] In the clear cell RCC cohort, 21 patients have been enrolled. Most of the population was male (91%), intermediate risk (57%) by International Metastatic RCC Database Consortium Risk Score ("IDMC") and had lung (71%) and nodal (100%) metastases. Close to 40% had liver (n=8) and bone disease (n=7) which generally correlate with worse prognosis. All patients were required to have had prior VEGF targeted therapy and PD-1 blockade alone or in combination (Table 5).

Thirteen (13) patients were evaluable for investigator assessed RECISTv1.1 response (FIGs. 11A-11B). Disease control rate defined as CR/PR + SD was 31% including one patient with a confirmed partial response. Progressive disease was best response in 71%. The patient with a partial response experienced target lesion tumor shrinkage of 45%, which was confirmed at C6 and the patient remains on study at cycle 9.

Table 5: Part B, ccRCC Demographics and Baseline Characteristics (All patients, N = 21)

Median age, years (range)	61 (42, 78)
Sex, n (%)	
Male	19 (90.5%)
Female	2 (9.5%)
ECOG PS at baseline, n (%)	
0	10 (47.6%)
1	11 (52.4%)
Median time since initial diagnosis, months (range)	55 (26, 119)
Number of prior systemic therapies, n (%)	
1	0 (0%)
2	5 (23.8%)
3-4	16 (76.2%)
Prior aPD-1/aPD-L1, n (%)	
Yes	21 (100%)
No	0 (0%)
IDMC (one or more patients are missing data)	
Favorable	4 (19%)
Intermediate	12 (57.1%)
Poor	2 (9.5%)

[0406] In the treatment-refractory HCC cohort, 17 patients were enrolled in a monotherapy expansion. It was an advanced treatment refractory population with a median progression free survival (PFS) of 7.2 weeks (6.3, NE). Of the 16 response evaluable patients, 31% (n=5) experienced stable disease and 69% (n=11) progressive disease as best response by RECISTv1.1 (FIGs. 12A-12B). Interrogation of baseline demographics highlights the advanced nature of the population enrolled: 53 % 3-4 lines of prior therapy, 18% Child Pugh B7, 77% BCLC Stage C, 94% with ECOG 1, 59% AFP $\geq$ 400. Only 18% ever had prior PR and 18% were primary treatment refractory to all prior lines of therapy (Table 6).

Table 6: Part B, HCC Demographics and Baseline Characteristics (All patients, N = 17)

Median age, years (range)	64 (39, 77)
Sex, n (%)	
Male	13 (76.5%)
Female	4 (23.5%)
ECOG PS at baseline, n (%)	
0	1 (5.9%)
1	15 (94.1%)

Median time since initial diagnosis, months (range)	27 (1, 137)
Number of prior systemic therapies, n (%)	
1	1 (5.9%)
2	7 (41.2%)
3-4	9 (52.9%)
≥5	0 (0%)
Prior aPD-1/aPD-L1, n (%)	
Yes	12 (70.6%)
No	5 (29.4%)

Example 4: Determination of Anti-IL-27 Antibodies in Human Serum by Enzyme-Linked Immunosorbent Assay (ELISA)

[0407] An immunoassay method was used for the detection of anti-IL-27 Ab1 in human serum. In the sandwich ELISA, microtiter plates (96-well MaxiSorp plates, Cat #439454) were coated with recombinant human IL-27 (Peprotech, Lot#1215589) and stored at 4°C overnight. The plates were washed and blocked for at least one hour at room temperature. Samples, including standards and quality controls (QCs), were diluted at a minimum required dilution (MRD) of 1:25 in assay buffer (1% bovine serum albumin, BSA, in phosphate-buffered saline/tween, PBST) then added onto the plate for one hour at room temperature. Anti-IL-27 Ab1 is detected by anti-human IgG1 antibody conjugated to horseradish peroxidase (HRP) (Southern Biotech, Lot# G4015-Q168B). KPL SureBlue™ peroxidase is used as a substrate for HRP. The reaction is stopped by 1N Hydrochloric acid. The color intensity is proportional to the quantity of anti-IL-27 Ab1.

Example 5: Determination of pSTAT Inhibition in Human Whole Blood

[0408] Whole blood samples from patients administered the anti-IL-27 antibody (anti-IL-27 Ab1) were evaluated in an assay to measure IL-27-mediated phosphorylation of STAT1. EDTA anticoagulated whole human blood, shipped overnight at room temperature, was used in this assay. 450 µL blood was distributed into each of three 15 mL conical tubes and warmed for 30 minutes at 37°C in a 37°C incubator. Anti-IL-27 antibody was diluted to 1 mg/mL in endotoxin-free PBS (Teknova #P0300) and 10 µL was added to one tube to serve as an antibody-spiked control. 10 µL PBS alone was added to the other two tubes for unstimulated and stimulated controls. Tubes were incubated for 30 minutes in a 37°C incubator.

[0409] A 10 µg vial of recombinant human IL-27 (R&D Systems# 2526-IL) was reconstituted to 100 µg/mL by adding 100µL PBS + 0.1 % BSA (made from 10% BSA Sigma #A1595). A working stock of the recombinant hIL-27 (rhIL-27) was prepared by dilution to 2µg/mL in endotoxin free PBS. After the 30-minute incubation, 50 µL of 2 µg/mL rhIL-27 was

added to anti-IL-27 antibody-spiked and stimulated tubes. 50 μ L PBS was added to unstimulated tube. The tubes were mixed and incubated for 30 minutes at 37°C.

After the 30-minute incubation, cells were fixed. Lyse/Fix reagent (BD #558049) was diluted 1:5 in sterile water (Hyclone #SH3052902) and warmed to 37°C in a water bath. 5 mL diluted Lyse/Fix reagent was added to each tube and the tubes were mixed well by inversion. The tubes were incubated for 15 min at 37°C. After the 15-minute incubation, the tubes were centrifuged for 5 minutes at 1500 RPM at room temperature and supernatant was discarded by decanting. 5 mL of endotoxin-free PBS was added per tube and samples were mixed by pipetting up and down. The tubes were centrifuged for 5 minutes at 1500 RPM at room temperature and supernatant was discarded by careful aspiration.

[0410] The cell pellets were loosened by flicking the tube and then resuspended in 500 μ L Perm III (stored at -20°C) (BD #558050) with pipetting. The tubes were incubated overnight at -20°C. After the incubation, 1 mL Stain Buffer with BSA (BD #554657) was added and the tubes were centrifuged at 1500 RPM for 5 minutes at room temperature. The supernatant was discarded by careful aspiration and the cells were resuspended in 100 μ L staining cocktail prepared in Stain Buffer with BSA as described in Table 7 below:

Table 7

BD Catalog#	Antibody	Color	Dilution
561811	CD3	FITC	1:20
562069	pSTAT1 Y701	PE	1:50

[0411] The tubes were incubated for 1 hour at room temperature in the dark. After the 1 hour incubation, 200 μ L Stain Buffer with BSA was added to each tube and samples were centrifuged at 1500 RPM for 5 minutes at room temperature. The supernatant was discarded from the plate by decanting and the cells were resuspended in 300 μ L Stain Buffer with BSA for analysis by flow cytometry.

[0412] Administration of 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg anti-IL-27 antibody resulted in at least 90% pSTAT1 signaling inhibition (FIGs. 13A-13D). This effect was most pronounced in subjects administered the 3 mg/kg dose of the anti-IL-27 antibody (FIG. 13D). Repeated administration of the anti-IL-27 antibody once every four weeks showed repeated decreases in pSTAT signaling (FIGs. 13B-13D).

Example 6: IL-27 Signaling Drives a Type 1 Interferon-like Gene Expression Program of Immunoregulatory Pathways Associated with Cancer Progression

[0413] Gene expression changes induced by IL-27 were examined in activated human CD4⁺ T cells, human PBMCs, and the IL-27RA-expressing lung cancer cell line NCI-H2228 by microarray or single cell RNA-sequencing. The resulting IL-27 signature genes were interrogated by gene enrichment analysis, including single cell RNA-seq analysis of the tumor microenvironment, from patients with NSCLC.

[0414] IL-27 induced a robust gene expression program in human immune cells that included several inhibitory receptors and canonical interferon regulated genes such as guanylate-binding proteins (GBPs) and interferon regulatory factors (IRFs). Gene set enrichment analysis (GSEA) and interferon signature analysis showed a striking overlap with those genes regulated by interferon-beta, a cytokine known to drive immune suppression associated with chronic viral infection that is used therapeutically for controlling inflammation associated with the autoimmune disease multiple sclerosis. Moreover, interferon regulated pathways have recently emerged as a mechanism of resistance to immune checkpoint blockade in cancer. Exploration of the IL-27 gene signature in published datasets showed enrichment in macrophage populations associated with progressive disease in patients with NSCLC. While many of the properties of IL-27-mediated immune regulation have focused on hematopoietic cells, IL-27RA is also expressed on tumor cells from NSCLC patients with progressive disease as well as lung cancer cell lines in which IL-27 can upregulate PD-L1, IDO1 and other canonical interferon regulated genes.

[0415] These studies elucidate the transcriptional networks that are engaged after IL-27 signaling in immune and cancer cells and highlight the parallels with interferon-associated immune regulation. Blockade of IL-27 provides a novel therapeutic strategy to alleviate a gene transcriptional program implicated in immune suppression and checkpoint resistance.

Example 7: Anti-IL-27 Ab1 Chemokine/Cytokine Multiplex Assays

[0416] Blood serum samples were collected from patients enrolled on the anti-IL-27 Ab1 clinical trial (*see* Example 2) at the following scheduled visits and timepoints: C1D1 pre-dose and 6 hours post-dose; C1D8; C2D1 pre-dose and 6 hours post-dose; and pre-dose for C3D1 and every subsequent treatment cycle. Serum protein expression was measured based on electrochemiluminescence (ECL) detection assays using commercially available multiplex chemokine and cytokine kits from Meso Scale Diagnostics (MSD; Rockville, MD, USA) across the following 4 panels: V-PLEX Plus Chemokine Panel 1 (human) Kit, V-PLEX Plus

Proinflammatory Panel 1 (human Kit), V-PLEX Plus Cytokine Panel 1 (human) Kit, and V-PLEX PLUS TH17 Panel 1 (human) Kit.

[0417] Individual circulating chemokine and cytokine measurements relative to fold-change over baseline levels (i.e., C1D1 pre-dose sample) were examined for any correlative relationships with clinical response data to anti-IL-27 Ab1 monotherapy. From this analysis, an increased fold-change over baseline was observed in Eotaxin-1 (CCL11) levels at the C1D1 6-hour post-dose timepoint in a patient (902-002) that had experienced a confirmed partial response (PR) to anti-IL-27 Ab1 monotherapy when compared to the fold changes seen in other patients that had been clinically classified as having either progressive disease (PD) or stable disease (SD) (FIG. 14A). Further longitudinal analysis through cycle 3 demonstrated a sustained elevated fold change over baseline level of Eotaxin-1 (CCL11) in this patient with PR when compared with the other patients with PD and SD (FIG. 14B).

[0418] Circulating levels of IL-27 relative to fold-change over baseline levels (i.e., C1D1 pre-dose sample) were examined in patients from each SRF388 monotherapy dose cohort (0.003 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg). IL-27 fold-change over baseline levels trend upward for most patients but does not appear to be a dose-dependent phenomenon (FIG. 15). These observations have been described for other therapeutic antibodies against cytokines (Yang J.C. et al. 2003; NEJM; Bocci G. et al. 2004; Cancer Research) including bevacizumab and its effects on circulating levels of VEGF and attributed to decreased receptor-mediated clearance.

[0419] Circulating levels of IFN γ relative to fold-change over baseline levels (i.e., C1D1 pre-dose sample) were examined in patients from the anti-IL-27 Ab1 monotherapy patients. IFN γ fold-change levels over baseline appeared to increase in a large proportion of patients in the 10 mg/kg monotherapy cohort patients consistent with anti-IL-27 Ab1 mechanism of action (FIG. 16).

[0420] Additional clinical correlative analyses demonstrated further potential relationships with several other chemokines and cytokines and response to anti-IL-27 Ab1 monotherapy, including TARC (CCL17; FIG. 17A), VEGF-A (FIG. 17B), IL-7 (FIG. 17C), IL-8 (FIG. 17D), MCP-1 (FIG. 17E), and MCP-4 (FIG. 17F). Similar to Eotaxin-1 (CCL11), we observed a fold change over baseline at the C1D1 6-hour post-dose in this set of proteins that was consistently elevated in the patient with PR when compared to the majority of patients in the PD and SD RECISTv1.1 response categories. Moreover, we noted that one of the patients with SD (901-008) also exhibited similar elevated fold change over baseline levels in this set of 6 proteins when

compared to the remaining PD and SD patients. Although this patient did not meet RECIST response criteria to be classified as a PR, this patient did experience demonstrable tumor shrinkage in response to anti-IL-27 Ab1 monotherapy (FIG. 17G). Longitudinal analyses of these chemokines and cytokines in these two patients through cycle 3 demonstrated that these fold-change elevations over baseline appeared to be relatively sustained, albeit to varying degrees over time (FIGs. 18A-18B).

Example 8: Analysis of Immunoregulatory Impact of IL-27 Signaling

[0421] IL-27 is a heterodimeric immunoregulatory cytokine that consists of 2 subunits: p28 and Epstein-Barr virus-induced gene 3 (EBI3). IL-27 signals through a heterodimeric receptor composed of glycoprotein 130 (gp130) and the IL-27 receptor subunit alpha, IL-27RA (WSX-1), which activates the JAK-STAT pathway to limit the duration and intensity of T cell-mediated immunity. IL-27 signaling through the JAK-STAT pathway results in altered immunoregulatory receptor expression and decreased proinflammatory cytokine secretion. The present example characterizes the immunoregulatory impact of IL-27 signaling by gene expression profiling.

[0422] To identify genes regulated by IL-27 signaling, PBMCs were isolated from healthy donors and stimulated in vitro for 3 days with anti-CD3 antibody (0.25 µg/mL, clone UCHT1) in the presence or absence of recombinant human IL-27 (100 ng/ml), recombinant human EBI3 (100 ng/ml), or recombinant human IL-25 (100 ng/ml) in 96-well plates. After this culture period, CD4⁺ CD8⁻ T cells were isolated by fluorescence activated cell sorting followed by RNA purification and processing for hybridization to HuGene 1.0ST arrays. Raw microarray data were normalized and differential gene expression was determined by comparing cytokine treatment to control conditions in two individual donors (FIG. 19). Genes that showed increased expression after IL-27 treatment were used for gene set enrichment analysis (GSEA). Several gene signatures from GSEA (*e.g.*, hallmark IFNα signature) were then used to highlight the overlap in gene expression with the IL-27 signature.

[0423] CD4⁺ T cells were isolated from activated PBMC cultures after treatment with rhIL-27, rhEBI3, or rhIL-35 cytokines at 100 ng/ml. The IL-27 heterodimer (FIG. 20A), but neither EBI3 alone (FIG. 20B) nor IL-35 (FIG. 20C), elicits robust gene expression changes in human CD4⁺ T cells from PBMCs.

[0424] Gene set enrichment analysis of the IL-27 gene signature from CD4⁺ T cells shows an enrichment of mRNA signatures associated with interferon signaling (FIGs. 21A-21B).

Hallmark IFN α signature genes (Table 8) are highlighted in FIG. 21B. Note that IL-27 does not increase the expression of interferon- γ (IFN γ) transcript or protein in these conditions.

Table 8: Enrichment of interferon-regulated genes.

Gene Set Name	# Genes In Gene Set (K)	# Genes in Overlap (k)	k/K	p-value	FDR q-value
GSE13485_CTRL_VS_DAY7_YF17D_VACCINE_PBMC_DN	200	46	0.23	1.00E-82	1.04E-78
HALLMARK_INTERFERON_GAMMA_RESPONSE	200	44	0.22	5.61E-78	1.94E-74
HALLMARK_INTERFERON_ALPHA_RESPONSE	97	37	0.3814	1.82E-75	3.76E-72
GSE13485_PRE_VS_POST_YF17D_VACCINATION_PBMC_DN	200	39	0.195	1.85E-66	2.73E-63
GSE10325_CD4_TCELL_VS_LUPUS_CD4_TCELL_DN	200	37	0.185	5.38E-62	5.06E-59
HECKER_IFNB1_TARGETS	95	26	0.2737	3.09E-48	1.78E-45
BROWNE_INTERFERON_RESPONSIVE_GENES	68	24	0.3529	1.16E-47	6.33E-45
MOSERLE_IFNA_RESPONSE	31	20	0.6452	7.69E-47	3.98E-44

[0425] Single-cell RNA-sequencing analysis of human PBMCs identifies several immune cell populations exhibiting upregulation of interferon-stimulated genes (ISGs) after IL-27 stimulation (FIG. 22A). PBMCs were isolated from healthy donors then pooled and stimulated *in vitro* for 16 hours with anti-CD3 antibody (0.25 μ g/mL, clone UCHT1) in the presence or absence of recombinant human IL-27 (100 ng/ml). Cells were then processed (10x Genomics), RNA was sequenced (Illumina, San Diego, CA), data was processed (Seurat), and subsequently visualized and analyzed (BBrowser, BioTuring, San Diego, CA). Differential gene expression was determined using the Venice algorithm within the differential expression module. Gene expression changes by IL-27 were determined in total PBMCs and also in defined cell subsets including NK cells, CD4⁺ T cells, B cells, monocytes, CD8⁺ T cells, and Treg cells. IL-27-mediated gene expression changes were identified in the total PBMC population and included many interferon-stimulated genes (FIG. 22B). Further, IL-27 upregulates ISGs in NK cells (FIG. 22C), monocytes (FIG. 22F), CD4⁺ T cells (FIG. 22D), CD8⁺ T cells (FIG. 22G), B cells (FIG. 22E), and Treg cells (FIG. 22H).

[0426] Interferon gene expression signatures from PBMCs stimulated with IFN α 2, IFN β 1, and IFN γ (Wadell et al. 2018) were used to compare to the IL-27 gene signature identified from the scRNA-seq PBMC data set described in example 2. The IL-27 signature is enriched for IFN β stimulated genes. Values in Tables 9A-9F represent the differential gene expression from total PBMCs in IL-27 stimulated vs control conditions.

Table 9A: Common IFN α 2, INF β 1, and IFN γ Genes

Gene Symbol	log2 (Fold-Change)	-log10 (FDR)
GBP1	0.761	254.34757
GBP2	0.756	239.99398
CD38	0.506	189.86262
STAT1	0.513	170.09093
PSMB9	0.452	143.37069
RGS1	0.456	122.82467
TNFSF10	0.53	103.62998
UBE2L6	0.451	98.20054
TAP1	0.451	95.66504
SOCS1	0.474	94.35918
AIM2	0.344	78.81771
OAS1	0.228	67.60822
SP100	0.317	64.70467
FAS	0.196	50.84631
IFI44	0.18	48.28002
STAT2	0.209	43.92146
LAP3	0.275	40.79373
CXCL10	0.564	32.29484
CXCL9	0.743	26.66933
APOL3	0.207	23.87797
OAS3	0.115	22.34989
IDO1	0.646	19.79276
JAK2	0.112	16.70246
SERPINC1	0.155	13.51017
GCH1	0.1	12.66507

Table 9B: INF β 1 Unique Genes

Gene Symbol	log2 (Fold-Change)	-log10 (FDR)
PSMB8	0.33	39.0291
TAPBP	0.182	32.91509
IRF9	0.177	32.74853
NCF1	0.283	25.87378
USP15	0.175	23.59477
IRF4	0.193	21.39749
NBN	0.097	9.49568
CFLAR	0.102	9.45277
PDE4B	0.099	8.77495

Table 9C: IFN γ Unique Genes

Gene Symbol	log2 (Fold-Change)	-log10 (FDR)
XRN1	0.462	135.99373
IRF8	0.306	28.03915

Table 9D: IFN α 2 Unique Genes

Gene Symbol	log2 (Fold-Change)	-log10 (FDR)
IFI44L	0.567	222.48149

Table 9E: Common IFN β 1 and IFN γ Genes

Gene Symbol	log2 (Fold-Change)	-log10 (FDR)
IRF1	0.686	254.34757
TBX21	0.36	123.32113
RALB	0.09	17.76183
FCGR1A	0.162	14.95528

Table 9F: Common IFN α 2 and INF β 1 Genes

Gene Symbol	log2 (Fold-Change)	-log10 (FDR)
ISG20	1.029	254.34757
ISG15	0.849	254.34757
IFI35	0.546	181.42095
MX1	0.606	171.79254
IFI6	0.585	138.02846
TRIM22	0.455	133.97689
BST2	0.516	133.83498
XAF1	0.487	131.1769
IFI16	0.488	110.10541
LY6E	0.437	84.82341
CD69	0.5	73.174
OAS2	0.267	67.99451
SAT1	0.319	62.81838
IRF7	0.255	60.96008
EIF2AK2	0.288	55.70977
NUB1	0.283	55.62562
MX2	0.179	45.90871
SP110	0.181	42.14114
PLSCR1	0.198	39.5995
IFITM3	0.304	37.3479
NMI	0.237	37.25722
LGALS3BP	0.146	33.17046
IFITM1	0.125	31.44208
ADAR	0.197	25.79626
KLF6	0.183	25.47153
DYNLT1	0.08	24.62869
LAG3	0.294	24.13571
MCL1	0.13	23.40519
RBCK1	0.202	23.25179
LAMP3	0.06	21.92573
TRIM21	0.123	20.70122
IRF2	0.155	19.3035
IFITM2	0.244	14.66585
GUK1	0.162	12.74087
PML	0.093	10.64515
IFIT5	0.067	9.6502

[0427] PBMCs from healthy donors were stimulated in vitro with anti-CD3 antibody (0.25 μ g/mL) for 4 days in the absence (control) or presence of anti-PD-1 antibody (Pembrolizumab, 1 μ g/mL) and various cytokines. Supernatants were then collected and tested for the presence of IL-

17A (FIG. 23A) or IFN- γ (FIG. 23B) by MSD. Both IL-27 and IFN β inhibited cytokine production after anti-PD-1 blockade.

[0428] NSCLC patients with progressive disease show an enrichment of a macrophage population that expresses several ISGs and IL-27. Graphical abstract from Maynard et al. (NCBI BioProject #PRJNA591860, which is incorporated by reference herein in its entirety) highlights the macrophage population (MF2) with high expression of IDO1 and GBP5 shows increased prevalence in patients with progressive disease (PD) compared to those with residual disease (RD) and treatment naïve (TN) patients. Single cell RNA-seq analysis of IL-27 transcript from Maynard et al. shows prominent expression in macrophage compared to other cell types in the NSCLC tumor microenvironment. Several genes from the MF2 signature (green highlights, Maynard et al. Table S4) are enriched in IL-27 positive macrophages compared to IL-27 negative macrophages. Macrophages from patients with progressive disease have more IL-27 transcript expression compared to those with RD or TN patients. IL-27 transcript is increased in macrophages from primary tumor and metastatic sites compared to macrophages from normal lung tissue. IL-27 transcript in macrophages is increased in patients with stage IV disease. The MF2 signature was also highlighted on an independent gene expression profile (Swaminathan et al 2013, GSE44955) comparing IL-27 cultured macrophages vs control condition. This data shows that most MF2 signature genes can be upregulated in macrophages by IL-27.

[0429] Single-cell RNA-seq analysis shows IL-27 is expressed in macrophages of the NSCLC tumor microenvironment (TME) and is increased in a macrophage subpopulation (MF2) associated with progressive disease (FIG. 24A). Further, the MF2 signature is highly enriched in IL27⁺ macrophages as compared to IL27⁻ macrophages (FIG. 24B). IL-27 is increased in macrophages from patients with progressive disease (FIG. 24C); in macrophages from metastatic and primary tumors compared to normal tissue (FIG. 24D); and in macrophages from patients with Stage IV disease (FIG. 24D). In addition, the MF2 signature is upregulated in macrophages by IL27 (FIG. 24F, gray data points).

[0430] IL-27-positive macrophages were detected in the tumor microenvironment (TME) of lung adenocarcinoma (FIG. 24G; AdenoCa) and lung squamous cell carcinoma (FIG. 24H; SCC) by immunohistochemistry (IHC). IHC on formalin-fixed, paraffin-embedded (FFPE) tissue samples of NSCLC was performed by staining tissue microarrays (TMAs) from US Biomax (Derwood, MD) with an affinity purified goat polyclonal antibody against recombinant human IL-27 (p28 and EBI3) from R&D Systems at 10 microg/mL. Slides were deparaffinized, dewaxed,

and rehydrated and stained in a Leica Bond RX automated stainer (Leica Biosystems, Wetzlar, Germany). Antigen retrieval was performed with Bond Epitope Retrieval Solution 2 (EDTA, pH 9) at 100°C for 10 min. Slides were manually dehydrated and coverslipped and digitally scanned with an Aperio Versa 2000 scanner

[0431] Single cell RNA-seq analysis of IL27RA transcript from Maynard et al. (NCBI BioProject #PRJNA591860) shows expression in several cell types in the NSCLC tumor microenvironment including some tumor cells (FIG. 25A). IL27RA expression was observed across various cell types within the NSCLC tumor microenvironment, including higher expression in dendritic cells, T cells, and tumor cells (FIG. 25B). For tumor tissue, the expression of IL27RA was higher in patients with progressive disease compared to those with residual disease or patients that are treatment naïve (FIG. 25C).

[0432] Data from the Cancer Cell Line Encyclopedia (CCLE) shows IL27RA transcript expression in lung cancer cell lines, including NCI-H2228 (FIG. 26A). Culturing NCI-H2228 cells *in vitro* with various concentrations of recombinant human IL-27 leads to the dose dependent increase in STAT1 phosphorylation (downstream of IL-27RA signaling) and PD-L1 expression by flow cytometry (FIGs. 26B-26C). NCI-H2228 cells were also cultured *in vitro* in the presence or absence of recombinant human IL-27 (100 ng/ml) for 48hrs followed by RNA purification and processing for hybridization to HuGene 1.0ST arrays. Raw microarray data were normalized and differential gene expression was determined by comparing IL-27 treatment (y-axis) to control conditions (x-axis) (FIG. 26D). IL-27 upregulated several ISGs including IDO1 and GBP5.

