

~~What is claimed is:~~Claims

1. ~~An isolated monoclonal antibody that specifically binds to 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 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.~~

2. ~~The isolated monoclonal antibody, or antigen binding portion thereof, of claim 1, 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.~~

3. ~~The isolated monoclonal antibody, or antigen binding portion thereof, of claims 1 or 2, wherein the antibody or antigen binding portion thereof binds to murine IL-27.~~

41. An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1 consisting of N-GFTFXXXX-C (SEQ ID NO: 408), heavy chain CDR2 consisting of N-ISSSXXYI-C (SEQ ID NO: 409), and heavy chain CDR3 sequence set forth in SEQ ID NO: 163; and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 169, 170 and 171, respectively; or

(ii) heavy chain CDR1 consisting of N-FTFXXXXMN-C (SEQ ID NO: 410), heavy chain CDR2 consisting of N-XISSSXXYIXYADSVKG-C (SEQ ID NO: 411), and heavy chain CDR3 sequence set forth in SEQ ID NO: 166; and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 172, 173 and 174, respectively.

52. The isolated monoclonal antibody of claim 41, wherein: the heavy chain CDR1 consists of N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 412) and the heavy chain CDR2 consists of N-ISSS[S/G][S/A]YI-C (SEQ ID NO: 413); or the heavy chain CDR1 consists of N-FTF[S/A/R][S/R][T/Y][G/S]MN-C (SEQ ID NO: 414) and the heavy chain CDR2 consists N-[G/S]ISSS[S/G][S/A]YI[L/Y]YADSVKG-C (SEQ ID NO: 415).

6. ~~The isolated monoclonal antibody of claim 4, wherein:~~

~~(i) — the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 161, 162 and 163, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 169, 170 and 171, respectively;~~

~~(ii) — the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 164, 165 and 166, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 172, 173 and 174, respectively;~~

~~(iii) — the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 73, 74 and 75, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 81, 82 and 83, respectively;~~

~~(iv) — the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 76, 77 and 78, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 84, 85 and 86, respectively;~~

~~(v) — the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 95, 96 and 97, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 103, 104 and 105, respectively;~~

~~(vi) — the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 98, 99 and 100, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 106, 107 and 108, respectively;~~

~~(vii) — the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 117, 118 and 119, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 125, 126 and 127, respectively;~~

(viii) ~~the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 120, 121 and 122, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 128, 129 and 130, respectively;~~

(ix) ~~the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 139, 140 and 141, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 147, 148 and 149, respectively;~~

(x) ~~the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 142, 143 and 144, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 150, 151 and 152, respectively;~~

(xi) ~~the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 51, 52 and 53, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 59, 60 and 61, respectively; or~~

(xii) ~~the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 54, 55 and 56, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 62, 63 and 64, respectively.~~

7. ~~An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:~~

~~—— (i) heavy chain CDR1 consisting of N-GGSFSXYX-C (SEQ ID NO: 416), heavy chain CDR2 consisting of N-IDXSGXT-C (SEQ ID NO: 417), and heavy chain CDR3 sequence consisting of N-ARXXXY[Y][X]_{n=0-1}DSS[X]_{n=4-6}DX-C (SEQ ID NO: 418); and light chain CDR1 consisting of N-QXXSXY-C (SEQ ID NO: 419), light chain CDR2 consisting of N-DXS-C (SEQ ID NO: 420), and light chain CDR3 sequence consisting of N-QQXXDXPIT-C (SEQ ID NO: 421), respectively; or~~

~~—— (ii) heavy chain CDR1 consisting of N-GSFSXYXWS-C (SEQ ID NO: 422), heavy chain CDR2 consisting of N-SIDXSGXTXYNPSLKS-C (SEQ ID NO: 423), and heavy chain CDR3 sequence consisting of N-ARXXXY[Y][X]_{n=0-1}DSS[X]_{n=4-6}DX-C (SEQ ID NO: 418); and light chain CDR1 consisting of N-XASQXXSXYLX-C (SEQ ID NO: 424), light chain CDR2 consisting of N-DXSNXXT-C (SEQ ID NO: 425), and light chain CDR3 sequence consisting of N-QQXXDXPIT-C (SEQ ID NO: 421), respectively.~~

8. ~~The isolated monoclonal antibody of claim 7, wherein:~~

~~(i) the heavy chain CDR1 consists of N-GGSFS[R/D]Y[E/Y]-C (SEQ ID NO: 426), the heavy chain CDR2 consists of N-ID[W/Y]SG[I/S]T-C (SEQ ID NO: 427), heavy chain CDR3 sequence consisting of N-AR[D/L][P/G][M/V]YY[-/Y]DSS[VSTGSV/DLGF]D[V/I]-C (SEQ ID NO: 428); and light chain CDR1 consisting of N-Q[S/D][V/I]S[S/N]Y-C (SEQ ID NO: 429), light chain CDR2 consisting of N-D[S/A]S-C (SEQ ID NO: 430), and light chain CDR3 sequence consisting of N-QQ[D/Y][S/D]D[H/L]PIT-C (SEQ ID NO: 431), respectively; or~~

