

ANTI-IL-27 ANTIBODIES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/646,496, filed March 22, 2018, the entire contents of which are incorporated herein by reference.

FIELD

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

BACKGROUND

In recent years, an increasing body of evidence suggests that the immune system operates as a significant barrier to tumor formation and progression. The principle that naturally-occurring T cells with anti-tumor potential or activity exist in a patient with cancer has rationalized the development of immunotherapeutic approaches in oncology. Immune cells, such as T cells, macrophages, and natural killer cells, can exhibit anti-tumor activity and effectively control the occurrence and growth of malignant tumors. Tumor-specific or -associated antigens can induce immune cells to recognize and eliminate malignancies (Chen & Mellman, (2013) *Immunity* 39(1):1-10). In spite of the existence of tumor-specific immune responses, malignant tumors often evade or avoid immune attack through a variety of immunomodulatory mechanisms resulting in the failure to control tumor occurrence and progression (Motz & Coukos, (2013) *Immunity* 39(1):61-730). Indeed, an emerging hallmark of cancer is the exploitation of these immunomodulatory mechanisms and the disablement of anti-tumor immune responses, resulting in tumor evasion and escape from immunological killing (Hanahan and Weinberg (2011) *Cell* 144(5):646-674).

IL-27 is a heterodimeric cytokine, composed of two subunits (EBI3 and IL-27p28). IL-27 is structurally related to both the IL-12 and IL-6 cytokine families. IL-27 binds to and mediates signaling through a heterodimer receptor consisting of IL-27R α (WSX1) and gp130 chains, which mediate signaling predominantly through STAT1 and STAT3. Initial reports characterized IL-27 as an immune-enhancing cytokine that supports CD4⁺ T cell proliferation, T helper (Th)1 cell differentiation, and IFN- γ production, often acting in concert with IL-12. Subsequent studies have

shown that IL-27 displays complex immunomodulatory functions, resulting in either proinflammatory or anti-inflammatory effects depending on the biological context and experimental models being used. IL-27 may drive the expression of different immune-regulatory molecules in human cancer cells, which may support local derangement of the immune response *in vivo* (Fabbi et al., (2017) Mediators Inflamm 3958069. Published online 2017 Feb 1. doi:10.1155/2017/3958069, and references contained therein).

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

SUMMARY OF THE DISCLOSURE

Disclosed herein are antibodies, or antigen binding portions thereof, that specifically bind to and antagonize human IL-27 (Interleukin 27) with high affinity and specificity. Nucleic acid molecules encoding the antibody molecules, expression vectors, host cells and methods for making the antibody molecules are also provided. Pharmaceutical compositions comprising the antibody molecules are also provided. The anti-IL-27 antibodies, or antigen binding portions thereof, disclosed herein can be used (alone or in combination with other therapeutic agents or procedures) to treat, prevent and/or diagnose disorders, including immune disorders and cancer. Thus, compositions and methods for treating and/or diagnosing various disorders, including cancer and immune disorders, using the anti-IL-27 antibody molecules are disclosed herein.

In some embodiments, the disclosure provides 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 inhibition of CD161 expression in a cell; (v) inhibits or reduces PD-L1 and/or TIM-3 expression in a cell; (vi) induces or enhances PD-1 mediated secretion of one or more cytokines from a cell; and (vii) a combination of (i)-(vi).

In some embodiments, the isolated monoclonal antibody, or antigen binding portion thereof, binds to human IL-27 with an equilibrium dissociation constant (K_D) of 15 nM or less.

In some embodiments, the isolated monoclonal antibody, or antigen binding portion thereof, binds to recombinant human IL-27 or to murine IL-27.

In one aspect, the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof has heavy and light chain CDRs that are: (i) heavy chain CDR1 is N-GFTFXXXX-C (SEQ ID NO: 408), heavy chain CDR2 is N-ISSSXXYI-C (SEQ ID NO: 409), and heavy chain CDR3 sequence is SEQ ID NO: 163; light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 169, 170 and 171, respectively; or (ii) heavy chain CDR1 is N-FTFXXXXMN-C (SEQ ID NO: 410), heavy chain CDR2 is N-XISSSXXYIXYADSVKG-C (SEQ ID NO: 411), and heavy chain CDR3 sequence is SEQ ID NO: 166; light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 172, 173 and 174, respectively.

In one embodiment, the heavy chain CDR1 is N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 412) and the heavy chain CDR2 is N-ISSS[S/G][S/A]YI-C (SEQ ID NO: 413); or the heavy chain CDR1 is N-FTF[S/A/R][S/R][T/Y][G/S]MN-C (SEQ ID NO: 414) and the heavy chain CDR2 is N-[G/S]ISSS[S/G][S/A]YI[L/Y]YADSVKG-C (SEQ ID NO: 415).

In another embodiment, the respective heavy chain and light chain CDRs are: (i) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 161, 162 and 163, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 169, 170 and 171, respectively; (ii) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 164, 165 and 166, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 172, 173 and 174, respectively; (iii) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 73, 74 and 75, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 81, 82 and 83, respectively; (iv) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 76, 77 and 78, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 84, 85 and 86, respectively; (v) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 95, 96 and 97, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 103, 104 and 105, respectively; (vi) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 98, 99 and 100, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 106, 107 and 108, respectively; (vii) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 117, 118 and 119, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 125, 126 and 127, respectively; (viii) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 120, 121 and 122, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs:

128, 129 and 130, respectively; (ix) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 139, 140 and 141, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 147, 148 and 149, respectively; (x) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 142, 143 and 144, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 150, 151 and 152, respectively; (xi) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 51, 52 and 53, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 59, 60 and 61, respectively; or (xii) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 54, 55 and 56, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 62, 63 and 64, respectively.

Another aspect of the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof includes heavy and light chain CDRs that are: (i) heavy chain CDR1 is N-GGSFSXYX-C (SEQ ID NO: 416), heavy chain CDR2 is N-IDXSGXT-C (SEQ ID NO: 417), and heavy chain CDR3 is N-ARXXXYY[X]_{n=0-1}DSS[X]_{n=4-6}DX-C (SEQ ID NO: 418); and light chain CDR1 is N-QXXSXY-C (SEQ ID NO: 419), light chain CDR2 is N-DXS-C (SEQ ID NO: 420), and light chain CDR3 is N-QQXXDXPIT-C (SEQ ID NO: 421), respectively; or (ii) heavy chain CDR1 is N-GSFSXYXWS-C (SEQ ID NO: 422), heavy chain CDR2 is N-SIDXSGXTXYNPSLKS-C (SEQ ID NO: 423), and heavy chain CDR3 sequence is N-ARXXXYY[X]_{n=0-1}DSS[X]_{n=4-6}DX-C (SEQ ID NO: 418); and light chain CDR1 is N-XASQXXSXYLX-C (SEQ ID NO: 424), light chain CDR2 is N-DXSNXXT-C (SEQ ID NO: 425), and light chain CDR3 is N-QQXXDXPIT-C (SEQ ID NO: 421), respectively.

In certain embodiments, (i) the heavy chain CDR1 is N-GGSFS[R/D]Y[E/Y]-C (SEQ ID NO: 426), the heavy chain CDR2 is N-ID[W/Y]SG[I/S]T-C (SEQ ID NO: 427), the heavy chain CDR3 is N-AR[D/L][P/G][M/V]YY[-/Y]DSS[VSTGSV/DLGF]D[V/I]-C (SEQ ID NO: 428); and the light chain CDR1 is N-Q[S/D][V/I]S[S/N]Y-C (SEQ ID NO: 429), the light chain CDR2 is N-D[S/A]S-C (SEQ ID NO: 430), and the light chain CDR3 is N-QQ[D/Y][S/D]D[H/L]PIT-C (SEQ ID NO: 431), respectively; or (ii) the heavy chain CDR1 is N-GSFS[R/D]Y[E/Y]WS-C (SEQ ID NO: 432), the heavy chain CDR2 is N-SID[W/Y]SG[I/S]T[N/E]YNPSLKS-C (SEQ ID NO: 433), the heavy chain CDR3 is N-AR[D/L][P/G][M/V]YY[-/Y]DSS[VSTGSV/DLGF]D[V/I]-C (SEQ ID NO: 428); and the light chain CDR1 is N-

[Q/R]ASQ[S/D][V/I]S[S/N]YL[N/A]-C (SEQ ID NO: 434), the light chain CDR2 is N-D[S/A]SN[R/L][A/E]T-C (SEQ ID NO: 435), and the light chain CDR3 is N-QQ[D/Y][S/D]D[H/L]PIT-C (SEQ ID NO: 431), respectively.

In some embodiments, (i) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 229, 230 and 231, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 237, 238 and 239, respectively; or (ii) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 232, 233 and 234, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 240, 241 and 242, respectively.

In certain embodiments, (i) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 251, 252 and 253, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 259, 260 and 261, respectively; or (ii) the heavy chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 254, 255 and 256, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are SEQ ID NOs: 262, 263 and 264, respectively.

Another aspect of the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof includes heavy and light chain CDRs that are heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 23, 24 and 25, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 26, 27 and 28, respectively.

An additional aspect of the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof includes heavy and light chain CDRs that are: (i) heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 339, 340 and 341, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 347, 348 and 349, respectively; or (ii) heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 342, 343 and 344, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 350, 351 and 352, respectively.

Another aspect of the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof includes heavy and light chain CDRs that are: (i) heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 185, 186 and 187, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 193, 194 and 195, respectively; or (ii)

heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 188, 189 and 190, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 196, 197 and 198, respectively.

One aspect of the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof includes heavy and light chain CDRs that are: (i) heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 207, 208 and 209, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 215, 216 and 217, respectively; or (ii) heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 210, 211 and 212, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 218, 219 and 220, respectively.

An additional aspect of the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof includes heavy and light chain CDRs that are: (i) heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 273, 274 and 275, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 281, 282 and 283, respectively; or (ii) heavy chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 276, 277 and 278, respectively, and light chain CDR1, CDR2 and CDR3 sequences SEQ ID NOs: 284, 285 and 286, respectively.

One aspect of the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof includes heavy and light chain CDRs that are: (i) heavy chain CDR1 is N-GFTFSSYG-C (SEQ ID NO: 361), heavy chain CDR2 is N-IXXDGSXK-C (SEQ ID NO: 436), and heavy chain CDR3 is N-ARXAP[X]_{n=3-8}DV-C (SEQ ID NO: 437); and light chain CDR1 is N-QSXSSY-C (SEQ ID NO: 438), light chain CDR2 is N-XXS-C (SEQ ID NO: 439), and light chain CDR3 is N-QQXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 440), respectively; or (ii) heavy chain CDR1 is N-FTFSSYGMX-C (SEQ ID NO: 441), heavy chain CDR2 is N-XIXXDGSXKYYXDSVKG-C (SEQ ID NO: 442), and heavy chain CDR3 is N-ARXAP[X]_{n=3-8}DV-C (SEQ ID NO: 437); and light chain CDR1 is N-RASQSXSSYLX-C (SEQ ID NO: 443), light chain CDR2 is N-[X]_{n=1-2}SS[X]_{n=3-4}-C (SEQ ID NO: 444), and light chain CDR3 is N-QQXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 440), respectively.

In certain embodiments, (i) the heavy chain CDR1 is N-GFTFSSYG-C (SEQ ID NO: 361), heavy chain CDR2 is N-I[K/W][Q/Y]DGS[E/N]K-C (SEQ ID NO: 445), and heavy chain CDR3

is N-AR[D/G]AP[WDIYDYDM/EYV]DV-C (SEQ ID NO: 446); and light chain CDR1 is N-QS[I/V]SSY-C (SEQ ID NO: 447), light chain CDR2 is N-[A/D][A/S]S-C (SEQ ID NO: 448), and light chain CDR3 is N-QQ[S/Y][Y/S][V/L][P/Y]P[W/-]T-C (SEQ ID NO: 449), respectively; or (ii) the heavy chain CDR1 is N-FTFSSYGM[S/H]-C (SEQ ID NO: 450); heavy chain CDR2 is N-[N/V]I[K/W][Q/Y]DGS[E/N]KYY[V/A]DSVKG-C (SEQ ID NO: 451), and heavy chain CDR3 is N-AR[D/G]AP[WDIYDYDM/EYV]DV-C (SEQ ID NO: 446); and light chain CDR1 is N-RASQS[I/V]SSYL[N/A]-C (SEQ ID NO: 452), light chain CDR2 is N-[AA/D]SS[LQS/NRAT]-C (SEQ ID NO: 453), and light chain CDR3 is N-QQ[S/Y][Y/S][V/L][P/Y]P[W/-]T-C (SEQ ID NO: 449), respectively.

In some embodiments, (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.

In one embodiment, (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.

Another aspect of the instant disclosure provides an isolated monoclonal antibody that specifically binds to and antagonizes human IL-27, or antigen binding portion thereof, where the antibody or antigen binding portion thereof includes heavy and light chain CDRs that are: (i) heavy chain CDR1 is N-GFTFXXXX-C (SEQ ID NO: 408), heavy chain CDR2 is N-IXXXXXXXXXX-C (SEQ ID NO: 456), and heavy chain CDR3 is N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 458); and light chain CDR1 is N-QS[X]_{n=1-3}SS[X]_{n=0-4}Y-C (SEQ ID NO: 460), light chain CDR2 is N-XXS-C (SEQ ID NO: 462), and light chain CDR3 is N-QQXXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 464), respectively; or (ii) heavy chain CDR1 is N-FTFXXXXMX-C (SEQ ID NO: 466), heavy chain CDR2 is N-XIXXXXXXXXXXXYXDSVKG-C (SEQ ID NO: 468), and heavy chain CDR3 is N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 470); and light chain CDR1 is N-RASQSXSSYLY-C (SEQ ID NO: 472), light chain CDR2 is N-[X]_{n=1-2}S[X]_{n=4-5}-C (SEQ ID NO: 474), and light chain CDR3 is N-QQXXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 476), respectively.

In certain embodiments, (i) the heavy chain CDR1 is N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 454), heavy chain CDR2 is 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 is N-AR[DGGRTSYTATAHNWF/DAPWDIYDYYM/GAPEYV]D[P/V]-C (SEQ ID NO: 457); and light chain CDR1 is N-QS[VLF/I/V]SS[NNKN/-]Y-C (SEQ ID NO: 459), light chain CDR2 is N-[W/A/D][A/S]S-C (SEQ ID NO: 461), and light chain CDR3 is 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 is N-FTF[S/A/R][S/R][T/Y][G/S]M[N/S/H]-C (SEQ ID NO: 465), heavy chain CDR2 is N-[G/S/N/V]I[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 is N-AR[D/G][GGRTSYTATAHNWF/APWDIYDYYM/APEYV]D[P/V]-C (SEQ ID NO: 469); and light chain CDR1 is N-RASQS[I/V]SSYL[N/A]-C (SEQ ID NO: 471), light chain CDR2 is N-[WA/AA/D]S[TRES/SLQS/SNRAT]-C (SEQ ID NO: 473), and light chain CDR3 is N-QQ[H/S/Y][A/Y/S][S/V/L][A/P/Y]P[P/W/-]T-C (SEQ ID NO: 475), respectively.

In some embodiments, the isolated monoclonal antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell. In some embodiments, the cell is an immune cell. In some embodiments, the cell is a cancer cell.

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

In some embodiments, the isolated monoclonal antibody, or antigen binding portion thereof, inhibits or reduces IL-27-mediated PD-L1 and/or TIM-3 expression in a cell. In some embodiments, PD-L1 expression is inhibited or reduced. In some embodiments, TIM-3 expression is inhibited or reduced. In some embodiments, both PD-L1 expression and TIM-3 expression is reduced. In some embodiments, the cell is an immune cell.

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

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

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

In some embodiments, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, that binds to at least one of the amino acid residues comprising IL-27 bound by the antibody, or antigen binding portion thereof, according to any one of the aforementioned embodiments.

In some embodiments, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, wherein a mutation of the epitope on IL-27 bound by the antibody or antigen binding portion thereof inhibits, reduces, or blocks binding to both the antibody or antigen binding portion thereof and to the antibody or antigen binding portion thereof according to any one of the aforementioned embodiments.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 172, 173 and 174, respectively.

In some embodiments, the disclosure provides 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 amino acid sequences of heavy chain CDR1, CDR2 and CDR3 are SYSMS (SEQ ID NO: 23), YISYDGG SAYYPDTVKG (SEQ ID NO: 24) and HGDYDDDDAMDY (SEQ ID NO: 25), respectively, and wherein the amino acid sequences of light chain CDR1, CDR2 and CDR3 are RASENIYSYLA (SEQ ID NO: 26), NAETLTE (SEQ ID NO: 27) and QHHYGTPLT (SEQ ID NO: 28), respectively.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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, 223, 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.

In some embodiments, the disclosure provides 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, 223, 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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: 223 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.

In some embodiments, the disclosure provides 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: 223 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides a method to inhibit or reduce STAT1 and/or STAT3 phosphorylation in a cell, the method comprising contacting the cell with an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell.

In some embodiments, the disclosure provides a method to inhibit or reduce IL-27 mediated inhibition of CD161 expression in a cell, the method comprising contacting the cell with an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or reduces inhibition of CD161 expression in a cell.

In some embodiments, the disclosure provides a method to inhibit or reduce IL-27 mediated expression of PD-L1 and/or TIM-3 expression in a cell, the method comprising contacting the cell with an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or PD-L1 and/or TIM-3 expression in a cell.

In some embodiments, the disclosure provides 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, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, induces or enhances PD-1 mediated secretion of one or more cytokines from a cell.

In some embodiments, the disclosure provides a method of stimulating an immune response in a subject, the method comprising administering to the subject an effective amount of

an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to and antagonizes IL-27, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier.

In some embodiments, the disclosure provides a method of treating a cancer in a subject, the method comprising administering to the subject an effective amount an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to and antagonizes IL-27, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier.

In some embodiments, the disclosure provides 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 an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier, 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.

In some embodiments, the disclosure provides 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 an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition, inhibits or reduces IL-27 mediated inhibition of CD161 expression in a cell, thereby stimulating the immune response, or treating the cancer.