[0433] These data show that IL-27 induced robust gene expression in human immune cells that included several inhibitory receptors and canonical interferon-regulated genes such as guanylate-binding proteins and interferon regulatory factors. Gene Set Enrichment Analysis and interferon signature analysis demonstrated a striking overlap with those genes regulated by interferon-beta, a cytokine known to drive immune suppression associated with chronic viral infection. Interferon-beta is used therapeutically for controlling inflammation associated with the autoimmune disease multiple sclerosis.

[0434] Both IL-27 and IFN β can counteract some of the immune stimulatory properties of PD-1 blockade. Interferon-regulated pathways have recently emerged as a mechanism of resistance to immune checkpoint blockade in cancer. Exploration of the IL-27 gene signature in published datasets showed enrichment in macrophage populations associated with progressive disease in patients with NSCLC. While many of the properties of IL-27-mediated immune regulation have

focused on hematopoietic cells, there is demonstrated IL-27RA expression on tumor cells from NSCLC patients with progressive disease. IL-27RA is also expressed on lung cancer cell lines in which IL-27 can upregulate PD-L1, *IDO1*, and other canonical interferon-regulated genes.

[0435] These studies elucidate the transcriptional networks that are engaged after IL-27 signaling in immune and cancer cells and highlight the parallels with interferon-associated immune regulation.

What is claimed is:

1. A method of stimulating an immune response in a subject, the method comprising administering to the subject an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof specifically binds to an epitope comprising one or more amino acids of (i) amino acids 37 to 56 corresponding to SEQ ID NO: 2 (IL-27p28), (ii) amino acids 142 to 164 corresponding to SEQ ID NO: 2 (IL-27p28), or (iii) both (i) and (ii); wherein the antibody or antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg.
2. A method of treating a cancer in a subject in need thereof comprising administering to the subject an antibody that antagonizes human IL-27, or an antigen binding portion thereof, wherein the antibody or antigen binding portion thereof specifically binds to an epitope comprising one or more amino acids of (i) amino acids 37 to 56 corresponding to SEQ ID NO: 2 (IL-27p28), (ii) amino acids 142 to 164 corresponding to SEQ ID NO: 2 (IL-27p28), or (iii) both (i) and (ii); wherein the antibody or antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg.
3. The method of claim 1 or 2, wherein the antibody or antigen binding portion thereof is administered at a dose of at least about 0.003 mg/kg, at least about 0.006 mg/kg, at least about 0.009 mg/kg, at least about 0.03 mg/kg, at least about 0.06 mg/kg, at least about 0.09 mg/kg, at least about 0.3 mg/kg, at least about 0.6 mg/kg, at least about 0.9 mg/kg, at least about 1.0 mg/kg, at least about 2 mg/kg, at least about 3 mg/kg, at least about 4 mg/kg, at least about 5 mg/kg, at least about 6 mg/kg, at least about 7 mg/kg, at least about 8 mg/kg, at least about 9 mg/kg, at least about 10 mg/kg, at least about 11 mg/kg, at least about 12 mg/kg, at least about 13 mg/kg, at least about 14 mg/kg, at least about 15 mg/kg, at least about 16 mg/kg, at least about 17 mg/kg, at least about 18 mg/kg, at least about 19 mg/kg, or at least about 20 mg/kg.
4. The method of any one of claims 1 to 3, wherein the antibody or antigen binding portion thereof is administered once about every week, once about every two weeks, once about every three weeks, once about every four weeks, once about every 6 weeks, once about every 8 weeks, or once about every 12 weeks.

5. The method of any one of claims 1 to 4, wherein the antibody or antigen binding portion thereof is administered once about every four weeks.
6. The method of any one of claims 1 to 5, wherein the antibody or antigen binding portion thereof is administered at a dose of about 0.3 mg/kg once about every four weeks.
7. The method of any one of claims 1 to 5, wherein the antibody or antigen binding portion thereof is administered at a dose of about 1 mg/kg once about every four weeks.
8. The method of any one of claims 1 to 5, wherein the antibody or antigen binding portion thereof is administered at a dose of about 3 mg/kg once about every four weeks.
9. The method of any one of claims 1 to 5, wherein the antibody or antigen binding portion thereof is administered at a dose of about 6 mg/kg once about every four weeks.
10. The method of any one of claims 1 to 5, wherein the antibody or antigen binding portion thereof is administered at a dose of about 10 mg/kg once about every four weeks.
11. The method of any one of claims 1 to 5, wherein the antibody or antigen binding portion thereof is administered at a dose of about 13 mg/kg once about every four weeks.
12. The method of any one of claims 1 to 5, wherein the antibody or antigen binding portion thereof is administered at a dose of about 16 mg/kg once about every four weeks.
13. The method of any one of claims 1 to 5, wherein the antibody or antigen binding portion thereof is administered at a dose of about 20 mg/kg once about every four weeks.
14. The method of any one of claims 1 to 4, wherein the antibody or antigen binding portion thereof is administered once about every three weeks.
15. The method of any one of claims 1 to 4 and 14, wherein the antibody or antigen binding portion thereof is administered at a dose of about 0.3 mg/kg once about every three weeks.
16. The method of any one of claims 1 to 4 and 14, wherein the antibody or antigen binding portion thereof is administered at a dose of about 1 mg/kg once about every three weeks.
17. The method of any one of claims 1 to 4 and 14, wherein the antibody or antigen binding portion thereof is administered at a dose of about 3 mg/kg once about every three weeks.

18. The method of any one of claims 1 to 4 and 14, wherein the antibody or antigen binding portion thereof is administered at a dose of about 6 mg/kg once about every three weeks.
19. The method of any one of claims 1 to 4 and 14, wherein the antibody or antigen binding portion thereof is administered at a dose of about 10 mg/kg once about every three weeks.
20. The method of any one of claims 1 to 4 and 14, wherein the antibody or antigen binding portion thereof is administered at a dose of about 13 mg/kg once about every three weeks.
21. The method of any one of claims 1 to 4 and 14, wherein the antibody or antigen binding portion thereof is administered at a dose of about 16 mg/kg once about every three weeks.
22. The method of any one of claims 1 to 4 and 14, wherein the antibody or antigen binding portion thereof is administered at a dose of about 20 mg/kg once about every three weeks.
23. The method of any one of claims 1 to 22, wherein the antibody or antigen binding portion thereof inhibits or reduces IL-27-dependent STAT1 and/or STAT3 phosphorylation in a cell in the subject.
24. The method of any one of claims 1 to 23, wherein the antibody or antigen binding portion thereof inhibits or reduces inhibition of CD161 expression in a cell in the subject.
25. The method of any one of claims 1 to 24, wherein the antibody or antigen binding portion thereof inhibits or reduces PD-L1 expression in a cell in the subject.
26. The method of any one of claims 1 to 25, wherein the antibody or antigen binding portion thereof induces or enhances PD-1 mediated secretion of one or more cytokines from a cell in the subject.
27. The method of any one of claims 1 to 26, wherein the antibody or antigen binding portion thereof alters the expression of TIM-3 in a cell in the subject.
28. The method of any one of claims 1 to 27, wherein the cell is a tumor cell or an immune cell.
29. The method of any one of claims 1 to 28, wherein the epitope comprises one or more amino acids of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143,

Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, or Glu164 of SEQ ID NO: 2 (IL-27p28).

30. The method of any one of claims 1 to 29, wherein the epitope comprises Asp146, Arg149, and/or Phe153 of SEQ ID NO: 2 (IL-27p28).
31. The method of any one of claims 1 to 30, wherein the epitope further comprises His150 and/or Leu156 of SEQ ID NO: 2 (IL-27p28).
32. The method of any one of claims 1 to 31, wherein the epitope further comprises Gln37, Leu38, Glu42, Leu142, and/or Glu164 of SEQ ID NO: 2 (IL-27p28).
33. The method of any one of claims 1 to 32, wherein the epitope further comprises Glu46, Val49, Ser50, and/or Leu162 of SEQ ID NO: 2 (IL-27p28).
34. The method of any one of claims 1 to 33, wherein the epitope consists or consists essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu142, Asp146, Arg149, His150, Phe153, Leu156, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28).
35. The method of any one of claims 1 to 34, wherein the epitope further comprises one or more amino acids of Leu53, Lys56, Asp143, Leu147, Arg152, Ala157, Gly159, Phe160, or Asn161 of SEQ ID NO: 2 (IL-27p28).
36. The method of any one of claims 1 to 35, wherein the epitope further comprises one or more amino acids of Leu53, Lys56, Asp143, Arg145, Leu147, Arg152, Ala157, Gly159, Phe160, Asn161, or Pro163 of SEQ ID NO: 2 (IL-27p28).
37. The method of any one of claims 1 to 36, wherein the epitope consists or consists essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, and Glu164 of SEQ ID NO: 2 (IL-27p28).
38. The method of any one of claims 1 to 37, wherein the epitope consists or consists essentially of Gln37, Leu38, Glu42, Glu46, Val49, Ser50, Leu53, Lys56, Leu142, Asp143, Arg145, Asp146, Leu147, Arg149, His150, Arg152, Phe153, Leu156, Ala157, Gly159, Phe160, Asn161, Leu162, Pro163, and Glu164, of SEQ ID NO: 2 (IL-27p28).

39. The method of any one of claims 1 to 38, wherein the antibody or the antigen binding portion thereof comprise heavy chain CDR1, heavy chain CDR2, heavy chain CDR3, light chain CDR1, light chain CDR2, and light chain CDR3, wherein (i) light chain CDR1 consists of N-XXXXXXLFSSNXXXYXX-C, light chain CDR3 consists of N-XXXASAXXX-C, heavy chain CDR2 consists of N-XXSSXSXYXXXXXXXXX-C, and heavy chain CDR3 consists of N-XXXXGRTSYTATXHNXXXXX-C, wherein X is any amino acids.
40. The method of any one of claims 1 to 39, wherein the antibody or the antigen binding portion thereof comprises a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 121 or 124.
41. The method of any one of claims 1 to 40, wherein the antibody or the antigen binding portion thereof comprises a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 120 or 123.
42. The method of any one of claims 1 to 41, wherein the antibody or the antigen binding portion thereof comprises a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 119 or 122.
43. The method of any one of claims 1 to 42, wherein the antibody or the antigen binding portion thereof comprises a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 129 or 132.
44. The method of any one of claims 1 to 43, wherein the antibody or the antigen binding portion thereof comprises a light chain CDR2 comprising the sequence set forth in SEQ ID NO: 128 or 131.
45. The method of any one of claims 1 to 44, wherein the antibody or the antigen binding portion thereof comprises a light chain CDR1 comprising the sequence set forth in SEQ ID NO: 127 or 130.
46. The method of any one of claims 1 to 45, wherein the antibody or the antigen binding portion thereof comprises:

- (a) a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, and a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121; or
 - (b) a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 123, and a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124.
47. The method of any one of claims 1 to 46, wherein the antibody or the antigen binding portion thereof comprises:
- (a) a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129; or
 - (b) a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132.
48. The method of any one of claims 1 to 47, wherein the antibody or the antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 119, a heavy chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 120, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 121, a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129.
49. The method of any one of claims 1 to 48, wherein the antibody or the antigen binding portion thereof comprises: a heavy chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 122, a heavy chain CDR2 comprising the amino acid sequence set

forth in SEQ ID NO: 123, a heavy chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124 a light chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a light chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131, and a light chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132.

50. The method of any one of claims 1 to 49, wherein the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 125.
51. The method of any one of claims 1 to 50, wherein the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125.
52. The method of any one of claims 1 to 51, wherein the antibody or the antigen binding portion thereof comprises a light chain variable region comprising an amino acid sequence that has at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 133.
53. The method of any one of claims 1 to 52, wherein the antibody or the antigen binding portion thereof comprises a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133.
54. The method of any one of claims 1 to 53, wherein the antibody or the antigen binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133.
55. The method of any one of claims 1 to 54, wherein the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 135.

56. The method of any one of claims 1 to 55, wherein the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 139.
57. The method of any one of claims 1 to 56, wherein the antibody or the antigen binding portion thereof comprises a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137.
58. The method of any one of claims 1 to 57, wherein the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 135 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137.
59. The method of any one of claims 1 to 58, wherein the antibody or the antigen binding portion thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 139 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 137.
60. The method of any one of claims 2 to 59, wherein the cancer is selected from lung cancer (e.g., non-small cell lung cancer), sarcoma, testicular cancer, ovarian cancer, pancreas cancer, breast cancer (e.g., triple-negative breast cancer), melanoma, head and neck cancer (e.g., squamous head and neck cancer), colorectal cancer, bladder cancer, endometrial cancer, prostate cancer, thyroid cancer, hepatocellular carcinoma (HCC), gastric cancer, brain cancer, lymphoma (e.g., DL-BCL), leukemia (e.g., AML), renal cancer (e.g., renal cell carcinoma (RCC), e.g., clear cell RCC and/or non-clear cell RCC), and any combination thereof.
61. The method of any one of claims 1 to 60, further comprising administering an additional therapeutic agent to the subject.
62. The method of claim 61, wherein the additional therapeutic agent is administered before the antibody or antigen-binding portion thereof, after the antibody or antigen-binding portion thereof, or concurrently with the antibody or antigen-binding portion thereof.

63. The method of claim 61 or 62, wherein the additional therapeutic agent comprises a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, a cellular immunotherapy, a biologic agent, or a combination thereof.
64. The method of any one of claims 61 to 63, wherein the additional therapeutic agent comprises a PD-1 antagonist, a PD-L1 inhibitor, a TIM-3 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, a CD112R inhibitor, a TAM inhibitor, a STING agonist, a 4-1BB agonist, a multityrosine kinase inhibitor (*e.g.*, a VEGFR inhibitor), an anti-VEGF blocking antibody, a CTLA-4 antagonist, a HIF2 antagonist, a TGFb antagonist, an mTOR inhibitor, an adenosine pathway inhibitor (*e.g.*, an anti-CD73 antibody, an anti-CD39 antibody, an anti-A2AR antibody, an anti-A2BR, or any combination thereof), an anti-CCR8 antibody, a cytokine-based regimen (*e.g.*, IL-2 or IFN- α), a PARP inhibitor, or a combination thereof.
65. The method of any one of claims 61 to 64, wherein the additional therapeutic agent comprises a PD-1 antagonist.
66. The method of claim 65, wherein the PD-1 antagonist is selected from the group consisting of: PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224.
67. The method of claim 66, wherein the PD-L1 inhibitor is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559.
68. The method of claim 67, wherein the additional therapeutic agent is selected from the group consisting of Sunitinib (SUTENT[®]), Cabozantinib (CABOMETYX[®]), Axitinib (INLYTA[®]), Lenvatinib (LENVIMA[®]), Everolimus (AFINITOR[®]), Bevacizumab (AVASTIN[®]), epacadostat, NKTR-214 (CD-122-biased agonist), Tivozanib (FOTIVDA[®]), abexinostat, Ipilimumab (YERVOY[®]), tremelimumab, Pazopanib (VOTRIENT[®]), Sorafenib (NEXAVAR[®]), Temsirolimus (TORISEL[®]), Ramucirumab (CYRAMZA[®]), niraparib, savolitinib, vorolanib (X-82), Regorafenib (STIVARGO[®]), Donafenib (multikinase inhibitor), Camrelizumab (SHR-1210), pexastimogene devacirepvec (JX-594), Ramucirumab (CYRAMZA[®]), apatinib (YN968D1), encapsulated doxorubicin (THERMODOX[®]), Tivantinib (ARQ197), ADI-PEG 20, binimetinib, apatinib

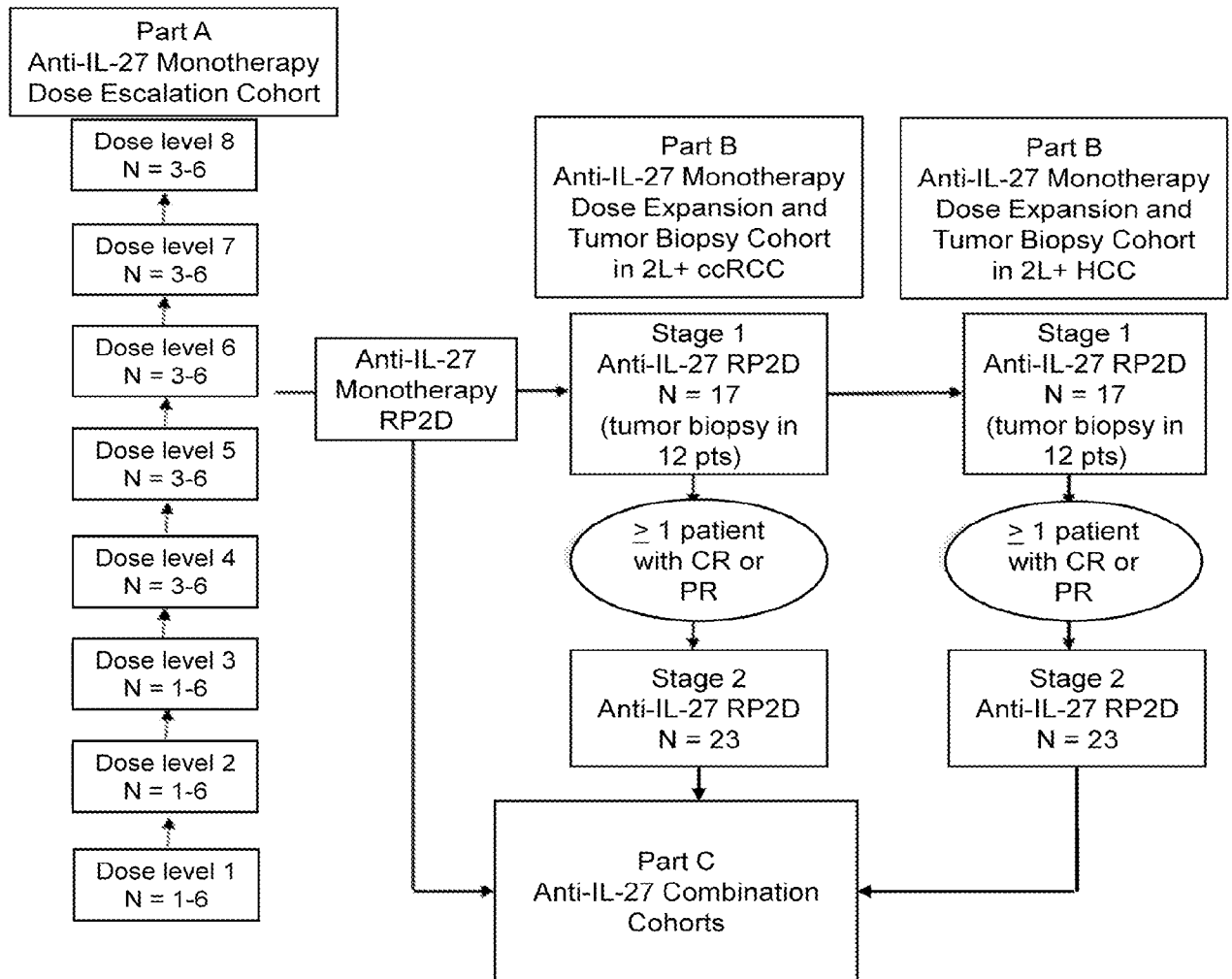
mesylate, nintedanib, lirilumab, Nivolumab (OPDIVO[®]), Pembrolizumab (KEYTRUDA[®]), Atezolizumab (TECENTRIQ[®]), Avelumab (BAVENCIO[®]), Durvalumab (IMFIMZI[®]), Cemiplimab-rwlc (LIBTAYO[®]), tislelizumab, and spartalizumab.

69. The method of claim 64, wherein the additional therapeutic agent is a TIM-3 inhibitor.
70. The method of claim 69, wherein the TIM-3 inhibitor is MGB453 or TSR-022.
71. The method of claim 64, wherein the additional therapeutic agent is a LAG-3 inhibitor.
72. The method of claim 71, wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, and TSR-033.
73. The method of claim 64, wherein the additional therapeutic agent is a TIGIT inhibitor.
74. The method of claim 64, wherein the additional therapeutic agent is a CD112R inhibitor.
75. The method of claim 64, wherein the additional therapeutic agent is a TAM (Axl, Mer, Tyro) inhibitor.
76. The method of claim 64, wherein the additional therapeutic agent is a 4-1BB agonist.
77. The method of claim 64, wherein the additional therapeutic agent is a Tyrosine Kinase Inhibitor (TKI).
78. The method of any one of claims 1 to 77, wherein following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of one or more biomarkers selected from the group consisting of EBI3, IL-27, TNF α , MIP-1 α (CCL3), IFN γ , IL-10, IL-6, and any combination thereof, wherein the increased expression of the one or more biomarkers is relative to the expression of the one or more biomarker prior to the administration.
79. The method of any one of claims 1 to 78, wherein following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of EBI3; wherein the increased expression EBI3 is relative to the expression EBI3 prior to the administration.

80. The method of any one of claims 1 to 79, wherein following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of one or more biomarkers selected from the group consisting of Eotaxin-1 (CCL11), TARC (CCL17), VEGF-A, IL-7, IL-8, MCP-1, MCP-4, and any combination thereof; wherein the increased expression of the one or more biomarkers is relative to the expression of the one or more biomarker prior to the administration.
81. The method of any one of claims 1 to 79, wherein following administration antibody or antigen binding portion thereof, the subject exhibits increased expression of Eotaxin-1 (CCL11), wherein the increased expression of Eotaxin-1 (CCL11) is relative to the expression of Eotaxin-1 (CCL11) prior to the administration.
82. The method of any one of claims 1 to 81, wherein following administration antibody or antigen binding portion thereof, the subject exhibits an increased circulating level of IFN γ , relative to the circulating level of IFN γ prior to the administration.

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FIG. 1A



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FIG. 1B

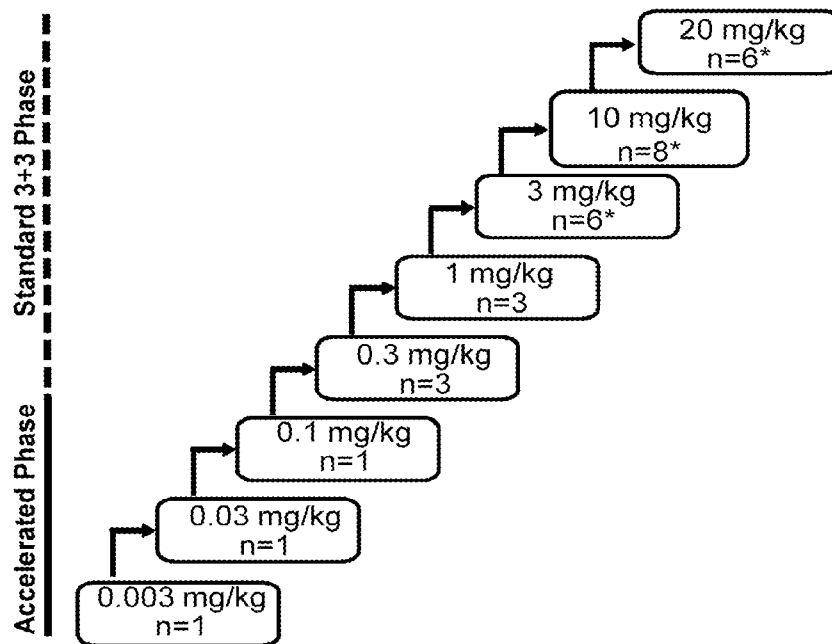
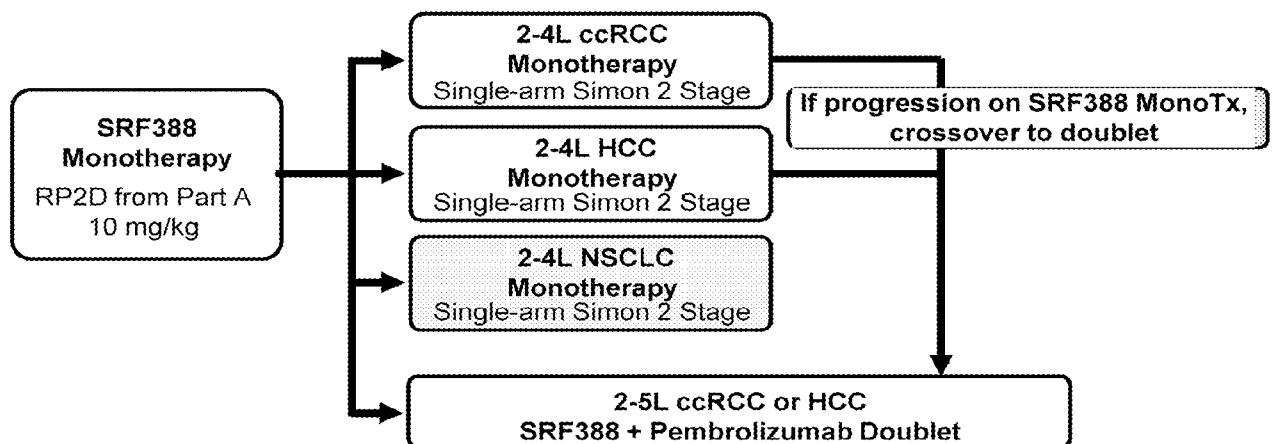
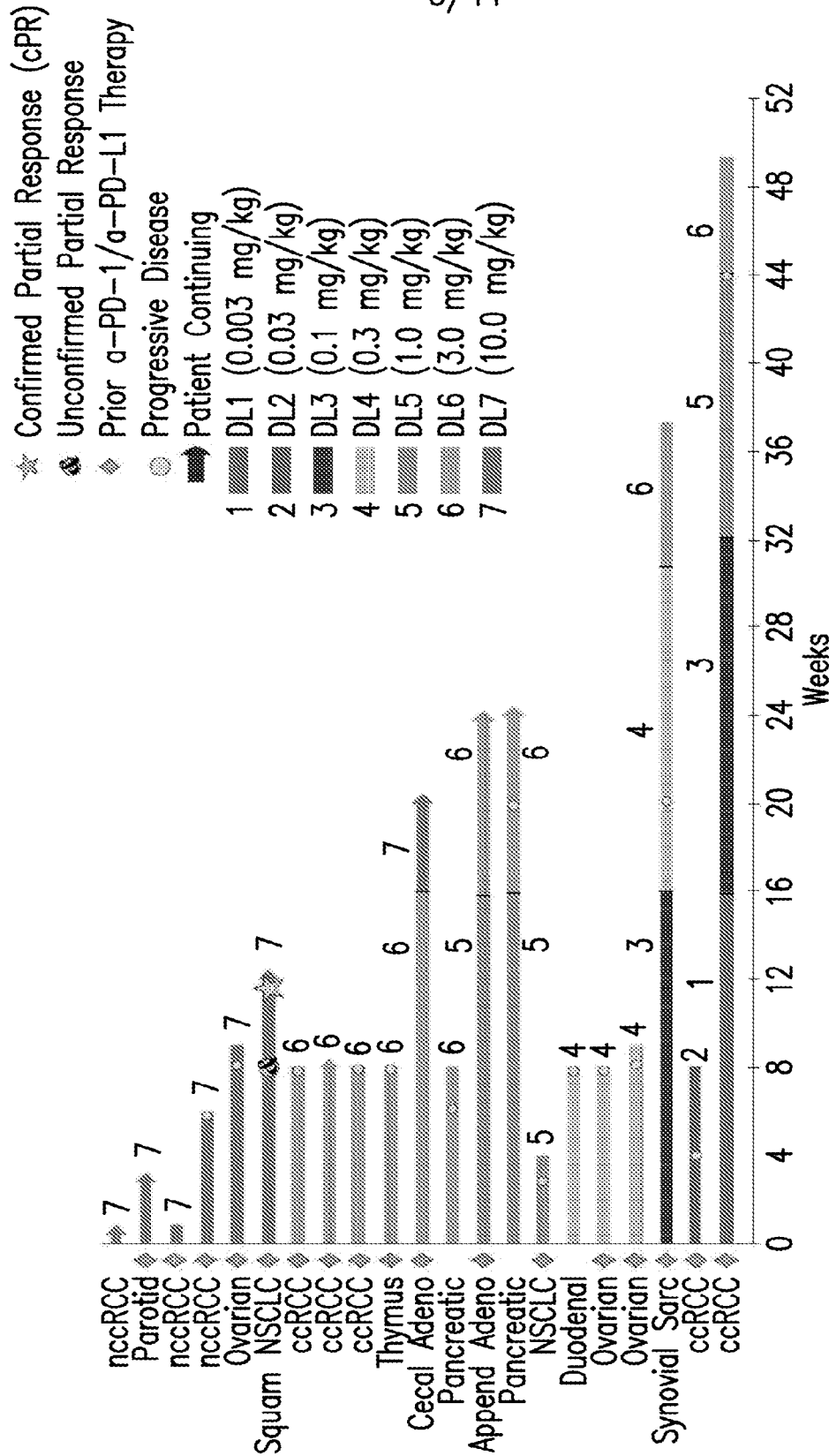