~~(ii) the heavy chain CDR1 consists of N-GSFS[R/D]Y[E/Y]WS-C (SEQ ID NO: 432), the heavy chain CDR2 consists of N-SID[W/Y]SG[I/S]T[N/E]YNPSLKS-C (SEQ ID NO: 433), heavy chain CDR3 sequence consisting of N-AR[D/L][P/G][M/V]YY[-/Y]DSS[VSTGSV/DLGF]D[V/I]-C (SEQ ID NO: 428); and light chain CDR1 consisting of N-[Q/R]ASQ[S/D][V/I]S[S/N]YL[N/A]-C (SEQ ID NO: 434), light chain CDR2 consisting of N-D[S/A]SN[R/L][A/E]T-C (SEQ ID NO: 435), and light chain CDR3 sequence consisting of N-QQ[D/Y][S/D]D[H/L]PIT-C (SEQ ID NO: 431), respectively.~~

9. ~~The isolated monoclonal antibody of claim 7, wherein:~~

~~(i) the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 229, 230 and 231, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 237, 238 and 239, respectively; or~~

~~(ii) the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 232, 233 and 234, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 240, 241 and 242, respectively.~~

10. ~~The isolated monoclonal antibody of claim 7, wherein:~~

~~(i) the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 251, 252 and 253, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 259, 260 and 261, respectively; or~~

~~(ii) the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 254, 255 and 256, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 262, 263 and 264, respectively.~~

11. — An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 23, 24 and 25, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 26, 27 and 28, respectively.

12. — An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 339, 340 and 341, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 347, 348 and 349, respectively; or

(ii) heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 342, 343 and 344, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 350, 351 and 352, respectively.

13. — An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 185, 186 and 187, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 193, 194 and 195, respectively; or

(ii) heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 188, 189 and 190, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 196, 197 and 198, respectively.

14. — An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 207, 208 and 209, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 215, 216 and 217, respectively; or

(ii) heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 210, 211 and 212, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 218, 219 and 220, respectively.

15. — An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:

(i) heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 273, 274 and 275, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 281, 282 and 283, respectively; or

(ii) heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 276, 277 and 278, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 284, 285 and 286, respectively.

16. — An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:

—— (i) heavy chain CDR1 consisting of N-GFTFSSYG-C (SEQ ID NO: 361), heavy chain CDR2 consisting of N-IXXDGSXK-C (SEQ ID NO: 436), and heavy chain CDR3 sequence consisting of N-ARXAP[X]_{n=3-8}DV-C (SEQ ID NO: 437); and light chain CDR1 consisting of N-QSXSSY-C (SEQ ID NO: 438), light chain CDR2 consisting of N-XXS-C (SEQ ID NO: 439), and light chain CDR3 sequence consisting of N-QQXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 440), respectively; or

—— (ii) heavy chain CDR1 consisting of N-FTFSSYGMX-C (SEQ ID NO: 441), heavy chain CDR2 consisting of N-XIXXDGSXKYYXDSVKG-C (SEQ ID NO: 442), and heavy chain CDR3 sequence consisting of N-ARXAP[X]_{n=3-8}DV-C (SEQ ID NO: 437); and light chain CDR1 consisting of N-RASQSXSSYLX-C (SEQ ID NO: 443), light chain CDR2 consisting of N-[X]_{n=1}

~~${}_{2}\text{SS}[\text{X}]_{n=3-4}\text{-C}$ (SEQ ID NO: 444), and light chain CDR3 sequence consisting of $\text{N-QQXXXXP}[\text{X}]_{n=0-1}\text{-T-C}$ (SEQ ID NO: 440), respectively.~~

17. ~~The isolated monoclonal antibody of claim 16, wherein:~~

~~(i) the heavy chain CDR1 consists of N-GFTFSSYG-C (SEQ ID NO: 361), heavy chain CDR2 consists of $\text{N-I}[\text{K/W}][\text{Q/Y}]\text{DGS}[\text{E/N}]\text{K-C}$ (SEQ ID NO: 445), and heavy chain CDR3 sequence consists of $\text{N-AR}[\text{D/G}]\text{AP}[\text{WDIYDY YM/EYV}]\text{DV-C}$ (SEQ ID NO: 446); and light chain CDR1 consists of $\text{N-QS}[\text{I/V}]\text{SSY-C}$ (SEQ ID NO: 447), light chain CDR2 consists of $\text{N-[A/D]}[\text{A/S}]\text{S-C}$ (SEQ ID NO: 448), and light chain CDR3 sequence consists of $\text{N-QQ}[\text{S/Y}][\text{Y/S}][\text{V/L}][\text{P/Y}]\text{P}[\text{W/-}]\text{T-C}$ (SEQ ID NO: 449), respectively; or (ii) the heavy chain CDR1 consists of $\text{N-FTFSSYGM}[\text{S/H}]\text{-C}$ (SEQ ID NO: 450), heavy chain CDR2 consists of $\text{N-[N/V]}[\text{K/W}][\text{Q/Y}]\text{DGS}[\text{E/N}]\text{KYY}[\text{V/A}]\text{DSVKG-C}$ (SEQ ID NO: 451), and heavy chain CDR3 sequence consists of $\text{N-AR}[\text{D/G}]\text{AP}[\text{WDIYDY YM/EYV}]\text{DV-C}$ (SEQ ID NO: 446); and light chain CDR1 consists of $\text{N-RASQS}[\text{I/V}]\text{SSYL}[\text{N/A}]\text{-C}$ (SEQ ID NO: 452), light chain CDR2 consists of $\text{N-[AA/D]SS[LQS/NRAT]C}$ (SEQ ID NO: 453), and light chain CDR3 sequence consists of $\text{N-QQ}[\text{S/Y}][\text{Y/S}][\text{V/L}][\text{P/Y}]\text{P}[\text{W/-}]\text{T-C}$ (SEQ ID NO: 449), respectively.~~