In some embodiments, the disclosure provides 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 an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition, inhibits or reduces IL-27 mediated expression of PD-L1 and/or TIM-3 expression in a cell, thereby stimulating the immune response, or treating the cancer.

In some embodiments, the disclosure provides 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 an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier, 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.

In some embodiments, 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 (including, e.g., uveal melanoma, etc.), 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).

In some embodiments, the disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to and antagonizes IL-27, provided by the disclosure, in combination with one or more additional therapeutic agents or procedure, wherein the second therapeutic agent or procedure is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy (including, e.g., Tyrosine Kinase Inhibitors (TKIs), 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.

In some embodiments, 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.

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

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

In certain embodiments, the instant disclosure provides a pharmaceutical composition that includes an anti-PD-1 antibody and/or an anti-PD-L1 antibody, and an antibody or antigen binding portion thereof as disclosed herein (e.g., an anti-IL-27 antibody), and a pharmaceutically acceptable carrier.

In a related embodiment, the instant disclosure provides a kit that includes an anti-PD-1 antibody and/or an anti-PD-L1 antibody, and an antibody or antigen binding portion thereof as disclosed herein (e.g., an anti-IL-27 antibody), for concurrent or sequential administration, and instructions for its use.

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

In some embodiments, 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.

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

In some embodiments, the disclosure provides a method of detecting IL-27 in a sample from a subject, the method comprising (a) contacting a sample from the subject with a detection antibody under conditions to permit the detection antibody to form a detection antibody-IL-27 complex, if IL-27 is present in the sample, wherein the detection antibody is an antibody, or antigen

binding fragment thereof, provided by the disclosure; and (b) detecting the presence of the complex, if any, produced in step (a).

In some embodiments, the disclosure provides 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-IL-27 complex, if IL-27 is present in the sample, wherein the detection antibody is an antibody, or antigen binding portion thereof, provided by the disclosure; and (b) detecting the presence of the complex, if any, produced in step (a). In some embodiments, the detection antibody is coupled to a detectable label. In some embodiments, the method further comprises contacting the sample with a capture antibody to produce a complex comprising IL-27 and the capture antibody, if IL-27 is present in the sample, wherein the capture antibody is an antibody, or antigen binding portion thereof, provided by the disclosure.

In some embodiments, the detection antibody or the capture antibody comprises heavy and light chain CDRs, wherein the amino acid sequences of heavy chain CDR1, CDR2 and CDR3 are SYSMS (SEQ ID NO: 23), YISYDGGSAAYPDTVKG (SEQ ID NO: 24) and HGDYDDDDAMDY (SEQ ID NO: 25), respectively, and wherein the amino acid sequences of light chain CDR1, CDR2 and CDR3 are RASENIYSYLA (SEQ ID NO: 26), NAETLTE (SEQ ID NO: 27) and QHHYGTPLT (SEQ ID NO: 28), respectively.

In some embodiments, the detection antibody or the capture antibody comprises heavy and light chain variable regions comprising amino acid sequences set forth in SEQ ID NO: 1 and SEQ ID NO: 3, respectively.

In some embodiments, the capture antibody is immobilized on a solid support. In some embodiments, the sample is contacted with the capture antibody before the detection antibody. In some embodiments, the sample is a body fluid sample. In some embodiments, the fluid sample is blood, serum, plasma, cell lysates or tissue lysates.

In some embodiments, the cancer is selected from renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), lung cancer, gastroesophageal cancer, ovarian cancer, endometrial cancer, melanoma, leukemia and lymphoma. In some embodiments, the cancer is renal cell carcinoma (RCC). In other embodiments, the cancer is hepatocellular carcinoma (HCC).

In some embodiments, the cancer is selected from leukemia and lymphoma. In some embodiments, the cancer is acute myeloid leukemia (AML).

Definitions

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

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

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

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

polypeptide. The potency of an agonist is usually defined by its EC₅₀ value (concentration required to activate 50% of the agonist response). The lower the EC₅₀ value the greater the potency of the agonist and the lower the concentration that is required to activate the maximum biological response.

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

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

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

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

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

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

When referring to a protein, mRNA or a marker, such as those described herein, the terms "level of expression" or "expression level" in general are used interchangeably and generally refer

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

As used herein, the term "angiogenesis" or "neovascularization" refers to the process by which new blood vessels develop from pre-existing vessels (Varner et al., (1999) *Angiogen.* 3:53-60; Mousa et al., (2000) *Angiogen. Stim. Inhib.* 35:42-44; Kim et al., (2000) *Amer. J. Path.* 156:1345-1362; Kim et al., (2000) *J. Biol. Chem.* 275:33920-33928; Kumar et al. (2000) *Angiogenesis: From Molecular to Integrative Pharm.* 169-180). Endothelial cells from pre-existing blood vessels or from circulating endothelial stem cells (Takahashi et al., (1995) *Nat. Med.* 5:434-438; Isner et al., (1999) *J. Clin. Invest.* 103:1231-1236) become activated to migrate, proliferate, and differentiate into structures with lumens, forming new blood vessels, in response to growth factor or hormonal cues, or hypoxic or ischemic conditions. During ischemia, such as occurs in cancer, the need to increase oxygenation and delivery of nutrients apparently induces the secretion of angiogenic factors by the affected tissue; these factors stimulate new blood vessel formation. Several additional terms are related to angiogenesis.

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

For example, a functional assay may comprise contacting a polypeptide with a candidate antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the polypeptide. The potency of an antagonist is usually defined by its IC₅₀ value (concentration required to inhibit 50% of the agonist response). The lower the IC₅₀ value the greater the potency of the antagonist and the lower the concentration that is required to inhibit the maximum biological response.

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

As used herein, the term "anti-IL-27 antagonist antibody" (interchangeably termed "anti-IL-27 antibody") refers to an antibody that specifically binds to IL-27 and inhibits IL-27 biological activity and/or downstream pathway(s) mediated by IL-27 signaling or other IL-27-mediated function. An anti-IL-27 antagonist antibody encompasses antibodies that block, antagonize, suppress, inhibit or reduce an IL-27 biological activity (e.g., ligand binding, enzymatic activity), including downstream pathways mediated by IL-27 signaling or function, such as receptor binding and/or elicitation of a cellular response to IL-27 or its metabolites. In some embodiments, an anti-IL-27 antagonist antibody provided by the disclosure binds to human IL-27 and prevents, blocks, or inhibits binding of human IL-27 to its cognate or normal receptor (e.g., IL-27 receptor), or one or more receptor subunits (e.g., gp130 and/or IL-27R α (also known as WSX1/TCCR)). In some embodiments, the anti-IL-27 antagonist antibody prevents, blocks, or inhibits the binding of human IL-27 to the gp130. In some embodiments, the anti-IL-27 antagonist antibody prevents, blocks, or inhibits the binding of human IL-27 to the IL-27R α . In some embodiments, the anti-IL-27 antagonist antibody prevents, blocks, or inhibits the dimerization of IL-27 monomers. In some embodiments, the anti-IL-27 antibody specifically binds to the EBI3 monomer. In some embodiments, the anti-IL-27 antibody specifically binds to the IL-27p28 monomer. In some embodiments, the anti-IL-27 antibody specifically binds to both IL-27 monomers. In some

embodiments, the anti-IL-27 antibody specifically binds to a non-contiguous epitope comprising both EBI3 and P28. In some embodiments, the anti-IL-27 antibody inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell. In some embodiments, the anti-IL-27 antibody inhibits or reduces inhibition of CD161 expression in a cell (e.g., ameliorates or relieves IL-27 mediated inhibition of CD161 expression in a cell). In some embodiments, the anti-IL-27 antibody inhibits or reduces PD-L1 and/or TIM-3 expression in a cell. In some embodiments, the anti-IL-27 induces or enhances PD-1-mediated secretion of one or more cytokines from a cell. In some embodiments, an anti-IL-27 antagonist antibody binds to human IL-27 and stimulates or enhances an anti-tumor response. In some embodiments, the anti-IL-27 antagonist antibody binds to human IL-27 with an affinity of 15nM or less. In some embodiments, the anti-IL-27 antagonist antibody binds to human IL-27 and comprises a wild type or mutant IgG1 heavy chain constant region or a wild type or mutant IgG4 heavy chain constant region. Examples of anti-IL-27 antagonist antibodies are provided herein.

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

Marasco, (1997) *Annu. Rev. Microbiol.* 51:257-283, the disclosures of each of which are incorporated herein by reference in their entirety.

As used herein, the term “antibody fragment” also includes, e.g., single domain antibodies such as camelized single domain antibodies. See, e.g., Muyldermans et al., (2001) *Trends Biochem. Sci.* 26:230-235; Nuttall et al., (2000) *Curr. Pharm. Biotech.* 1:253-263; Reichmann et al., (1999) *J. Immunol. Meth.* 231:25-38; PCT application publication nos. WO 94/04678 and WO 94/25591; and U.S. patent no. 6,005,079, all of which are incorporated herein by reference in their entireties. In some embodiments, the disclosure provides single domain antibodies comprising two VH domains with modifications such that single domain antibodies are formed.

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

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

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

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

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

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

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

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

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been

produced using leucine zippers. See, e.g., Kostelny et al. (1992) *J Immunol* 148(5):1547-1553. The leucine zipper peptides from the Fos and Jun proteins may be linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers may be reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al. (1993) *Proc Natl Acad Sci USA* 90:6444-6448 has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the VH and VL domains of one fragment are forced to pair with the complementary VL and VH domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (scFv) dimers has also been reported. See, e.g., Gruber et al. (1994) *J Immunol* 152:5368. Alternatively, the antibodies can be "linear antibodies" as described in, e.g., Zapata et al. (1995) *Protein Eng.* 8(10):1057-1062. Briefly, these antibodies comprise a pair of tandem Fd segments (VH-CH1-VH-CH1) which form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

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

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

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

As used herein, the term "cancer-specific immune response" refers to the immune response induced by the presence of tumors, cancer cells, or cancer antigens. In certain embodiments, the response includes the proliferation of cancer antigen specific lymphocytes. In certain embodiments, the response includes expression and upregulation of antibodies and T-cell receptors and the formation and release of lymphokines, chemokines, and cytokines. Both innate and acquired immune systems interact to initiate antigenic responses against the tumors, cancer cells, or cancer antigens. In certain embodiments, the cancer-specific immune response is a T cell response.

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

As used herein, the term "CD112R" refers to a member of poliovirus receptor-like proteins and is a co-inhibitory receptor for human T cells. CD112R is preferentially expressed on T cells and inhibits T cell receptor-mediated signals. CD112, widely expressed on antigen-presenting cells and tumor cells, is the ligand for CD112R. CD112R competes with CD226 to bind to CD112. Disrupting the CD112R-CD112 interaction enhances human T cell response. CD112R as a novel checkpoint for human T cells via interaction with CD112. As used herein the term "CD112R

inhibitor” refers to an agent that disrupts, blocks or inhibits the biological function or activity of CD112R.

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

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

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

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

EBI3 is also believed to have biological functions independent of p28 or the IL-27 heterodimer. For example, EBI3 also interacts with p35 to form the heterodimeric cytokine IL-35 (Yoshida et al. (2015) *Annu. Rev Immunol.* 33:417-43) and has been shown to be selectively overexpressed in certain cell types without a corresponding increase in p28 or IL-27 (Larousserie et al. (2005) *Am. J. Pathol.* 166(4):1217-28).

An amino acid sequence of an exemplary human EBI3 protein is provided in SEQ ID NO: 698 (NCBI Reference Sequence: NP_005746.2; N-MTPQLLLALVLWASCPGSGRKGPPAALTLPRVQCRASRYPIAVDCSWTLPPAPNSTSPV SFIATYRLGMAARGHSWPCLQQTPTSTSCITTDVQLFSMAPYVLNVTAVHPWGSSSSSFV PFITEHIIKPDPPEGVRLSPLAERQLQVQWEPPGSWPFPEIFSLKYWIRYKRQGAARFHRV GPIEATSFILRAVRPRARYYVQVAAQDLTDYGELSDWSLPATATMSLGK-C). An amino acid sequence of an exemplary human p28 protein is provided in SEQ ID NO: 699 (NCBI Reference Sequence: NP_663634.2; N-MGQTAGDLGWRLSLLLLPLLLVQAGVWGFPRPPGRPQLSLQELRREFTVSLHLARKLLS EVRGQAHRFAESHLPGVNLYLLPLGEQLPDVSLTFQAWRRLSDPERLCFISTTLQPFHAL LGGLGTQGRWTNMQRLWAMRLDLRDLQRHLRFQVLAAGFNLPEEEEEEEEEEEEEEE RKGLLPALGSALQGPAQVSWPQLLSTYRLLHSLELVLSRAVRELLLLSKAGHSVWPLG FPTLSPQP-C). An amino acid sequence of an exemplary human WSX1 protein is provided in SEQ ID NO: 700 (NCBI Reference Sequence: NP_004834.1; N-MRGGRGAPFWLWPLPKLALLPLLWVLFQRTRPQGSAGPLQCYGVGPLGDLNCSWEPL GDLGAPSELHLQSQKYRSNKTQTVAVAAGRSWVAIPREQLTMSDKLLVWGKAGQPL WPPVFNLETQMKNAPRLGPDVDFSEDDPLEATVHWAPPTWPSHKVLICQFHYYRCQ EAAWTLLEPELKTIPLTPVEIQDLELATGYKVYGRCRMEEKEDLWGEWSPILSFQTPPSA

PKDVWVSGNLCGTPGGEEPLLLWKAPGPCVQVSYKVWFWVGGRELSPEGITCCCSLIPS
 GAEWARVSAVNATSWEPLTNLSLVCLDSASAPRSVAVSSIAGSTELLVTWQPGPGEPLE
 HVVDWARDGDPLEKLNWVRLPPGNLSALLPGNFTVGVPYRITVTAVSASGLASASSVW
 GFREELAPLVGPTLWRLQDAPPGTPAIAWGEVPRHQLRGHLTHYTLCAQSGTSPSVCM
 NVSGNTQSVTLPLDPWGPCELWVTASTIAGQGPPGPILRLHLPDNTLRWKVLPGLFLW
 GLFLLGCGLSLATSGRCYHLRHKVLPRWVWEKVPDPANSSSGQPHMEQVPEAQPLGDL
 PILEVEEMEPPPMESSQPAQATAPLD SGYEKHFLPTPEELGLLGPPRPQVLA-C). An

amino acid sequence of an exemplary human gp130 protein is provided in SEQ ID NO: 701 (NCBI

Reference Sequence: NP_002175.2; N-

MLTLQTWLVQALFIFLTTESTGELLDP CGYISPESPVVQLHSNFTAVCVLKEKCMDYFH
 VNANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIIS
 GLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPT
 SCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVKNPPHNLSVINSEELSSIL
 KLTWTNPSIKSVILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRC
 MKEDGKGYWSDWSEEASGITYEDRPSKAPSFYKIDPSHTQGYRTVQLVWKTLPPEA
 NGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL TIP
 ACDFQATHPVMDLKAFPKNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQED
 GTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKN
 EAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETA VNVDSSHTEYTLSSLTSDTLYMVRM
 AAYTDEGGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFLLTLLGVLF CFNKRDLIKKHIWP
 NVPDPSKSHIAQWSPHTPPRHNFN SKDQMYSDGNFTDVS VVEIEANDKKPFPEDLKSLD
 LFKKEKINTEGHSSGIGGSSCMSSSRPSISSSDENESSQNTSSTVQYSTVVHSGYRHQVPS
 VQVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCSQHESPDISHFER
 SKQVSSVNEEDFVRLKQQISDHISQSCGSGQM KMFQEVSAADAFGPGTEGQVERFETVG
 MEAATDEGMPKSYLPQTVRQGGYMPQ-C).

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

reference antigen-binding protein (e.g., a reference antibody) to a common antigen (e.g., IL-27 or a fragment thereof).

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

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

In certain embodiments, there is one amino acid difference between a starting polypeptide sequence and the sequence derived there from. Identity or similarity with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical (i.e., same residue) with the starting amino acid residues, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. In certain embodiments, a polypeptide consists of, consists essentially of, or comprises an amino acid sequence selected from a sequence set forth in Table 12. In certain embodiments, a polypeptide includes an amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence selected from a sequence set forth in Table 12. In certain embodiments, a polypeptide includes a contiguous amino acid sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a contiguous amino acid

sequence selected from a sequence set forth in Table 12. In certain embodiments, a polypeptide includes an amino acid sequence having at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 300, 400, or 500 (or any integer within these numbers) contiguous amino acids of an amino acid sequence selected from a sequence set forth in Table 12.

In certain embodiments, the antibodies of the disclosure are encoded by a nucleotide sequence. Nucleotide sequences of the invention can be useful for a number of applications, including: cloning, gene therapy, protein expression and purification, mutation introduction, DNA vaccination of a host in need thereof, antibody generation for, e.g., passive immunization, PCR, primer and probe generation, and the like. In certain embodiments, the nucleotide sequence of the invention comprises, consists of, or consists essentially of, a nucleotide sequence selected from a sequence set forth in Table 12. In certain embodiments, a nucleotide sequence includes a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a nucleotide sequence selected from a sequence set forth in Table 12. In certain embodiments, a nucleotide sequence includes a contiguous nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a contiguous nucleotide sequence selected from a sequence set forth in Table 12. In certain embodiments, a nucleotide sequence includes a nucleotide sequence having at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 300, 400, or 500 (or any integer within these numbers) contiguous nucleotides of a nucleotide sequence selected from a sequence set forth in Table 12.

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

The antibodies suitable for use in the methods disclosed herein may comprise conservative amino acid substitutions at one or more amino acid residues, e.g., at essential or non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid

residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a nonessential amino acid residue in a binding polypeptide is preferably replaced with another amino acid residue from the same side chain family. In certain embodiments, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members. Alternatively, in certain embodiments, mutations may be introduced randomly along all or part of a coding sequence, such as by saturation mutagenesis, and the resultant mutants can be incorporated into binding polypeptides of the invention and screened for their ability to bind to the desired target.