FIG. 1C



* No DLTs, additional slots per cohort to increase experience at this dose

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*cPR scan confirmation data received after 16 APR 2021 data snapshot
 nccRCC, non-clear cell renal carcinoma; NSCLC, non-small cell lung cancer

FIG.2

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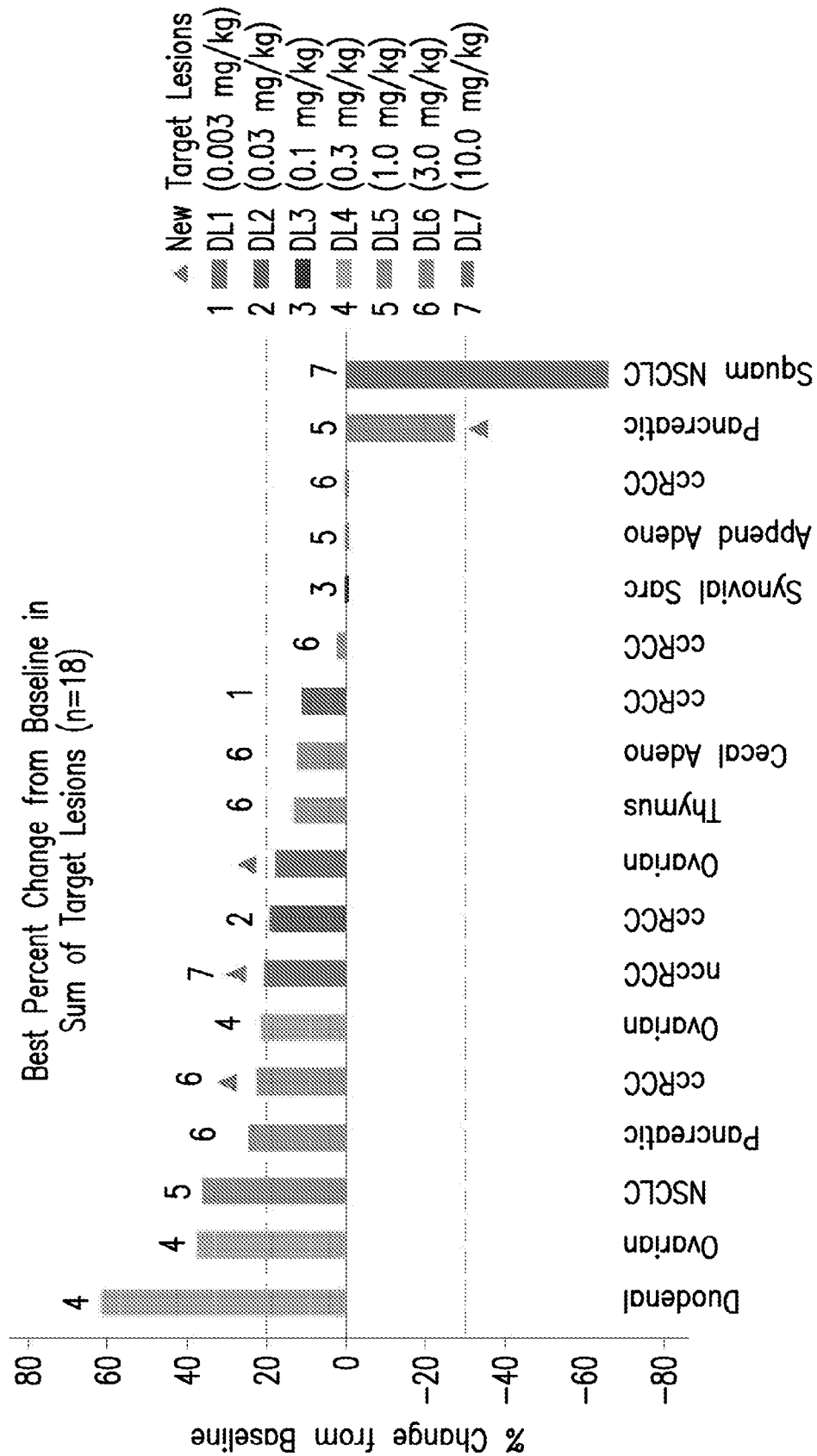
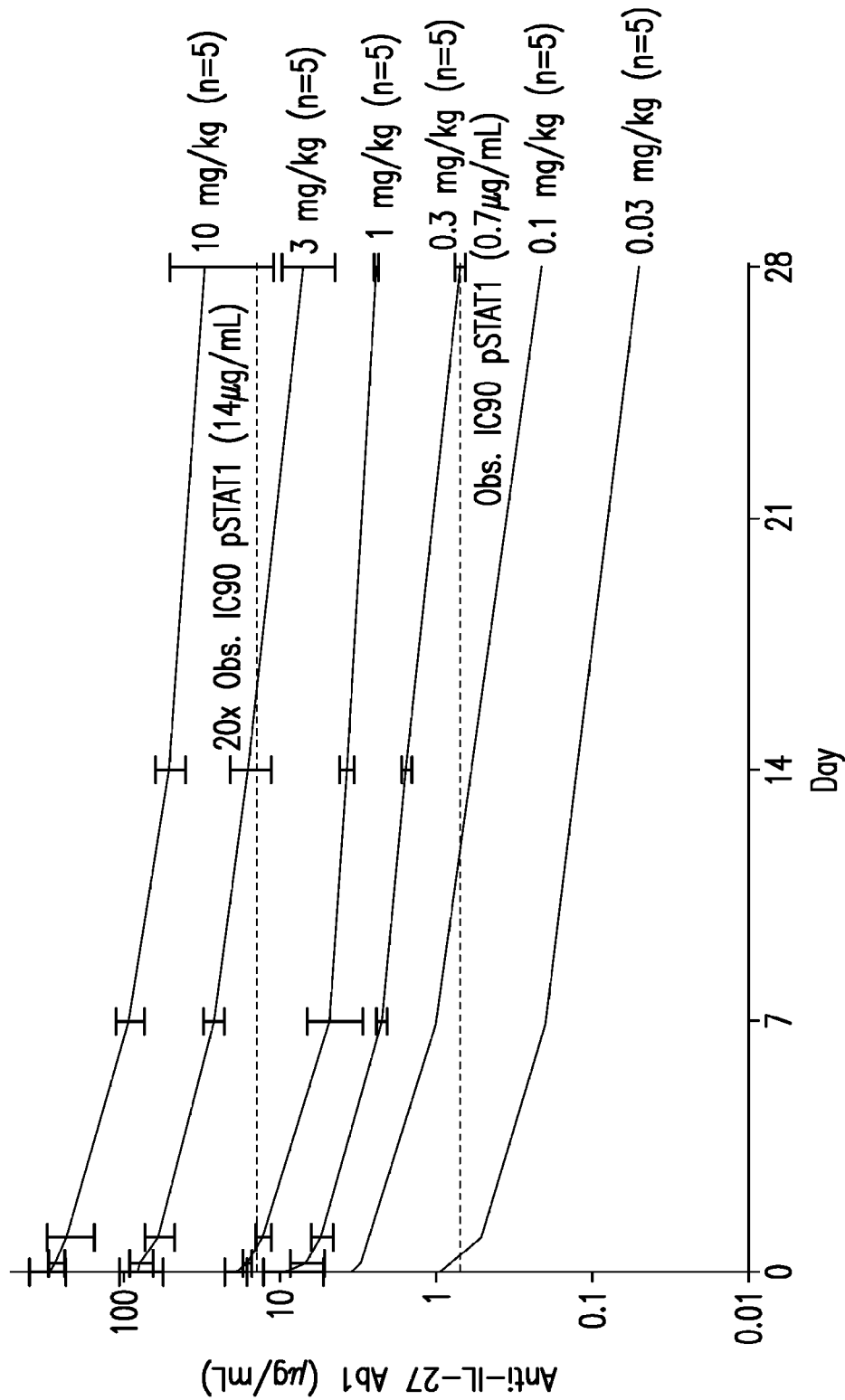


FIG.3

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Note: DL1, 0.003 mg/kg was below level of quantification during cycle 1

FIG.4

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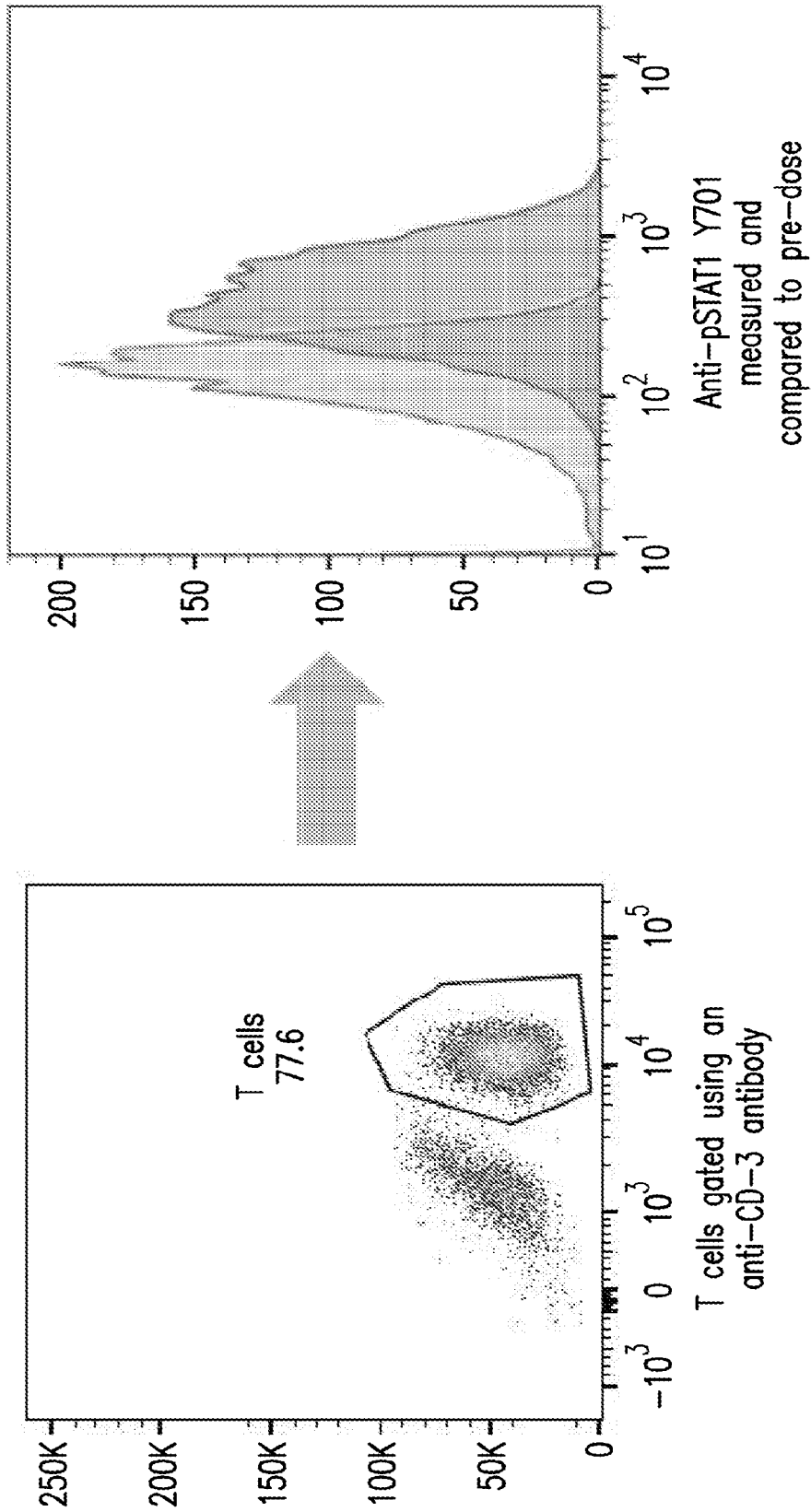


FIG. 5B

FIG. 5A

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FIG. 5C

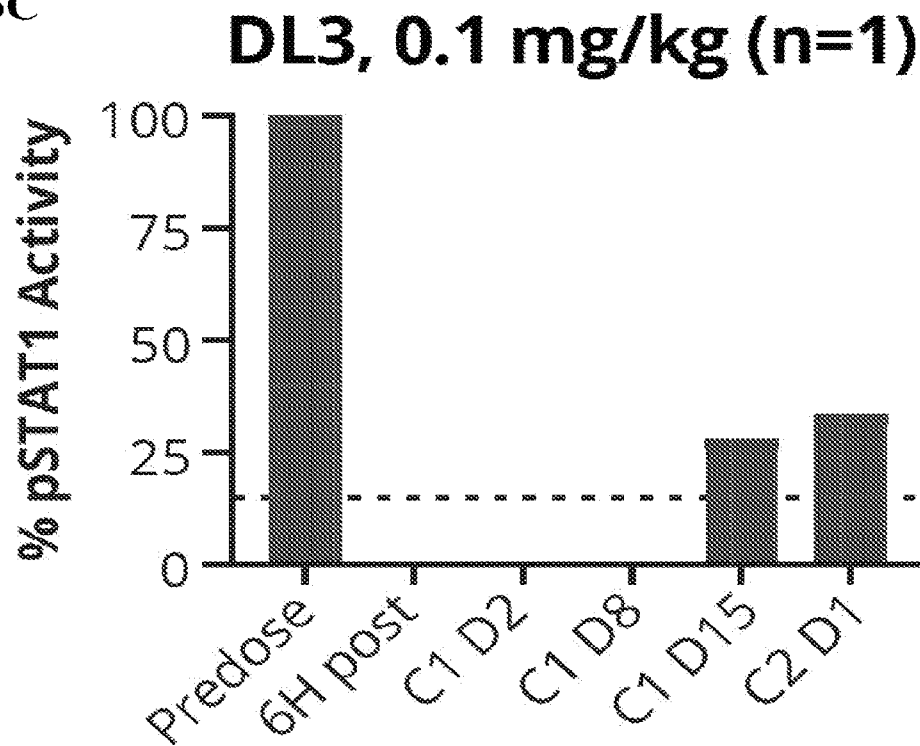


FIG. 5D

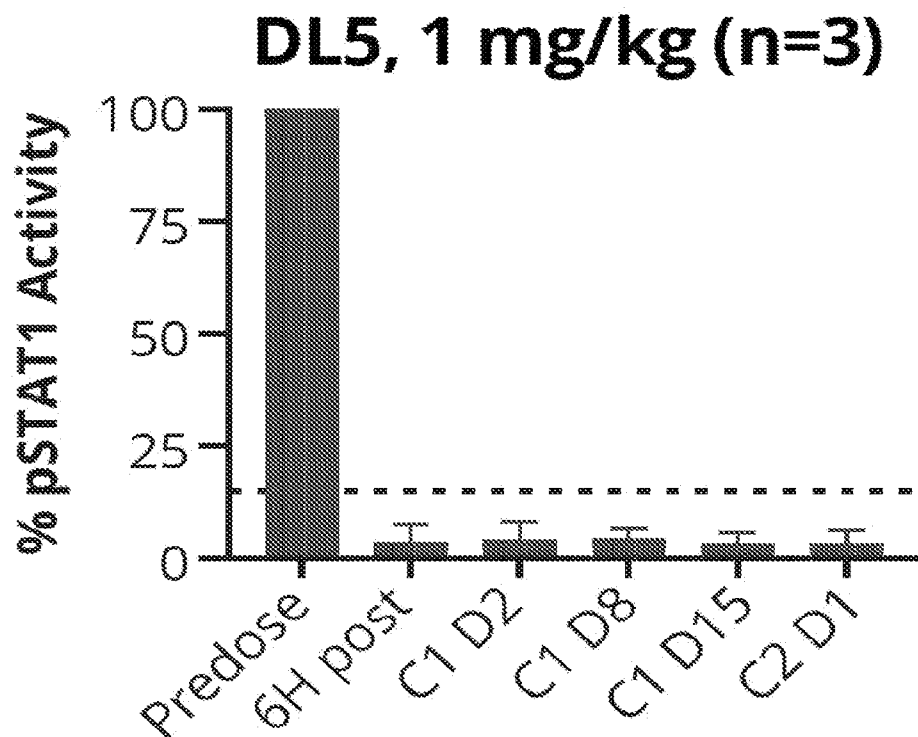


FIG. 6C



FIG. 6B

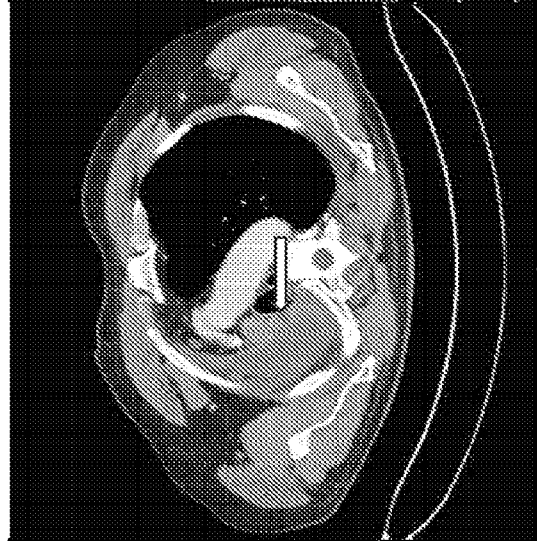


FIG. 6A



FIG. 6F



FIG. 6E

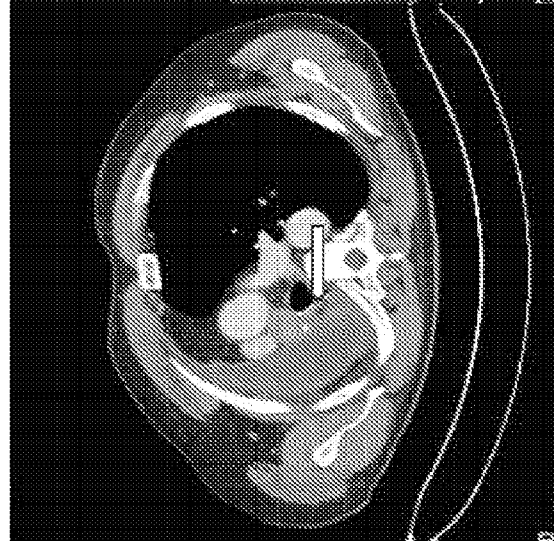
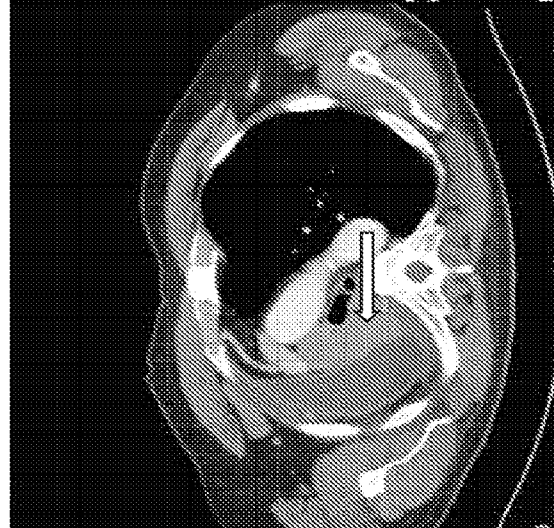


FIG. 6D



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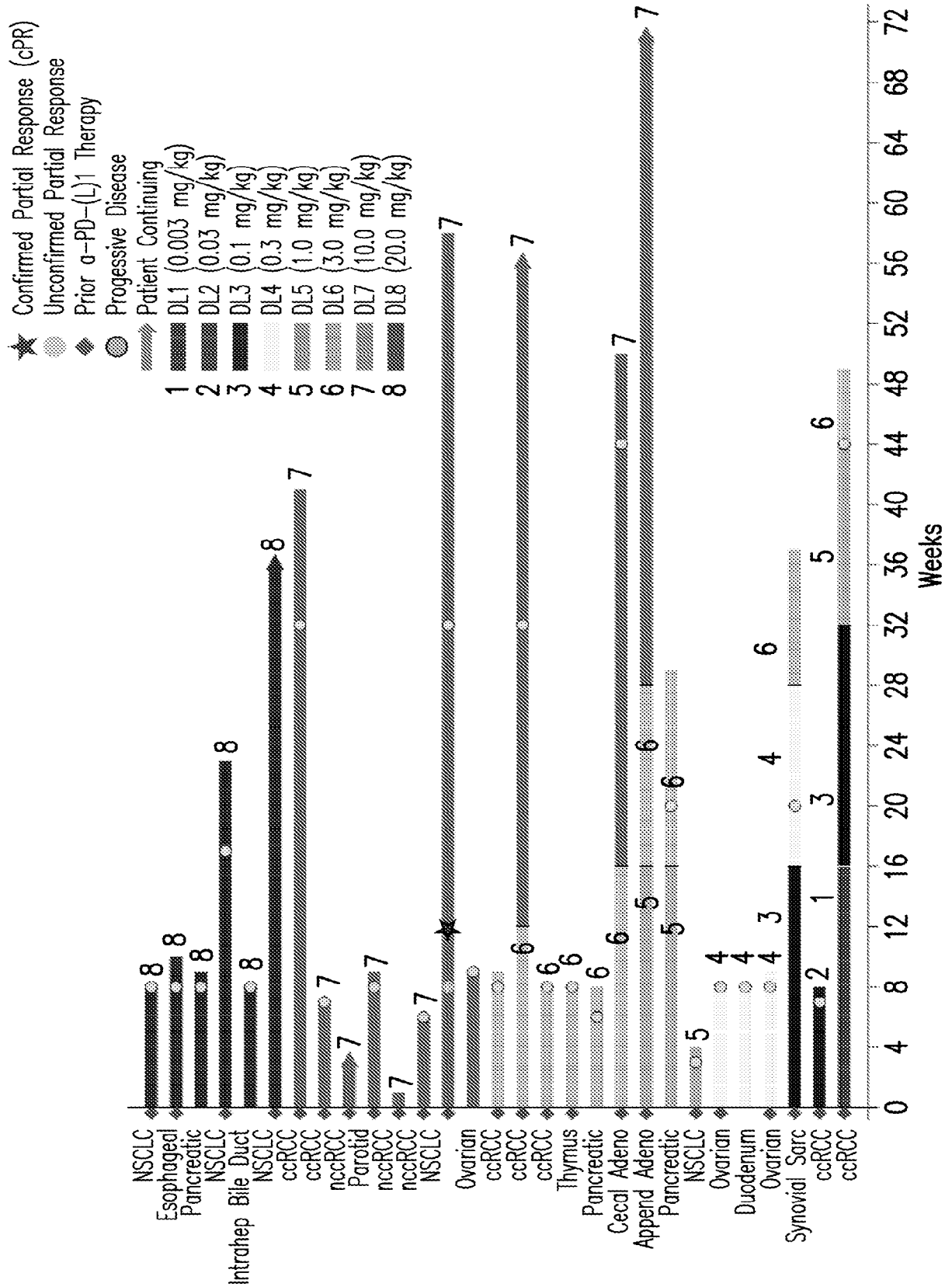


