

## Claims

1. 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.

2. The isolated monoclonal antibody of claim 1, 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).

3. The isolated monoclonal antibody, or antigen binding portion thereof, of claim 1, wherein:

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

(b) the antibody or antigen binding portion thereof inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell, optionally wherein the cell is an immune cell or a cancer cell;

(c) the antibody or antigen binding portion thereof inhibits or reduces inhibition of CD161 expression in a cell;

(d) the antibody or antigen binding portion thereof inhibits or reduces PD-L1 and/or TIM-3 expression in a cell;

(e) the antibody or antigen binding portion thereof induces or enhances the PD-1-mediated secretion of one or more cytokines from a cell;

(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;

(g) the antibody comprises an Fc domain comprising at least one mutation, optionally wherein the antibody comprises a mutant IgG1 heavy chain constant region 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 $\gamma$ , IL-17, TNF  $\alpha$ , 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.

9. The isolated monoclonal antibody of claim 1, 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.
15. 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: 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.

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.