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

As used herein, the term “cross-reacts” refers to the ability of an antibody of the disclosure to bind to IL-27 from a different species. For example, an antibody of the present disclosure which binds human IL-27 may also bind another species of IL-27. As used herein, cross-reactivity is measured by detecting a specific reactivity with purified antigen in binding assays (e.g., SPR, ELISA) or binding to, or otherwise functionally interacting with, cells physiologically expressing IL-27. Methods for determining cross-reactivity include standard binding assays as described herein, for example, by Biacore™ surface plasmon resonance (SPR) analysis using a Biacore™ 2000 SPR instrument (Biacore AB, Uppsala, Sweden), or flow cytometric techniques.

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

As used herein, the term “dendritic cell” or “DC” refers to type of antigen-presenting cells that are bone marrow (BM)-derived leukocytes and are the most potent type of antigen-presenting cells. DCs capture and process antigens, converting proteins to peptides that are presented on major histocompatibility complex (MHC) molecules recognized by T cells. DCs are heterogeneous, e.g. myeloid and plasmacytoid DCs; although all DCs are capable of antigen uptake, processing and presentation to naive T cells, the DC subtypes have distinct markers and

differ in location, migratory pathways, detailed immunological function and dependence on infections or inflammatory stimuli for their generation. During the development of an adaptive immune response, the phenotype and function of DCs play a role in initiating tolerance, memory, and polarized T-helper 1 (Th1), Th2 and Th17 differentiation.

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

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

As used herein, the term “effective dose” or “effective dosage” is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term “therapeutically effective dose” is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts effective for this use will depend upon the severity of the disorder being treated and the general state of the patient’s own immune system.

As used herein, the term “epitope” or “antigenic determinant” refers to a site on an antigen to which an immunoglobulin or antibody specifically binds. The term “epitope mapping” refers to a process or method of identifying the binding site, or epitope, of an antibody, or antigen binding fragment thereof, on its target protein antigen. Epitope mapping methods and techniques are provided herein. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by

tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods for determining what epitopes are bound by a given antibody (*i.e.*, epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation assays, wherein overlapping or contiguous peptides from IL-27 are tested for reactivity with the given anti-IL-27 antibody. Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance (see, *e.g.*, *Epitope Mapping Protocols in Methods in Molecular Biology*, Vol. 66, G. E. Morris, Ed. (1996)).

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

Also encompassed by the present disclosure are antibodies that bind the same epitope and/or antibodies that compete for binding to human IL-27 with the antibodies described herein. Antibodies that recognize the same epitope or compete for binding can be identified using routine techniques. Such techniques include, for example, an immunoassay, which shows the ability of one antibody to block the binding of another antibody to a target antigen, *i.e.*, a competitive binding assay. Competitive binding is determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as IL-27. Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli *et al.*, *Methods in Enzymology* 9:242 (1983)); solid phase direct biotin-avidin EIA (see Kirkland *et al.*, *J. Immunol.* 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press (1988)); solid phase direct label RIA using I-125 label (see Morel *et al.*, *Mol. Immunol.* 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung *et al.*, *Virology* 176:546 (1990)); and direct labeled RIA. (Moldenhauer *et al.*, *Scand. J. Immunol.* 32:77 (1990)). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test

immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70% 70-75% or more.

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

As used herein, the term “Fc-mediated effector functions” or “Fc effector functions” refer to the biological activities of an antibody other than the antibody’s primary function and purpose. For example, the effector functions of a therapeutic agnostic antibody are the biological activities other than the activation of the target protein or pathway. Examples of antibody effect functions include C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); lack of activation of platelets that express Fc receptor; and B cell activation. Many effector functions begin with Fc binding to an Fc γ receptor. In some embodiments, the tumor antigen-targeting antibody has effector function, e.g., ADCC activity. In some embodiments, a tumor antigen-targeting antibody described herein comprises a variant constant region having increased effector function (e.g. increased ability to mediate ADCC) relative to the unmodified form of the constant region.

As used herein, the term “Fc receptor” refers to a polypeptide found on the surface of immune effector cells, which is bound by the Fc region of an antibody. In some embodiments, the Fc receptor is an Fc γ receptor. There are three subclasses of Fc γ receptors, Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIII (CD16). All four IgG isotypes (IgG1, IgG2, IgG3 and IgG4) bind and activate

Fc receptors FcγRI, FcγRIIA and FcγRIIIA. FcγRIIB is an inhibitory receptor, and therefore antibody binding to this receptor does not activate complement and cellular responses. FcγRI is a high affinity receptor that binds to IgG in monomeric form, whereas FcγRIIA and FcγRIIA are low affinity receptors that bind IgG only in multimeric form and have slightly lower affinity. The binding of an antibody to an Fc receptor and/or C1q is governed by specific residues or domains within the Fc regions. Binding also depends on residues located within the hinge region and within the CH2 portion of the antibody. In some embodiments, the agonistic and/or therapeutic activity of the antibodies described herein is dependent on binding of the Fc region to the Fc receptor (e.g., FcγR). In some embodiments, the agonistic and/or therapeutic activity of the antibodies described herein is enhanced by binding of the Fc region to the Fc receptor (e.g., FcγR).

A list of certain Fc receptor sequences employed in the instant disclosure is set forth as Table 13 below.

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

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

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

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

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

As used herein, the terms “inhibits”, “reduces” or “blocks” (*e.g.*, referring to inhibition or reduction of human IL-27-mediated phosphorylation of STAT1 and/or STAT3 in a cell) are used interchangeably and encompass both partial and complete inhibition/blocking. The inhibition/blocking of IL-27 reduces or alters the normal level or type of activity that occurs without inhibition or blocking. Inhibition and blocking are also intended to include any measurable decrease in the binding affinity of IL-27 when in contact with an anti-IL-27 antibody as compared to IL-27 not in contact with an anti-IL-27 antibody, *e.g.*, inhibits binding of IL-27 by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% , 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%.

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

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

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

The term “*in vivo*” refers to processes that occur in a living organism.

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

As used herein, the term “isolated nucleic acid molecule” refers to nucleic acids encoding antibodies or antibody portions (*e.g.*, V_H, V_L, CDR3) that bind to IL-27, is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the antibody or antibody portion are free of other nucleotide sequences encoding antibodies or antibody portions that bind antigens other than IL-27, which other sequences may naturally flank the nucleic acid in human genomic DNA. For example, a sequence selected from a sequence set forth in Table 12 corresponds to the nucleotide sequences comprising the heavy chain (V_H) and light chain (V_L) variable regions of anti-IL-27 antibody monoclonal antibodies described herein.

As used herein, “isotype” refers to the antibody class (*e.g.*, IgM or IgG1) that is encoded by heavy chain constant region genes. In some embodiments, a human monoclonal antibody of the disclosure is of the IgG1 isotype. In some embodiments, a human monoclonal antibody of the disclosure is of the IgG2 isotype. In some embodiments, a human monoclonal antibody of the disclosure is of the IgG3 isotype. In some embodiments, a human monoclonal antibody of the

disclosure is of the IgG4 isotype. As is apparent to a skilled artisan, identification of antibody isotypes (e.g., IgG1, IgG2, IgG3, IgG4, IgM, IgA1 IgA2, IgD, and IgE) is routine in the art and commonly involves a combination of sequence alignments with known antibodies, published Fc variant sequences and conserved sequences.

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

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

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

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

As used herein, the term “leukocyte” refers to a type of white blood cell involved in defending the body against infective organisms and foreign substances. Leukocytes are produced in the bone marrow. There are 5 main types of white blood cells, subdivided between 2 main groups: polymorphonuclear leukocytes (neutrophils, eosinophils, basophils) and mononuclear leukocytes (monocytes and lymphocytes).

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

As used herein, the terms "linked," "fused", or "fusion", are used interchangeably. These terms refer to the joining together of two more elements or components or domains, by whatever

means including chemical conjugation or recombinant means. Methods of chemical conjugation (e.g., using heterobifunctional crosslinking agents) are known in the art.

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

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

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

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

As used herein, the term “natural killer (NK) cell” refers to a type of cytotoxic lymphocyte. These are large, usually granular, non-T, non-B lymphocytes, which kill certain tumor cells and play an important in innate immunity to viruses and other intracellular pathogens, as well as in antibody-dependent cell-mediated cytotoxicity (ADCC).

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

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

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

Polynucleotides used herein can be composed of any polyribonucleotide or polydeoxribonucleotide, which can be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double- stranded regions, single- and double- stranded RNA, and RNA that is mixture of single- and double- stranded regions, hybrid molecules comprising DNA and RNA that can be single- stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide can also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified"

bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

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

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

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

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

The term "percent identity," in the context of two or more nucleic acid or polypeptide sequences, refer to two or more sequences or subsequences that have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned for maximum correspondence, as measured using one of the sequence comparison algorithms described below (e.g., BLASTP and BLASTN or other algorithms available to persons of skill) or by visual inspection. Depending on the application, the "percent identity" can exist over a region of the sequence being compared, e.g., over a functional domain, or, alternatively, exist over the full

length of the two sequences to be compared. For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

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

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

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

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

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

amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

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

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

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

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

PD-1 is known as an immune-inhibitory protein that negatively regulates TCR signals (Ishida, Y. et al. (1992) EMBO J. 11:3887-3895; Blank, C. et al. (Epub 2006 Dec. 29) Immunol. Immunother. 56(5):739-745). The interaction between PD-1 and PD-L1 can act as an immune checkpoint, which can lead to a decrease in T-cell receptor mediated proliferation (Dong et al.

(2003) *J. Mol. Med.* 81:281-7; Blank et al. (2005) *Cancer Immunol. Immunother.* 54:307-314; Konishi et al. (2004) *Clin. Cancer Res.* 10:5094-100). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1 or PD-L2; the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai et al. (2002) *Proc. Nat'l. Acad. Sci. USA* 99:12293-7; Brown et al. (2003) *J. Immunol.* 170:1257-66).

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

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

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

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

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

As used herein, the term “recombinant human antibody” includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art (see, *e.g.*, Lonberg (2005) *Nature Biotech.* 23(9):1117-1125), the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (*i.e.*, isotype switch). Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen may not have sequence

identity with the original nucleic acid molecules, but instead will be substantially identical or similar (*i.e.*, have at least 80% identity).

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

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

antibody specific for an antigen” are used interchangeably herein with the term “an antibody which binds specifically to an antigen.”

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

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

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

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

For nucleic acids, the term “substantial homology” indicates that two nucleic acids, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least about 80% of the nucleotides, usually at least about 90% to 95%, and more preferably at least about 98% to 99.5% of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to the complement of the strand.

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

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

The nucleic acid and protein sequences of the present disclosure can further be used as a “query sequence” to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the protein molecules of the invention. To obtain gapped alignments

for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.

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

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

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

The term “T cell” refers to a type of white blood cell that can be distinguished from other white blood cells by the presence of a T cell receptor on the cell surface. There are several subsets of T cells, including, but not limited to, T helper cells (a.k.a. T_H cells or CD4⁺ T cells) and subtypes, including T_{H1}, T_{H2}, T_{H3}, T_{H17}, T_{H9}, and T_{FH} cells, cytotoxic T cells (a.k.a T_C cells, CD8⁺ T cells, cytotoxic T lymphocytes, T-killer cells, killer T cells), memory T cells and subtypes, including

central memory T cells (T_{CM} cells), effector memory T cells (T_{EM} and T_{EMRA} cells), and resident memory T cells (T_{RM} cells), regulatory T cells (a.k.a. T_{reg} cells or suppressor T cells) and subtypes, including CD4⁺ FOXP3⁺ T_{reg} cells, CD4⁺FOXP3⁻ T_{reg} cells, Tr1 cells, Th3 cells, and T_{reg}17 cells, natural killer T cells (a.k.a. NKT cells), mucosal associated invariant T cells (MAITs), and gamma delta T cells (γδ T cells), including Vγ9/Vδ2 T cells. Any one or more of the aforementioned or unmentioned T cells may be the target cell type for a method of use of the invention.

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

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

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

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

The terms “treat,” “treating,” and “treatment,” as used herein, refer to therapeutic or preventative measures described herein. The methods of “treatment” employ administration to a

subject, in need of such treatment, a human antibody of the present disclosure, for example, a subject in need of an enhanced immune response against a particular antigen or a subject who ultimately may acquire such a disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

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

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

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

of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the presently disclosed methods and compositions. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a table that provides affinity data for anti-IL-27 antibodies, as indicated. Affinity measurements were performed using ForteBio and Meso Scale Discovery methods.

FIG. 2 is a graph depicting the binding of anti-IL-27 antibodies, as indicated, to plate-bound recombinant IL-27 as measured by ELISA.

FIGS. 3A-3E are a bar chart, two graphs, a bar chart, and a graph, respectively. **FIG. 3A** is a graph depicting the inhibition of IL-27-mediated phosphorylation of STAT1 in human whole blood by anti-IL-27 antibodies, as indicated, as measured by flow cytometry. **FIG. 3B** is a graph depicting the inhibition of IL-27-mediated phosphorylation of STAT1 in human PBMCs by anti-IL-27 antibodies, as indicated, as measured by flow cytometry. **FIG. 3C** is a graph depicting the inhibition of IL-27-mediated phosphorylation of STAT1 in U937 cells by anti-IL-27 antibodies, as indicated, as measured by flow cytometry. **FIG. 3D** is a graph depicting the inhibition of IL-27-mediated phosphorylation of STAT1 in HUT-78 cells by anti-IL-27 antibodies, as indicated, as measured by flow cytometry. **FIG. 3E** is graph showing that SRF388 inhibits IL-27-mediated pSTAT1 in human whole blood T cells.

FIG. 4 is a graph depicting the reversal of IL-27-mediated inhibition of CD161 expression in T cells by a range of concentrations of anti-IL-27 antibodies, as indicated. CD161 expression was determined using flow cytometry.

FIG. 5A is a graph depicting the extent of anti-IL-27 antibodies to enhance the PD-1-mediated secretion of TNF α in human PBMCs as measured by ELISA. **FIG. 5B** is a graph depicting the extent of anti-IL-27 antibodies to enhance the PD-1-mediated secretion of IL-6 in human PBMCs as measured by ELISA. **FIG. 5C** is a dotplot showing that SRF388 in combination

with PD-1 blockade leads to increased cytokine production in PBMCs from healthy donors and patients with RCC (Abbreviations: CBA = Cytometric Bead Array, IFN γ = interferon gamma, MSD = Meso Scale Discovery, PBMCs = peripheral blood mononuclear cells, PD-1 = programmed death receptor-1, RCC = renal cell carcinoma, TNF α = tumor necrosis factor alpha). **FIG. 5D** shows that IL-27 inhibits cytokine production following PD-1 blockade and is restored in combination with SRF388 (Abbreviations: Ctrl = control, ns = not significant, PBMCs = peripheral blood mononuclear cells, rhIL-27 = recombinant human IL-27). **FIG. 5E** summarizes observed cytokine induction (specifically, TNF α , IFN γ , IL-6 and IL-17A) in PBMC culture for various indicated types of cells, when such cells were contacted with SRF388 antibody, α PD-1 antibody, or a combination of SRF388 and α PD-1 antibodies. **FIG. 5F** shows the impact upon pSTAT1 signal in U937 (lymphoma) cells of varying concentrations of the individual antibodies indicated (SRF405, SRF410, SRF411, SRF414, SRF416, SRF536, SRF543, SRF529, SRF381, SRF388 and Ab7). **FIG. 5G** shows the impact upon pSTAT1 signal in PBMCs (peripheral blood mononuclear cells) of varying concentrations of these individual antibodies. **FIG. 5H** shows the impact upon CD161 signal in PBMCs (peripheral blood mononuclear cells) of varying concentrations of these individual antibodies. **FIG. 5I** shows the impact upon PD-L1 signal in CD4 T lymphocytes (CD4 cells) of varying concentrations of these individual antibodies (excluding SRF414). **FIG. 5J** shows the impact upon PD-L1 signal in monocytes of varying concentrations of these individual antibodies (excluding SRF529). **FIG. 5K** shows the impact upon TIM-3 signal in monocytes of varying concentrations of these individual antibodies (excluding SRF529).

FIG. 6A is a graph depicting the inhibition of IL-27-mediated expression of PD-L1 by treatment of human monocytes with anti-IL-27 antibody as determined by flow cytometry. **FIG. 6B** is a graph depicting the dose-dependent inhibition of IL-27-mediated expression of PD-L1 by treatment of human monocytes with a range of concentrations of an anti-IL-27 antibody that specifically binds to the EBI3 monomer, as determined by flow cytometry. **FIG. 6C** is a graph depicting the inhibition of IL-27-mediated expression of TIM3 by treatment of human monocytes with anti-IL-27 antibody, as determined by flow cytometry. **FIG. 6D** is a graph depicting the inhibition of IL-27-mediated expression of PD-L1 by treatment of resting human T cells with anti-IL-27 antibody, as determined by flow cytometry.

FIG. 7A is a dotplot depicting the number of surface lung B16F10 metastatic nodules (pulmonary nodules) from B16F10 tumor-bearing mice treated with anti-IL27 antibody (SRF388), isotype control antibody, α WSX-1 antibody or combined α PD-1 and α CTLA-4 antibodies, as indicated, as determined by visual counting of nodules from lungs isolated from mice. **FIG. 7B** provides a graph depicting the growth kinetics of bioluminescent B16-Luc tumors in mice treated with anti-IL-27 antibody (SRF388) or isotype control antibody, as determined by bioluminescent imaging analysis. **FIG. 7C** shows a series of images of fixed, sectioned lung tissue stained with hematoxylin and eosin isolated from B16F10 tumor-bearing mice treated with anti-IL27 antibody (SRF388), isotype control antibody, α WSX-1 antibody or combined α PD-1 and α CTLA-4 antibodies, as indicated. **FIG. 7D** is a dotplot depicting the total tumor area as a percentage of total tissue area of fixed, sectioned lung tissue B16F10 tumor tissue stained with hematoxylin and eosin isolated from B16F10 tumor-bearing mice treated with anti-IL27 antibody (SRF388), isotype control antibody, α WSX-1 antibody or combined α PD-1 and α CTLA-4 antibodies, as indicated, as determined by image analysis software. A similar reduction in surface lung metastasis number and total tumor area was observed with IL-27RA (WSX-1) mediated antibody blockade and with anti-PD-1 + anti-CTLA-4 combination therapy.