FIG.7

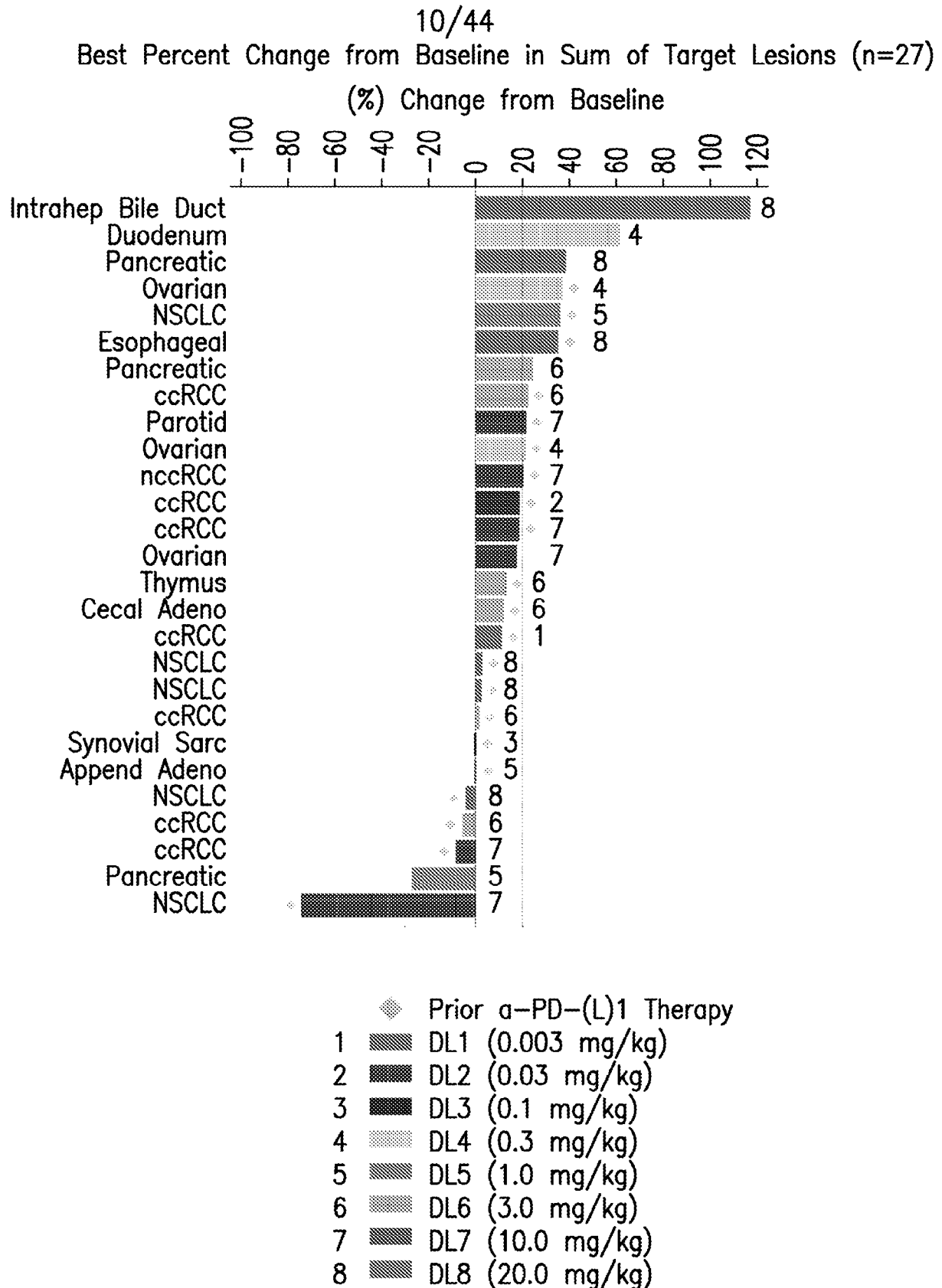


FIG.8A

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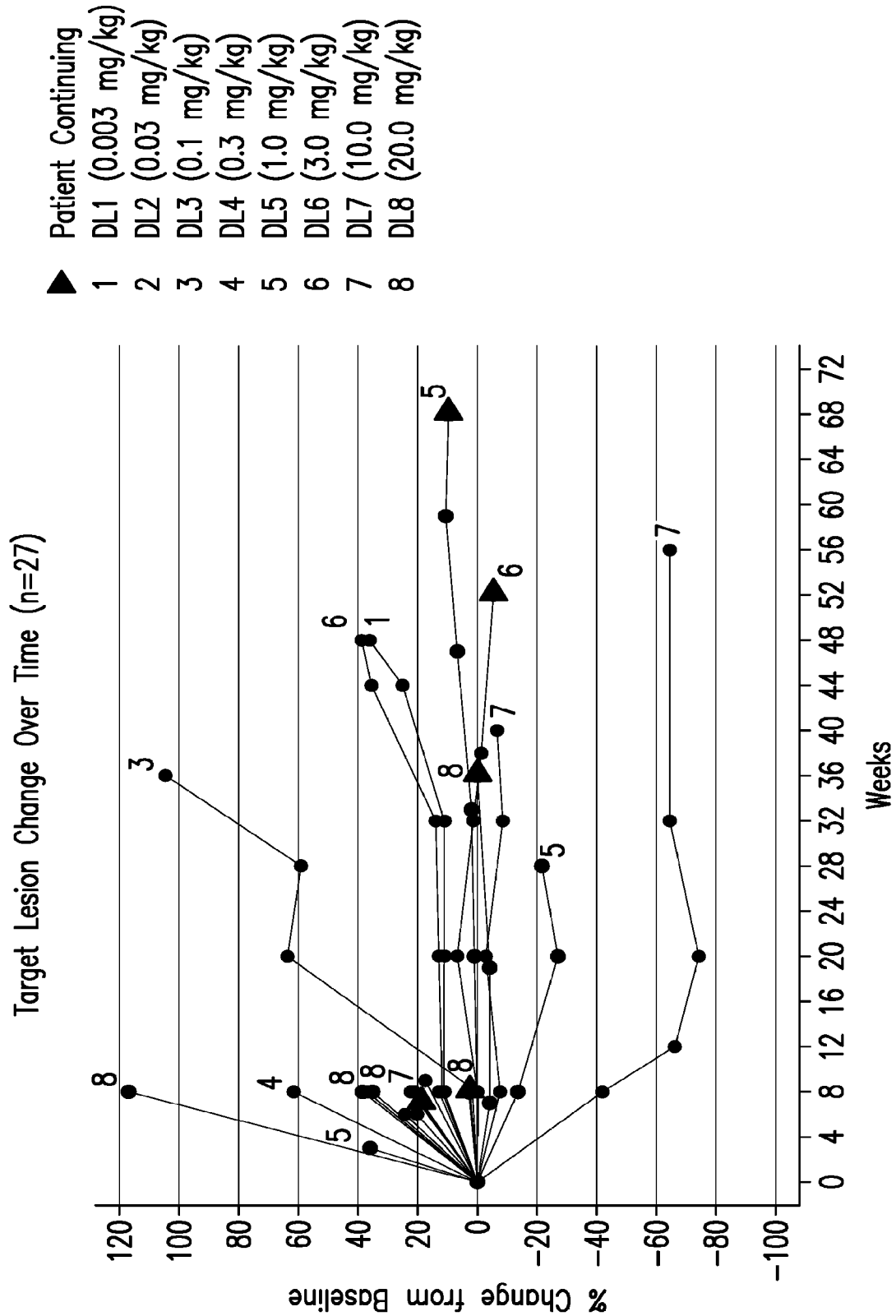


FIG.8B

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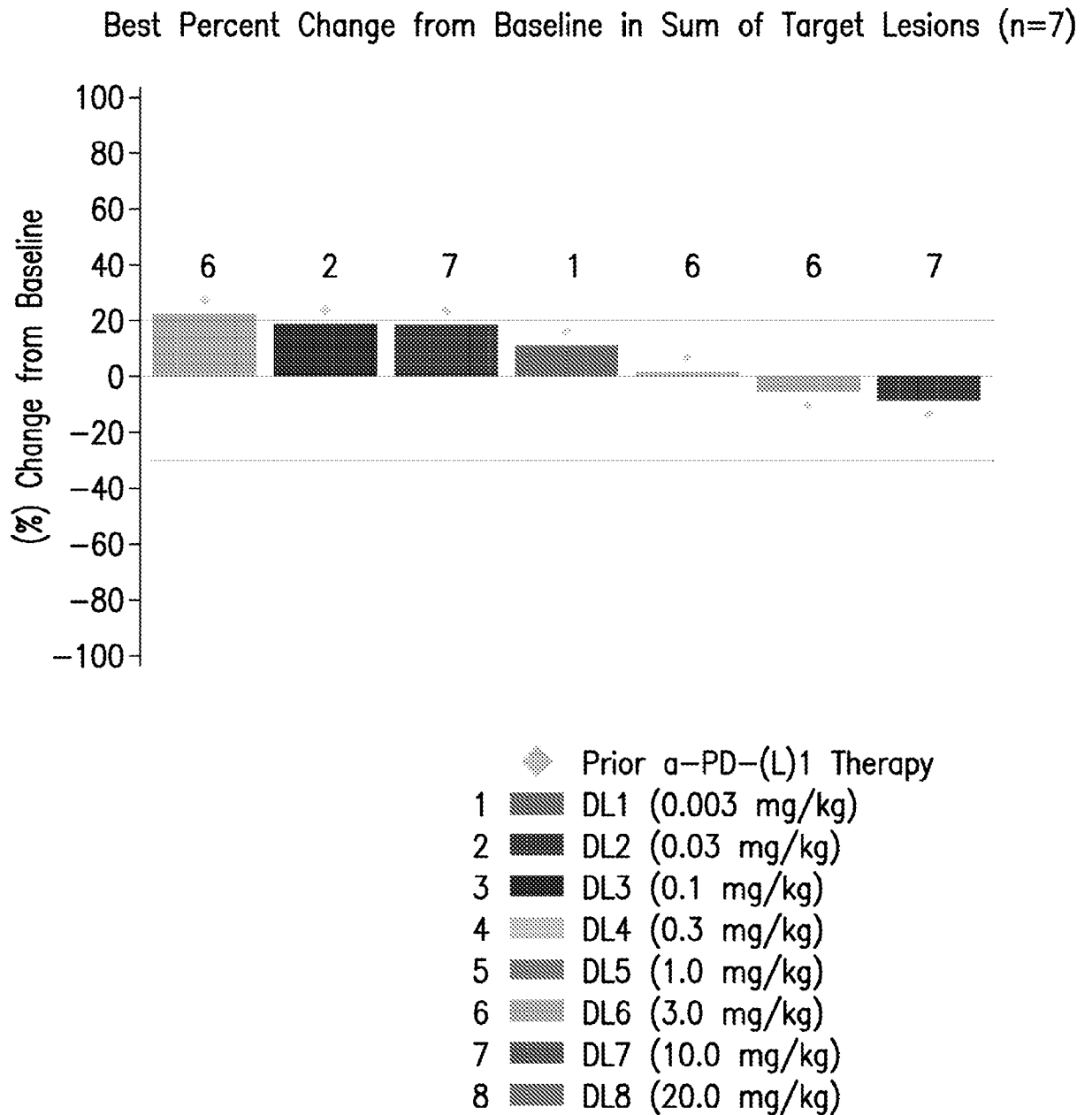


FIG.9A

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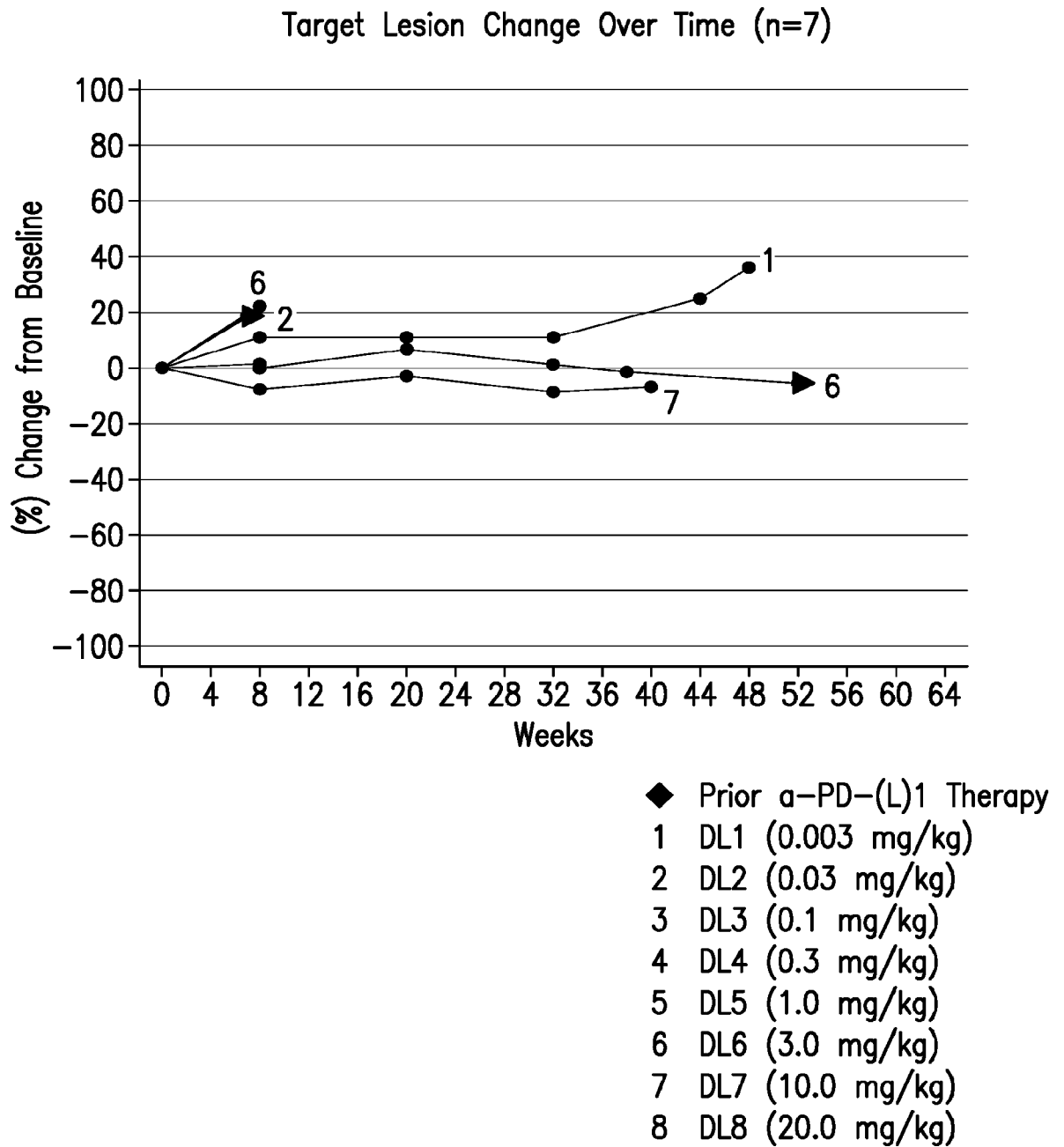
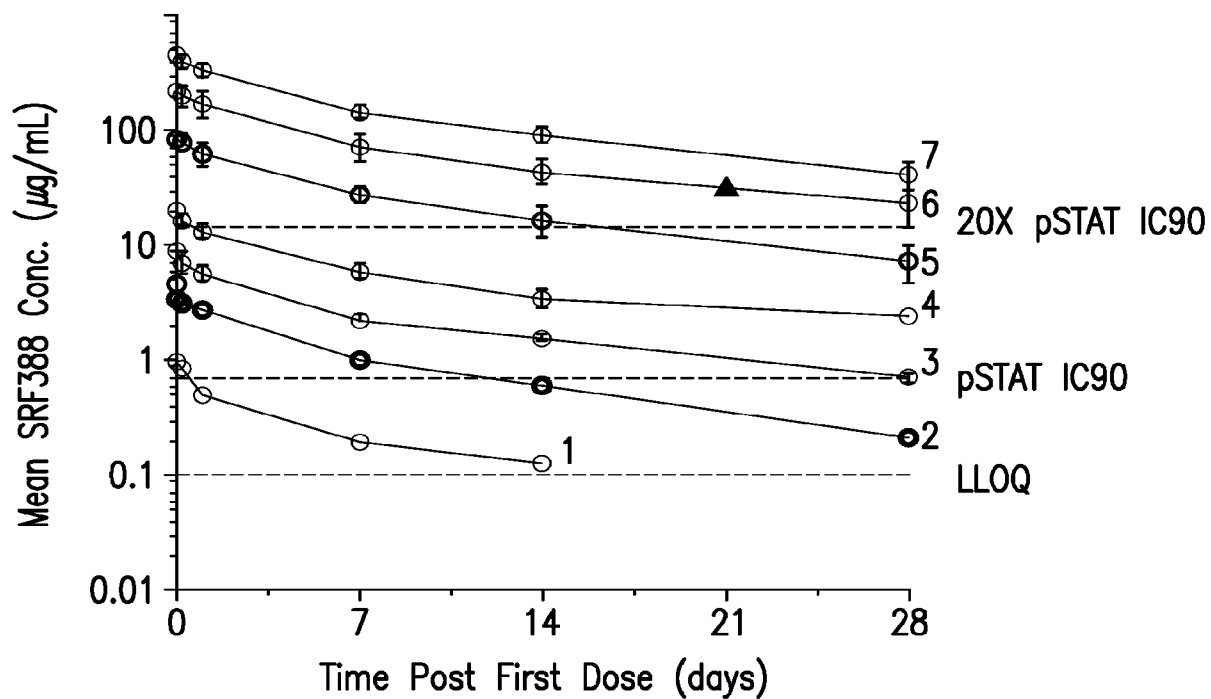


FIG.9B

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Note: 0.003 mg/kg Cycle 1 Samples below the limit of quantitation

FIG. 10A

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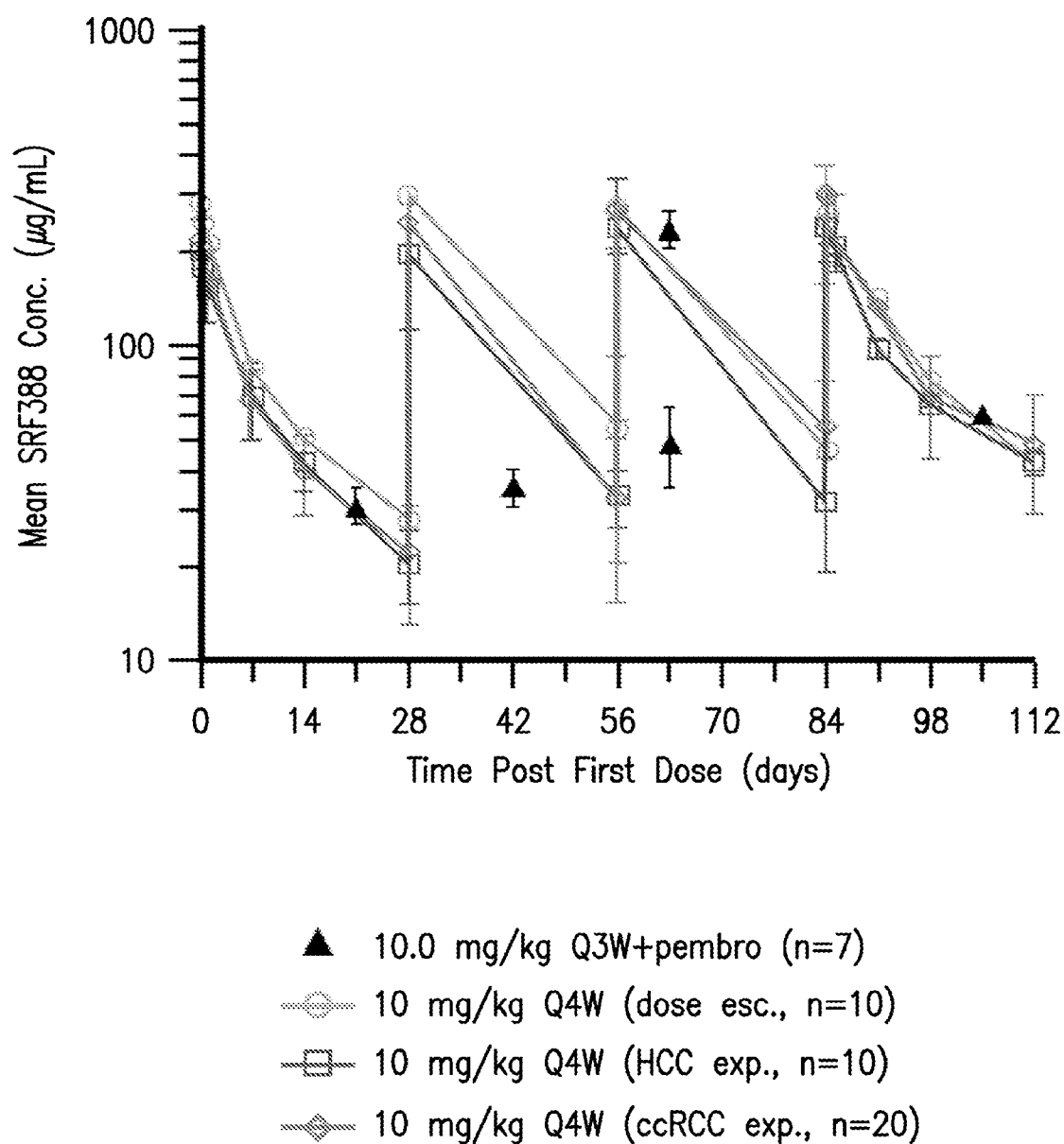


FIG.10B

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Best Percent Change from Baseline in Sum of Target Lesions (n=13)

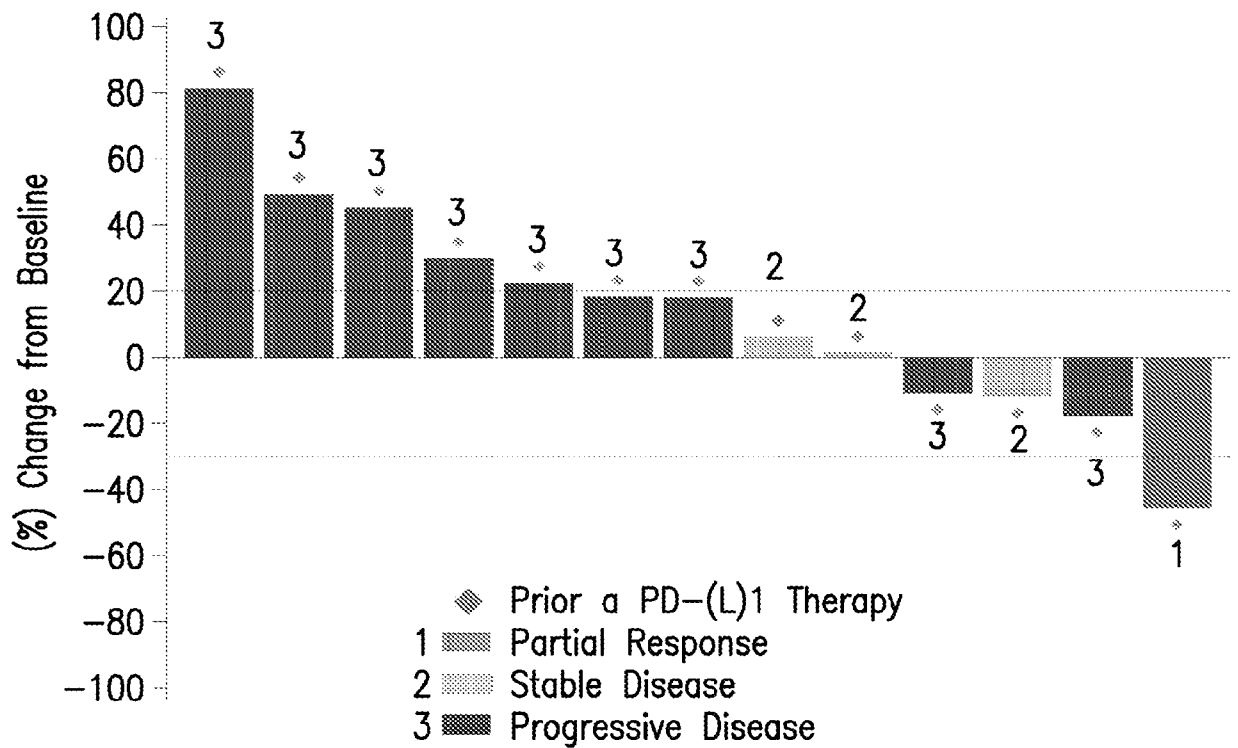


FIG. 11A

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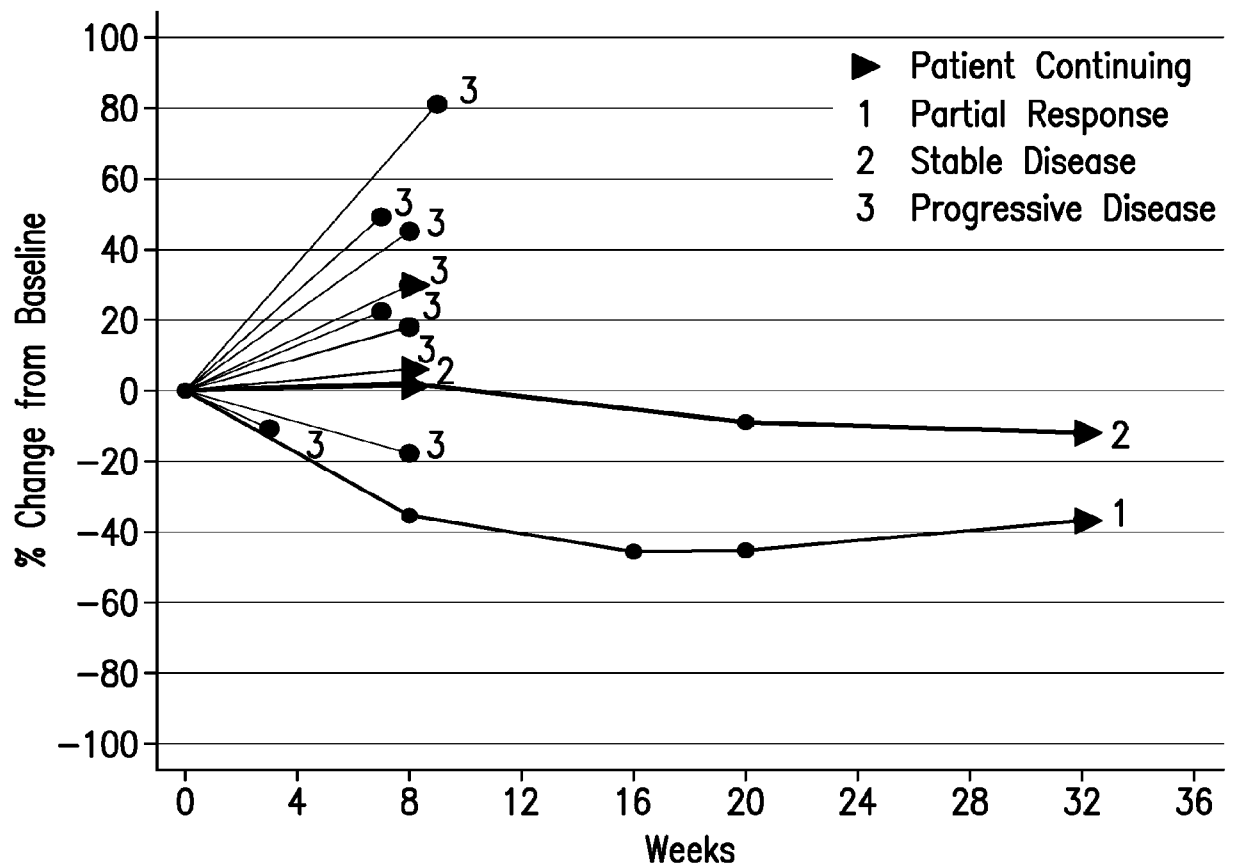