18. ~~The isolated monoclonal antibody of claim 16, wherein:~~

~~(i) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 361, 362 and 363, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 369, 370 and 371, respectively; or~~

~~(ii) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 364, 365 and 366, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 372, 373 and 374, respectively.~~

19. ~~The isolated monoclonal antibody of claim 16, wherein:~~

~~(i) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 383, 384 and 385, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 391, 392 and 393, respectively; or~~

(ii) ~~the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 386, 387 and 388, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 394, 395 and 396, respectively.~~

20. ~~An isolated monoclonal antibody that specifically binds human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain CDRs selected from the group consisting of:~~

~~—— (i) heavy chain CDR1 consisting of N-GFTFXXXX-C (SEQ ID NO: 408), heavy chain CDR2 consisting of N-IXXXXXXXXX-C (SEQ ID NO: 456), and heavy chain CDR3 sequence consisting of N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 458); and light chain CDR1 consisting of N-QS[X]_{n=1-3}SS[X]_{n=0-4}Y-C (SEQ ID NO: 460), light chain CDR2 consisting of N-XXS-C (SEQ ID NO: 462), and light chain CDR3 sequence consisting of N-QQXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 464), respectively; or~~

~~—— (ii) heavy chain CDR1 consisting of N-FTFXXXXMX-C (SEQ ID NO: 466), heavy chain CDR2 consisting of N-XIXXXXXXXXXXYXDSVKG-C (SEQ ID NO: 468), and heavy chain CDR3 sequence consisting of N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 470); and light chain CDR1 consisting of N-RASQSXSSYLX-C (SEQ ID NO: 472), light chain CDR2 consisting of N-[X]_{n=1-2}S[X]_{n=4-5}-C (SEQ ID NO: 474), and light chain CDR3 sequence consisting of N-QQXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 476), respectively.~~

21. ~~The isolated monoclonal antibody of claim 20, wherein:~~

~~(i) the heavy chain CDR1 consists of N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 454), heavy chain CDR2 consists of N-I[S/K/W][S/Q/Y][S/D][S/G][S/A][Y/E/N][I/K]-C (SEQ ID NO: 455), and heavy chain CDR3 sequence consists of N-AR[DGGRTSYTATAHNWF/DAPWDIYDYDM/GAPEYV]D[P/V]-C (SEQ ID NO: 457); and light chain CDR1 consists of N-QS[VLF/I/V]SS[NNKN/-]Y-C (SEQ ID NO: 459), light chain CDR2 consists of N-[W/A/D][A/S]S-C (SEQ ID NO: 461), and light chain CDR3 sequence consists of N-QQ[H/S/Y][A/Y/S][S/V/L][A/P/Y]P[P/W/-]T-C (SEQ ID NO: 463), respectively; or~~

~~(ii) the heavy chain CDR1 consists of N-FTF[S/A/R][S/R][T/Y][G/S]M[N/S/H]-C (SEQ ID NO: 465), heavy chain CDR2 consists of N-~~

[G/S/N/V][S/K/W][S/Q/Y][S/D][S/G][S/A][Y/E/N][I/K][L/Y]Y[V/A]DSVKG-C (SEQ ID NO: 467), and heavy chain CDR3 sequence consists of N-AR[D/G][GGRTSYTATAHNWF/APWDIYDYYM/APEYV]D[P/V]-C (SEQ ID NO: 469); and light chain CDR1 consists of N-RASQS[I/V]SSYL[N/A]-C (SEQ ID NO: 471), light chain CDR2 consists of N-[WA/AA/D]S[TRES/SLQS/SNRAT]-C (SEQ ID NO: 473), and light chain CDR3 sequence consists of N-QQ[H/S/Y][A/Y/S][S/V/L][A/P/Y]P[P/W/]-T-C (SEQ ID NO: 475), respectively.

