

What is claimed is:

1. An isolated 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); and

comprises 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.
2. The antibody, or antigen binding portion thereof, of claim 1, 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).
3. The antibody, or antigen binding portion thereof, of claim 1 or 2, wherein the epitope comprises Asp146, Arg149, and/or Phe153 of SEQ ID NO: 2 (IL-27p28).
4. The antibody, or antigen binding portion thereof, of claim 3, wherein the epitope further comprises His150 and/or Leu156 of SEQ ID NO: 2 (IL-27p28).
5. The antibody, or antigen binding portion thereof, of claim 3 or 4, wherein the epitope further comprises Gln37, Leu38, Glu42, Leu142, and/or Glu164 of SEQ ID NO: 2 (IL-27p28).
6. The antibody, or antigen binding portion thereof, of any one of claims 3 to 5, wherein the epitope further comprises Glu46, Val49, Ser50, and/or Leu162 of SEQ ID NO: 2 (IL-27p28).

7. The antibody, or antigen binding portion thereof, of any one of claims 1 to 6, 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).

8. The antibody, or antigen binding portion thereof, of any one of claims 1 to 6, 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).

9. The antibody, or antigen binding portion thereof, of any one of claims 1 to 6, 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).

10. The antibody, or antigen binding portion thereof, of any one of claims 1 to 6, 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).

11. The antibody, or antigen binding portion thereof, of any one of claims 1 to 6, 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).

12. The antibody, or antigen binding portion thereof, of any one of claims 1 to 11, 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 IL-27-mediated inhibition of CD161 expression in a cell;
- (v) inhibits or reduces IL-27-mediated PD-L1 and/or TIM-3 expression in a cell; and

- (vi) induces or enhances PD-1-mediated secretion of one or more cytokines from a cell.
13. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 12, wherein the antibody or antigen binding portion thereof binds to human IL-27 with an equilibrium dissociation constant (K_D) of 15 nM or less.
14. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 13, wherein the antibody or antigen binding portion thereof inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell.
15. The isolated antibody, or antigen binding portion thereof, of claim 14, wherein the cell is an immune cell or a cancer cell.
16. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 15, wherein the antibody or antigen binding portion thereof inhibits or reduces inhibition of CD161 expression in a cell.
17. The isolated antibody, or antigen binding portion thereof, of claim 16, wherein the cell is an immune cell.
18. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 17, wherein the antibody or antigen binding portion thereof inhibits or reduces PD-L1 and/or TIM-3 expression in a cell.
19. The isolated antibody, or antigen binding portion thereof, of claim 18, wherein the cell is an immune cell.
20. The isolated antibody, or antigen binding portion thereof, of claim 19, wherein the cell is a cancer cell.

21. The isolated antibody, or antigen binding portion thereof, of claim 20, wherein the cell is a cancer cell, wherein the antibody or antigen binding portion thereof inhibits or reduces PD-L1 expression in a cancer cell.
22. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 21, wherein the antibody or antigen binding portion thereof induces or enhances the PD-1-mediated secretion of one or more cytokines from a cell.
23. The isolated antibody, or antigen binding portion thereof, of claim 22, wherein the one or more cytokines is IFN γ (or IFN γ), IL-17, or TNF α (or TNF α).
24. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 23, wherein the antibody 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.
25. The isolated antibody, or antigen binding portion thereof, according to claim 24, wherein the antibody is an IgG1 antibody or an IgG4 antibody.
26. The isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 25, wherein the antibody comprises an Fc domain comprising at least one mutation.
27. A pharmaceutical composition comprising an isolated antibody or antigen binding portion thereof, of any one of the preceding claims, and a pharmaceutically acceptable carrier.
28. A nucleic acid comprising a nucleotide sequence encoding the light chain, heavy chain, or both light and heavy chains of the isolated antibody, or antigen binding portion thereof, of any one of claims 1 to 26.
29. An expression vector comprising the nucleic acid of claim 28.
30. A cell transformed with an expression vector of claim 29.

31. A method for producing a antibody that specifically binds human IL-27, or an antigen binding portion thereof, the method comprising maintaining an isolated cell according to claim 30 under conditions permitting expression of the monoclonal antibody or antigen binding portion thereof.