FIG.11B

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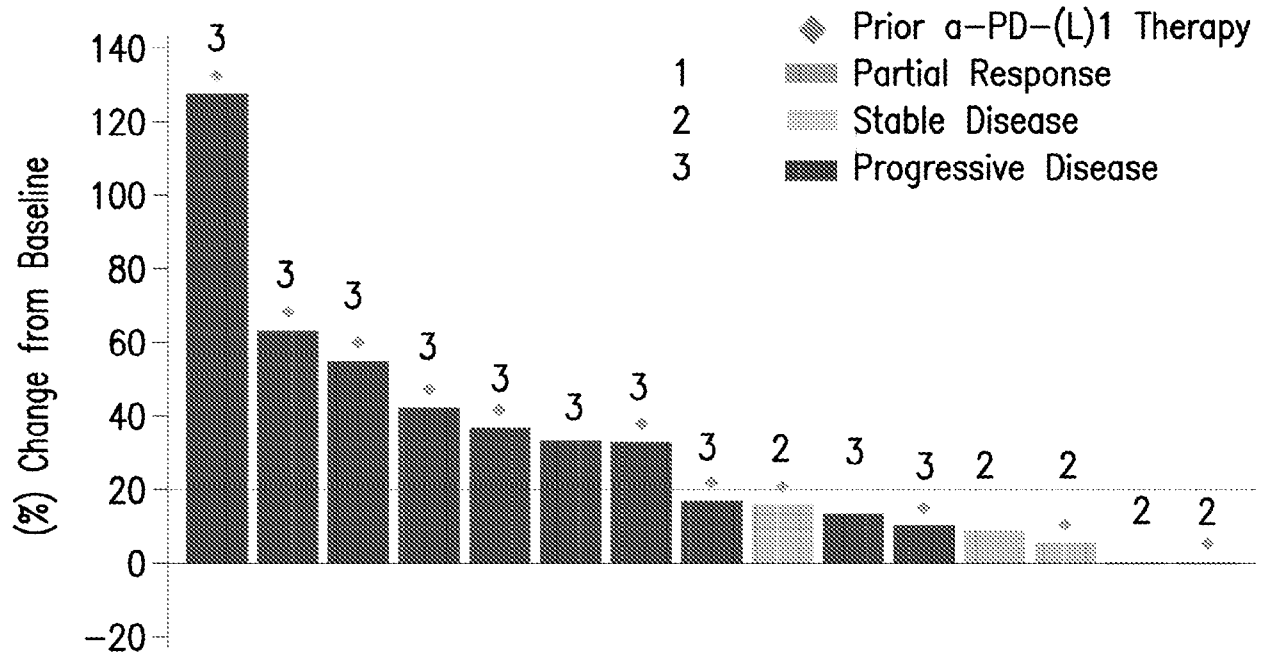


FIG. 12A

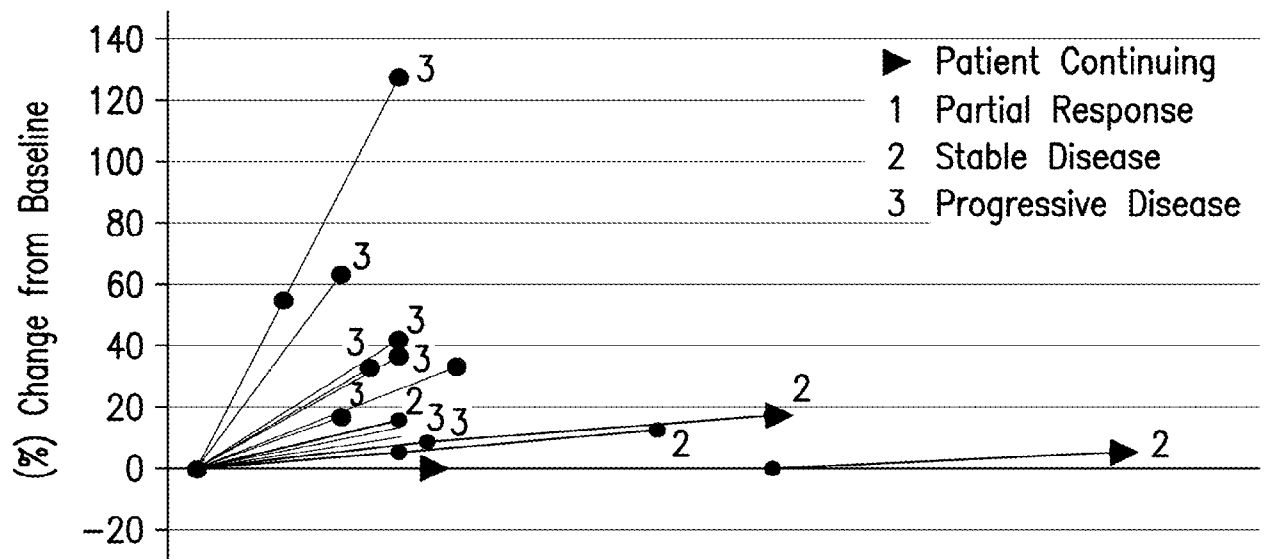
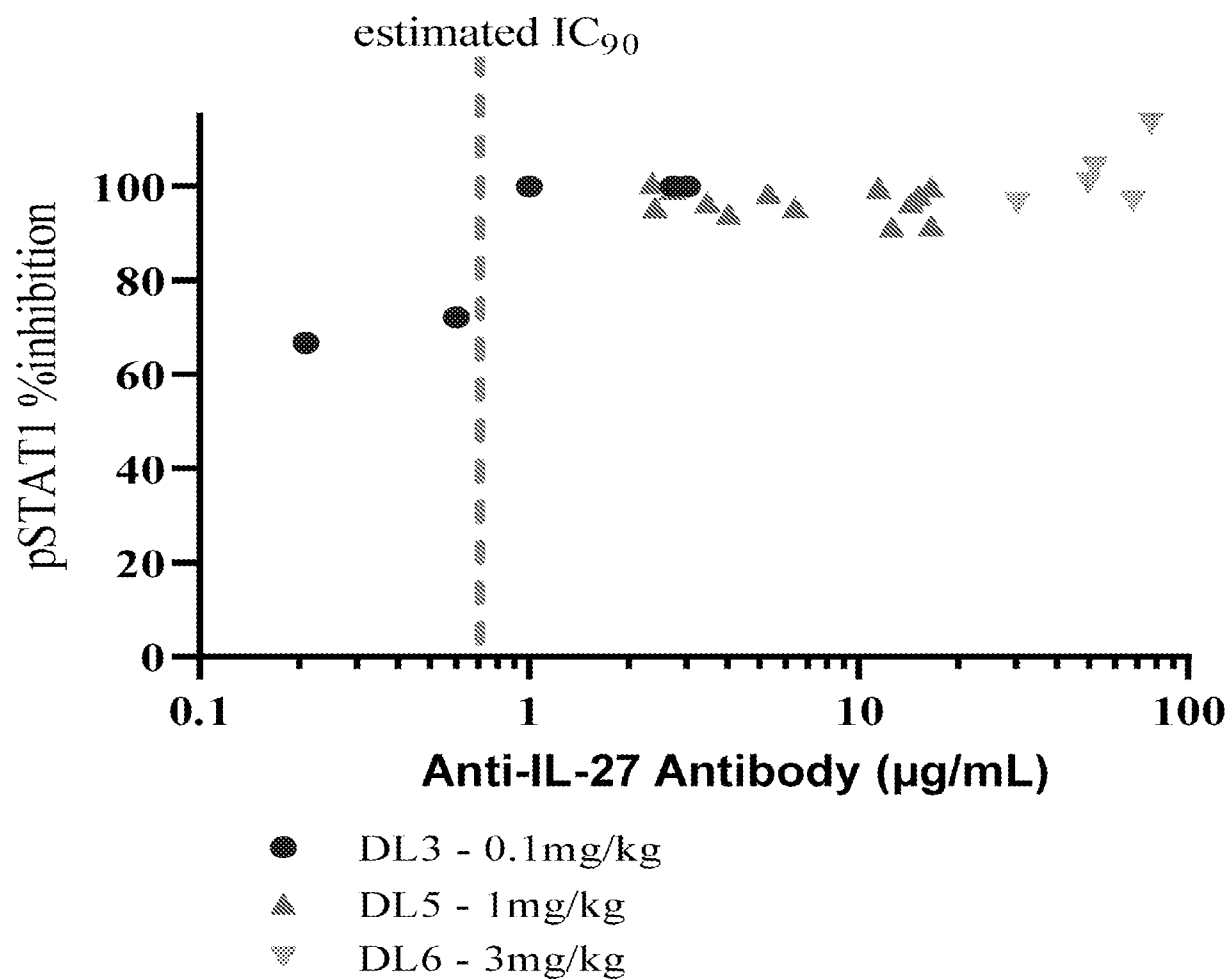


FIG. 12B

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FIG. 13A

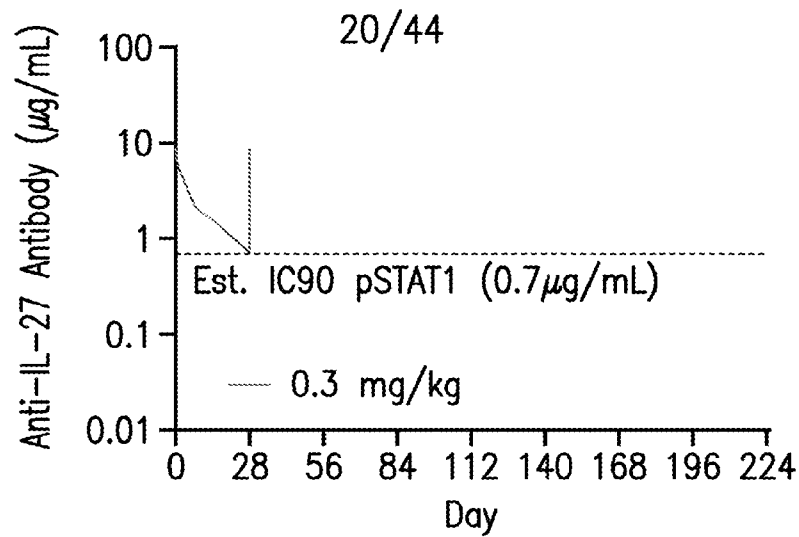


FIG. 13B

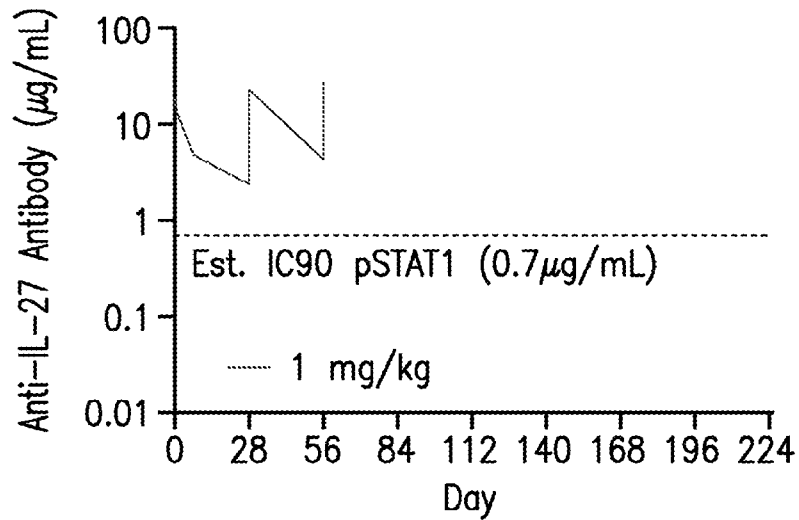


FIG. 13C

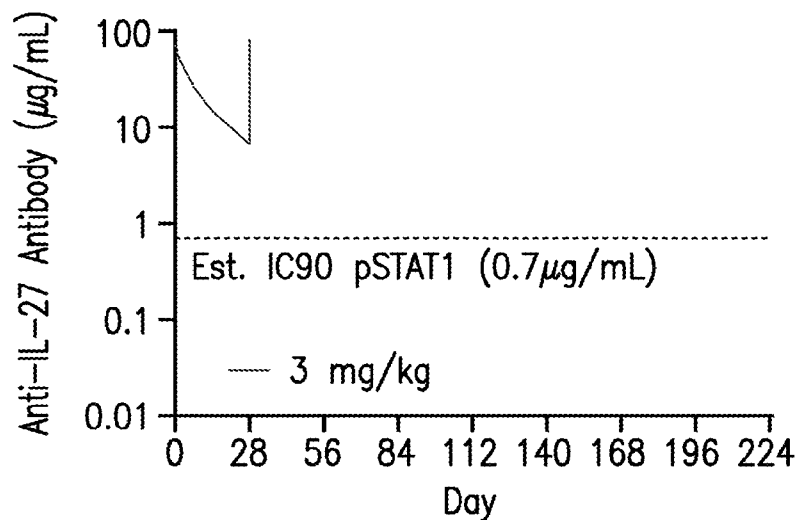


FIG. 13D

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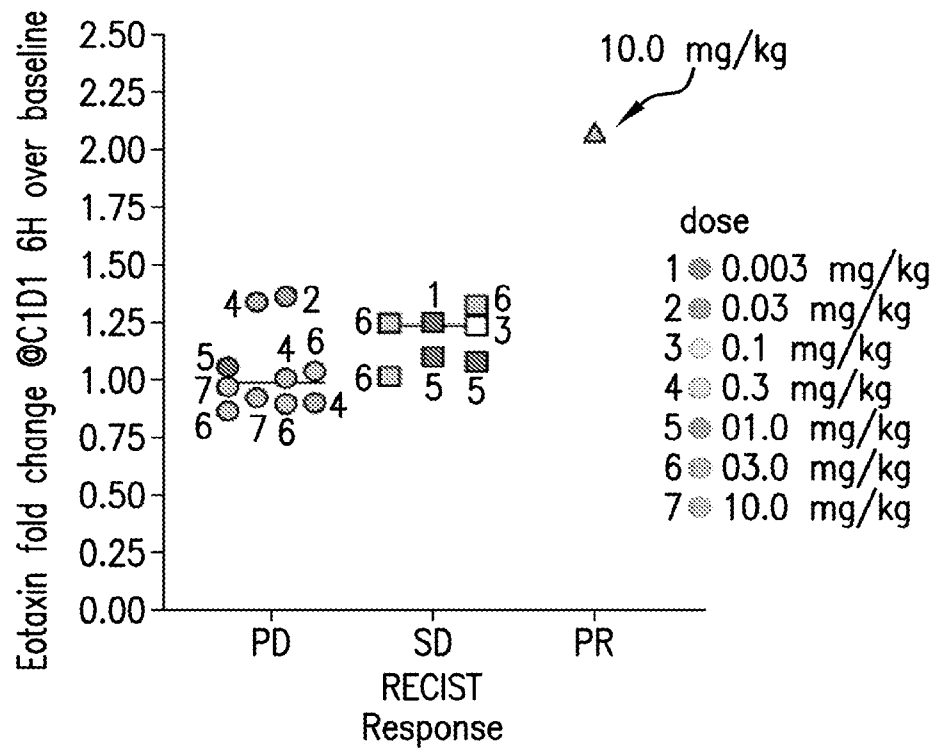


FIG. 14A

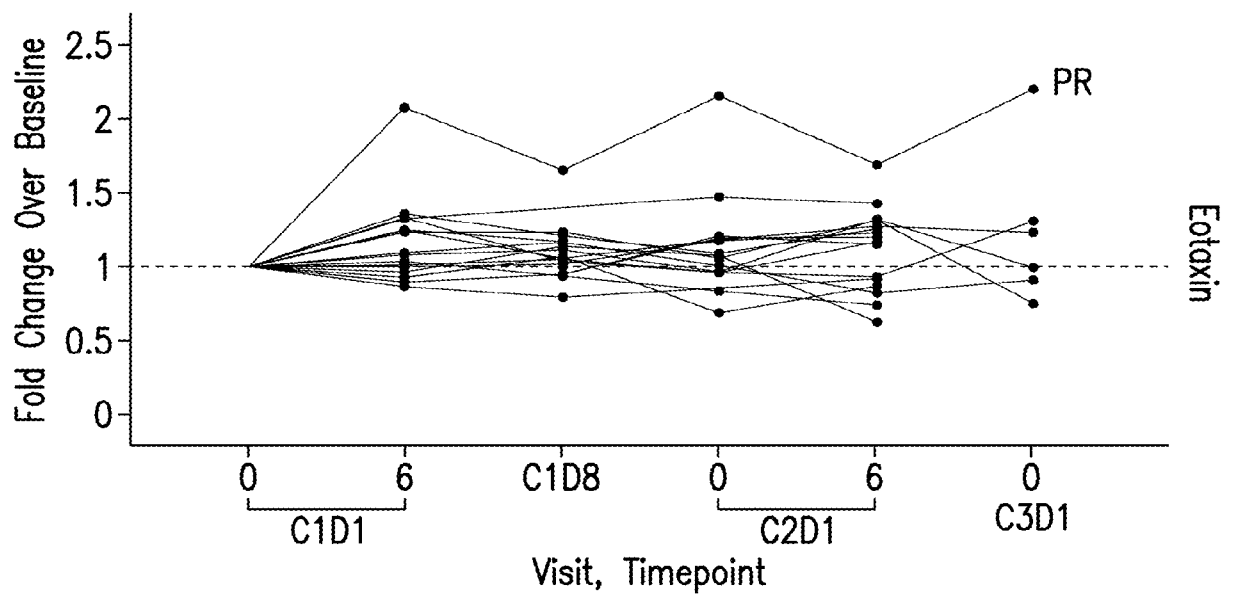
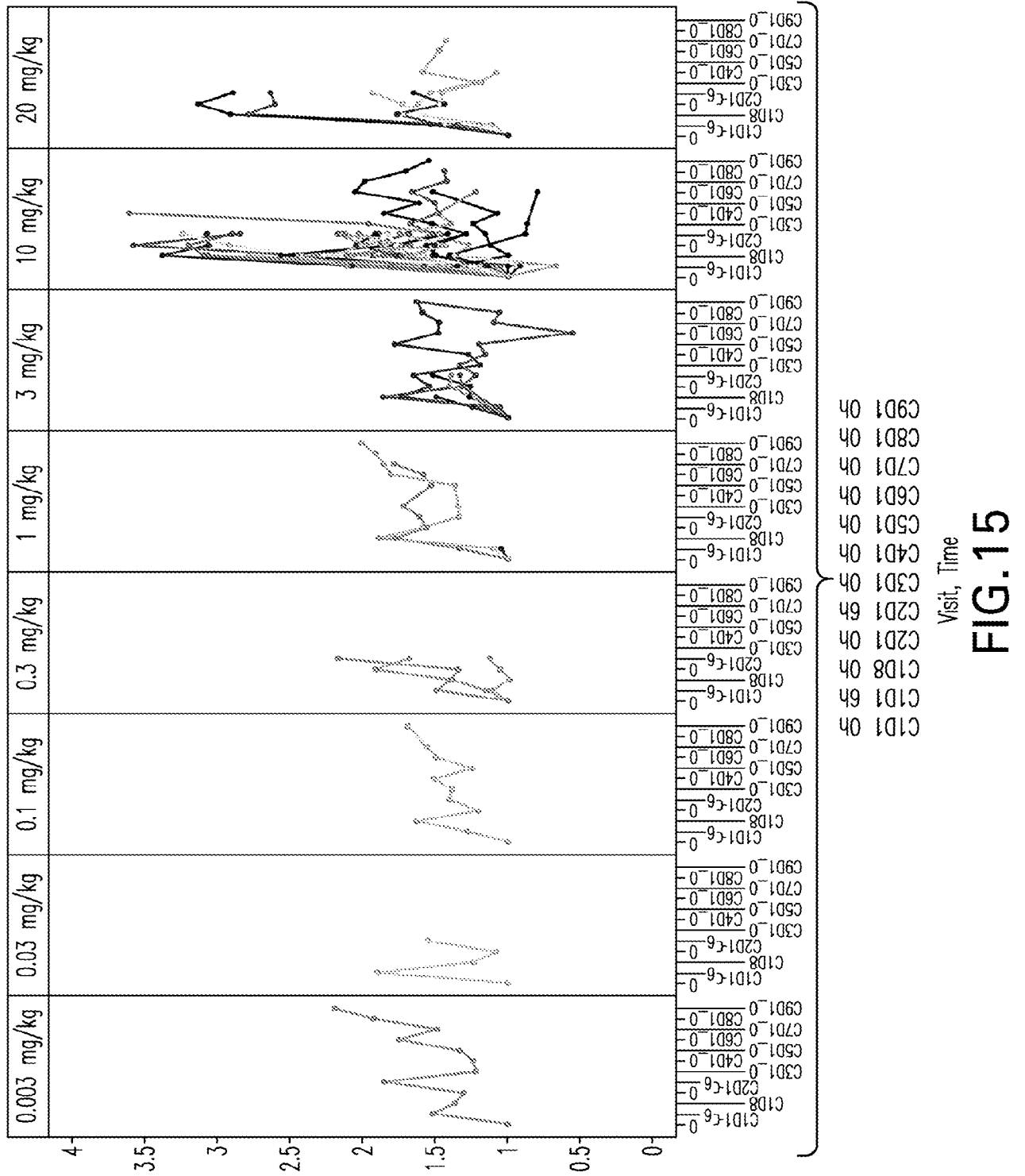