223. The isolated monoclonal antibody, or antigen binding portion thereof, of ~~any one of claims 1-21~~ claim 1, wherein:

(a) the antibody or antigen binding portion thereof antagonizes IL-27; and/or

23. ~~The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-22, wherein~~ (b) the antibody or antigen binding portion thereof inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell;

24. ~~The isolated monoclonal antibody, or antigen binding portion thereof, of claim 23,~~ optionally wherein the cell is an immune cell;

25. ~~The isolated monoclonal antibody, or antigen binding portion thereof, of claim 23, wherein the cell is~~ or a cancer cell;

26. ~~The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-25, wherein~~ (c) the antibody or antigen binding portion thereof inhibits or reduces inhibition of CD161 expression in a cell;

27. ~~The isolated monoclonal antibody, or antigen binding portion thereof, of claim 26, wherein the cell is an immune cell.~~

~~28. — The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-27, wherein (d) the antibody or antigen binding portion thereof inhibits or reduces PD-L1 and/or TIM-3 expression in a cell;~~

~~29. — The isolated monoclonal antibody, or antigen binding portion thereof, of claim 28, wherein the cell is an immune cell.~~

~~30. — The isolated monoclonal antibody, or antigen binding portion thereof, of claim 29, wherein the cell is a cancer cell.~~

~~31. — The isolated monoclonal antibody, or antigen binding portion thereof, of claim 29, 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.~~

~~32. — The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-31, wherein (e) the antibody or antigen binding portion thereof induces or enhances the PD-1-mediated secretion of one or more cytokines from a cell;~~

~~33. — The isolated monoclonal antibody, or antigen binding portion thereof, of claim 32, wherein the one or more cytokines is IFN γ , TNF α or IL-6.~~

~~34. — The isolated monoclonal antibody, or antigen binding portion thereof, of claim 33, wherein the one or more cytokines is IFN γ , IL-17, TNF α or IL-6.~~

~~35. — The isolated monoclonal antibody, or antigen binding portion thereof, of claim 33, wherein the one or more cytokines is TNF α .~~

~~36. — The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 32-35, wherein the cell is an immune cell.~~

~~37. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-36, wherein (f) 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;~~

~~38. The isolated monoclonal antibody, or antigen binding portion thereof, according to claim 37, wherein the antibody is an IgG1 antibody or an IgG4 antibody.~~

~~39. The isolated monoclonal antibody, or antigen binding portion thereof, according to claim 38, wherein the antibody comprises a wild type IgG1 heavy chain constant region.~~

~~40. The isolated monoclonal antibody, or antigen binding portion thereof, according to claim 38, wherein the antibody comprises a wild type IgG4 heavy chain constant region.~~

~~41. The isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-40, wherein (g) the antibody comprises an Fc domain comprising at least one mutation;~~

~~42. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 41, optionally wherein the antibody comprises a mutant IgG1 heavy chain constant region;~~

~~43. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 41, wherein the antibody comprises or a mutant IgG4 heavy chain constant region; or (h) any combination of (a)-(g).~~

4. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 1, wherein the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 161, the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 162, the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 163 the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 169, the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 170, and the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 171.

5. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 1, wherein the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 164, the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 165, the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 166 the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 172, the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 173, and the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 174.

6. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 3, wherein the cell is an immune cell or a cancer cell.

7. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 3, wherein the one or more cytokines comprise IFN γ , IL-17, TNF α , IL-6, or any combination thereof.

8. The isolated monoclonal antibody of claim 1, wherein the antibody comprises an IgG1 heavy chain constant region or an IgG4 heavy chain constant region.

~~449.~~ The isolated monoclonal antibody, ~~or antigen binding portion thereof,~~ of claim ~~431,~~ wherein the mutant IgG4 heavy chain constant region comprises any one of the substitutions S228P, L235E, L235A, or a combination thereof, according to EU numbering.

10. The isolated antibody, or antigen-binding portion thereof, of claim 1, wherein the heavy chain variable region comprises an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 167.

11. The isolated antibody, or antigen-binding portion thereof, of claim 1, wherein the light chain variable region comprises an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 175.

12. The isolated antibody, or antigen-binding portion thereof, of claim 1, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 167, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 175.

13. The isolated antibody, or antigen-binding portion thereof, of claim 1, which comprises an IgG1 heavy chain constant region or an IgG4 heavy chain constant region.

14. The isolated antibody, or antigen-binding portion thereof, of claim 12, which comprises (i) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 177, and (ii) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 179.

~~45. An isolated monoclonal antibody, or antigen binding portion thereof, that binds to substantially the same epitope as the antibody, or antigen binding portion thereof, according to any one of claims 1-44.~~

~~46. An isolated monoclonal antibody, or antigen binding portion thereof, that binds to at least one of the amino acid residues bound by the antibody, or antigen binding portion thereof, according to any one of claims 1-44.~~

~~47. An isolated monoclonal antibody, or antigen binding portion thereof, wherein a mutation of the epitope 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 claims 1-44.~~

~~48. An isolated monoclonal antibody, or antigen binding portion thereof, that binds to an epitope on IL-27, wherein the epitope is the same or is similar to the epitope bound by an antibody molecule described in Table 12.~~

~~49. An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises 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: 51, 52 and 53, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 59, 60 and 61, respectively;

(ii) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 73, 74 and 75, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 81, 82 and 83, respectively;