FIG. 8A provides a scatterplot depicting microarray data of genes with an expression change $> 1.0 \log_2$ fold change (black dots) in splenocytes isolated from mice overexpressing IL-27 following treatment with IL-27 minicircles. **FIG. 8B** provides a graph depicting the expression level of select immunomodulatory genes, as indicated, in splenocytes as in **FIG. 8A**. **FIG. 8C** shows ectopic expression of human IL-27 induces inhibitory receptor expression on murine T cells in vivo and that SRF388 reduces inhibitory receptor expression on T cells in vivo after IL-27 minicircle treatment. Six-week-old female Balb/c mice were injected with empty vector (control) or hIL-27 minicircle. (top left and right panels) PBMCs and (bottom left and right panels) total splenocytes were collected 5 days after transfection and cells were stained and analyzed by flow cytometry. Expression of the indicated markers were analyzed on CD4⁺ T cells (top left and bottom left panels) and CD8⁺ T cells (top right and bottom right panels). Analysis was performed using FlowJo software. **FIG. 8D** shows that SRF388 inhibits detection of minicircle-derived human IL-27 in murine plasma.

FIG. 9 presents a tabulated summary of select monoclonal antibody properties.

FIG. 10A presents a chart of antibody sequences, with sequence partitioning reflecting NT numbering. **FIG. 10B** presents a chart of antibody sequences (corresponding to the sequence chart of **FIG. 10A**), with sequence partitioning reflecting ImMunoGeneTics (IMGT) numbering. In both **FIG. 10A** and **FIG. 10B**, highlighted amino acids in CDR sequences show mutations from germline-encoded sequence. As will be apparent to the skilled artisan, antibody numbering, including determination of CDR sequences, framework sequences, etc., can be performed in a number of art-recognized manners, including *via* the NT and IMGT numbering systems presented in **FIG. 10A** and **FIG. 10B** and employed elsewhere herein.

DETAILED DESCRIPTION

The present disclosure provides, at least in part, antibody molecules that bind to human IL-27 with high affinity and specificity. In one embodiment, disclosed herein are human antibodies that bind to IL-27. The terms “IL-27” and “IL27” as used herein refer interchangeably to the heterodimeric cytokine, IL-27 that is composed of two distinct subunits, encoded by two different genes: Epstein-Barr virus-induced gene 3 (EBI3) and IL-27p28. IL-27 has both pro- and anti-inflammatory properties with diverse effects on - hematopoietic and non-hematopoietic cells.

Accordingly, in one aspect, the disclosure provides a 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;
 - (vi) induces or enhances PD-1 mediated secretion of one or more cytokines from a cell;
- and
- (vii) a combination of (i)-(vi).

In other aspects, the disclosure provides a monoclonal antibody or antigen binding portion thereof that specifically binds human IL-27 and inhibits or reduces an IL-27 biological activity or IL-27 signaling.

Additional aspects of the invention include nucleic acid molecules encoding the antibody molecules, expression vectors, host cells and methods for making the antibody molecules. Immunoconjugates, multi- or bispecific molecules and pharmaceutical compositions comprising the antibody molecules are also provided. The anti-IL-27 antibody molecules disclosed herein can be used to treat, prevent and/or diagnose cancerous or malignant disorders, e.g., solid and liquid tumors (e.g., leukemia, e.g., lymphoma, e.g., AML), lung cancer (e.g., non-small cell lung cancer), pancreatic cancer, breast cancer (e.g., triple-negative breast cancer), melanoma, testicular cancer, sarcoma, head and neck cancer (e.g., squamous head and neck cancer), liver cancer (e.g., hepatocellular carcinoma (HCC)), colorectal cancer, ovarian cancer, brain cancer (e.g., glioblastoma multiforme), or renal cancer (e.g., renal cell carcinoma, e.g. renal clear cell carcinoma).

Anti-IL-27 Antibodies and Antigen-binding Fragments Thereof

The present disclosure provides antibodies, and antigen binding portions thereof, that specifically bind to and antagonize IL-27, in particular human IL-27. Provided herein are isolated monoclonal antibodies or antigen binding portion thereof that specifically bind to human IL-27, comprising heavy and light chain CDRs and variable sequences as set forth in Table 12.

In some embodiments, the disclosure provides 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 inhibition of CD161 expression in a cell; (v) inhibits or reduces PD-L1 and/or TIM-3 expression in a cell; (vi) induces or enhances PD-1 mediated secretion of one or more cytokines from a cell; and (vii) a combination of (i)-(vi).

In some embodiments, the isolated monoclonal antibody, or antigen binding portion thereof, binds to human IL-27 with an equilibrium dissociation constant (K_D) of 15 nM or less.

In some embodiments, the isolated monoclonal antibody, or antigen binding portion thereof, binds to recombinant human IL-27 or to murine IL-27.

In some embodiments, the isolated monoclonal antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell. In some embodiments, the cell is an immune cell. In some embodiments, the cell is a cancer cell.

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

In some embodiments, the isolated monoclonal antibody, or antigen binding portion thereof, inhibits or reduces PD-L1 and/or TIM-3 expression in a cell. In some embodiments, PD-L1 expression is inhibited or reduced. In some embodiments, TIM-3 expression is inhibited or reduced. In some embodiments, both PD-L1 expression and TIM-3 expression is reduced. In some embodiments, the cell is an immune cell.

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

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

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

In some embodiments, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, that binds to at least one of the amino acid residues comprising IL-27 bound by the antibody, or antigen binding portion thereof, according to any one of the aforementioned embodiments.

In some embodiments, the disclosure provides an isolated monoclonal antibody, or antigen binding portion thereof, wherein a mutation of the epitope on IL-27 bound by the antibody or antigen binding portion thereof inhibits, reduces, or blocks binding to both the antibody or antigen binding portion thereof and to the antibody or antigen binding portion thereof according to any one of the aforementioned embodiments.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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, respectively, and the light chain CDR1, CDR2 and CDR3 sequences are set forth in SEQ ID NOs: 172, 173 and 174, respectively.

In some embodiments, the disclosure provides 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 amino acid sequences of heavy chain CDR1, CDR2 and CDR3 are SYSMS (SEQ ID NO: 23), YISYDGG SAYYPDTVKG (SEQ ID NO: 24) and HGDYDDDDAMDY (SEQ ID NO: 25), respectively, and wherein the amino acid sequences of light chain CDR1, CDR2 and CDR3 are RASENIYSYLA (SEQ ID NO: 26), NAETLTE (SEQ ID NO: 27) and QHHYGTPLT (SEQ ID NO: 28), respectively.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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, 223, 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.

In some embodiments, the disclosure provides 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, 223, 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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: 223 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.

In some embodiments, the disclosure provides 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: 223 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

In some embodiments, the disclosure provides 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.

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

The disclosure also features methods for producing any of the anti-IL-27 antibodies or antigen-binding fragments thereof described herein. In some embodiments, methods for preparing an antibody described herein can include immunizing a subject (e.g., a non-human mammal) with

an appropriate immunogen. Suitable immunogens for generating any of the antibodies described herein are set forth herein. For example, to generate an antibody that binds to IL-27, a skilled artisan can immunize a suitable subject (e.g., a non-human mammal such as a rat, a mouse, a gerbil, a hamster, a dog, a cat, a pig, a goat, a horse, or a non-human primate) with IL-27. In some embodiments, a full-length human IL-27 EBI3 monomer polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 97 is used as the immunogen. In some embodiments, a full-length human IL-27p28 monomer polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 98 is used as the immunogen.

A suitable subject (e.g., a non-human mammal) can be immunized with the appropriate antigen along with subsequent booster immunizations a number of times sufficient to elicit the production of an antibody by the mammal. The immunogen can be administered to a subject (e.g., a non-human mammal) with an adjuvant. Adjuvants useful in producing an antibody in a subject include, but are not limited to, protein adjuvants; bacterial adjuvants, e.g., whole bacteria (BCG, *Corynebacterium parvum* or *Salmonella minnesota*) and bacterial components including cell wall skeleton, trehalose dimycolate, monophosphoryl lipid A, methanol extractable residue (MER) of tubercle *bacillus*, complete or incomplete Freund's adjuvant; viral adjuvants; chemical adjuvants, e.g., aluminum hydroxide, and iodoacetate and cholesteryl hemisuccinate. Other adjuvants that can be used in the methods for inducing an immune response include, e.g., cholera toxin and parapoxvirus proteins. See also Bieg et al. (1999) *Autoimmunity* 31(1):15-24. See also, e.g., Lodmell et al. (2000) *Vaccine* 18:1059-1066; Johnson et al. (1999) *J Med Chem* 42:4640-4649; Baldrige et al. (1999) *Methods* 19:103-107; and Gupta et al. (1995) *Vaccine* 13(14): 1263-1276.

In some embodiments, the methods include preparing a hybridoma cell line that secretes a monoclonal antibody that binds to the immunogen. For example, a suitable mammal such as a laboratory mouse is immunized with a IL-27 polypeptide as described above. Antibody-producing cells (e.g., B cells of the spleen) of the immunized mammal can be isolated two to four days after at least one booster immunization of the immunogen and then grown briefly in culture before fusion with cells of a suitable myeloma cell line. The cells can be fused in the presence of a fusion promoter such as, e.g., vaccinia virus or polyethylene glycol. The hybrid cells obtained in the fusion are cloned, and cell clones secreting the desired antibodies are selected. For example, spleen cells of Balb/c mice immunized with a suitable immunogen can be fused with cells of the myeloma cell line PAI or the myeloma cell line Sp2/0-Ag 14. After the fusion, the cells are expanded in

suitable culture medium, which is supplemented with a selection medium, for example HAT medium, at regular intervals in order to prevent normal myeloma cells from overgrowing the desired hybridoma cells. The obtained hybrid cells are then screened for secretion of the desired antibodies, e.g., an antibody that binds to human IL-27 and In some embodiments, a skilled artisan can identify an anti-IL-27 antibody from a non-immune biased library as described in, e.g., U.S. patent no. 6,300,064 (to Knappik et al.; Morphosys AG) and Schoonbroodt et al. (2005) *Nucleic Acids Res* 33(9):e81.

In some embodiments, the methods described herein can involve, or be used in conjunction with, e.g., phage display technologies, bacterial display, yeast surface display, eukaryotic viral display, mammalian cell display, and cell-free (e.g., ribosomal display) antibody screening techniques (see, e.g., Etz et al. (2001) *J Bacteriol* 183:6924-6935; Cornelis (2000) *Curr Opin Biotechnol* 11:450-454; Klemm et al. (2000) *Microbiology* 146:3025-3032; Kiecke et al. (1997) *Protein Eng* 10:1303-1310; Yeung et al. (2002) *Biotechnol Prog* 18:212-220; Boder et al. (2000) *Methods Enzymology* 328:430-444; Grabherr et al. (2001) *Comb Chem High Throughput Screen* 4:185-192; Michael et al. (1995) *Gene Ther* 2:660-668; Pereboev et al. (2001) *J Virol* 75:7107-7113; Schaffitzel et al. (1999) *J Immunol Methods* 231:119-135; and Hanes et al. (2000) *Nat Biotechnol* 18:1287-1292).

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

patent nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108.

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

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

A subpopulation of antibodies screened using the above methods can be characterized for their specificity and binding affinity for a particular antigen (e.g., human IL-27) using any immunological or biochemical based method known in the art. For example, specific binding of an antibody to IL-27, may be determined for example using immunological or biochemical based

methods such as, but not limited to, an ELISA assay, SPR assays, immunoprecipitation assay, affinity chromatography, and equilibrium dialysis as described above. Immunoassays which can be used to analyze immunospecific binding and cross-reactivity of the antibodies include, but are not limited to, competitive and non-competitive assay systems using techniques such as Western blots, RIA, ELISA (enzyme linked immunosorbent assay), “sandwich” immunoassays, immunoprecipitation assays, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays. Such assays are routine and well known in the art.

It is understood that the above methods can also be used to determine if, e.g., an anti-IL-27 antibody does not bind to full-length, human IL-27 and/or IL-27 proteins.

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

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

In one embodiment, the anti-IL-27 antibodies described herein comprise an IgG4 heavy chain constant region. In one embodiment, the IgG4 heavy chain constant region is a wild type IgG4 heavy chain constant region. In another embodiment, the IgG4 constant region comprises a mutation, e.g., one or both of S228P and L235E or L235A, e.g., according to EU numbering (Kabat, E.A., et al., supra). Representative sequences for use in antibodies of the disclosure of wild-type and mutant IgG4 constant regions are set forth in Table 12. In one embodiment, the anti-IL-27 antibodies described herein comprise an IgG1 constant region. In one embodiment, the IgG1 heavy chain constant region is a wild type IgG1 heavy chain constant region. In another embodiment, the IgG1 heavy chain constant region comprises a mutation. Representative sequences for use in antibodies of the disclosure of wild-type and mutant IgG4 constant regions are set forth in Table 12.

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

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

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

Recombinant Antibody Expression and Purification

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

Several possible vector systems are available for the expression of cloned heavy chain and light chain polypeptides from nucleic acids in mammalian cells. One class of vectors relies upon the integration of the desired gene sequences into the host cell genome. Cells which have stably

integrated DNA can be selected by simultaneously introducing drug resistance genes such as *E. coli* gpt (Mulligan and Berg (1981) *Proc Natl Acad Sci USA* 78:2072) or *Tn5* neo (Southern and Berg (1982) *Mol Appl Genet* 1:327). The selectable marker gene can be either linked to the DNA gene sequences to be expressed, or introduced into the same cell by co-transfection (Wigler et al. (1979) *Cell* 16:77). A second class of vectors utilizes DNA elements which confer autonomously replicating capabilities to an extrachromosomal plasmid. These vectors can be derived from animal viruses, such as bovine papillomavirus (Sarver et al. (1982) *Proc Natl Acad Sci USA*, 79:7147), cytomegalovirus, polyoma virus (Deans et al. (1984) *Proc Natl Acad Sci USA* 81:1292), or SV40 virus (Lusky and Botchan (1981) *Nature* 293:79).

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

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

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

The antibodies and fragments thereof can be produced from the cells by culturing a host cell transformed with the expression vector containing nucleic acid encoding the antibodies or fragments, under conditions, and for an amount of time, sufficient to allow expression of the proteins. Such conditions for protein expression will vary with the choice of the expression vector and the host cell, and will be easily ascertained by one skilled in the art through routine experimentation. For example, antibodies expressed in *E. coli* can be refolded from inclusion bodies (see, e.g., Hou et al. (1998) *Cytokine* 10:319-30). Bacterial expression systems and methods for their use are well known in the art (see Current Protocols in Molecular Biology, Wiley

& Sons, and Molecular Cloning--A Laboratory Manual --3rd Ed., Cold Spring Harbor Laboratory Press, New York (2001)). The choice of codons, suitable expression vectors and suitable host cells will vary depending on a number of factors, and may be easily optimized as needed. An antibody (or fragment thereof) described herein can be expressed in mammalian cells or in other expression systems including but not limited to yeast, baculovirus, and *in vitro* expression systems (see, e.g., Kaszubska et al. (2000) *Protein Expression and Purification* 18:213-220).

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

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

Modification of the Antibodies or Antigen-Binding Fragments Thereof

The antibodies or antigen-binding fragments thereof can be modified following their expression and purification. The modifications can be covalent or non-covalent modifications. Such modifications can be introduced into the antibodies or fragments by, e.g., reacting targeted amino acid residues of the polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues. Suitable sites for modification can be chosen using any of a variety of criteria including, e.g., structural analysis or amino acid sequence analysis of the antibodies or fragments.

In some embodiments, the antibodies or antigen-binding fragments thereof can be conjugated to a heterologous moiety. The heterologous moiety can be, e.g., a heterologous polypeptide, a therapeutic agent (e.g., a toxin or a drug), or a detectable label such as, but not limited to, a radioactive label, an enzymatic label, a fluorescent label, a heavy metal label, a luminescent label, or an affinity tag such as biotin or streptavidin. Suitable heterologous polypeptides include, e.g., an antigenic tag (FLAG (DYKDDDDK (SEQ ID NO: 405)), polyhistidine (6-His; HHHHHH (SEQ ID NO: 406), hemagglutinin (HA; YPYDVPDYA (SEQ ID NO: 407)), glutathione-S-transferase (GST), or maltose-binding protein (MBP)) for use in purifying the antibodies or fragments. Heterologous polypeptides also include polypeptides (e.g., enzymes) that are useful as diagnostic or detectable markers, for example, luciferase, a fluorescent protein (e.g., green fluorescent protein (GFP)), or chloramphenicol acetyl transferase (CAT). Suitable radioactive labels include, e.g., ^{32}P , ^{33}P , ^{14}C , ^{125}I , ^{131}I , ^{35}S , and ^3H . Suitable fluorescent labels include, without limitation, fluorescein, fluorescein isothiocyanate (FITC), green fluorescent protein (GFP), DyLight™ 488, phycoerythrin (PE), propidium iodide (PI), PerCP, PE-Alexa Fluor® 700, Cy5, allophycocyanin, and Cy7. Luminescent labels include, e.g., any of a variety of luminescent lanthanide (e.g., europium or terbium) chelates. For example, suitable europium chelates include the europium chelate of diethylene triamine pentaacetic acid (DTPA) or tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). Enzymatic labels include, e.g., alkaline phosphatase, CAT, luciferase, and horseradish peroxidase.

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

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

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

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

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

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

Pharmaceutical Compositions and Formulations

In certain embodiments, the invention provides for a pharmaceutical composition comprising an anti-IL-27 antibody with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, the formulation material(s) are for s.c. and/or I.V. administration. In certain embodiments, the pharmaceutical composition can contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolality, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In certain embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen- sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta- cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending

agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company (1995). In certain embodiments, the formulation comprises PBS; 20 mM NaOAC, pH 5.2, 50 mM NaCl; and/or 10 mM NAOAC, pH 5.2, 9% Sucrose. In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, Remington's Pharmaceutical Sciences, *supra*. In certain embodiments, such compositions may influence the physical state, stability, rate of *in vivo* release and/or rate of *in vivo* clearance of the anti-IL-27 antibody.