FIG. 14B

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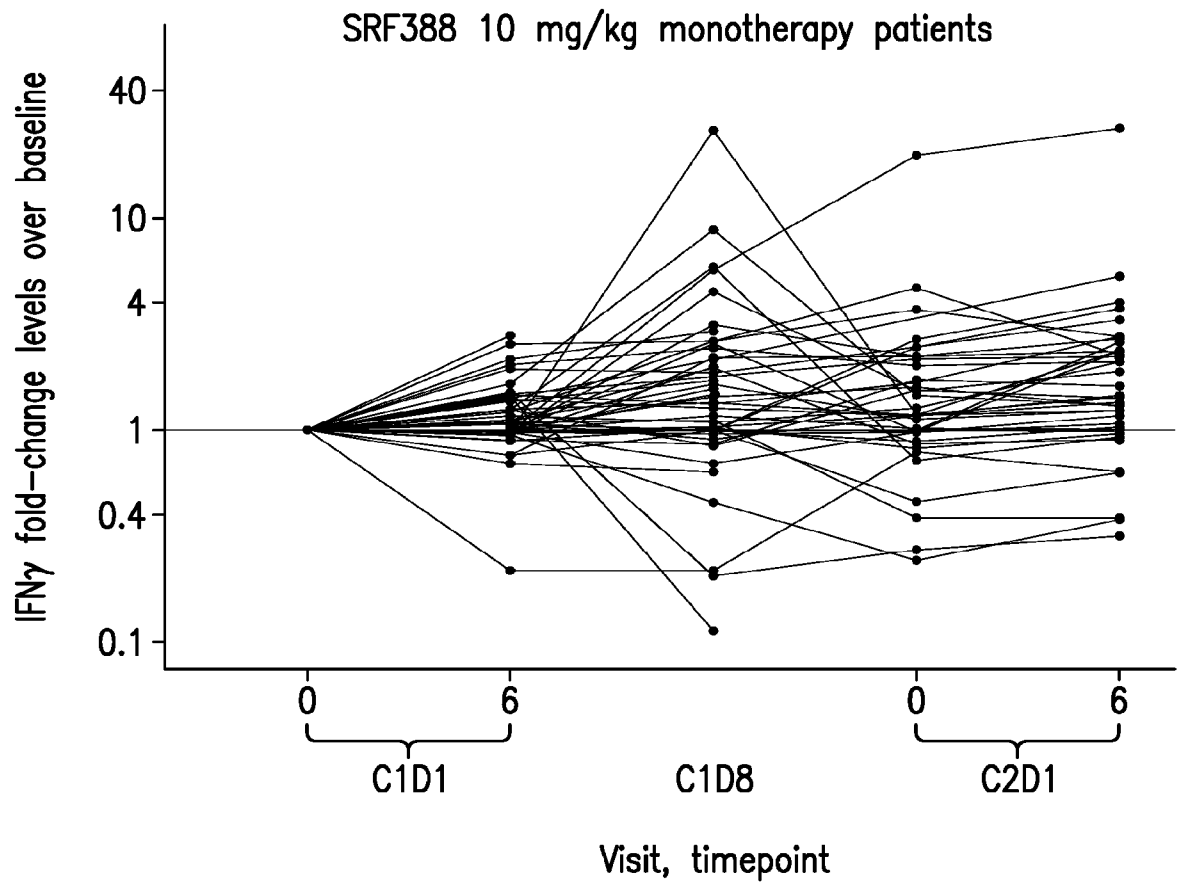
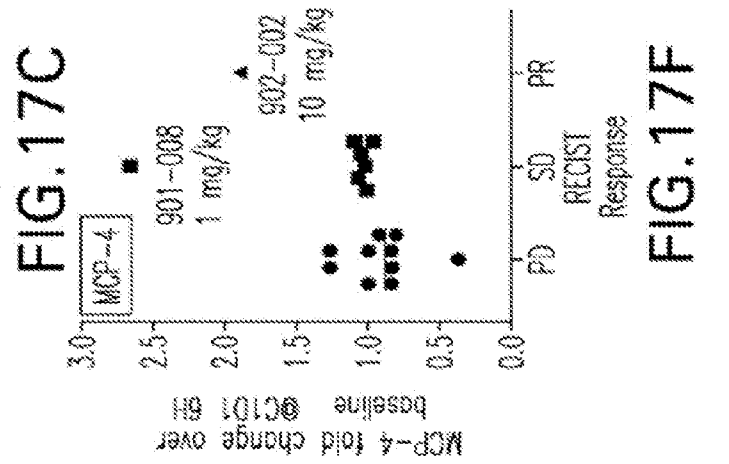
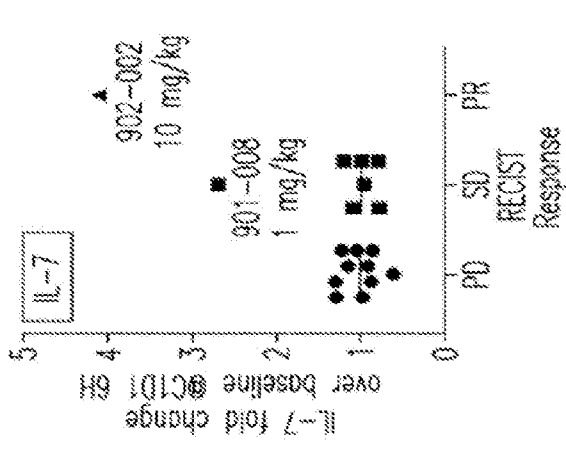
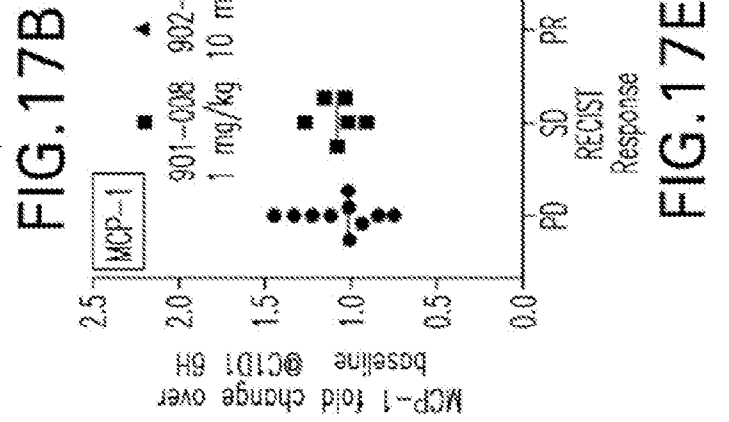
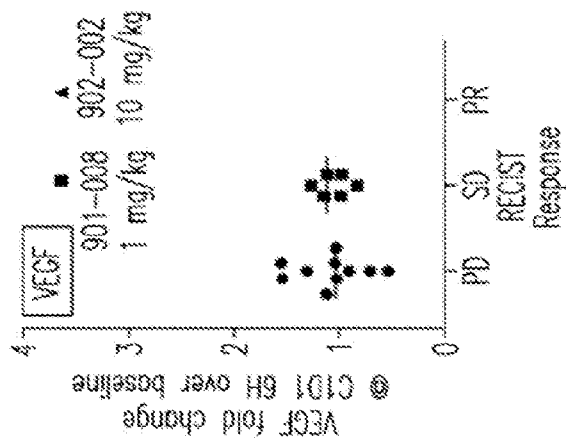
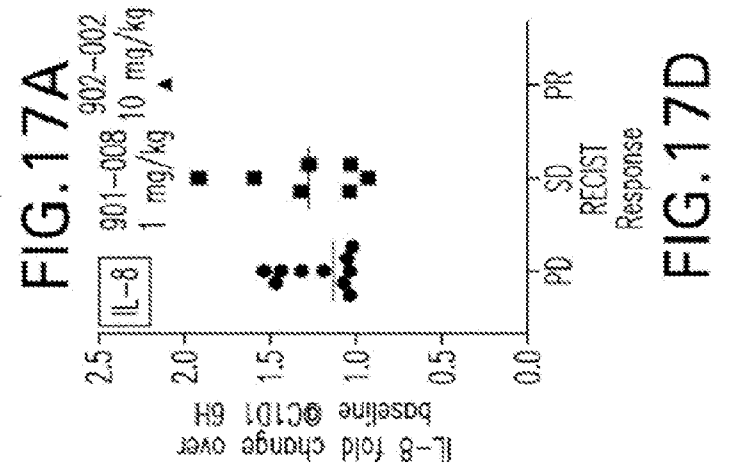
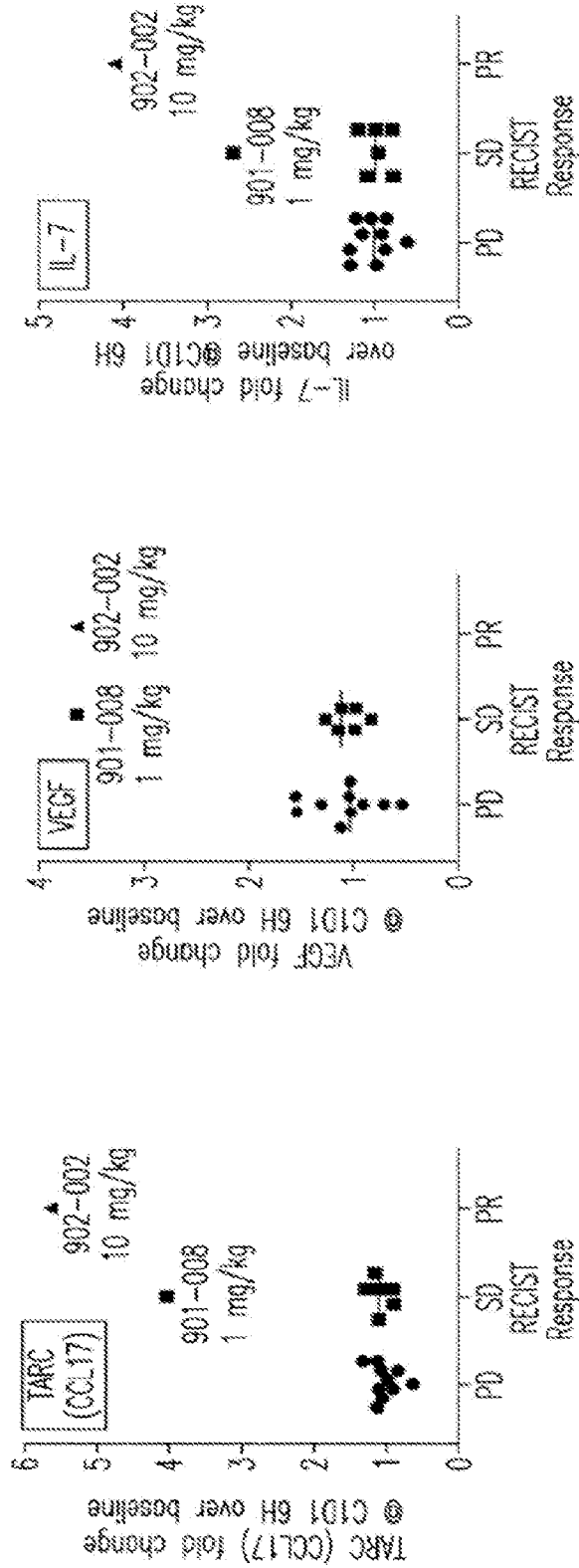


FIG.16



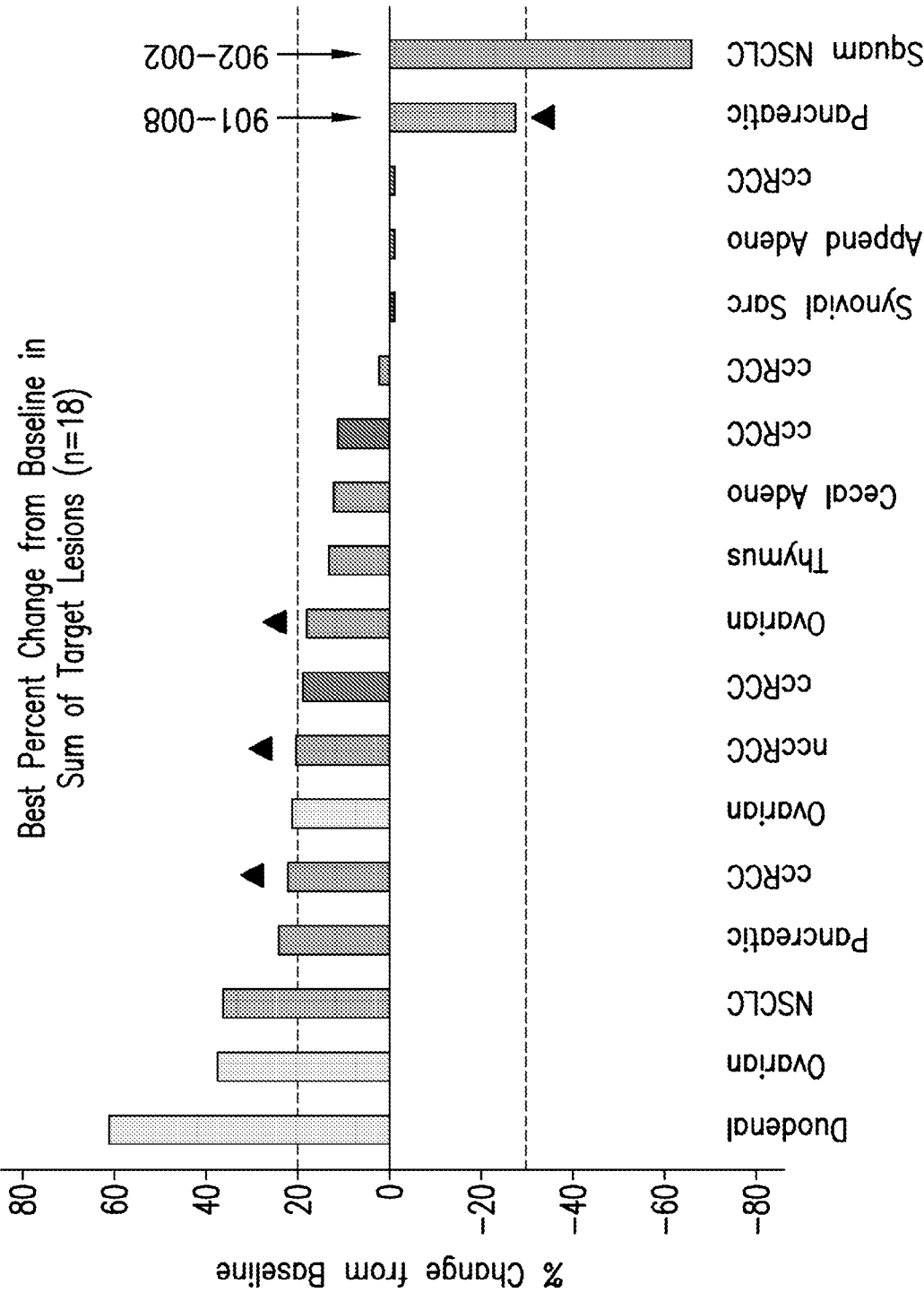


FIG.17G

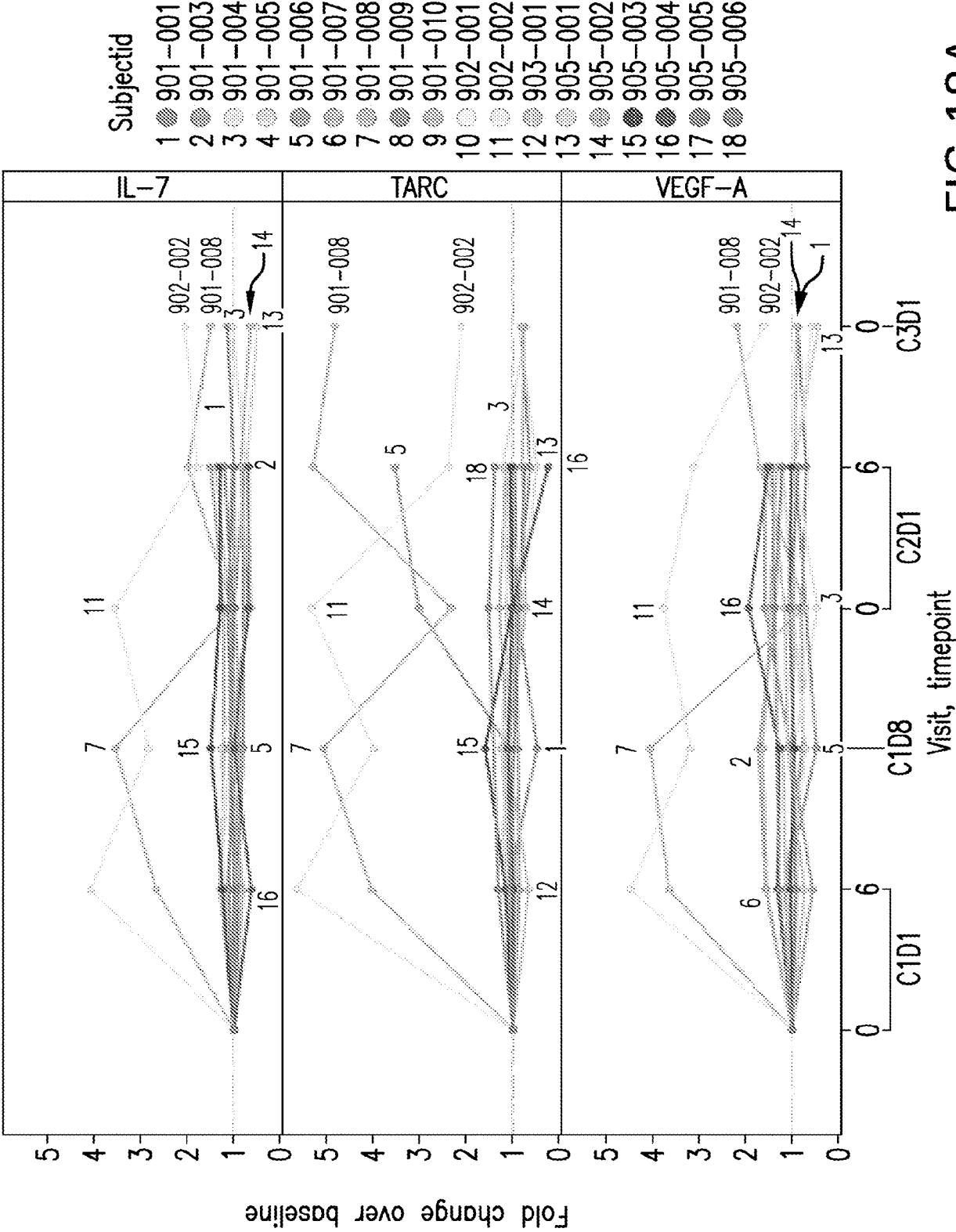


FIG.18A

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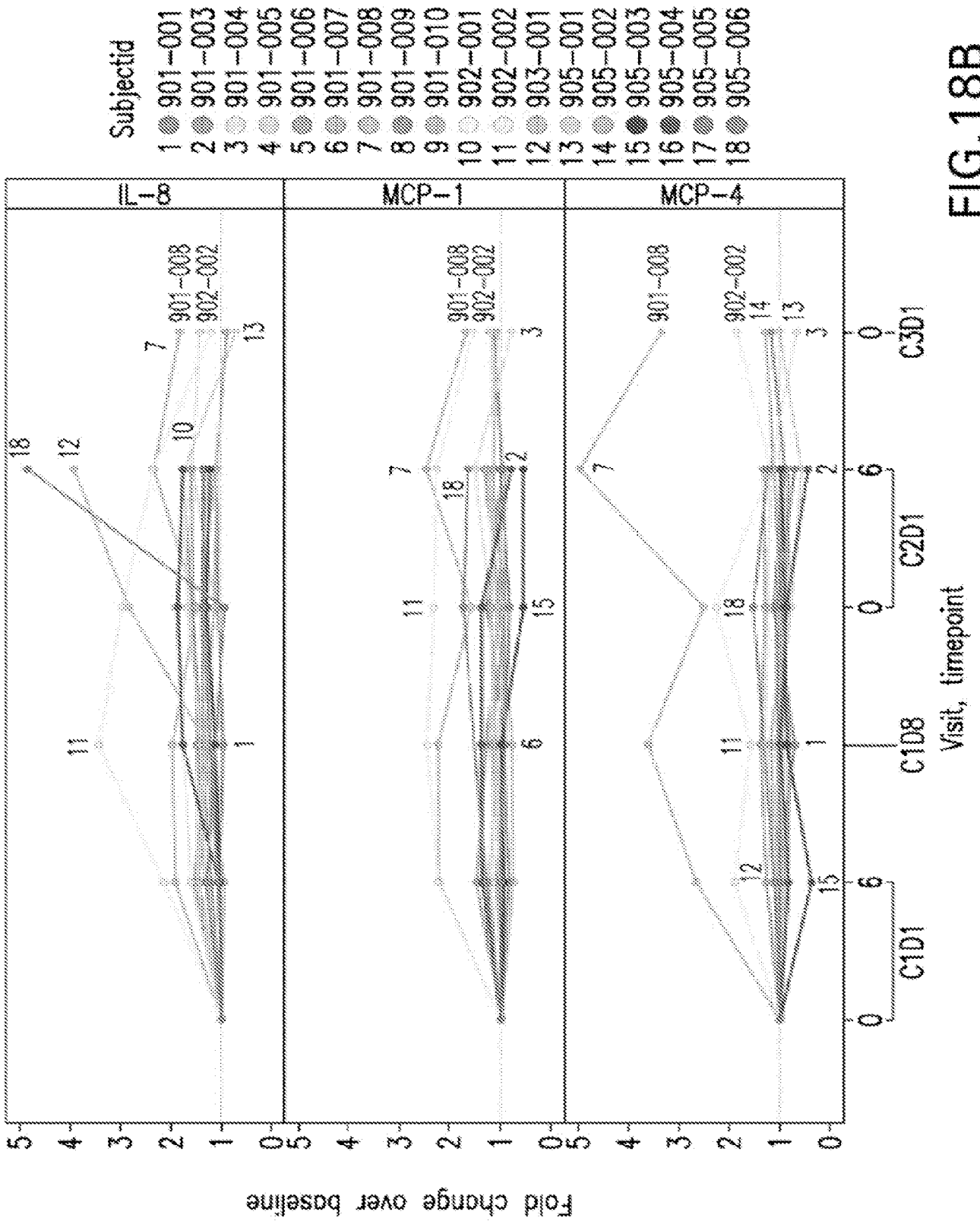


FIG.18B

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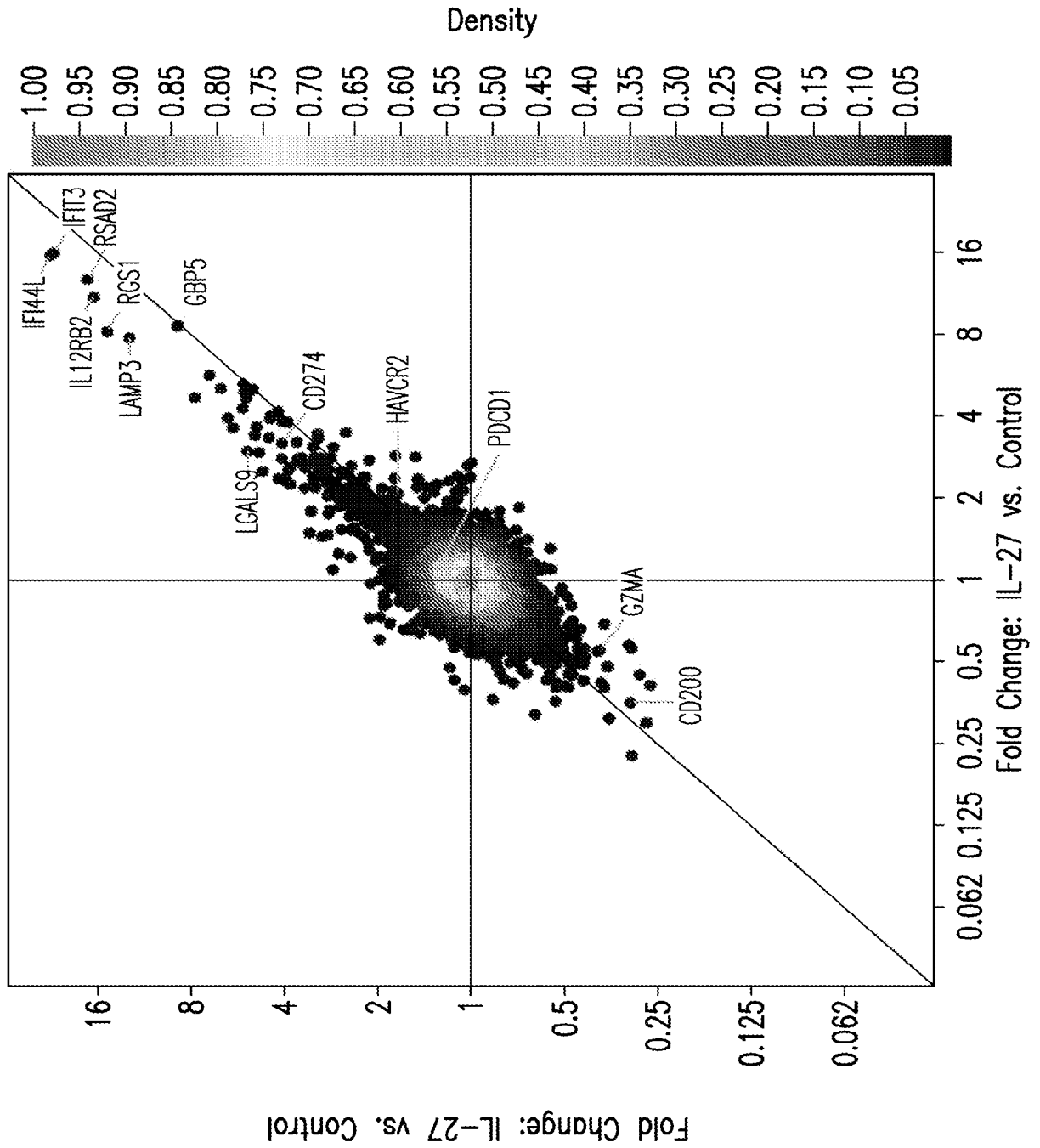


FIG.19

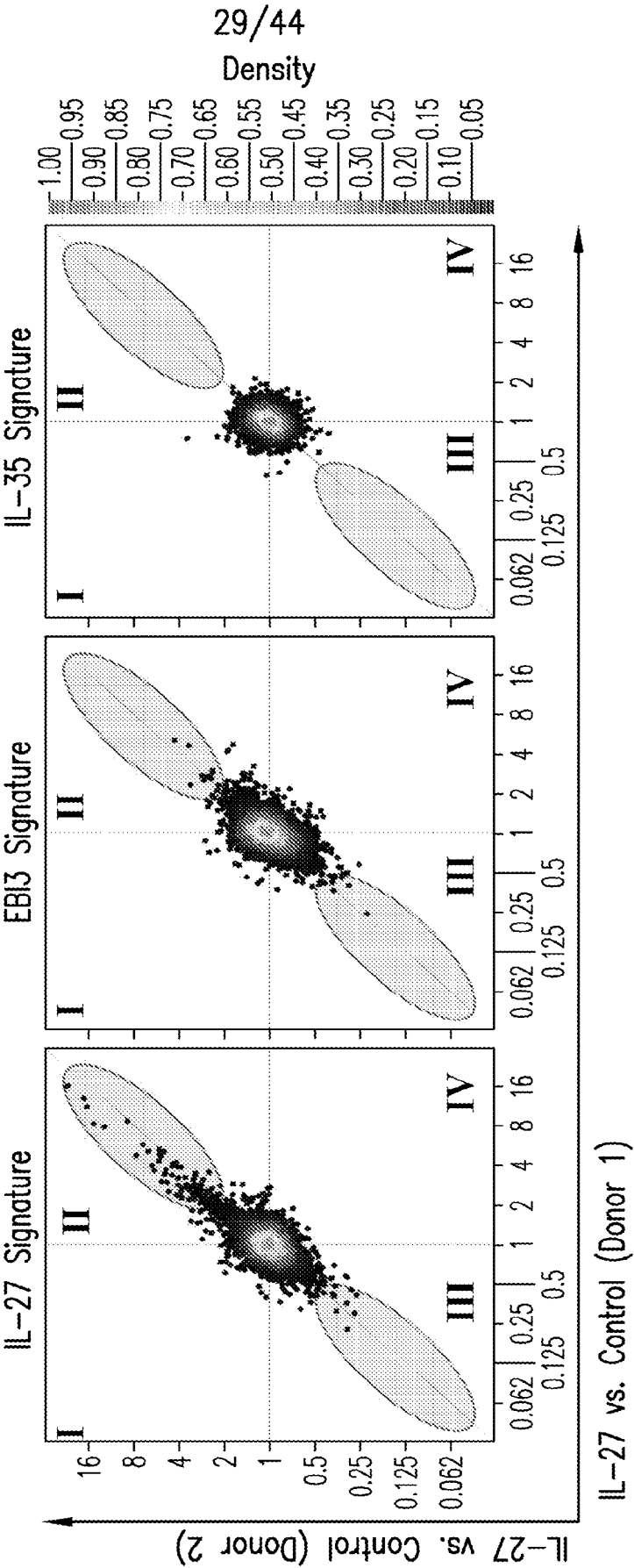


FIG.20A

FIG.20B

FIG.20C

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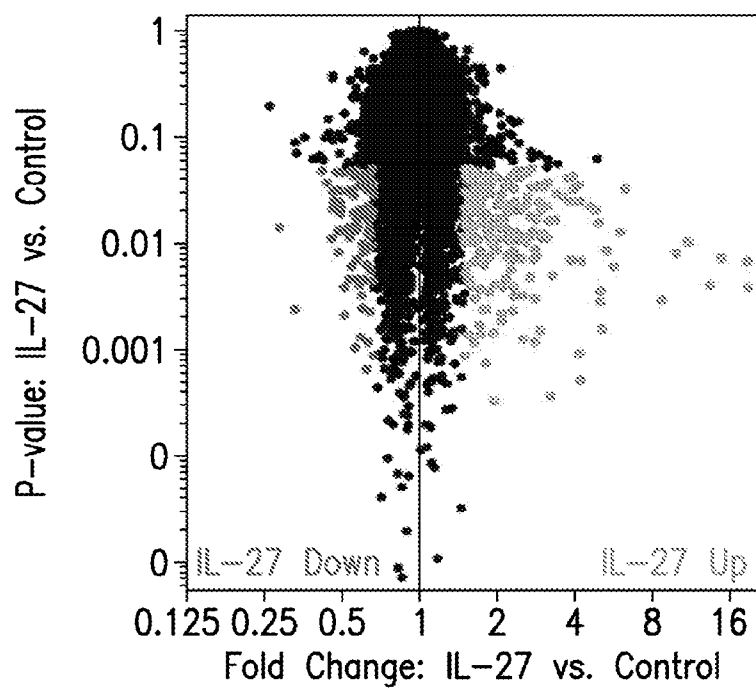