(iii) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 95, 96 and 97, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 103, 104 and 105, respectively;

(iv) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 117, 118 and 119, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 125, 126 and 127, respectively;

(v) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 139, 140 and 141, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 147, 148 and 149, respectively;

(vi) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 161, 162 and 163, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 169, 170 and 171, respectively;

(vii) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 185, 186 and 187, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 193, 194 and 195, respectively;

(viii) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 207, 208 and 209, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 215, 216 and 217, respectively;

(ix) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 229, 230 and 231, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 237, 238 and 239, respectively;

(x) — heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 251, 252 and 253, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 259, 260 and 261, respectively;

(xi) ~~heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 273, 274 and 275, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 281, 282 and 283, respectively;~~

(xii) ~~heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 295, 296 and 297, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 303, 304 and 305, respectively;~~

(xiii) ~~heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 317, 318 and 319, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 325, 326 and 327, respectively;~~

(xiv) ~~heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 339, 340 and 341, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 347, 348 and 349, respectively;~~

(xv) ~~heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 361, 362 and 363, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 369, 370 and 371, respectively; and~~

(xvi) ~~heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 383, 384 and 385, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 391, 392 and 393, respectively.~~

50. ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL 27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises 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: 54, 55 and 56, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 62, 63 and 64, respectively;~~

~~(ii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 76, 77 and 78, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 84, 85 and 86, respectively;~~

~~(iii) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 98, 99 and 100, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 106, 107 and 108, respectively;~~

(iv)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 120, 121 and 122, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 128, 129 and 130, respectively;

(v)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 142, 143 and 144, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 150, 151 and 152, respectively;

(vi)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 164, 165 and 166, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 172, 173 and 174, respectively;

(vii)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 188, 189 and 190, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 196, 197 and 198, respectively;

(viii)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 210, 211 and 212, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 218, 219 and 220, respectively;

(ix)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 232, 233 and 234, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 240, 241 and 242, respectively;

(x)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 254, 255 and 256, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 262, 263 and 264, respectively;

(xi)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 276, 277 and 278, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 284, 285 and 286, respectively;

(xii)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 298, 299 and 300, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 306, 307 and 308, respectively;

(xiii)——heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 320, 321 and 322, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 328, 329 and 330, respectively;

~~(xiv) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 342, 343 and 344, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 350, 351 and 352, respectively;~~

~~(xv) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 364, 365 and 366, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 372, 373 and 374, respectively; and~~

~~(xvi) heavy chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 386, 387 and 388, respectively, and light chain CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NOs: 394, 395 and 396, respectively.~~

~~5415.~~ An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein

the antibody or antigen binding portion thereof comprises heavy and light chain CDRs, wherein the heavy chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: ~~164, 165 and 166~~ 161, 162 and 163, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: ~~172, 173 and 174~~ 169, 170 and 171, respectively.

16. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 15, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain comprising an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 167.

17. The isolated monoclonal antibody of claim 15, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a variable light chain comprising an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 175.

18. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 15, wherein the antibody or antigen binding portion thereof comprises a variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 167, and a variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 175.

19. The isolated monoclonal antibody of claim 15, wherein the antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 177, and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 179.

~~52. An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 57, 79, 101, 123, 145, 167, 191, 213, 235, 257, 279, 301, 323, 345, 367 and 389; and wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 65, 87, 109, 131, 153, 175, 199, 221, 243, 265, 287, 309, 331, 353, 375 and 397.~~

~~53. An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences selected from the group consisting of:~~

- ~~(i) SEQ ID NO: 57 and 65, respectively;~~
- ~~(ii) SEQ ID NO: 79 and 87, respectively;~~
- ~~(iii) SEQ ID NO: 101 and 109, respectively;~~
- ~~(iv) SEQ ID NO: 123 and 131, respectively;~~
- ~~(v) SEQ ID NO: 145 and 153, respectively;~~
- ~~(vi) SEQ ID NO: 167 and 175, respectively;~~
- ~~(vii) SEQ ID NO: 191 and 199, respectively;~~
- ~~(viii) SEQ ID NO: 213 and 221, respectively;~~
- ~~(ix) SEQ ID NO: 235 and 243, respectively;~~
- ~~(x) SEQ ID NO: 257 and 265, respectively;~~
- ~~(xi) SEQ ID NO: 279 and 287, respectively;~~
- ~~(xii) SEQ ID NO: 301 and 309, respectively;~~
- ~~(xiii) SEQ ID NO: 323 and 331, respectively;~~
- ~~(xiv) SEQ ID NO: 345 and 353, respectively;~~

(xv) — SEQ ID NO: 367 and 375, respectively; and

(xvi) — SEQ ID NO: 389 and 397, respectively.

54. — An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 57, 79, 101, 123, 145, 167, 191, 213, 235, 257, 279, 301, 323, 345, 367 and 389; and wherein the light chain variable region comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 65, 87, 109, 131, 153, 175, 199, 221, 243, 265, 287, 309, 331, 353, 375 and 397.