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

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

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

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

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

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

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

Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving an anti-IL-27 antibody in sustained- or controlled-delivery formulations. In certain embodiments, techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See for example, PCT Application No. PCT/US93/00829 which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. In certain embodiments, sustained-release preparations can include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides (U.S. Pat. No. 3,773,919 and EP 058,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., *Biopolymers*, 22:547-556 (1983)), poly (2-hydroxyethyl-methacrylate) (Langer et al., *J. Biomed. Mater. Res.*, 15: 167-277 (1981) and Langer, *Chem. Tech.*, 12:98- 105 (1982)), ethylene vinyl acetate (Langer et al., *supra*) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). In certain embodiments, sustained release compositions can also include liposomes, which can be prepared by any of several methods known in the art. See, e.g., Eppstein et al, *Proc. Natl. Acad. Sci. USA*, 82:3688-3692 (1985); EP 036,676; EP 088,046 and EP 143,949.

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

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

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

In certain embodiments, the effective amount of a pharmaceutical composition comprising an anti-IL-27 antibody to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment, according to certain embodiments, will thus vary depending, in part, upon the molecule delivered, the indication for which an anti-IL-27 antibody is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect.

In certain embodiments, the frequency of dosing will take into account the pharmacokinetic parameters of an anti-IL-27 antibody in the formulation used. In certain embodiments, a clinician will administer the composition until a dosage is reached that achieves the desired effect. In certain embodiments, the composition can therefore be administered as a single dose or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. In certain embodiments, appropriate dosages can be ascertained through use of appropriate dose-response data.

In certain embodiments, the route of administration of the pharmaceutical composition is in accord with known methods, e.g. orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, subcutaneously, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain embodiments, the compositions can be administered by bolus

injection or continuously by infusion, or by implantation device. In certain embodiments, individual elements of the combination therapy may be administered by different routes.

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

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

Applications

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

in an assay to identify additional compounds (e.g., small molecules, aptamers, or antibodies) that reduce or abrogate IL-27 production. The compositions can also be used in therapeutic methods as elaborated on below.

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

Kits

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

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

Methods of Use

The compositions of the present invention have numerous *in vitro* and *in vivo* utilities involving the detection and/or quantification of IL-27 and/or the antagonism of IL-27 function.

In some embodiments, the disclosure provides a method to inhibit or reduce STAT1 and/or STAT3 phosphorylation in a cell, the method comprising contacting the cell with an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or reduces STAT1 and/or STAT3 phosphorylation in a cell.

In some embodiments, the disclosure provides a method to inhibit or reduce inhibition of CD161 expression in a cell, the method comprising contacting the cell with an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or reduces inhibition of CD161 expression in a cell.

In some embodiments, the disclosure provides a method to inhibit or reduce PD-L1 and/or TIM-3 expression in a cell, the method comprising contacting the cell with an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, inhibits or PD-L1 and/or TIM-3 expression in a cell.

In some embodiments, the disclosure provides 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, provided by the disclosure, wherein the antibody, or antigen binding portion thereof, induces or enhances PD-1 mediated secretion of one or more cytokines from a cell.

In some embodiments, the disclosure provides a method of stimulating an immune response in a subject, the method comprising administering to the subject an effective amount of an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to and antagonizes IL-27, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier.

In some embodiments, the disclosure provides a method of treating a cancer in a subject, the method comprising administering to the subject an effective amount an isolated monoclonal antibody, or antigen binding portion thereof, that specifically binds to and antagonizes IL-27, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier.

In some embodiments, the disclosure provides 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 an isolated monoclonal antibody, or antigen binding fragment, provided by

the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier, 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.

In some embodiments, the disclosure provides 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 an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier, 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.

In some embodiments, the disclosure provides 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 an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier, wherein the antibody, or antigen binding portion thereof, or the pharmaceutical composition, inhibits or reduces PD-L1 and/or TIM-3 expression in a cell, thereby stimulating the immune response, or treating the cancer.

In some embodiments, the disclosure provides 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 an isolated monoclonal antibody, or antigen binding fragment, provided by the disclosure, or a pharmaceutical composition comprising the antibody or antigen binding portion thereof, and a pharmaceutically acceptable carrier, 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.

In some embodiments, 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).

The above-described compositions are useful in, *inter alia*, methods for treating or preventing a variety of cancers in a subject. The compositions can be administered to a subject, e.g., a human subject, using a variety of methods that depend, in part, on the route of administration. The route can be, e.g., intravenous injection or infusion (IV), subcutaneous injection (SC), intraperitoneal (IP) injection, intramuscular injection (IM), or intrathecal injection (IT). The injection can be in a bolus or a continuous infusion.

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

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

A suitable dose of an antibody or fragment thereof described herein, which dose is capable of treating or preventing cancer in a subject, can depend on a variety of factors including, e.g., the age, sex, and weight of a subject to be treated and the particular inhibitor compound used. For example, a different dose of a whole anti-IL-27 antibody may be required to treat a subject with cancer as compared to the dose of a IL-27-binding Fab' antibody fragment required to treat the same subject. Other factors affecting the dose administered to the subject include, e.g., the type or severity of the cancer. For example, a subject having metastatic melanoma may require administration of a different dosage of an anti-IL-27 antibody than a subject with glioblastoma. Other factors can include, e.g., other medical disorders concurrently or previously affecting the subject, the general health of the subject, the genetic disposition of the subject, diet, time of administration, rate of excretion, drug combination, and any other additional therapeutics that are

administered to the subject. It should also be understood that a specific dosage and treatment regimen for any particular subject will also depend upon the judgment of the treating medical practitioner (e.g., doctor or nurse). Suitable dosages are described herein.

A pharmaceutical composition can include a therapeutically effective amount of an anti-IL-27 antibody or antigen-binding fragment thereof described herein. Such effective amounts can be readily determined by one of ordinary skill in the art based, in part, on the effect of the administered antibody, or the combinatorial effect of the antibody and one or more additional active agents, if more than one agent is used. A therapeutically effective amount of an antibody or fragment thereof described herein can also vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody (and one or more additional active agents) to elicit a desired response in the individual, e.g., reduction in tumor growth. For example, a therapeutically effective amount of an anti-IL-27 antibody can inhibit (lessen the severity of or eliminate the occurrence of) and/or prevent a particular disorder, and/or any one of the symptoms of the particular disorder known in the art or described herein. A therapeutically effective amount is also one in which any toxic or detrimental effects of the composition are outweighed by the therapeutically beneficial effects.

Suitable human doses of any of the antibodies or fragments thereof described herein can further be evaluated in, e.g., Phase I dose escalation studies. See, e.g., van Gurp et al. (2008) *Am J Transplantation* 8(8):1711-1718; Hanouska et al. (2007) *Clin Cancer Res* 13(2, part 1):523-531; and Hetherington et al. (2006) *Antimicrobial Agents and Chemotherapy* 50(10): 3499-3500.

In some embodiments, the composition contains any of the antibodies or antigen-binding fragments thereof described herein and one or more (e.g., two, three, four, five, six, seven, eight, nine, 10, or 11 or more) additional therapeutic agents such that the composition as a whole is therapeutically effective. For example, a composition can contain an anti-IL-27 antibody described herein and an alkylating agent, wherein the antibody and agent are each at a concentration that when combined are therapeutically effective for treating or preventing a cancer (e.g., melanoma) in a subject.

Toxicity and therapeutic efficacy of such compositions can be determined by known pharmaceutical procedures in cell cultures or experimental animals (e.g., animal models of any of the cancers described herein). These procedures can be used, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of

the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50} . An antibody or antigen-binding fragment thereof that exhibits a high therapeutic index is preferred. While compositions that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue and to minimize potential damage to normal cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such antibodies or antigen-binding fragments thereof lies generally within a range of circulating concentrations of the antibodies or fragments that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For an anti-IL-27 antibody described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (i.e., the concentration of the antibody which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography. In some embodiments, e.g., where local administration (e.g., to the eye or a joint) is desired, cell culture or animal modeling can be used to determine a dose required to achieve a therapeutically effective concentration within the local site.

In some embodiments, the methods can be performed in conjunction with other therapies for cancer. For example, the composition can be administered to a subject at the same time, prior to, or after, radiation, surgery, targeted or cytotoxic chemotherapy, chemoradiotherapy, hormone therapy, immunotherapy, gene therapy, cell transplant therapy, precision medicine, genome editing therapy, or other pharmacotherapy.

As described above, the compositions described herein (e.g., anti-IL-27 compositions) can be used to treat a variety of cancers such as but not limited to: Kaposi's sarcoma, leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblasts promyelocyte myelomonocytic monocytic erythroleukemia, chronic leukemia, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, mantle cell lymphoma, primary central nervous system lymphoma, Burkitt's lymphoma and marginal zone B cell lymphoma, Polycythemia vera Lymphoma,

Hodgkin's disease, non-Hodgkin's disease, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, solid tumors, sarcomas, and carcinomas, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, osteosarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon sarcoma, colorectal carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatocellular carcinoma (HCC), hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, retinoblastoma, nasopharyngeal carcinoma, esophageal carcinoma, basal cell carcinoma, biliary tract cancer, bladder cancer, bone cancer, brain and central nervous system (CNS) cancer, cervical cancer, choriocarcinoma, colorectal cancers, connective tissue cancer, cancer of the digestive system, endometrial cancer, esophageal cancer, eye cancer, head and neck cancer, gastric cancer, intraepithelial neoplasm, kidney cancer, larynx cancer, liver cancer, lung cancer (small cell, large cell), melanoma, neuroblastoma; oral cavity cancer (for example lip, tongue, mouth and pharynx), ovarian cancer, pancreatic cancer, retinoblastoma, rhabdomyosarcoma, rectal cancer; cancer of the respiratory system, sarcoma, skin cancer, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, and cancer of the urinary system.

Combination Therapy

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

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

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

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

In some embodiments, the one or more additional therapeutic agents is a PD-1 antagonist, a TIM-3 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, a CD112R inhibitor, a TAM inhibitor, a STING agonist, a 4-1BB agonist, or a combination thereof.

In some embodiments, the one or more additional therapeutic agents is a PD-1 antagonist. In some embodiments, the PD-1 antagonist is selected from the group consisting of: PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224. In certain embodiments, the one or more additional therapeutic agents is a PD-L1 inhibitor. In some embodiments, the PD-L1 inhibitor is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559. In some embodiments, the

disclosure provides a method of enhancing one or more activities of an anti-PD-1 antibody (e.g., enhances PD-1-mediated cytokine secretion; enhances anti-PD-1 mediated TNF α secretion; enhances anti-PD-1 mediated IL-6 secretion from a cell exposed to anti-PD-1 antibodies), the method comprising exposing a cell to an antibody, or antigen binding portion thereof, provided by the disclosure, concurrently with or sequentially to an anti-PD-1 antibody, thereby to enhance one or more activities of the anti-PD1 antibody.

In some embodiments, the one or more additional therapeutic agents is sunitinib (Sutent[®]), Cabozantinib (Cabometyx[®]), Axitinib (Inlyta[®]), Lenvatinib (Lenvima[®]), Everolimus (Afinitor[®]), Bevacizumab (Avastin[®]), epacadostat, NKTR-214 (CD-122-biased agonist), tivozanib (Fotivda[®]), abexinostat, Ipilimumab (Yervoy[®]), tremelimumab, Pazopanib (Votrient[®]), Sorafenib (Nexavar[®]), Temsirolimus (Torisel[®]), Ramucirumab (Cyramza[®]), niraparib, savolitinib, vorolanib (X-82), Regorafenib (Stivargo[®]), Donafenib (multikinase inhibitor), Camrelizumab (SHR-1210), pexastimogene devacirepvec (JX-594), Ramucirumab (Cyramza[®]), apatinib (YN968D1), encapsulated doxorubicin (Thermodox[®]), Tivantinib (ARQ197), ADI-PEG 20, binimetinib, apatinib mesylate, nintedanib, lirilumab, Nivolumab (Opdivo[®]), Pembrolizumab (Keytruda[®]), Atezolizumab (Tecentriq[®]), Avelumab (Bavencio[®]), Durvalumab (Imfimi[®]), cemiplimab-rwlc (Libtayo[®]), tislelizumab, and/or spartalizumab.

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

In some embodiments, 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.

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

Combination with Chemotherapeutic Agents

Chemotherapeutic agents suitable for combination and/or co-administration with compositions of the present invention include, for example: taxol, cytochalasin B, gramicidin D,

ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxyanthrancindione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Further agents include, for example, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g. mechlorethamine, thioTEPA, chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II)(DDP), procarbazine, altretamine, cisplatin, carboplatin, oxaliplatin, nedaplatin, satraplatin, or triplatin tetranitrate), anthracycline (e.g. daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g. dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g. vincristine and vinblastine) and temozolomide.

Combination with PD-1/PD-L1 Antagonists

In some embodiments, the anti-IL-27 antibodies, or antigen binding portions thereof, provided by the disclosure are combined (e.g., administered in combination) with one or more PD-1 antagonist that specifically binds to human PD-1 or PD-L1 and inhibits PD-1/PD-L1 biological activity and/or downstream pathway(s) and/or cellular processes mediated by human PD-1/PD-L1 signaling or other human PD-1/PD-L1-mediated functions.

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

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

In some embodiments, the PD-1 antagonist inhibits PD-1 signaling or function. In some embodiments, the PD-1 antagonist blocks binding of PD-1 to PD-L1, PD-L2, or to both PD-L1

and PD-L2. In some embodiments, the PD-1 antagonist blocks binding of PD-1 to PD-L1. In some embodiments, the PD-1 antagonist blocks binding of PD-1 to PD-L2. In some embodiments, the PD-1 antagonist blocks the binding of PD-1 to PD-L1 and PD-L2. In some embodiments, the PD-1 antagonist specifically binds PD-1. In some embodiments, the PD-1 antagonist specifically binds PD-L1. In some embodiments, the PD-1 antagonist specifically binds PD-L2.

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

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

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

Examples of anti-human PD-1 monoclonal antibodies, or antigen binding fragments thereof, that may comprise the PD-1 antagonist in any of the compositions, methods, and uses provided by the disclosure include, but are not limited to: KEYTRUDA® (pembrolizumab, MK-3475, h409A11; see US8952136, US8354509, US8900587, and EP2170959, all of which are included herein by reference in their entirety; Merck), OPDIVO® (nivolumab, BMS-936558, MDX-1106, ONO-4538; see US7595048, US8728474, US9073994, US9067999, EP1537878, US8008449, US8779105, and EP2161336, all of which are included herein by reference in their entirety; Bristol Myers Squibb), MEDI0680 (AMP-514), BGB-A317 and BGB-108 (BeiGene), 244C8 and 388D4 (see WO2016106159, which is incorporated herein by reference in its entirety; Enumeral Biomedical), PDR001 (Novartis), and REGN2810 (Regeneron). Accordingly, in some

embodiments the PD-1 antagonist is pembrolizumab. In some embodiments, the PD-1 antagonist is nivolumab.

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

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

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

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

Combinations with TIM-3 Inhibitors

In some embodiments, an anti-IL-27 antibody, or antigen binding portion thereof, provided by the disclosure is combined (e.g., administered in combination) with a TIM-3 inhibitor. The

TIM-3 inhibitor may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or an oligopeptide. In some embodiments, the TIM-3 inhibitor is chosen from MGB453 (Novartis), TSR-022 (Tesaro), or LY3321367 (Eli Lilly). In some embodiments, the anti-IL-27 antibody, or antigen binding portion thereof, is administered in combination with MGB453. In some embodiments, the anti-IL-27 antibody, or antigen binding portion thereof, is administered in combination with TSR-022.

Combinations with LAG-3 Inhibitors

In some embodiments, an anti-IL-27 antibody, or antigen binding portion thereof, provided by the disclosure is combined (e.g., administered in combination) with a LAG-3 inhibitor. The LAG-3 inhibitor may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide. In some embodiments, the LAG-3 inhibitor is chosen from LAG525 (Novartis), BMS-986016 (Bristol-Myers Squibb), TSR-033 (Tesaro), MK-4280 (Merck & Co), or REGN3767 (Regeneron).

Other Combinations

In some embodiments, an anti-IL-27 antibody, or antigen binding portion thereof, provided by the disclosure is combined (e.g., administered in combination) with a TIGIT inhibitor, a kinase inhibitor (e.g., a tyrosine kinase inhibitor (TKI)), a CD112R inhibitor, a TAM receptor inhibitor, a STING agonist and/or a 4-1BB agonist, or a combination thereof.

Methods of Detection

In some embodiments, an anti-IL-27 antibody or an antigen-binding fragment thereof described herein can be employed in methods of detection and/or quantification of human IL-27 in a biological sample. Accordingly, an anti-IL-27 antibody, or an antigen-binding fragment thereof, as described herein is useful to diagnose, prognose and/or determine progression of disease (e.g., cancer) in a patient.

Monitoring a subject (e.g., a human patient) for an improvement in a cancer, as defined herein, means evaluating the subject for a change in a disease parameter, e.g., a reduction in tumor growth. In some embodiments, the evaluation is performed at least one (1) hour, e.g., at least 2, 4, 6, 8, 12, 24, or 48 hours, or at least 1 day, 2 days, 4 days, 10 days, 13 days, 20 days or more, or

at least 1 week, 2 weeks, 4 weeks, 10 weeks, 13 weeks, 20 weeks or more, after an administration. The subject can be evaluated in one or more of the following periods: prior to beginning of treatment; during the treatment; or after one or more elements of the treatment have been administered. Evaluation can include evaluating the need for further treatment, e.g., evaluating whether a dosage, frequency of administration, or duration of treatment should be altered. It can also include evaluating the need to add or drop a selected therapeutic modality, e.g., adding or dropping any of the treatments for a cancer described herein.

In some embodiments, the disclosure provides a method of detecting IL-27 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-IL-27 complex, if IL-27 is present in the sample, wherein the detection antibody is an antibody, or antigen binding fragment thereof, provided by the disclosure; and (b) detecting the presence of the complex, if any, produced in step (a).