32. The method of claim 31, further comprising obtaining the antibody or antigen binding portion thereof.

33. An in vitro method to inhibit or reduce STAT1 and/or STAT3 phosphorylation in a cell, the method comprising contacting the cell with the isolated antibody, or antigen binding fragment, of any one claims 1 to 33, wherein the antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell.

34. An in vitro method to inhibit or reduce inhibition of CD161 expression in a cell, the method comprising contacting the cell with the isolated antibody, or antigen binding fragment, of any one claims 1 to 33, wherein the antibody, or antigen binding portion thereof, inhibits or reduces inhibition of CD161 expression in a cell.

35. An in vitro method to inhibit or reduce PD-L1 and/or TIM-3 expression in a cell, the method comprising contacting the cell with the isolated antibody, or antigen binding fragment, of any one claims 1 to 33, wherein the antibody, or antigen binding portion thereof, inhibits or PD-L1 and/or TIM-3 expression in a cell.

36. An in vitro method to induce or enhance secretion of one or more cytokines from a cell, the method comprising contacting the cell with the isolated antibody, or antigen binding fragment, of any one claims 1 to 33, wherein the antibody, or antigen binding portion thereof, induces or enhances PD-1 mediated secretion of one or more cytokines from a cell.

37. The antibody, or antigen binding portion thereof, of any one of claims 1-25, or the pharmaceutical composition of claim 27, for use in a method of stimulating an immune response in a subject, the method comprising administering to the subject an effective amount of the isolated antibody, or antigen binding portion thereof, or the pharmaceutical composition.

38. The antibody, or antigen binding portion thereof, of any one of claims 1-25, or the pharmaceutical composition of claim 27, for use in method of treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated antibody, or antigen binding portion thereof, or the pharmaceutical composition.

39. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 37 or 38, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell, thereby stimulating the immune response, or treating the cancer.

40. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 37 or 38, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition inhibits or reduces inhibition of CD161 expression in a cell, thereby stimulating the immune response, or treating the cancer.

41. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 37 or 38, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition inhibits or reduces PD-L1 and/or TIM-3 expression on a cell, thereby stimulating the immune response, or treating the cancer.

42. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 37 or 38, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition induces or enhances PD-1-mediated secretion of one or more cytokines from a cell, thereby stimulating the immune response, or treating the cancer.

43. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to any one of claims 38 to 42, wherein 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., renal clear cell carcinoma).

44. An in vitro 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, of any one of claims 1 to 26, concurrently with or sequentially to an anti-PD-1 antibody, thereby to enhance one or more activities of anti-PD1 antibodies.

45. A pharmaceutical composition comprising an anti-PD-1 antibody and an antibody, or antigen binding portion thereof, of any one of claims 1 to 26, and a pharmaceutically acceptable carrier.

46. A kit comprising an anti-PD-1 antibody and an antibody, or antigen binding portion thereof, of any one of claims 1 to 26, for concurrent or sequential administration, and instructions for its use.

47. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to any one of claims 38 to 43, wherein the isolated antibody, or antigen binding portion thereof, is administered 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, or a combination thereof.

48. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 47, wherein the one or more additional therapeutic agents is 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.

49. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein the one or more additional therapeutic agents is a PD-1 antagonist.

50. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 49, 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.

51. The method of claim 48, wherein the PD-L1 inhibitor is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559.

52. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein the one or more additional therapeutic agents 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.

53. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein the one or more additional therapeutic agents is a TIM-3 inhibitor, optionally wherein the TIM-3 inhibitor is MGB453 or TSR-022.

54. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein 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.

55. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein the one or more additional therapeutic agents is a TIGIT inhibitor.

56. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein the one or more additional therapeutic agents is a CD112R inhibitor.

57. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein the one or more additional therapeutic agents is a TAM (Axl, Mer, Tyro) inhibitor.

58. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein the one or more additional therapeutic agents is a 4-1BB agonist.

59. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 48, wherein the one or more additional therapeutic agents is a Tyrosine Kinase Inhibitor (TKI).

60. A kit comprising the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1 to 26 or the pharmaceutical composition of claim 27 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.

61. A kit comprising the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1 to 26 and instructions for use in detecting IL-27 in a sample from a subject, optionally with instructions for use to detect an IL-27-associated cancer in a subject.

62. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 47, wherein the one or more additional therapeutic agents is a tyrosine kinase inhibitor, a CD39 antagonist, a CD73 antagonist, a A2AR antagonist, A2BR antagonist, a dual A2AR/A2BR antagonist, a CCR8 antagonist, a CTLA4 antagonist, a VEG-F inhibitor, or a combination thereof.

63. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 47, wherein the one or more additional therapeutic agents is 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 tyrosine kinase inhibitor, a CD39 antagonist, a CD73 antagonist, a A2AR antagonist, A2BR antagonist, a dual A2AR/A2BR antagonist, a CCR8 antagonist, a CTLA4 antagonist, a VEG-F inhibitor, or a combination thereof.

64. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 63, wherein the one or more additional therapeutic agents is a PD-1 antagonist, a PD-L1 inhibitor, a VEG-F inhibitor, or a combination thereof.

65. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to any one of claims 37 to 44, 47 to 59, or 63 to 64, further comprising measuring an expression of TNFSF15 following the administering.

66. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 65, further comprising measuring an expression of TNFSF15 prior to the administering.

67. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 66, comprising administering an additional dose to the subject exhibiting no change in or decreased expression of TNFSF15 following the administering as compared to the expression of TNFSF15 prior to the administering.

68. The antibody, or antigen binding portion thereof, or the pharmaceutical composition for use according to claim 66, comprising administering an additional dose to the subject exhibiting

increased expression of TNFSF15 following the administering as compared to the expression of TNFSF15 prior to the administering.

69. A method for producing an antibody, or an antigen binding portion thereof, comprising culturing an isolated mammalian cell to express the antibody or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises:

- (a) a heavy chain CDR1 comprising an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 9, 31, 53, 75, 97, or 119;
- (b) a heavy chain CDR2 comprising an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 10, 32, 54, 76, 98, or 120;
- (c) a heavy chain CDR3 comprising an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 11, 33, 55, 77, 99, or 121;
- (d) a light chain CDR1 comprising an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 17, 39, 61, 83, 105, or 127;
- (e) a light chain CDR2 comprising an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 18, 40, 62, 84, 106, or 128; and
- (f) a light chain CDR3 comprising an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 19, 41, 63, 85, 107, or 129.

70. A method for producing an antibody, or an antigen binding portion thereof, comprising culturing an isolated mammalian cell to express the antibody or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein:

- (a) the light chain CDR1 consists of N-XXXXXXLFSSNKKYXX-C;
 - (b) the light chain CDR2 consists of the sequence set forth in SEQ ID NO: 131;
 - (c) the light chain CDR3 consists of N-XXXASAXXX-C;
 - (d) the heavy chain CDR1 consists of the sequence set forth in SEQ ID NO: 122;
 - (e) the heavy chain CDR2 consists of N- XXSSXSXYXXXXXXXXX-C; and
 - (f) the heavy chain CDR3 consists of N- XXXXGRTSYTATXHNXXXX-C;
- wherein X is any amino acid.

71. The method of claim 69 or 70, wherein the antibody 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.
72. The method of claim 71, wherein the antibody is an IgG1 antibody or an IgG4 antibody.
73. The method of claim 69 or 70, wherein the antibody comprises an IgG1 heavy chain constant region or an IgG4 heavy chain constant region.
74. The method of claim 69 or 70, wherein the antibody comprises an Fc domain comprising at least one mutation.
75. The method of claim 74, wherein the antibody comprises an IgG4 heavy chain comprising a substitution selected from the group consisting of S228P, L235E, L235A, and any combination thereof, according to EU numbering.
76. The method of claim 69 or 70, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain comprising an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 15, 37, 59, 81, 103, and 125.
77. The method of claim 69 or 70, wherein the antibody or antigen binding portion thereof comprises a variable light chain comprising an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 23, 45, 67, 89, 111, and 133.
78. The method of claim 69 or 70, further comprising purifying the antibody or antigen binding portion thereof.
79. The method of claim 78, wherein the purifying comprises using a chromatographic technique selected from ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse-phase HPLC chromatography, or a combination thereof.
80. The method of claim 78, wherein the purifying comprises using an immunological technique.

81. The method of claim 78, wherein the purifying comprises using a protein-A chromatography column.
82. The method of claim 69 or 70, further comprising conjugating a therapeutic agent to the antibody or antigen binding portion thereof.
83. The method of claim 69 or 70, wherein the antibody or antigen binding portion thereof is glycosylated.
84. The method of claim 69 or 70, further comprising PEGylating the antibody or antigen binding portion thereof.