55. — An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:

- (i) — SEQ ID NO: 57 and 65, respectively;
- (ii) — SEQ ID NO: 79 and 87, respectively;
- (iii) — SEQ ID NO: 101 and 109, respectively;
- (iv) — SEQ ID NO: 123 and 131, respectively;
- (v) — SEQ ID NO: 145 and 153, respectively;
- (vi) — SEQ ID NO: 167 and 175, respectively;
- (vii) — SEQ ID NO: 191 and 199, respectively;
- (viii) — SEQ ID NO: 213 and 221, respectively;
- (ix) — SEQ ID NO: 235 and 243, respectively;
- (x) — SEQ ID NO: 257 and 265, respectively;
- (xi) — SEQ ID NO: 279 and 287, respectively;
- (xii) — SEQ ID NO: 301 and 309, respectively;
- (xiii) — SEQ ID NO: 323 and 331, respectively;
- (xiv) — SEQ ID NO: 345 and 353, respectively;

(xv) ~~SEQ ID NO: 367 and 375, respectively; and~~

(xvi) ~~SEQ ID NO: 389 and 397, respectively.~~

56. ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences set forth in SEQ ID NO: 167 and 175, respectively.~~

57. ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises heavy and light chain variable regions comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 167 and 175, respectively.~~

58. ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 67, 89, 111, 133, 155, 177, 201, 243, 245, 267, 289, 311, 333, 355, 377 and 399; and wherein the light chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 69, 91, 113, 135, 157, 179, 203, 225, 247, 269, 291, 313, 335, 357, 379 and 401.~~

59. ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain, wherein the heavy chain comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 67, 89, 111, 133, 155, 177, 201, 243, 245, 267, 289, 311, 333, 355, 377 and 399; and wherein the light chain comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 69, 91, 113, 135, 157, 179, 203, 225, 247, 269, 291, 313, 335, 357, 379 and 401.~~

60. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 71, 93, 115, 137, 159, 181, 205, 227, 249, 271, 293, 315, 337, 359, 381 and 403; and wherein the light chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 69, 91, 113, 135, 157, 179, 203, 225, 247, 269, 291, 313, 335, 357, 379 and 401.~~

61. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain, wherein the heavy chain comprises 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, 93, 115, 137, 159, 181, 205, 227, 249, 271, 293, 315, 337, 359, 381 and 403; and wherein the light chain comprises an amino acid sequence which is at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 69, 91, 113, 135, 157, 179, 203, 225, 247, 269, 291, 313, 335, 357, 379 and 401.~~

62. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences selected from the group consisting of:~~

- ~~—— (i) — SEQ ID NO: 67 and 69, respectively;~~
- ~~(ii) — SEQ ID NO: 89 and 91, respectively;~~
- ~~(iii) — SEQ ID NO: 111 and 113, respectively;~~
- ~~(iv) — SEQ ID NO: 133 and 135, respectively;~~
- ~~(v) — SEQ ID NO: 155 and 157, respectively;~~
- ~~(vi) — SEQ ID NO: 177 and 179, respectively;~~
- ~~(vii) — SEQ ID NO: 201 and 203, respectively;~~
- ~~(viii) — SEQ ID NO: 243 and 225, respectively;~~
- ~~(ix) — SEQ ID NO: 245 and 247, respectively;~~
- ~~(x) — SEQ ID NO: 267 and 269, respectively;~~

- (xi) — SEQ ID NO: 289 and 291, respectively;
- (xii) — SEQ ID NO: 311 and 313, respectively;
- (xiii) — SEQ ID NO: 333 and 335, respectively;
- (xiv) — SEQ ID NO: 355 and 357, respectively;
- (xv) — SEQ ID NO: 377 and 379, respectively; and
- (xvi) — SEQ ID NO: 399 and 401, respectively.

63. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:~~

- (i) — SEQ ID NO: 67 and 69, respectively;
- (ii) — SEQ ID NO: 89 and 91, respectively;
- (iii) — SEQ ID NO: 111 and 113, respectively;
- (iv) — SEQ ID NO: 133 and 135, respectively;
- (v) — SEQ ID NO: 155 and 157, respectively;
- (vi) — SEQ ID NO: 177 and 179, respectively;
- (vii) — SEQ ID NO: 201 and 203, respectively;
- (viii) — SEQ ID NO: 243 and 225, respectively;
- (ix) — SEQ ID NO: 245 and 247, respectively;
- (x) — SEQ ID NO: 267 and 269, respectively;
- (xi) — SEQ ID NO: 289 and 291, respectively;
- (xii) — SEQ ID NO: 311 and 313, respectively;
- (xiii) — SEQ ID NO: 333 and 335, respectively;
- (xiv) — SEQ ID NO: 355 and 357, respectively;
- (xv) — SEQ ID NO: 377 and 379, respectively; and
- (xvi) — SEQ ID NO: 399 and 401, respectively.

64. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof~~

~~comprises a heavy and a light chain comprising amino acid sequences selected from the group consisting of:~~

- ~~—— (i) — SEQ ID NO: 71 and 69, respectively;~~
- ~~(ii) — SEQ ID NO: 93 and 91, respectively;~~
- ~~(iii) — SEQ ID NO: 115 and 113, respectively;~~
- ~~(iv) — SEQ ID NO: 137 and 135, respectively;~~
- ~~(v) — SEQ ID NO: 159 and 157, respectively;~~
- ~~(vi) — SEQ ID NO: 181 and 179, respectively;~~
- ~~(vii) — SEQ ID NO: 205 and 203, respectively;~~
- ~~(viii) — SEQ ID NO: 227 and 225, respectively;~~
- ~~(ix) — SEQ ID NO: 249 and 247, respectively;~~
- ~~(x) — SEQ ID NO: 271 and 269, respectively;~~
- ~~(xi) — SEQ ID NO: 293 and 291, respectively;~~
- ~~(xii) — SEQ ID NO: 315 and 313, respectively;~~
- ~~(xiii) — SEQ ID NO: 337 and 335, respectively;~~
- ~~(xiv) — SEQ ID NO: 359 and 357, respectively;~~
- ~~(xv) — SEQ ID NO: 381 and 379, respectively; and~~
- ~~(xvi) — SEQ ID NO: 403 and 401, respectively.~~

~~65. — An isolated monoclonal antibody that specifically binds to and antagonizes human IL 27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences selected from the group consisting of:~~

- ~~—— (i) — SEQ ID NO: 71 and 69, respectively;~~
- ~~(ii) — SEQ ID NO: 93 and 91, respectively;~~
- ~~(iii) — SEQ ID NO: 115 and 113, respectively;~~
- ~~(iv) — SEQ ID NO: 137 and 135, respectively;~~
- ~~(v) — SEQ ID NO: 159 and 157, respectively;~~
- ~~(vi) — SEQ ID NO: 181 and 179, respectively;~~
- ~~(vii) — SEQ ID NO: 205 and 203, respectively;~~
- ~~(viii) — SEQ ID NO: 227 and 225, respectively;~~

- (ix) — SEQ ID NO: 249 and 247, respectively;
- (x) — SEQ ID NO: 271 and 269, respectively;
- (xi) — SEQ ID NO: 293 and 291, respectively;
- (xii) — SEQ ID NO: 315 and 313, respectively;
- (xiii) — SEQ ID NO: 337 and 335, respectively;
- (xiv) — SEQ ID NO: 359 and 357, respectively;
- (xv) — SEQ ID NO: 381 and 379, respectively; and
- (xvi) — SEQ ID NO: 403 and 401, respectively.

66. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences set forth in SEQ ID NO: 177 and 179, respectively.~~

67. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 177 and 179, respectively.~~

68. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy and a light chain comprising amino acid sequences set forth in SEQ ID NO: 181 and 179, respectively.~~

69. — ~~An isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, wherein the antibody or antigen binding portion thereof comprises a heavy chain and a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in SEQ ID NO: 181 and 179, respectively.~~

70. — ~~A pharmaceutical composition comprising an isolated monoclonal antibody or antigen binding portion thereof, of any one of the preceding claims, and a pharmaceutically acceptable carrier.~~

71. — ~~A nucleic acid comprising a nucleotide sequence encoding the light chain, heavy chain, or both light and heavy chains of the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1-69.~~

72. — ~~An expression vector comprising the nucleic acid of claim 71.~~

73. — ~~A cell transformed with an expression vector of claim 72.~~

74. — ~~A method for producing a monoclonal antibody that specifically binds human IL-27, or an antigen binding portion thereof, the method comprising maintaining a cell according to claim 73 under conditions permitting expression of the monoclonal antibody or antigen binding portion thereof.~~

75. — ~~The method of claim 74, further comprising obtaining the monoclonal antibody or antigen binding portion thereof.~~

76. — ~~A method to inhibit or reduce STAT1 and/or STAT3 phosphorylation in a cell, the method comprising contacting the cell with the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69, wherein the antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell.~~

77. — ~~A method to inhibit or reduce inhibition of CD161 expression in a cell, the method comprising contacting the cell with the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69, wherein the antibody, or antigen binding portion thereof, inhibits or reduces inhibition of CD161 expression in a cell.~~

78. — ~~A method to inhibit or reduce PD-L1 and/or TIM-3 expression in a cell, the method comprising contacting the cell with the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69, wherein the antibody, or antigen binding portion thereof, inhibits or PD-L1 and/or TIM-3 expression in a cell.~~

79. — ~~A method to induce or enhance secretion of one or more cytokines from a cell, the method comprising contacting the cell with the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69, wherein the antibody, or antigen binding portion thereof, induces or enhances PD-1 mediated secretion of one or more cytokines from a cell.~~

80. — ~~A method of stimulating an immune response in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69 or the pharmaceutical composition of claim 70.~~

81. — ~~A method of treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69 or the pharmaceutical composition of claim 70.~~

82. — ~~A method of stimulating an immune response, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69 or the pharmaceutical composition of claim 70, 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.~~

83. — ~~A method of stimulating an immune response, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69 or the pharmaceutical composition of claim 70, 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.~~