In some embodiments, the disclosure provides 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-IL-27 complex, if IL-27 is present in the sample, wherein the detection antibody is an antibody, or antigen binding portion thereof, provided by the disclosure; and (b) detecting the presence of the complex, if any, produced in step (a). In some embodiments, the detection antibody is coupled to a detectable label. In some embodiments, the method further comprises contacting the sample with a capture antibody to produce a complex comprising IL-27 and the capture antibody, if IL-27 is present in the sample, wherein the capture antibody is an antibody, or antigen binding portion thereof, provided by the disclosure.

In some embodiments, the capture antibody is immobilized on a solid support. In some embodiments, the sample is contacted with the capture antibody before the detection antibody. In some embodiments, the sample is a body fluid sample. In some embodiments, the fluid sample is blood, serum, plasma, cell lysates or tissue lysates.

In some embodiments, the cancer is selected from renal cell carcinoma (RCC), hepatocellular carcinoma, lung cancer, gastroesophageal cancer, ovarian cancer, endometrial cancer, melanoma, leukemia and lymphoma. In some embodiments, the cancer is renal cell

carcinoma (RCC). In other embodiments, the cancer is hepatocellular carcinoma (HCC). In some embodiments, the cancer is selected from leukemia and lymphoma. In some embodiments, the cancer is acute myeloid leukemia (AML).

EXAMPLES

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

Example 1: Generation and Characterization of Anti-IL-27 Antibodies that Specifically Bind the IL-27 EBI3 Monomer

This Example describes the production of anti-IL-27 antibodies that specifically bind to the EBI3 subunit of human IL-27. Briefly, BALB/c mice were immunized with a human EBI3 immunization vector (Aldevron) and used in the generation and isolation of hybridomas expressing anti-EBI3 monoclonal antibodies. Isolated hybridomas included hybridomas expressing anti-IL-27 antibody molecules referred to herein as Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab8. Hybridoma supernatants were analyzed by flow cytometry on mammalian cells expressing a surface-targeted human EBI3. All the hybridoma clone supernatants tested bound to EBI3 expressing cells (data not shown).

An exemplary isolated anti-EBI3 antibody Ab7 (hereafter referred to as “Ab7”, comprising an immunoglobulin heavy chain variable region hereafter referred to as “Ab7-V_{H0}” and an immunoglobulin light chain variable region hereafter referred to as “Ab7-V_{L0}”) was sequenced and further characterized below (amino terminal signal peptide sequences are not shown).

The heavy chain variable region of the isolated Ab7 antibody (Ab7-V_{H0}) has the following sequence (**FR1**-CDR1-**FR2**-CDR2-**FR3**-CDR3-**FR4**-*Constant region*):

EVKLVE SGGGLVQPGGSLKLFCAASGFTFTSYSMSWVRQTPEKRLEWVAYISYDGGSAYYPDTV
KGRFSISRDN AKKTLYLQMSSLKSEDTAMYYCARHGDYDDDDAMDYWGQGTSVTVSS (SEQ ID
NO: 1).

A nucleic acid sequence encoding the heavy chain variable region Ab7-V_{H0} has the
following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GAGGTGAAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAAACTCTTCT
GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGACTCCAGAGAA
GAGGCTGGAGTGGGTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTACCCTGACACTGTG
AAGGGCCGGTTCTCCATCTCCAGAGACAATGCCAAGAAAACCCTGTATCTGCAAATGAGCAGCC
TGAAGTCTGAGGACACGGCCATGTATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO: 2).

The light chain variable region of the isolated Ab7 antibody (Ab7-V_{L0}) has the following
sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

DIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQQKQGKSPQLLVYNAETLTEGVPSRFSG
SGSGTQFSLKINSLQPEDFGNYCQHGYGTPLTFGAGTKLDLK (SEQ ID NO: 3).

The heavy chain of the isolated Ab7 antibody (Ab7-V_{H0}-mIgG2a) has the following
sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

EVKLVE SGGGLVQPGGSLKLFCAASGFTFTSYSMSWVRQTPEKRLEWVAYISYDGGSAYYPDTV
KGRFSISRDN AKKTLYLQMSSLKSEDTAMYYCARHGDYDDDDAMDYWGQGTSVTVSSAKTTAPS
VYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVT
SSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVL
ISLSPIVTCVVVDVSEDDPDVQISW FVNNVEVHTAQTQTHREDYNSTLRVVSALPIQH QDWMSG
KEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLLTCMVTDFMPEDIYVE
WTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRT
PGK (SEQ ID NO: 183).

A nucleic acid sequence encoding the light chain variable region Ab7-V_{L0} has the following
sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GACATCCAGATGACCCAGTCTCCAGCCTCCCTGTCTGCATCTGTAGGAGAACTGTCACCATCA
CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAGCATGGTATCAGCAGAAACAGGGGAAATC

TCCTCAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
AGTGGATCTGGGACACAATTCTCTCTCAAGATCAACAGTCTGCAACCTGAAGATTTTGGGAATT
ACTACTGTCAACATCATTACGGTACCCCGCTCACATTTCGGCGCTGGGACCAAGCTGGATCTGAA
A (SEQ ID NO: 4).

The light chain of the isolated Ab7 antibody (Ab7-V_{L0}-mKappa) has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

DIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQQKQKGKSPQLLVYNAETLTEGVPSRFSG
SGSGTQFSLKINSLQPEDFGNYYCQHHYGTPLTFGAGTKLDLKADAAPTVSIFPPSSEQLTSGG
ASVVCFLNNFYPKDINVKKIDGSERQNGVLNSWTDQDSKDYMSSTLTTLTKDEYERHNSYT
CEATHKTSTSPIVKSFNRNEC (SEQ ID NO: 184).

Humanized Ab7 antibodies were designed using methods known in the art. Briefly, the V region gene sequences encoding the mouse monoclonal Ab7 antibody were used to construct a series of fully humanized antibodies. Variable region genes were cloned into vectors encoding a human IgG1 heavy chain constant domain and a human kappa light chain constant domain. Chimeric and humanized antibodies were transiently expressed in mammalian cells. Humanization of the isolated Ab7 heavy chain variable region resulted in 5 humanized heavy chain variable region variants (hereafter referred to as “Ab7-V_{H1},” “Ab7-V_{H2},” “Ab7-V_{H3},” “Ab7-V_{H4},” and “Ab7-V_{H5}”). Humanization of the isolated Ab7 light chain variable region resulted in 4 humanized light chain variable region variants (hereafter referred to as “Ab7-V_{L1},” “Ab7-V_{L2},” “Ab7-V_{L3},” and “Ab7-V_{L4}”).

The protein sequences defining the humanized Ab7 variant variable regions, and nucleotide sequences encoding the humanized Ab7 variant variable regions, are summarized below (amino terminal signal peptide sequences are not shown).

The heavy chain variable region Ab7-V_{H1} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

EVKLVESGGGLVQPGGSLRLSCAASGFTFTSYSMSWVRQAPGKGLEWVAYISYDGGSAYYPDTV
KGRFTISRDN SKKTLYLQMSSLKSEDTAMYYCARHGDYDDDDAMDYWGQGTSTVTVSS (SEQ ID
NO: 5).

A nucleic acid sequence encoding the heavy chain variable region Ab7-V_{H1} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GAGGTGAAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGGTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTACCCTGACACTGTG
AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAAACCCTGTATCTGCAAATGAGCAGCC
TGAAGTCTGAGGACACGGCCATGTATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO: 6).

The heavy chain variable region Ab7-V_{H2} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYSMSWVRQAPGKGLEWVAYISYDGGSAIYPDTV
KGRFTISRDN SKNTLYLQMSSLKSEDTAMYYCARHGDYDDDDAMDYWGQGTTLVTVSS (SEQ ID
NO: 7).

A nucleic acid sequence encoding the heavy chain variable region Ab7-V_{H2} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGGTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTACCCTGACACTGTG
AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTGCAAATGAGCAGCC
TGAAGTCTGAGGACACGGCCATGTATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 8).

The heavy chain variable region Ab7-V_{H3} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

EVKLVESGGGLVQPGGSLRLSCAASGFTFTSYSMSWVRQAPGKGLEWVAYISYDGGSAIYPDTV
KGRFTISRDN SKKTLYLQMNSLRAEDTAVYYCARHGDYDDDDAMDYWGQGTTLVTVSS (SEQ ID
NO: 9).

A nucleic acid sequence encoding the heavy chain variable region Ab7-V_{H3} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GAGGTGAAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGGTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTATCCTGACACTGTG
AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAAACCCTGTATCTGCAAATGAACAGCC

TGAGAGCCGAGGACACGGCCGTATATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 10).

The heavy chain variable region Ab7-V_{H4} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYSMSWVRQAPGKGLEWVAYISYDGGSAIYPDTV
KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARHGDYDDDDAMDYWGQGTLVTVSS (SEQ ID
NO: 11).

A nucleic acid sequence encoding the heavy chain variable region Ab7-V_{H4} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGGTGCGATACATTAGTTATGATGGTGGTAGCGCCTACTATCCTGACACTGTG
AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTGCAAATGAACAGCC
TGAGAGCCGAGGACACGGCCGTATATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 12).

The heavy chain variable region Ab7-V_{H5} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYSMSWVRQAPGKGLEWVSYISYDGGSAIYPDTV
KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARHGDYDDDDAMDYWGQGTLVTVSS (SEQ ID
NO: 13).

A nucleic acid sequence encoding the heavy chain variable region Ab7-V_{H5} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGGTGTCTTACATTAGTTATGATGGTGGTAGCGCCTACTATCCTGACACTGTG
AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTGCAAATGAACAGCC
TGAGAGCCGAGGACACGGCCGTATATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 14).

The light chain variable region Ab7-V_{L1} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKQGKAPKLLVYNAETLTEGVPSRFSG
SGSGTDFTLTISSLQPEDFANYYCQHHYGTPLTFGQGTKLDIK (SEQ ID NO: 15).

A nucleic acid sequence encoding the light chain variable region Ab7-V_{L1} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAGCATGGTATCAGCAGAAACAGGGGAAAGC
CCCTAAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAAATT
ACTACTGTCAACATCATTACGGTACCCCGCTCACATTCGGCCAAGGGACCAAGCTGGATATCAA
A (SEQ ID NO: 16).

The light chain variable region Ab7-V_{L2} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLVYNAETLTEGVPSRFSG
SGSGTDFTLTISSLQPEDFANYYCQHHYGTPLTFGQGTKLEIK (SEQ ID NO: 17).

A nucleic acid sequence encoding the light chain variable region Ab7-V_{L2} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAGCATGGTATCAGCAGAAACCAGGGAAAGC
CCCTAAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAAATT
ACTACTGTCAACATCATTACGGTACCCCGCTCACATTCGGCCAAGGGACCAAGCTGGAAATCAA
A (SEQ ID NO: 18).

The light chain variable region Ab7-V_{L3} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLVYNAETLTEGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQHHYGTPLTFGQGTKLEIK (SEQ ID NO: 19).

A nucleic acid sequence encoding the light chain variable region Ab7-V_{L3} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAGCATGGTATCAGCAGAAACCAGGGAAAGC
CCCTAAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTT
ACTACTGTCAACATCATTACGGTACCCCGCTCACATTCGGCCAAGGGACCAAGCTGGAAATCAA
A (SEQ ID NO: 20).

The light chain variable region Ab7-V_{L4} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

DIQMTQSPSSLSASVGDRVITTCRASENIYSYLNWYQQKPGKAPKLLVYNAETLTEGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQHHYGTPLTFGQGTKLEIK (SEQ ID NO: 21).

A nucleic acid sequence encoding the light chain variable region Ab7-V_{L4} has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4**):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGC
CCCTAAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTT
ACTACTGTCAACATCATTACGGTACCCCGCTCACATTCGGCCAAGGGACCAAGCTGGAAATCAA
A (SEQ ID NO: 22).

The heavy chain and light chain CDR amino acid sequences of the isolated parental Ab7 antibody (Kabat definition) are shown in **Table 1**.

TABLE 1

Heavy Chain Variable Region	HCDR1	HCDR2	HCDR3
Ab7-V _{H0} (SEQ ID NO: 16)	SYSMS (SEQ ID NO: 23)	YISYDGGSAYYPDTVK G (SEQ ID NO: 24)	HGDYDDDDAMDY (SEQ ID NO: 25)

Light Chain Variable Region	LCDR1	LCDR2	LCDR3
Ab7-V _{L0} (SEQ ID NO: 29)	RASENIYSYLA (SEQ ID NO: 26)	NAETLTE (SEQ ID NO: 27)	QHHYGTPLT (SEQ ID NO: 28)

To create the complete chimeric and humanized heavy or light chain antibody sequences, each heavy chain variable region described above was combined with a human IgG1 constant region, and each light chain variable region described above was combined a human kappa constant region.

The protein sequences defining the complete heavy chain and light chain of the chimeric and humanized Ab7 variants are summarized below (amino terminal signal peptide sequences are not shown).

The heavy chain Ab7-V_{H0}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

EVKLVESSGGLVQPGGSLKLFCAASGFTFTSYSMSWVRQTPEKRLEWVAYISYDGGSAIYPDTV
KGRFSISRDNAAKKTLYLQMSSLKSEDTAMYYCARHGDYDDDDAMDYWGQGTSVTVSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPQVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVSMHEALHNHYTQKSLSLS
PGK (SEQ ID NO: 29).

A nucleic acid sequence encoding the heavy chain Ab7-V_{H0}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GAGGTGAAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAAACTCTTCT
GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGACTCCAGAGAA
GAGGCTGGAGTGGGTTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTACCCTGACACTGTG
AAGGGCCGGTTCTCCATCTCCAGAGACAATGCCAAGAAAACCTGTATCTGCAAATGAGCAGCC
TGAAGTCTGAGGACACGGCCATGTATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCTCAGTCACCGTCTCCTCAGCCTCCACCAAAGGCCCCAGC

GTCTTCCCCCTCGCGCCGTCTCCAAGTCCACCTCGGGTGGCACCGCCGCCCTGGGCTGCCTGG
TCAAGGACTACTTCCCGGAGCCTGTGACCGTGTCTGGAACCTCGGGCGCGCTCACGAGCGGCGT
ACACACCTTCCCGGCGGTGCTCCAGTCTTCCGGGCTGTACTCGCTCTCGTCGGTCGTCACGGTG
CCGTCTCTCTCCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCGTCCAACACCA
AGGTGGATAAGAAGGTCGAGCCCAAGTCGTGCGACAAGACGCACACGTGCCCCGCCGTGCCCGGC
CCCGGAGCTGCTGGGCGGCCCCCTCGGTCTTCTGTTCCTGTTCCCCCGAAGCCCAAGGATACGCTGATG
ATCTCCCGCACCCCCGGAGGTCACCTGCGTGGTGGTGGACGTCTCCCACGAGGACCCGGAGGTGA
AATTCAACTGGTACGTGACGGAGTGGAGGTCCACAACGCCAAGACCAAGCCCCGGGAGGAGCA
GTACAACTCCACGTACCGCGTCGTCTCCGTCTGACCGTCCTCCACCAGGACTGGCTGAACGGC
AAGGAGTACAAGTGTAAGGTCTCCAACAAGGCGCTGCCCCGCCCCCATCGAGAAGACCATCTCCA
AGGCAAAGGGTCAGCCGCGGGAGCCGCAGGTCTATACCCTCCCCCGTCCCGCGACGAGCTGAC
GAAAAACCAGGTCTCCCTGACCTGCCTGGTGAAGGGTTTCTACCCCTCCGACATCGCGGTGAG
TGGGAGTCGAACGGCCAGCCGGAGAACAACACTACAAGACCACCCCCCGTGCTCGACAGTGACG
GCTCGTTCTTCTGTACTCGAAGCTGACCGTCGACAAGTCGCGCTGGCAGCAGGGCAACGTCTT
CTCGTGCTCCGTTATGCACGAGGCCCTGCACAACCACTACACGCAGAAGAGTCTTTCGCTGTCC
CCGGGGAAGTGA (SEQ ID NO: 30).

The heavy chain Ab7-V_{H1}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

EVKLVESGGGLV**QPGG**SLRL**SCAASGFTFT**SYSMS**WVRQAPGKGLEW**VAYISYDGG**SAYYP**DTV
KGRFTISRDNSK**KTLYLQ**MSS**LKSEDTAMYYCAR**HGDYDDDD**AMDYWGQ**GS**SVTVSS**AST**KGPS**
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV
PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVSMHEALHNHYTQKSLSLS
PGK (SEQ ID NO: 31).

A nucleic acid sequence encoding the heavy chain Ab7-V_{H1}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GAGGTGAAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGGTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTACCCTGACACTGTG

AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAAACCCTGTATCTGCAAATGAGCAGCC
TGAAGTCTGAGGACACGGCCATGTATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCTCAGTCACCGTCTCCTCAGCCTCCACCAAAGGCCCCAGC
GTCTTCCCCCTCGCGCCGTCTCCAAGTCCACCTCGGGTGGCACCGCCGCCCTGGGCTGCCTGG
TCAAGGACTACTTCCCGGAGCCTGTGACCGTGTCTGGAACCTCGGGCGCGCTCACGAGCGGCGT
ACACACCTTCCCGGCGGTGCTCCAGTCCTCCGGGCTGTACTCGCTCTCGTCGGTCGTCACGGTG
CCGTCCTCCTCCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCGTCCAACACCA
AGGTGGATAAGAAGGTCGAGCCCAAGTCGTGCGACAAGACGCACACGTGCCCCGCCGTGCCCGGC
CCCGGAGCTGCTGGGCGGCCCTCGGTCTTCCTGTTCCCCCGAAGCCCAAGGATACGCTGATG
ATCTCCCGCACCCCCGGAGGTCACCTGCGTGGTGGTGGACGTCTCCACGAGGACCCGGAGGTGA
AATTCAACTGGTACGTCGACGGAGTGGAGGTCCACAACGCCAAGACCAAGCCCCGGGAGGAGCA
GTACAACCTCCACGTACCGCGTCGTCTCCGTCTGACCGTCCTCCACCAGGACTGGCTGAACGGC
AAGGAGTACAAGTGTAAGGTCTCCAACAAGGCGCTGCCCCGCCCCCATCGAGAAGACCATCTCCA
AGGCAAAGGGTCAGCCGCGGGAGCCGCAGGTCTATACCCTCCCCCGTCCCGCGACGAGCTGAC
GAAAAACCAGGTCTCCCTGACCTGCCTGGTGAAGGGTTTCTACCCCTCCGACATCGCGGTGAG
TGGGAGTCGAACGGCCAGCCGGAGAACAACACTACAAGACCACCCCCCGTGCTCGACAGTGACG
GCTCGTTCTTCCTGTACTCGAAGCTGACCGTCGACAAGTCGCGCTGGCAGCAGGGCAACGTCTT
CTCGTGCTCCGTTATGCACGAGGCCCTGCACAACCACTACACGCAGAAGAGTCTTTCGCTGTCC
CCGGGGAAGTGA (SEQ ID NO: 32).