FIG.21A

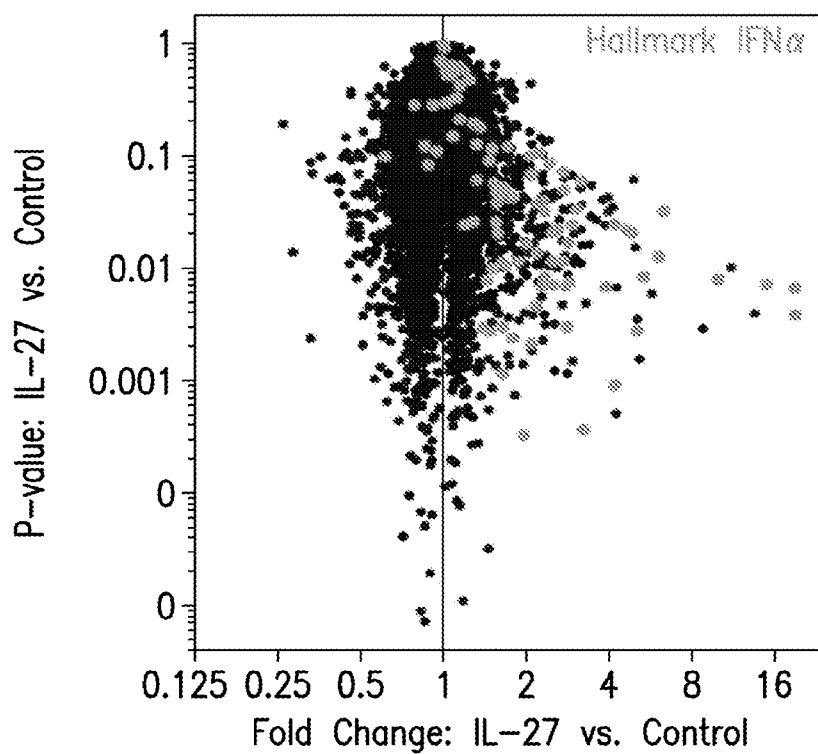


FIG.21B

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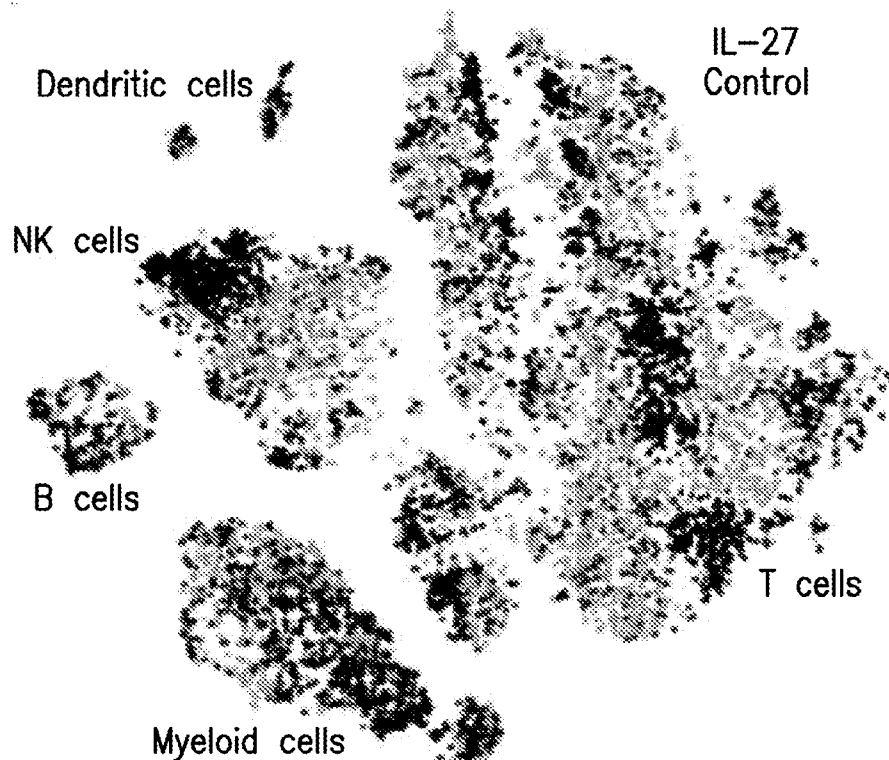


FIG.22A

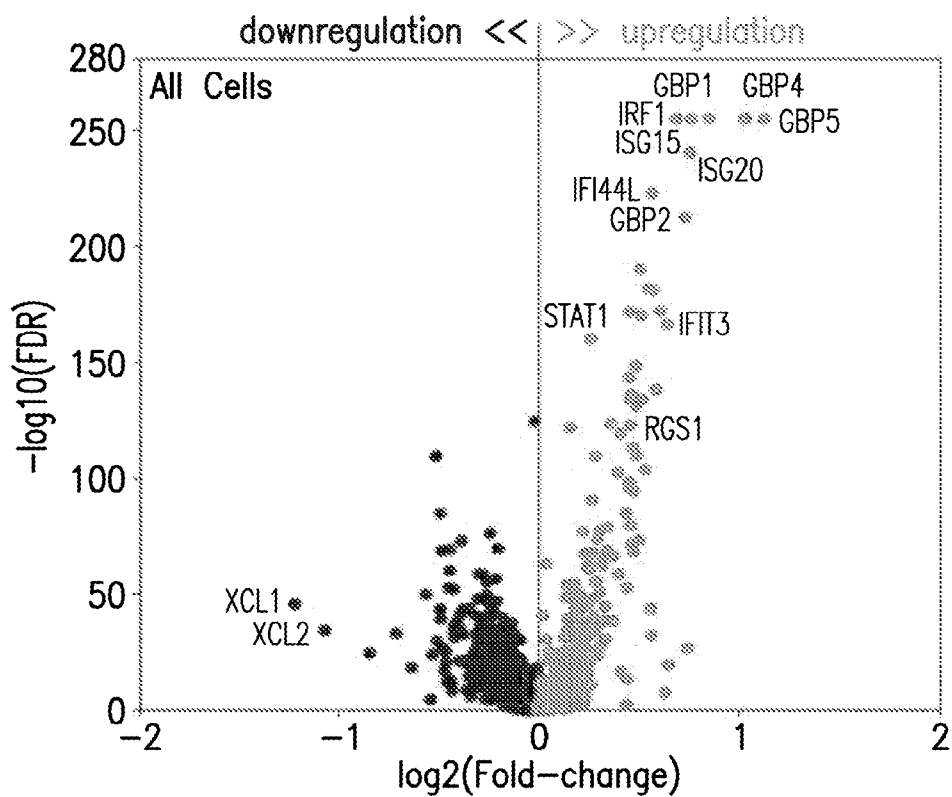


FIG.22B

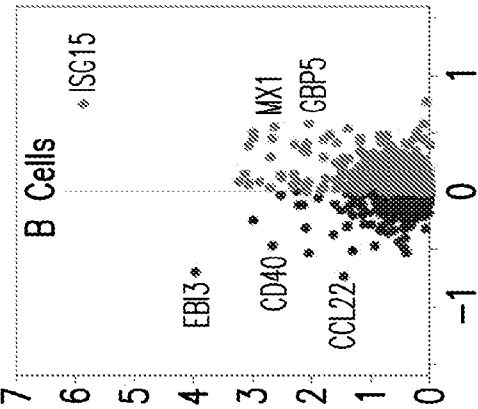


FIG.22E

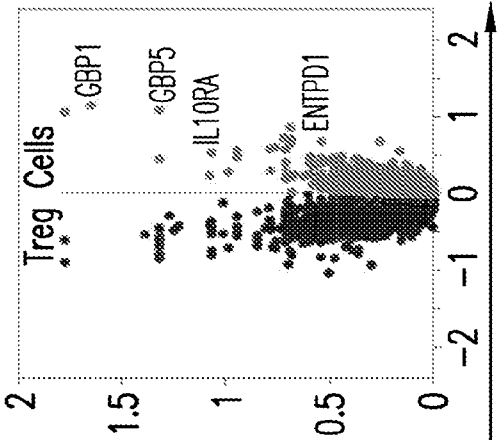


FIG.22H

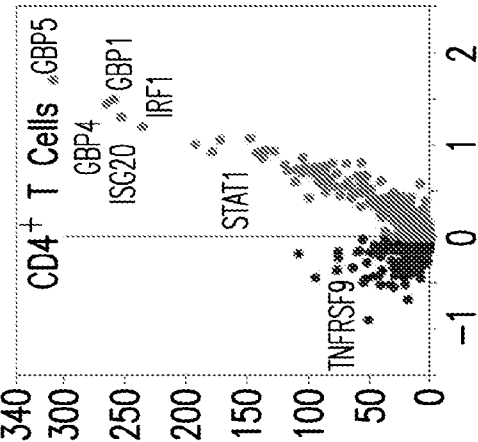


FIG.22D

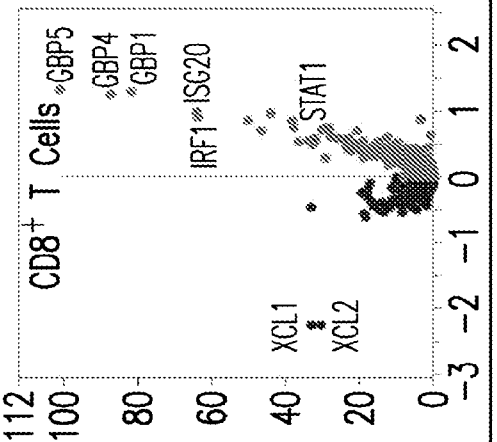


FIG.22G

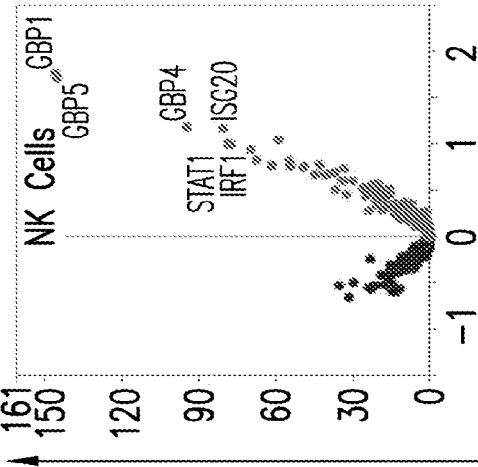


FIG.22C

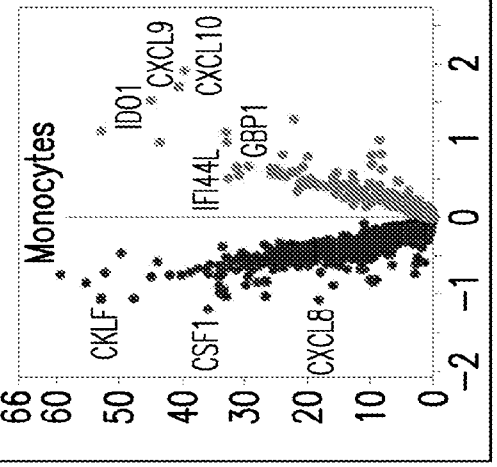


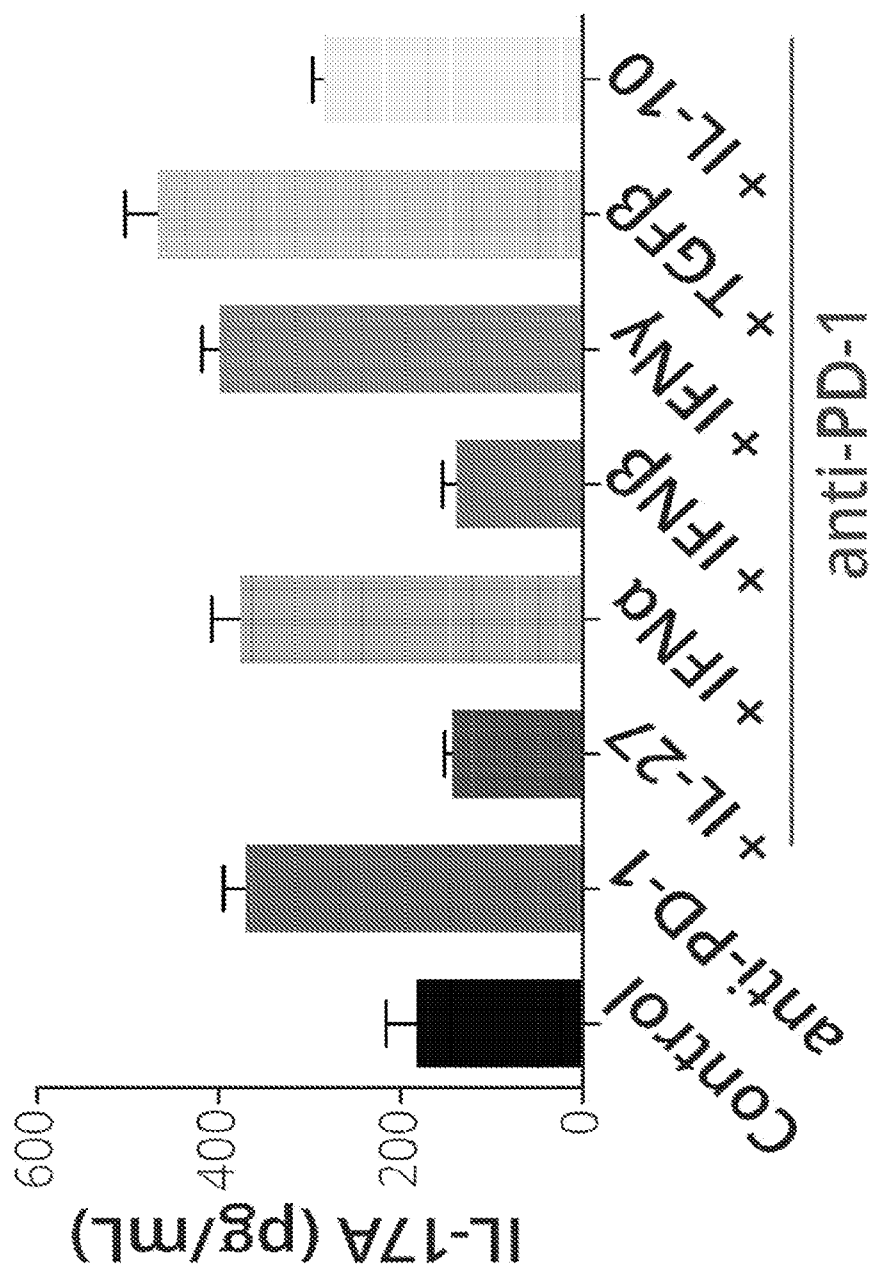
FIG.22F

$\log_2(\text{Fold-change})$

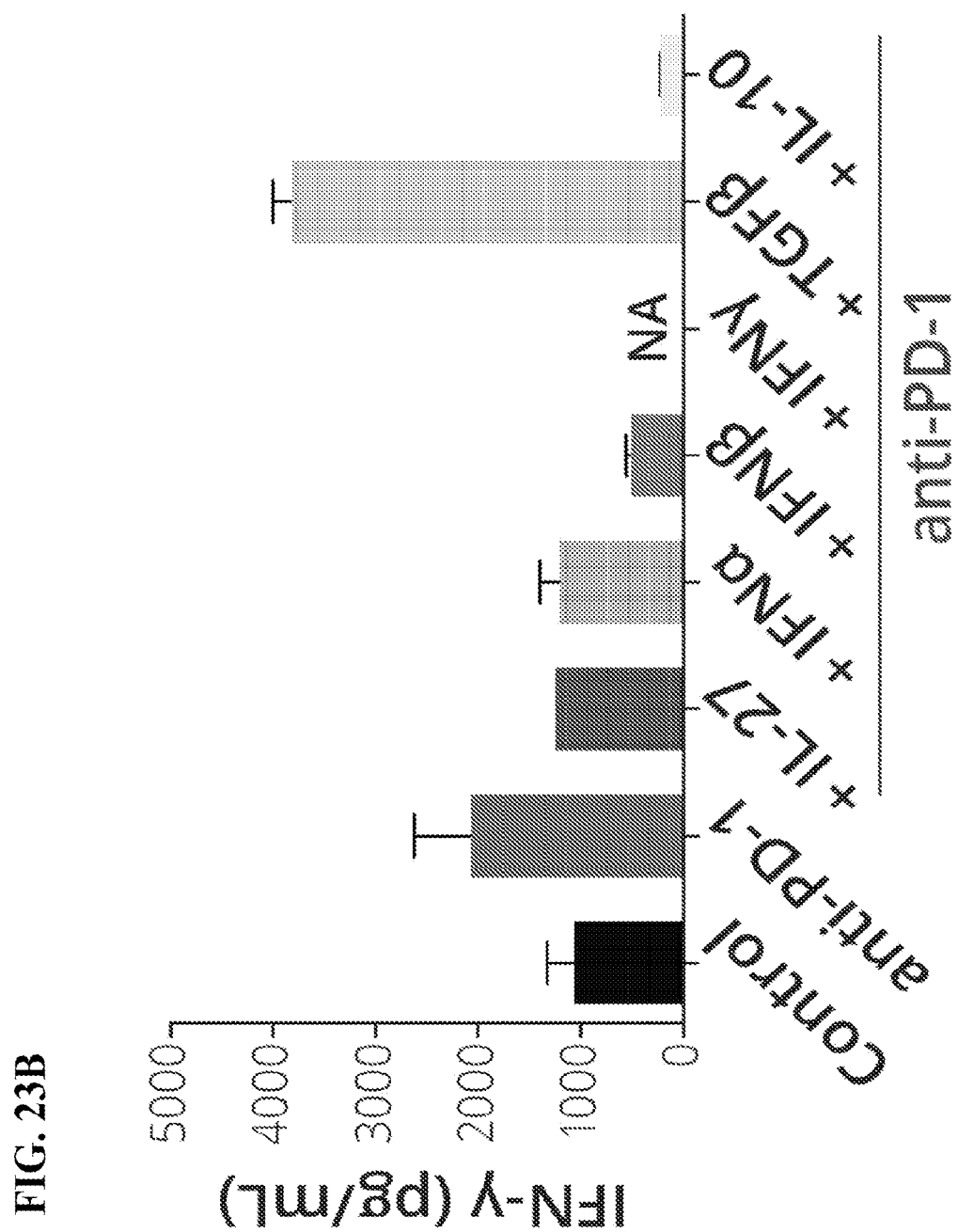
$-\log_{10}(\text{FDR})$

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FIG. 23A



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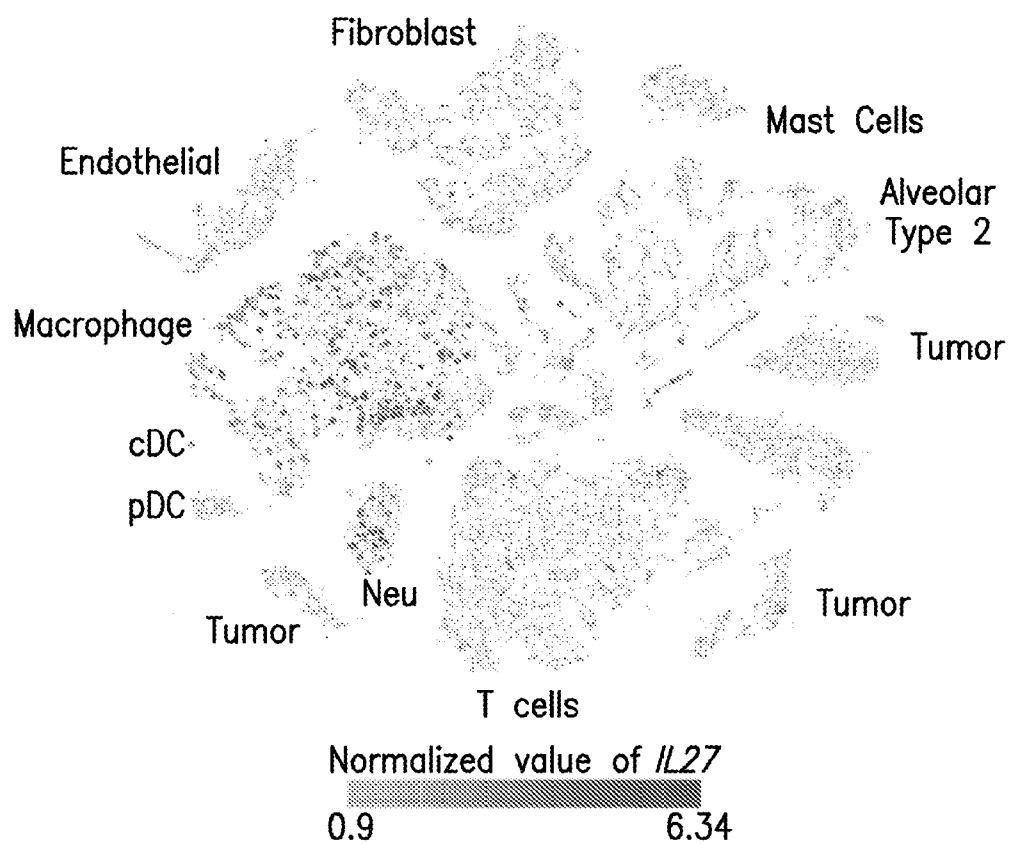


FIG.24A

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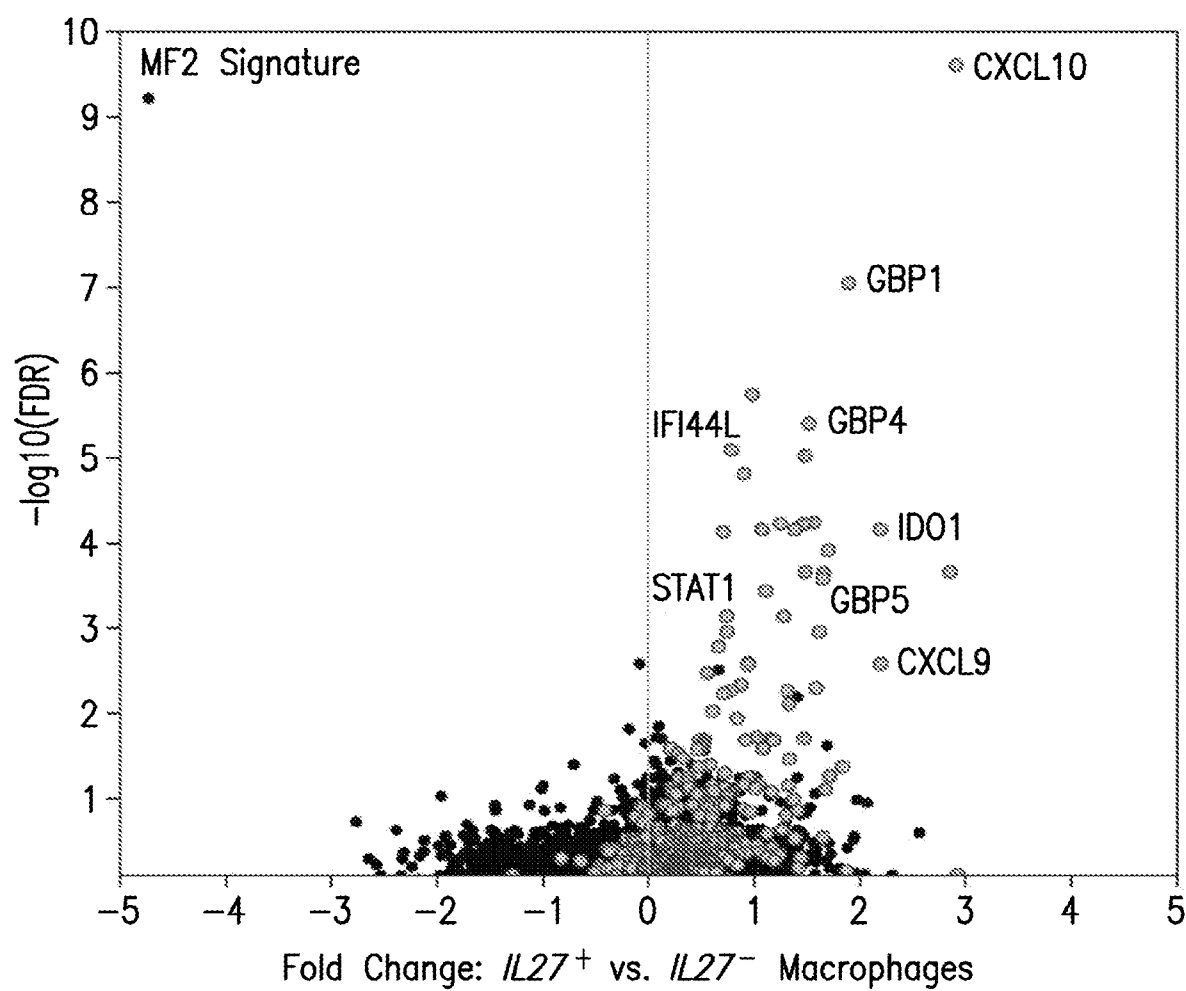


