

What is claimed is:

1. Use of an antibody that antagonizes human IL-27, or an antigen-binding portion thereof, in a method of stimulating an immune response in a subject, the method comprising administering to the subject the antibody or antigen binding portion thereof at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg, 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).
2. Use of an antibody that antagonizes human IL-27, or an antigen-binding portion thereof, in a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject the antibody or an antigen binding portion thereof at a dose of at least about 0.003 mg/kg to at least about 20 mg/kg, 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).
3. The use of claim 1 or 2, 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.
4. The use of claim 1 or 2, wherein the antibody or antigen binding portion thereof is administered at a dose of:
 - (i) about 0.3 mg/kg once about every four weeks;
 - (ii) about 1 mg/kg once about every four weeks;
 - (iii) about 3 mg/kg once about every four weeks;
 - (iv) about 6 mg/kg once about every four weeks;

- (v) about 10 mg/kg once about every four weeks;
 - (vi) about 13 mg/kg once about every four weeks;
 - (vii) about 16 mg/kg once about every four weeks; or
 - (viii) about 20 mg/kg once about every four weeks.
5. The use of claim 1 or 2, wherein the antibody or antigen binding portion thereof is administered at a dose of:
- (i) about 0.3 mg/kg once about every three weeks
 - (ii) about 1 mg/kg once about every three weeks;
 - (iii) about 3 mg/kg once about every three weeks;
 - (iv) about 6 mg/kg once about every three weeks;
 - (v) about 10 mg/kg once about every three weeks;
 - (vi) about 13 mg/kg once about every three weeks;
 - (vii) about 16 mg/kg once about every three weeks; or
 - (viii) about 20 mg/kg once about every three weeks.
6. The use of claim 1 or 2, wherein the antibody or antigen binding portion thereof:
- (i) inhibits or reduces IL-27-dependent STAT1 and/or STAT3 phosphorylation in a cell in the subject;
 - (ii) inhibits or reduces inhibition of CD161 expression in a cell in the subject;
 - (iii) inhibits or reduces PD-L1 expression in a cell in the subject;
 - (iv) induces or enhances PD-1 mediated secretion of one or more cytokines from a cell in the subject;

- (v) alters the expression of TIM-3 in a cell in the subject; or
 - (vi) any combination of (i) to (v).
- 7. The use of claim 1 or 2, wherein the cell is a tumor cell or an immune cell.
- 8. The use of claim 1 or 2, 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).
- 9. The use of claim 1 or 2, wherein the epitope consists or consists essentially of:
 - (i) 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); or
 - (ii) 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).
- 10. The use of claim 1 or 2, 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-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.
- 11. The use of claim 1 or 2, wherein the antibody or the antigen binding portion thereof comprises:
 - (i) 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; or

- (ii) 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.

12. The use of claim 1 or 2, wherein the antibody or the antigen binding portion thereof comprises:

- (a) 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;
- (b) 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;
or
- (c) both (a) and (b).

13. The use of claim 1 or 2, wherein the antibody or the antigen binding portion thereof comprises:

- (a) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 125;
 - (b) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 133; or
 - (c) both (a) and (b).
- 14. The use of claim 1 or 2, wherein the antibody or the antigen binding portion thereof comprises:
 - (a) 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; or
 - (b) 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.
- 15. The use of claim 2, 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.
- 16. The use of claim 1 or 2, wherein the method further comprises administering an additional therapeutic agent to the subject.
- 17. The use of claim 16, 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.

18. The use of claim 16, 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.
19. The use of claim 18, wherein: (i) the PD-1 antagonist is selected from the group consisting of: PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224; and (ii) the PD-L1 inhibitor is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559.
20. The use of claim 1 or 2, wherein following administration of the antibody or antigen binding portion thereof, the subject exhibits:
 - (i) 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;
 - (ii) increased expression of EBI3; wherein the increased expression EBI3 is relative to the expression EBI3 prior to the administration;
 - (iii) 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; and/or
 - (iv) an increased circulating level of IFN γ , relative to the circulating level of IFN γ prior to the administration.