The heavy chain Ab7-V_{H2}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYSMSWVRQAPGKGLEWVAYISYDGGSAIYPDTV
KGRFTISRDN SKNTLYLQMSSLKSEDTAMYYCARHGDYDDDDAMDYWGQGT LVT VSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV
PSSSLGTQTYICNVNHKPSNTKVDDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTP E V T C V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H Q D W L N G
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV F S C S V M H E A L H N H Y T Q K S L S L S
PGK (SEQ ID NO: 33).

A nucleic acid sequence encoding the heavy chain Ab7-V_{H2}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
 GTGCAGCCTCTGGATTACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
 GGGGCTGGAGTGGGTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTACCCTGACACTGTG
 AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACCTGTATCTGCAAATGAGCAGCC
 TGAAGTCTGAGGACACGGCCATGTATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
 GATGGACTACTGGGGCCAAGGAACCTGGTCACCGTCTCCTCAGCCTCCACCAAAGGCCCCAGC
 GTCTTCCCCCTCGCGCCGTCTCCAAGTCCACCTCGGGTGGCACCGCCGCCCTGGGCTGCCTGG
 TCAAGGACTACTTCCCGGAGCCTGTGACCGTGTCTTGGAACTCGGGCGCGCTCACGAGCGGCGT
 ACACACCTTCCCGGCGGTGCTCCAGTCCTCCGGGCTGTACTCGCTCTCGTCGGTCGTCACGGTG
 CCGTCCTCCTCCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCGTCCAACACCA
 AGGTGGATAAGAAGGTCGAGCCCAAGTCGTGCGACAAGACGCACACGTGCCCCGCCGTGCCCGGC
 CCCGGAGCTGCTGGGCGGCCCTCGGTCTTCCTGTTCCCCCGAAGCCCAAGGATACGCTGATG
 ATCTCCCGCACCCCGGAGGTCACCTGCGTGGTGGTGGACGTCTCCACGAGGACCCGGAGGTGA
 AATTCAACTGGTACGTCGACGGAGTGGAGGTCCACAACGCCAAGACCAAGCCCCGGGAGGAGCA
 GTACAACTCCACGTACCGCGTCGTCTCCGTCTGACCGTCCTCCACCAGGACTGGCTGAACGGC
 AAGGAGTACAAGTGTAAGGTCTCCAACAAGGCGCTGCCCGCCCCCATCGAGAAGACCATCTCCA
 AGGCAAAGGGTCAGCCGCGGGAGCCGCAGGTCTATACCCTCCCCCGTCCCGCGACGAGCTGAC
 GAAAAACCAGGTCTCCCTGACCTGCCTGGTGAAGGGTTTCTACCCCTCCGACATCGCGGTGAG
 TGGGAGTCGAACGGCCAGCCGGAGAACAATAAGACCACCCCCCCCCGTGCTCGACAGTGACG
 GCTCGTTCTTCCTGTACTCGAAGCTGACCGTCGACAAGTCGCGCTGGCAGCAGGGCAACGTCTT
 CTCGTGCTCCGTTATGCACGAGGCCCTGCACAACCACTACACGCAGAAGAGTCTTTCGCTGTCC
 CCGGGGAAGTGA (SEQ ID NO: 34).

The heavy chain Ab7-V_H3-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-
 FR3-CDR3-FR4-Constant region**):

EVKLVE SGGGLVQPGGSLRLSCAASGFTFTSY SMSWVRQAPGKGLEWVAYISYDGGSA YYPDTV
 KGRFTISRDN SKKTLYLQMNSLR AEDTAVYYCARHGDYDDDDAMDYWGQGT LVTVSSASTKGPS
 VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV
 PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
 KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE

WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLS
PGK (SEQ ID NO: 35).

A nucleic acid sequence encoding the heavy chain Ab7-V_{H3}-IgG1 has the following sequence (**FR1**-CDR1-**FR2**-CDR2-**FR3**-CDR3-**FR4**-*Constant region*):

GAGGTGAAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
GTGCAGCCTCTGGATTACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGGTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTATCCTGACACTGTG
AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAAACCTGTATCTGCAAATGAACAGCC
TGAGAGCCGAGGACACGGCCGTATATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCTGGTCACCGTCTCCTCAGCCTCCACCAAAGGCCCCAGC
GTCTTCCCCCTCGCGCCGTCTCCAAGTCCACCTCGGGTGGCACCGCCGCCCTGGGCTGCCTGG
TCAAGGACTACTTCCCGGAGCCTGTGACCGTGTCTTGGAACTCGGGCGCGCTCACGAGCGGCGT
ACACACCTTCCCGGCGGTGCTCCAGTCTTCCGGGCTGTACTCGCTCTCGTCGGTCGTCACGGTG
CCGTCCTCCTCCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCGTCCAACACCA
AGGTGGATAAGAAGGTCGAGCCCAAGTCGTGCGACAAGACGCACACGTGCCCCGCCGTGCCCGGC
CCCGGAGCTGCTGGGCGGCCCTCGGTCTTCTTCCCCCGAAGCCCAAGGATACGCTGATG
ATCTCCCGCACCCCGGAGGTCACCTGCGTGGTGGTGGACGTCTCCCACGAGGACCCGGAGGTGA
AATTCAACTGGTACGTCGACGGAGTGGAGGTCCACAACGCCAAGACCAAGCCCCGGGAGGAGCA
GTACAACTCCACGTACCGCGTCGTCTCCGTCTGACCGTCTTCCACCAGGACTGGCTGAACGGC
AAGGAGTACAAGTGTAAGGTCTCCAACAAGGCGCTGCCCCGCCCCCATCGAGAAGACCATCTCCA
AGGCAAAGGGTCAGCCGCGGGAGCCGCAGGTCTATACCCTCCCCCGTCCCGCGACGAGCTGAC
GAAAAACCAGGTCTCCCTGACCTGCCTGGTGAAGGGTTTCTACCCCTCCGACATCGCGGTGAG
TGGGAGTCGAACGGCCAGCCGGAGAACAATAAGACCACCCCCCGTGCTCGACAGTGACG
GCTCGTTCTTCTGTACTCGAAGCTGACCGTCGACAAGTCGCGCTGGCAGCAGGGCAACGTCTT
CTCGTGCTCCGTTATGCACGAGGCCCTGCACAACCACTACACGCAGAAGAGTCTTTCGCTGTCC
CCGGGGAAGTGA (SEQ ID NO: 36).

The heavy chain Ab7-V_{H4}-IgG1 has the following sequence (**FR1**-CDR1-**FR2**-CDR2-**FR3**-CDR3-**FR4**-*Constant region*):

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYSMSWVRQAPGKGLEWVAYISYDGGSAIYPDTV
KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARHGDYDDDDAMDYWGQGTLVTVSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV

PSSSLGTQTYICNVNHKPSNTKVDDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
PGK (SEQ ID NO: 37).

A nucleic acid sequence encoding the heavy chain Ab7-V_{H4}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
GTGCAGCCTCTGGATTACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGGTTCGCATACATTAGTTATGATGGTGGTAGCGCCTACTATCCTGACACTGTG
AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTGCAAATGAACAGCC
TGAGAGCCGAGGACACGGCCGTATATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
GATGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAAGGCCCCAGC
GTCTTCCCCCTCGCGCCGTCTCCAAGTCCACCTCGGGTGGCACCGCCGCCCTGGGCTGCCTGG
TCAAGGACTACTTCCCGGAGCCTGTGACCGTGTCTTGGAACTCGGGCGCGCTCACGAGCGGCGT
ACACACCTTCCCGGCGGTGCTCCAGTCTTCCGGGCTGTACTCGCTCTCGTCGGTCGTCACGGTG
CCGTCTCTCTCCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCGTCCAACACCA
AGGTGGATAAGAAGGTCGAGCCCAAGTCGTGCGACAAGACGCACACGTGCCCCGCCGTGCCCGGC
CCCGGAGCTGCTGGGCGGCCCCCTCGGTCTTCTCTGTTCCCCCGAAGCCCAAGGATACGCTGATG
ATCTCCCGCACCCCCGGAGGTCACCTGCGTGGTGGTGGACGTCTCCACGAGGACCCGGAGGTGA
AATTCAACTGGTACGTCGACGGAGTGGAGGTCCACAACGCCAAGACCAAGCCCCGGGAGGAGCA
GTACAACTCCACGTACCGCGTCGTCTCCGTCTGACCGTCTCTCCACCAGGACTGGCTGAACGGC
AAGGAGTACAAGTGTAAGGTCTCCAACAAGGCGCTGCCCCGCCCCCATCGAGAAGACCATCTCCA
AGGCAAAGGGTCAGCCGCGGGAGCCGCAGGTCTATACCCTCCCCCGTCCCGCGACGAGCTGAC
GAAAAACCAGGTCTCCCTGACCTGCCTGGTGAAGGGTTTCTACCCCTCCGACATCGCGGTGAG
TGGGAGTCGAACGGCCAGCCGGAGAACAATAAGACCACCCCCCGTGCTCGACAGTGACG
GCTCGTTCTTCTGTACTCGAAGCTGACCGTCGACAAGTCGCGCTGGCAGCAGGGCAACGTCTT
CTCGTGCTCCGTTATGCACGAGGCCCTGCACAACCACTACACGCAGAAGAGTCTTTCGCTGTCC
CCGGGGAAGTGA (SEQ ID NO: 38).

The heavy chain Ab7-V_{H5}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSYSMSWVRQAPGKGLEWVSYISYDGGSAYYPDTV
 KGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARHGDYDDDDAMDYWGQGTLLVTVSSASTKGPS
 VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
 PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
 KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLS
 PGK (SEQ ID NO: 39).

A nucleic acid sequence encoding the heavy chain Ab7-V_{H5}-IgG1 has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT
 GTGCAGCCTCTGGATTCACCTTTACCAGCTATTCCATGAGCTGGGTCCGCCAGGCTCCAGGGAA
 GGGGCTGGAGTGGGTGTCTTACATTAGTTATGATGGTGGTAGCGCCTACTATCCTGACACTGTG
 AAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTGCAAATGAACAGCC
 TGAGAGCCGAGGACACGGCCGTATATTACTGTGCAAGACATGGAGACTATGACGACGACGACGC
 GATGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAAGGCCCCAGC
 GTCTTCCCCCTCGCGCCGTCTCCAAGTCCACCTCGGGTGGCACCGCCGCCCTGGGCTGCCTGG
 TCAAGGACTACTTCCCGGAGCCTGTGACCGTGTCTTGGAACTCGGGCGCGCTCACGAGCGGCGT
 ACACACCTTCCCGGCGGTGCTCCAGTCTTCCGGGCTGTACTCGCTCTCGTCGGTCGTCACGGTG
 CCGTCTCTCTCCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCGTCCAACACCA
 AGGTGGATAAGAAGGTCGAGCCCAAGTCGTGCGACAAGACGCACACGTGCCCCGCCGTGCCCGGC
 CCCGGAGCTGCTGGGCGGCCCTCGGTCTTCTCTGTTCCCCCGAAGCCCAAGGATACGCTGATG
 ATCTCCCGCACCCCGGAGGTCACCTGCGTGGTGGTGGACGTCTCCACGAGGACCCGGAGGTGA
 AATTCAACTGGTACGTGACGGAGTGGAGGTCCACAACGCCAAGACCAAGCCCCGGGAGGAGCA
 GTACAACCTCCACGTACCGCGTCGTCTCCGTCTGACCGTCTCTCCACCAGGACTGGCTGAACGGC
 AAGGAGTACAAGTGTAAGGTCTCCAACAAGGCGCTGCCCGCCCCCATCGAGAAGACCATCTCCA
 AGGCAAAGGGTCAGCCGCGGGAGCCGCAGGTCTATACCCTCCCCCGTCCCGCGACGAGCTGAC
 GAAAAACCAGGTCTCCCTGACCTGCCTGGTGAAGGGTTTCTACCCCTCCGACATCGCGGTGAG
 TGGGAGTCGAACGGCCAGCCGGAGAACAATAAGACCACCCCCCCCCGTGCTCGACAGTGACG
 GCTCGTTCTTCTCTGTACTCGAAGCTGACCGTCGACAAGTCGCGCTGGCAGCAGGGCAACGTCTT

CTCGTGCTCCGTTATGCACGAGGCCCTGCACAACCACTACACGCAGAAGAGTCTTTCGCTGTCC
CCGGGGAAGTGA (SEQ ID NO: 40).

The light chain Ab7-V_{L0}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

DIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQQKQKGKSPQLLVYNAETLTEGVPSRFSG
SGSGTQFSLKINSLQPEDFGNYCYQHGYGTPLTFGAGTKLDLKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 41).

A nucleic acid sequence encoding the light chain Ab7-V_{L0}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GACATCCAGATGACCCAGTCTCCAGCCTCCCTGTCTGCATCTGTAGGAGAACTGTCACCATCA
CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAGCATGGTATCAGCAGAAACAGGGGAAATC
TCCTCAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
AGTGGATCTGGGACACAATTCTCTCTCAAGATCAACAGTCTGCAACCTGAAGATTTTGGAATT
ACTACTGTCAACATCATTACGGTACCCCGCTCACATTCGGCGCTGGGACCAAGCTGGATCTGAA
ACGAACGGTGGCCGCGCCGAGCGTCTTCATCTTCCCGCCTTCCGACGAGCAGCTCAAGTCCGGG
ACCGCCTCCGTAGTATGCCTCCTCAATAACTTCTACCCCCGGGAGGCGAAGGTCCAGTGGAAGG
TCGACAACGCCCTCCAATCGGGCAACTCCCAGGAGTCGGTGACCGAGCAGGATTCCAAGGACTC
GACCTACAGTCTAAGCTCCACCCTCACACTGTCGAAGGCGGACTACGAGAAGCACAAGGTGTAC
GCCTGCGAGGTCACCCACCAGGGCCTGAGCAGCCCCGGTCACCAAGTCCTTCAACCGGGGCGAGT
GCTGA (SEQ ID NO: 42).

The light chain Ab7-V_{L1}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

DIQMTQSPSSLSASVGDRVITITCRASENIYSYLAWYQQKQKGKAPKLLVYNAETLTEGVPSRFSG
SGSGTDFTLTISSLQPEDFANYCYQHGYGTPLTFGQGTKLDIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 43).

A nucleic acid sequence encoding the light chain Ab7-V_{L1}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
 CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAGCATGGTATCAGCAGAAACAGGGGAAAGC
 CCTAAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
 AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAAATT
 ACTACTGTCAACATCATTACGGTACCCCGCTCACATTCGGCCAAGGGACCAAGCTGGATATCAA
 ACGAACGGTGGCCGCGCCGAGCGTCTTCATCTTCCCGCCTTCCGACGAGCAGCTCAAGTCCGGG
 ACCGCCTCCGTAGTATGCCTCCTCAATAACTTCTACCCCCGGGAGGCGAAGGTCCAGTGGAAGG
 TCGACAACGCCCTCCAATCGGGCAACTCCCAGGAGTCGGTGACCGAGCAGGATTCCAAGGACTC
 GACCTACAGTCTAAGCTCCACCCTCACACTGTCGAAGGCGGACTACGAGAAGCACAAAGGTGTAC
 GCCTGCGAGGTCACCCACCAGGGCCTGAGCAGCCCCGGTCACCAAGTCCTTCAACCGGGGCGAGT
 GCTGA (SEQ ID NO: 44).

The light chain Ab7-V_{L2}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-
 FR3-CDR3-FR4-Constant region**):

DIQMTQSPSSLSASVGDRVITICRASENIYSYLAWYQQKPGKAPKLLVYNAETLTEGVPSRFSG
 SGSGTDFTLTISSLQPEDFANYYCQHHYGTPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSG
 TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVY
 ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 45).

A nucleic acid sequence encoding the light chain Ab7-V_{L2}-Kappa has the following
 sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
 CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAGCATGGTATCAGCAGAAACCAGGGGAAAGC
 CCTAAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
 AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAAATT
 ACTACTGTCAACATCATTACGGTACCCCGCTCACATTCGGCCAAGGGACCAAGCTGGAAATCAA
 ACGAACGGTGGCCGCGCCGAGCGTCTTCATCTTCCCGCCTTCCGACGAGCAGCTCAAGTCCGGG
 ACCGCCTCCGTAGTATGCCTCCTCAATAACTTCTACCCCCGGGAGGCGAAGGTCCAGTGGAAGG
 TCGACAACGCCCTCCAATCGGGCAACTCCCAGGAGTCGGTGACCGAGCAGGATTCCAAGGACTC
 GACCTACAGTCTAAGCTCCACCCTCACACTGTCGAAGGCGGACTACGAGAAGCACAAAGGTGTAC
 GCCTGCGAGGTCACCCACCAGGGCCTGAGCAGCCCCGGTCACCAAGTCCTTCAACCGGGGCGAGT
 GCTGA (SEQ ID NO: 46).

The light chain Ab7-V_{L3}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLVYNAETLTEGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQHGYGTPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 47).