84. — ~~A method of stimulating an immune response, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69 or the pharmaceutical composition of claim 70, 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.~~

85. — ~~A method of stimulating an immune response, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the isolated monoclonal antibody, or antigen binding fragment, of any one claims 1-69 or the pharmaceutical composition of claim 70, 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.~~

86. — ~~The method of any one of claims 81-85, 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).~~

87. — ~~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, of any one of claims 1-69, concurrently with or sequentially to an anti-PD-1 antibody, thereby to enhance one or more activities of anti-PD1 antibodies.~~

~~88. — A pharmaceutical composition comprising an anti PD-1 antibody and an antibody, or antigen-binding portion thereof, of any one of claims 1-69, and a pharmaceutically acceptable carrier.~~

~~89. — A kit comprising an anti PD-1 antibody and an antibody, or antigen-binding portion thereof, of any one of claims 1-69, for concurrent or sequential administration, and instructions for its use.~~

~~90. — The method of any one of claims 80-86, wherein the isolated monoclonal 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.~~

~~91. — The method of claim 90, 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.~~

~~92. — The method of claim 91, wherein the one or more additional therapeutic agents is a PD-1 antagonist.~~

~~93. — The method of claim 92, 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.~~

~~94. — The method of claim 91, wherein the PD-L1 inhibitor is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559.~~

95.— The method of claim 91, 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 (Imfinzi[®]), cemiplimab-rwlc (Libtayo[®]), tislelizumab, and spartalizumab.

96.— The method of claim 91, wherein the one or more additional therapeutic agents is a TIM-3 inhibitor, optionally wherein the TIM-3 inhibitor is MGB453 or TSR-022.

97.— The method of claim 91, 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.

98.— The method of claim 91, wherein the one or more additional therapeutic agents is a TIGIT inhibitor.

99.— The method of claim 91, wherein the one or more additional therapeutic agents is a CD112R inhibitor.

100.— The method of claim 91, wherein the one or more additional therapeutic agents is a TAM (Axl, Mer, Tyro) inhibitor.

101.— The method of claim 91, wherein the one or more additional therapeutic agents is a 4-1BB agonist.

~~102. The method of claim 91, wherein the one or more additional therapeutic agents is a Tyrosine Kinase Inhibitor (TKI).~~

~~103. A method of detecting IL-27 or EBI3 in a sample from a subject, the method comprising the (a) contacting a sample from the subject with a detection antibody under conditions to permit the detection antibody to form a detection antibody-EBI3 complex, if IL-27 or EBI3 is present in the sample, wherein the detection antibody is an antibody, or antigen binding fragment thereof, according to any one of claims 1-69; and (b) detecting the presence of the complex, if any, produced in step (a).~~

~~104. A method of detecting an IL-27 associated cancer in a subject, the method comprising the steps of: (a) contacting a sample from a subject suspected of having an IL-27 associated cancer with a detection antibody under conditions to permit the detection antibody to form a detection antibody-EBI3 complex, if IL-27 or EBI3 is present in the sample, wherein the detection antibody is an antibody, or antigen binding portion thereof, according to any one of claims 1-69; and (b) detecting the presence of the complex, if any, produced in step (a).~~

~~105. The method of claims 103 or 104, wherein the detection antibody is coupled to a detectable label.~~

~~106. The method of any one of claims 103-105, wherein the method further comprises contacting the sample with a capture antibody to produce a complex comprising IL-27 or EBI3 and the capture antibody, if IL-27 or EBI3 is present in the sample, wherein the capture antibody is an antibody, or antigen binding portion thereof, according to any one of claims 1-69.~~

~~107. The method of claim 106, wherein the capture antibody is immobilized on a solid support.~~

~~108. The method of any one of claims 103-107, wherein the sample is contacted with the capture antibody before the detection antibody.~~

~~109.— The method of any one of claims 103–108, wherein the sample is a body fluid sample.~~

~~110.— The method of claim 109, wherein the fluid sample is blood, serum, plasma, cell lysates or tissue lysates.~~

~~111.— The method of any one of claims 104–110, wherein the cancer is selected from renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), lung cancer, gastroesophageal cancer, ovarian cancer, endometrial cancer, melanoma, leukemia and lymphoma.~~

~~112.— The method of claim 111, wherein the cancer is renal cell carcinoma (RCC).~~

~~113.— The method of claim 111, wherein the cancer is hepatocellular carcinoma (HCC).~~

~~114.— The method of claim 111, wherein the cancer is selected from leukemia and lymphoma.~~

~~115.— The method of claim 111, wherein the cancer is ovarian cancer.~~

~~116.— Use of the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1–69 or the pharmaceutical composition of claim 70 for stimulating an immune response in a subject, or for treating cancer in a subject, optionally for use in combination with one or more additional therapeutic agents or procedure.~~

~~117.— A kit comprising the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1–69 or the pharmaceutical composition of claim 70 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.~~

~~118.— A kit comprising the isolated monoclonal antibody, or antigen binding portion thereof, of any one of claims 1–69 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.~~