FIG.24B

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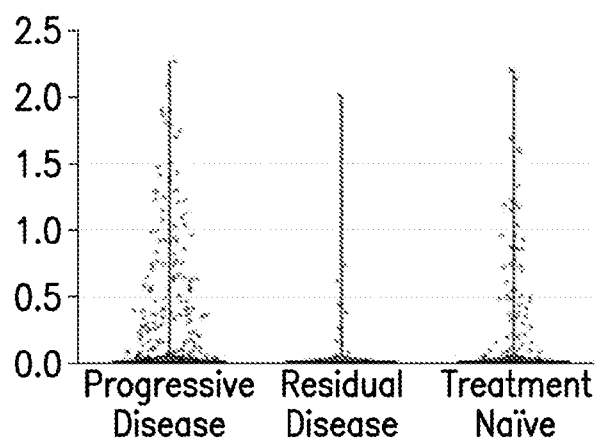


FIG. 24C

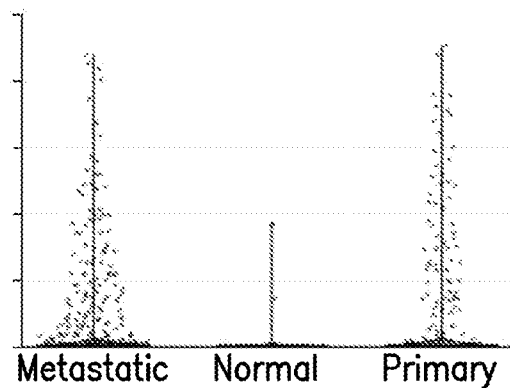


FIG. 24D

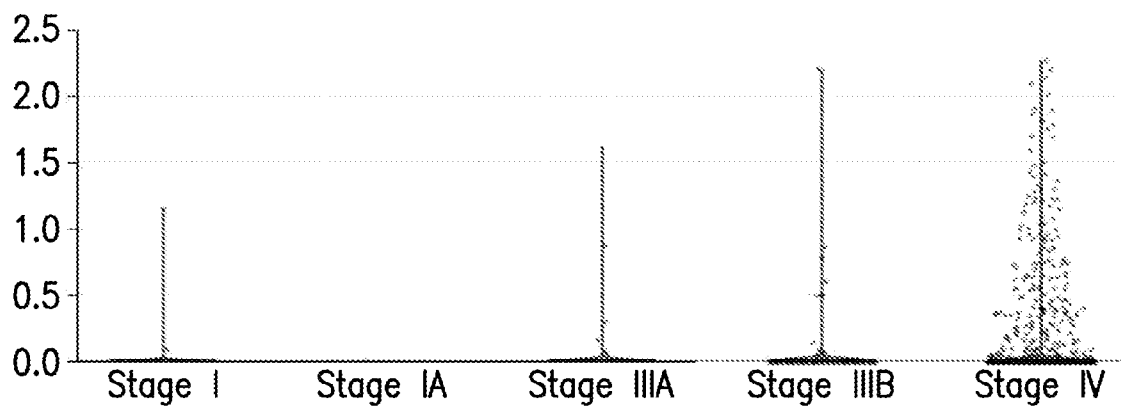


FIG. 24E

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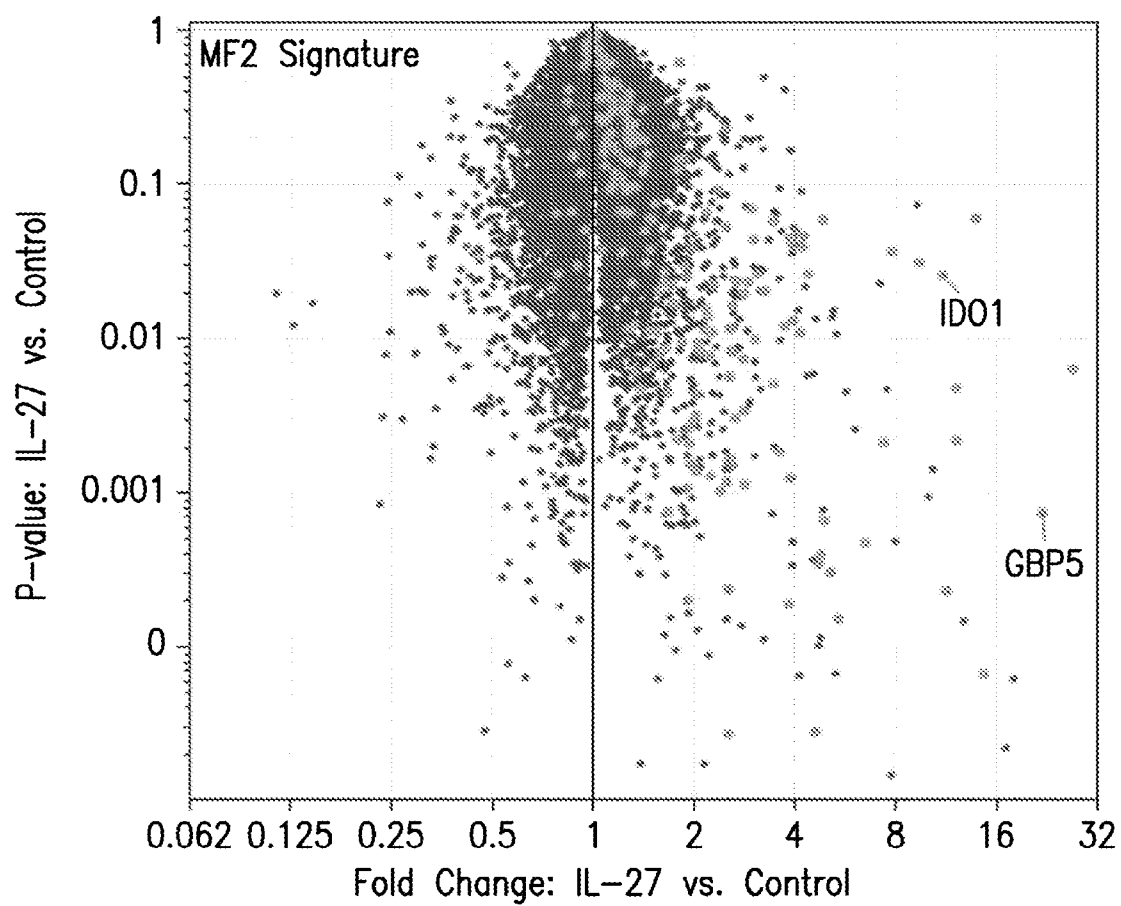


FIG.24F

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Lung AdenoCa

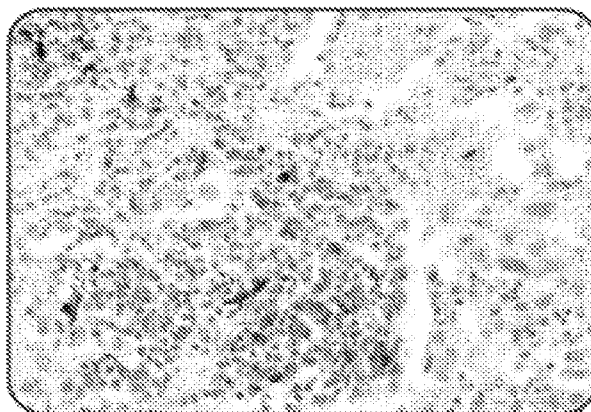


FIG.24G

Lung SCC

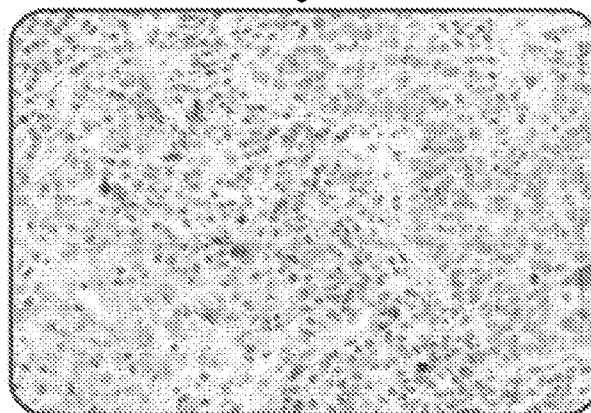


FIG.24H

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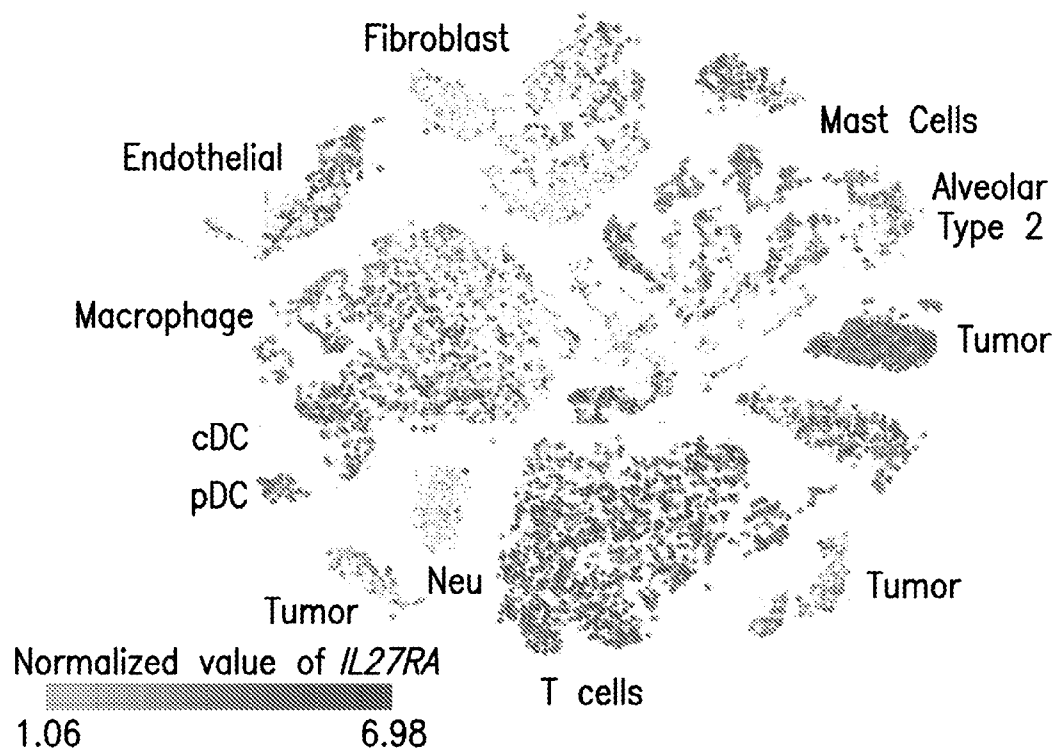


FIG.25A

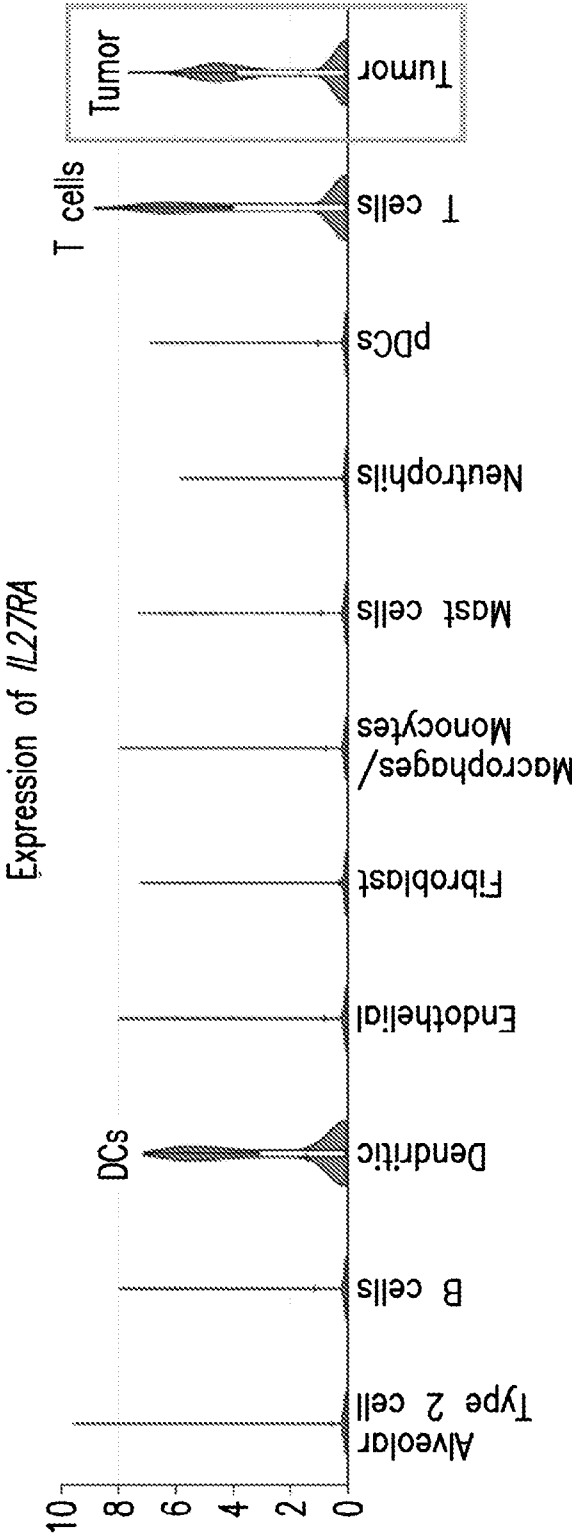


FIG.25B

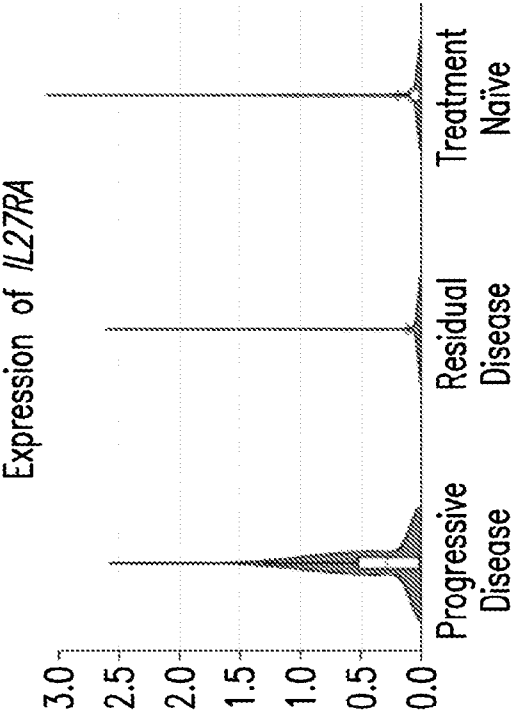


FIG.25C

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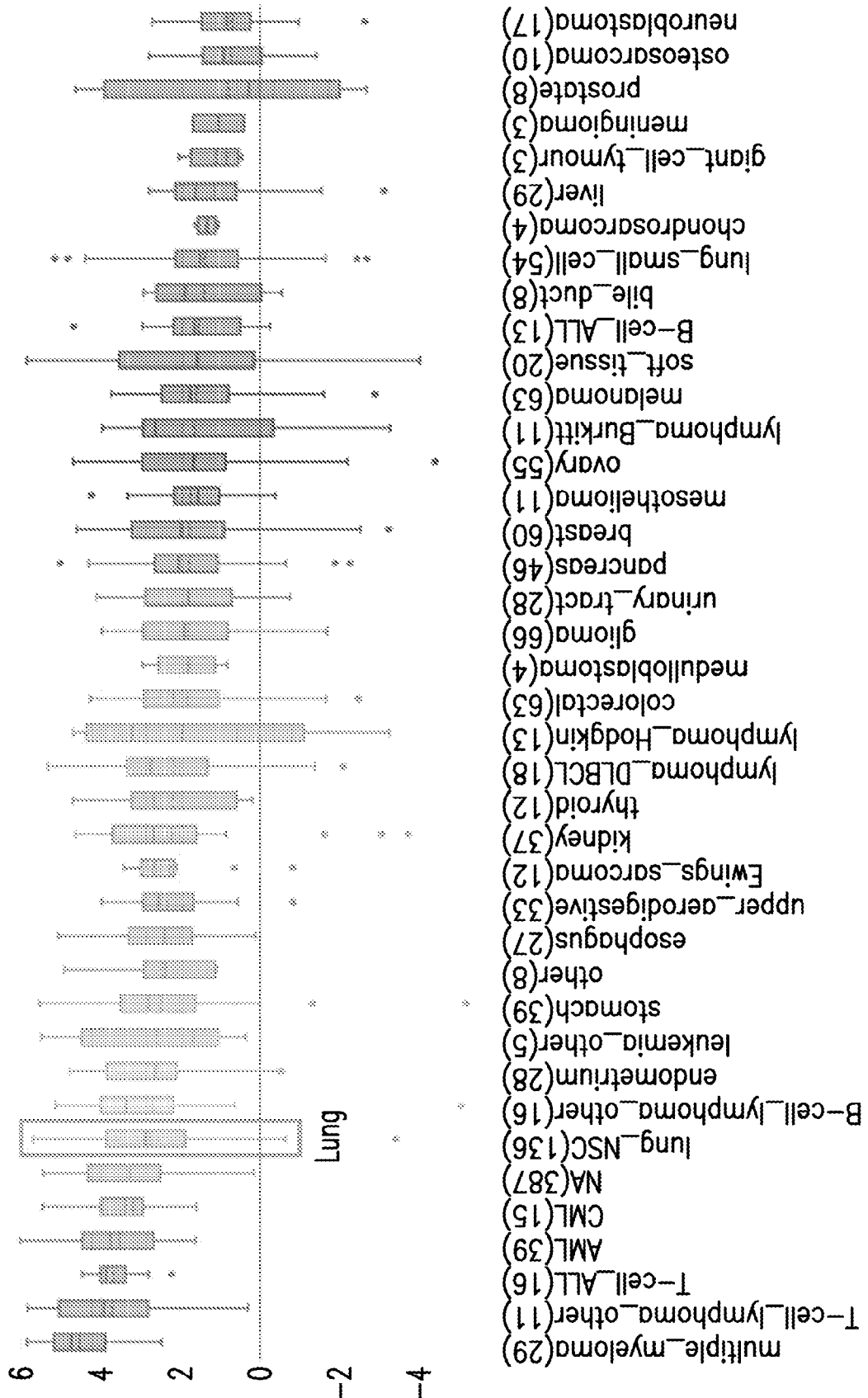


FIG. 26A

FIG. 26B

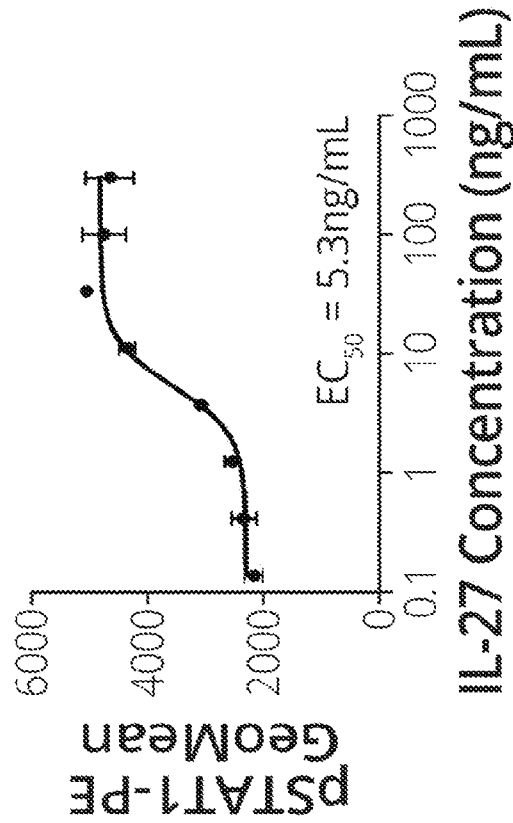
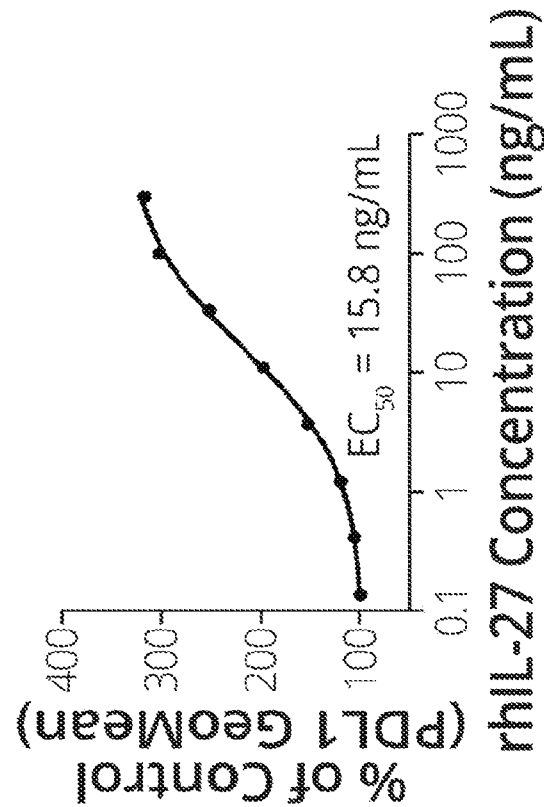


FIG. 26C



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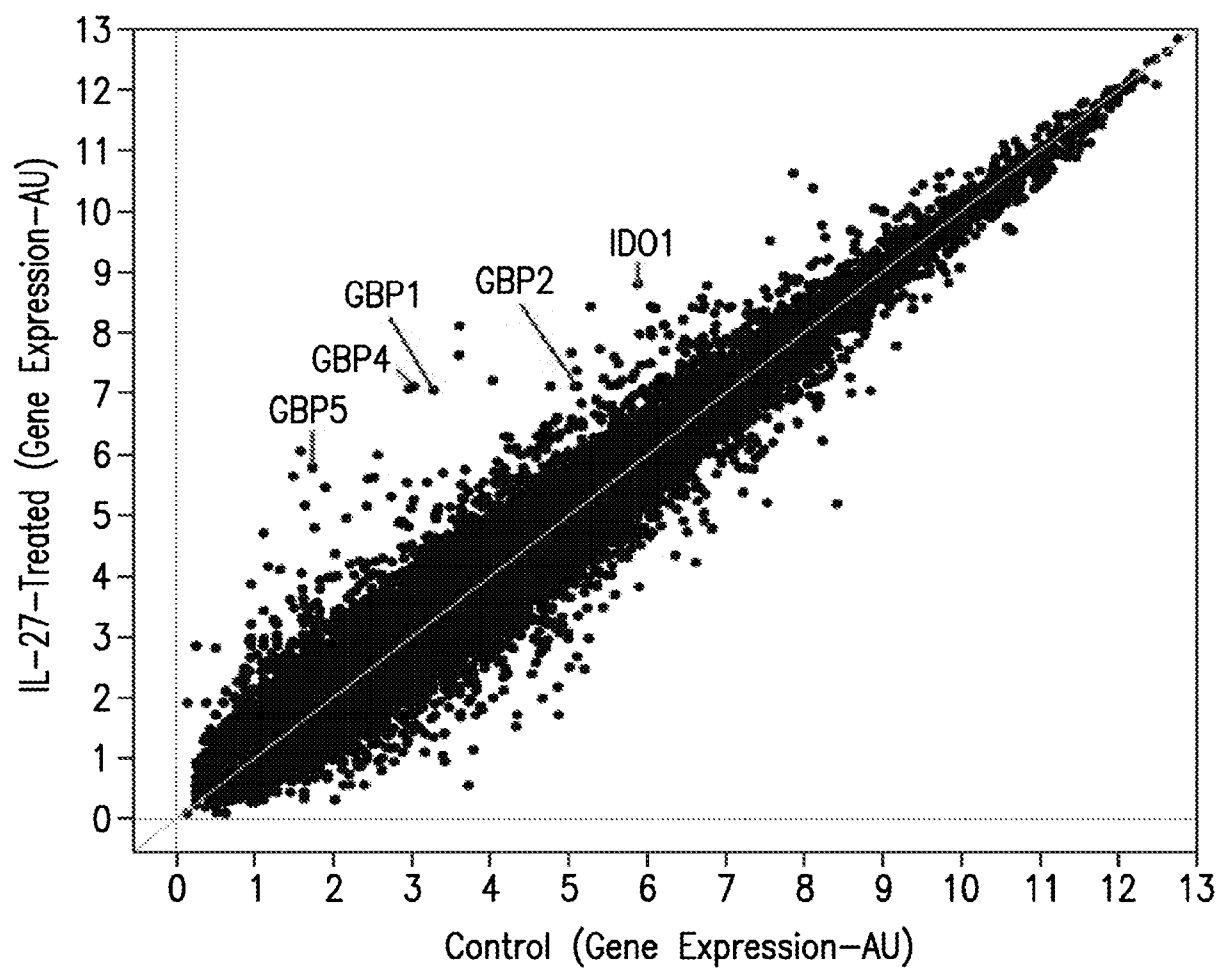


FIG.26D