A nucleic acid sequence encoding the light chain Ab7-V_{L3}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAGCATGGTATCAGCAGAAACCAGGGAAAGC
CCCTAAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC
AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTT
ACTACTGTCAACATCATTACGGTACCCCGCTCACATTTCGGCCAAGGGACCAAGCTGGAAATCAA
ACGAACGGTGGCCGCGCCGAGCGTCTTCATCTTCCCGCCTTCCGACGAGCAGCTCAAGTCCGGG
ACCGCCTCCGTAGTATGCCTCCTCAATAACTTCTACCCCCGGGAGGCGAAGGTCCAGTGGAAGG
TCGACAACGCCCTCCAATCGGGCAACTCCCAGGAGTCGGTGACCGAGCAGGATTCCAAGGACTC
GACCTACAGTCTAAGCTCCACCCTCACACTGTCTGAAGGCGGACTACGAGAAGCACAAGGTGTAC
GCCTGCGAGGTCACCCACCAGGGCCTGAGCAGCCCCGGTCACCAAGTCCTTCAACCGGGGCGAGT
GCTGA (SEQ ID NO: 48).

The light chain Ab7-V_{L4}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLNWYQQKPGKAPKLLVYNAETLTEGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQHGYGTPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 49).

A nucleic acid sequence encoding the light chain Ab7-V_{L4}-Kappa has the following sequence (**FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-Constant region**):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
CTTGCCGGGCAAGTGAGAACATTTACAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGC
CCCTAAGCTCCTGGTCTATAATGCAGAAACCTTGACAGAAGGGGTCCCATCAAGGTTTCAGCGGC

AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTT
 ACTACTGTCAACATCATTACGGTACCCCGCTCACATTCGGCCAAGGGACCAAGCTGGAAATCAA
 ACGAACGGTGGCCGCGCCGAGCGTCTTCATCTTCCCGCCTTCCGACGAGCAGCTCAAGTCCGGG
 ACCGCCTCCGTAGTATGCCTCCTCAATAACTTCTACCCCCGGGAGGCGAAGGTCCAGTGGAAGG
 TCGACAACGCCCTCCAATCGGGCAACTCCCAGGAGTCGGTGACCGAGCAGGATTCCAAGGACTC
 GACCTACAGTCTAAGCTCCACCCTCACACTGTCGAAGGCGGACTACGAGAAGCACAAAGGTGTAC
 GCCTGCGAGGTCACCCACCAGGGCCTGAGCAGCCCCGGTCACCAAGTCCTTCAACCGGGGCGAGT
 GCTGA (SEQ ID NO: 50).

It is also contemplated that the variable region sequences can be fused to other antibody constant region sequences to produce full length immunoglobulin heavy and light chains. For example, the Ab7-V_{H0}, Ab7-V_{H1}, Ab7-V_{H2}, Ab7-V_{H3}, Ab7-V_{H4}, or Ab7-V_{H5} heavy chain variable regions may be combined with a human IgG2, IgG3, IgG4, or an IgG4 comprising one or more amino acid substitutions in the constant region (e.g., IgG4mt, or IgG4mt2). Similarly, the Ab7-V_{L0}, Ab7-V_{L1}, Ab7-V_{L2}, Ab7-V_{L3} or Ab7-V_{L4} light chain variable regions may be combined with a human lambda constant region.

DNA fragments encoding the heavy and light chain variable regions of Ab7 and the humanized Ab7 variants described above were synthesized with flanking restriction enzyme sites for cloning into a pANT expression vector (Antitope) system for IgG1 heavy and kappa light chains. All constructs were confirmed by sequencing. Heavy and light chain combinations shown in **Table 2** were transiently transfected into HEK293 EBNA adherent cells (LGC Standards, Teddington, UK) using a PEI transfection method and incubated for seven days post-transfection.

Table 2

Antibody	Heavy Chain	Light Chain
Ab7.1	Ab7-V _{H0} -IgG1 (SEQ ID NO: 29)	Ab7-V _{L0} -Kappa (SEQ ID NO: 41)
Ab7.2	Ab7-V _{H0} -IgG1 (SEQ ID NO: 29)	Ab7-V _{L1} -Kappa (SEQ ID NO: 43)
Ab7.3	Ab7-V _{H1} -IgG1 (SEQ ID NO: 31)	Ab7-V _{L0} -Kappa (SEQ ID NO: 41)
Ab7.4	Ab7-V _{H1} -IgG1 (SEQ ID NO: 31)	Ab7-V _{L1} -Kappa (SEQ ID NO: 43)
Ab7.5	Ab7-V _{H1} -IgG1 (SEQ ID NO: 31)	Ab7-V _{L2} -Kappa (SEQ ID NO: 45)
Ab7.6	Ab7-V _{H1} -IgG1 (SEQ ID NO: 31)	Ab7-V _{L3} -Kappa (SEQ ID NO: 47)
Ab7.7	Ab7-V _{H1} -IgG1 (SEQ ID NO: 31)	Ab7-V _{L4} -Kappa (SEQ ID NO: 49)
Ab7.8	Ab7-V _{H2} -IgG1 (SEQ ID NO: 33)	Ab7-V _{L1} -Kappa (SEQ ID NO: 43)

Ab7.9	Ab7-V _{H2} -IgG1 (SEQ ID NO: 33)	Ab7-V _{L2} -Kappa (SEQ ID NO: 45)
Ab7.10	Ab7-V _{H2} -IgG1 (SEQ ID NO: 33)	Ab7-V _{L3} -Kappa (SEQ ID NO: 47)
Ab7.11	Ab7-V _{H2} -IgG1 (SEQ ID NO: 33)	Ab7-V _{L4} -Kappa (SEQ ID NO: 49)
Ab7.12	Ab7-V _{H3} -IgG1 (SEQ ID NO: 35)	Ab7-V _{L1} -Kappa (SEQ ID NO: 43)
Ab7.13	Ab7-V _{H3} -IgG1 (SEQ ID NO: 35)	Ab7-V _{L2} -Kappa (SEQ ID NO: 45)
Ab7.14	Ab7-V _{H3} -IgG1 (SEQ ID NO: 35)	Ab7-V _{L3} -Kappa (SEQ ID NO: 47)
Ab7.15	Ab7-V _{H3} -IgG1 (SEQ ID NO: 35)	Ab7-V _{L4} -Kappa (SEQ ID NO: 49)
Ab7.16	Ab7-V _{H4} -IgG1 (SEQ ID NO: 37)	Ab7-V _{L1} -Kappa (SEQ ID NO: 43)
Ab7.17	Ab7-V _{H4} -IgG1 (SEQ ID NO: 37)	Ab7-V _{L2} -Kappa (SEQ ID NO: 45)
Ab7.18	Ab7-V _{H4} -IgG1 (SEQ ID NO: 37)	Ab7-V _{L3} -Kappa (SEQ ID NO: 47)
Ab7.19	Ab7-V _{H4} -IgG1 (SEQ ID NO: 37)	Ab7-V _{L4} -Kappa (SEQ ID NO: 49)
Ab7.20	Ab7-V _{H5} -IgG1 (SEQ ID NO: 39)	Ab7-V _{L1} -Kappa (SEQ ID NO: 43)
Ab7.21	Ab7-V _{H5} -IgG1 (SEQ ID NO: 39)	Ab7-V _{L2} -Kappa (SEQ ID NO: 45)
Ab7.22	Ab7-V _{H5} -IgG1 (SEQ ID NO: 39)	Ab7-V _{L3} -Kappa (SEQ ID NO: 47)
Ab7.23	Ab7-V _{H5} -IgG1 (SEQ ID NO: 39)	Ab7-V _{L4} -Kappa (SEQ ID NO: 49)

Antibodies were purified from cell culture supernatants on Protein A-conjugated sepharose columns (GE Healthcare, Little Chalfont, UK), buffer exchanged into 1x DPBS pH 7.2 and quantified by OD_{280nm} using an extinction coefficient ($E_{c(0.1\%)}$) based on the predicted amino acid sequence. 1 µg of each antibody was analyzed by SDS-PAGE and bands corresponding to the profile of a typical antibody were observed (data not shown).

***In Vitro* Characterization of Anti-EBI3 Antibodies**

The Ab7 antibody and Ab7 antibody variants produced as described in Table 2 were tested in a series of *in vitro* assays to ascertain their biological characteristics and activities.

In order to assess the binding of the humanized Ab7 antibody variants relative to the chimeric Ab7.1 antibody, a binding competition ELISA was established. Assay plates were coated with 1 µg/mL of human IL-27 (hIL-27) (R&D Systems, Abingdon, UK) diluted in 1x DPBS pH 7.2 and incubated overnight at 4°C. All antibodies were diluted in 2% BSA/DPBS to 25 µg/mL and serially diluted three-fold down the plate to generate an eight point binding curve. Antibody dilutions were pre-mixed with biotinylated Ab7.1 antibody at a constant final concentration of 0.08 µg/mL. The antibody mixtures were then transferred onto the coated assay plates and incubated for 1 hour at room temperature. The binding of biotinylated Ab7.1 antibody was detected with streptavidin-peroxidase conjugate (Sigma-Aldrich, Gillingham, UK) and TMB substrate

(ThermoFisher, Loughborough, UK). The reaction was stopped with 1M HCl and absorbance read at 450 nm on a Dynex Technologies MRX TC II plate reader.

Absolute IC₅₀ values of the tested antibodies were determined using a four-parameter logistic curve. IC₅₀ normalized relative to the IC₅₀ of the chimeric antibody on each plate are summarized in **Table 3**. The results show that all humanized Ab7 variants generated, with the exception of variants containing the Ab7-V_{L4} light chain, have similar binding profiles to the chimeric Ab7.1 antibody, with most variants competing within two-fold of the chimeric Ab7.1 antibody.

Table 3

Antibody	Average Relative IC ₅₀ to Ab7.1	Standard Deviation	No. of Repeats
Ab7.1	1		
Ab7.2	0.76	0	2
Ab7.3	0.76	0.27	2
Ab7.4	0.97	0.46	2
Ab7.4	0.73	0.25	2
Ab7.5	1.39	0.13	2
Ab7.6	ND	-	1
Ab7.8	1.43	0.05	2
Ab7.9	1.85	0.21	2
Ab7.10	1.85	0.22	2
Ab7.11	ND	-	1
Ab7.12	1.33	0.21	2
Ab7.13	1.37	0.08	2
Ab7.14	1.48	0.07	2
Ab7.15	ND	-	1
Ab7.16	1.81	0.35	2
Ab7.17	1.55	0.44	2
Ab7.18	1.39	0.37	2
Ab7.19	ND	-	1
Ab7.20	1.6	0.06	2
Ab7.21	2.16	0.33	2
Ab7.22	2.50	0.95	2
Ab7.23	ND	-	1

The antibodies were further characterized by surface plasmon resonance (SPR). Kinetic experiments were performed on a Biacore T200 (GE Healthcare, Uppsala, Sweden). All experiments were run at 25°C with HBS-P+ running buffer (pH 7.4) (GE Healthcare, Little Chalfont, UK) using hIL-27 (R&D Systems, Abingdon, UK). Human IL-27 (hIL-27) antigen was captured on a CM5 chip to ~ 16 RU. Immobilization was carried out at a protein concentration of 1 µg/mL in 10 mM acetate buffer pH 5.0. A three point, three-fold dilution range from 3.3 nM to 30 nM of antibody diluted in HBS-P+ buffer without regeneration between each concentration was used. The association phase for the three injections of increasing concentrations of antibody was monitored for 75 seconds each time and a single dissociation phase was measured for 250 seconds following the last injection of antibody. Regeneration of the hIL-27 surface was conducted using a single injection of 2M MgCl₂ for 120s. Multiple repeats (n=4) of the chimeric antibody were performed throughout the assay to check the stability of the surface and analyte over the kinetic cycles.

Both 1:1 binding and bivalent analyte models were used to analyze the data due to the bivalent nature of the antibody. The results from the 1:1 binding model analysis are summarized in **Table 4** and results from the bivalent analyte model are summarized in **Table 5**.

Table 4

Antibody	k _a (1/Ms)	k _d (1/s)	K _D (M)	Chi ² (RU ²)	Relative K _D to Ab7.1
Ab7.1	1.4 x 10 ⁶	1.5 x 10 ⁻³	1.0 x 10 ⁻⁹	0.282	1.0
Ab7.2	1.5 x 10 ⁶	1.8 x 10 ⁻³	1.2 x 10 ⁻⁹	0.237	1.2
Ab7.3	1.5 x 10 ⁶	1.5 x 10 ⁻³	9.6 x 10 ⁻¹⁰	0.321	0.9
Ab7.4	1.5 x 10 ⁶	1.8 x 10 ⁻³	1.2 x 10 ⁻⁹	0.235	1.2
Ab7.4	1.5 x 10 ⁶	1.8 x 10 ⁻³	1.3 x 10 ⁻⁹	0.212	1.2
Ab7.5	1.5 x 10 ⁶	1.8 x 10 ⁻³	1.2 x 10 ⁻⁹	0.222	1.2
Ab7.6	-	-	-	-	-
Ab7.8	1.3 x 10 ⁶	1.8 x 10 ⁻³	1.5 x 10 ⁻⁹	0.0932	1.4
Ab7.9	1.3 x 10 ⁶	1.9 x 10 ⁻³	1.5 x 10 ⁻⁹	0.0953	1.5
Ab7.10	1.3 x 10 ⁶	1.8 x 10 ⁻³	1.4 x 10 ⁻⁹	0.105	1.4
Ab7.11	-	-	-	-	-
Ab7.12	1.5 x 10 ⁶	1.8 x 10 ⁻³	1.2 x 10 ⁻⁹	0.265	1.2
Ab7.13	1.5 x 10 ⁶	1.8 x 10 ⁻³	1.2 x 10 ⁻⁹	0.235	1.2
Ab7.14	1.5 x 10 ⁶	1.8 x 10 ⁻³	1.2 x 10 ⁻⁹	0.232	1.2
Ab7.15	-	-	-	-	-
Ab7.16	1.3 x 10 ⁶	1.8 x 10 ⁻³	1.5 x 10 ⁻⁹	0.092	1.4
Ab7.17	1.3 x 10 ⁶	1.9 x 10 ⁻³	1.5 x 10 ⁻⁹	0.101	1.5

Ab7.18	1.3×10^6	1.9×10^{-3}	1.5×10^{-9}	0.0969	1.4
Ab7.19	-	-	-	-	-
Ab7.20	1.3×10^6	1.8×10^{-3}	1.4×10^{-9}	0.109	1.4
Ab7.21	1.2×10^6	1.9×10^{-3}	1.5×10^{-9}	0.0793	1.5
Ab7.22	1.3×10^6	1.9×10^{-3}	1.5×10^{-9}	0.081	1.5
Ab7.23	-	-	-	-	-

Table 5

Analyte	ka1 (1/Ms)	ka2 (1/RUs)	kd1 (1/s)	kd2 (1/s)	Chi ² (RU ²)
Ab7.1	6.7×10^5	2.1×10^{-2}	2.2×10^{-3}	4.6×10^{-2}	0.138
Ab7.2	7.0×10^5	3.5×10^{-2}	2.7×10^{-3}	8.7×10^{-2}	0.108
Ab7.3	7.5×10^5	2.9×10^{-2}	2.2×10^{-3}	6.3×10^{-2}	0.132
Ab7.4	7.2×10^5	7.2×10^{-2}	2.6×10^{-3}	1.9×10^{-1}	0.106
Ab7.4	7.1×10^5	1.7×10^{-2}	2.5×10^{-3}	4.9×10^{-2}	0.103
Ab7.5	6.8×10^5	2.8×10^{-2}	2.7×10^{-3}	6.8×10^{-2}	0.104
Ab7.6	-	-	-	-	-
Ab7.8	5.8×10^5	6.4×10^{-2}	2.7×10^{-3}	1.5×10^{-1}	0.0514
Ab7.9	5.9×10^5	4.3×10^{-2}	2.8×10^{-3}	1.1×10^{-1}	0.0526
Ab7.10	6.0×10^5	8.4×10^{-2}	2.5×10^{-3}	2.0×10^{-1}	0.0573
Ab7.11	-	-	-	-	-
Ab7.12	7.5×10^5	1.1×10^{-1}	2.6×10^{-3}	2.9×10^{-1}	0.119
Ab7.13	7.4×10^5	2.0×10^{-2}	2.6×10^{-3}	5.3×10^{-2}	0.109
Ab7.14	7.0×10^5	3.9×10^{-2}	2.6×10^{-3}	9.9×10^{-2}	0.106
Ab7.15	-	-	-	-	-
Ab7.16	5.7×10^5	4.0×10^{-2}	2.7×10^{-3}	9.1×10^{-2}	0.0512
Ab7.17	5.8×10^5	3.9×10^{-2}	2.9×10^{-3}	9.0×10^{-2}	0.0569
Ab7.18	5.7×10^5	5.3×10^{-2}	2.8×10^{-3}	1.1×10^{-1}	0.054
Ab7.19	-	-	-	-	-
Ab7.20	6.2×10^5	3.6×10^{-2}	2.5×10^{-3}	8.6×10^{-2}	0.0604
Ab7.21	5.5×10^5	4.3×10^{-2}	2.7×10^{-3}	9.7×10^{-2}	0.0459
Ab7.22	5.8×10^5	4.9×10^{-1}	2.7×10^{-3}	1.11	0.0432
Ab7.23	-	-	-	-	-

Single cycle kinetics using the 1:1 model (**Table 4**) demonstrated that Ab7-V_{L4} humanized variants did not bind to hIL-27 and the remaining variants bound within two-fold of the chimeric antibody, consistent with results from the bivalent analyte model (**Table 5**) and the competition ELISA.

In summary, the binding affinity of the Ab7.1 chimeric antibody as determined by single cycle kinetics and using a 1:1 binding model was 1 nM. All of the humanized variants had a KD of 1.5 nM or lower, with the exception of the Ab7-V_{L4} containing variants in which binding was

abolished. These results demonstrate that the Ab7 antibody and the Ab7 antibody variants bind with high affinity to the EBI3 subunit of IL-27.

Example 2: Generation of Anti-IL-27 Antibodies In Yeast That Specifically Bind EBI3 and/or P28 Subunits of Human IL-27

Additional anti-IL-27 monoclonal antibodies representing multiple epitope bins were selected from eight naïve human synthetic yeast libraries using methods described below.

Materials and Methods

Eight naïve human synthetic yeast libraries each of $\sim 10^9$ diversity was propagated as previously described (see e.g., Xu et al., (2013) Protein Eng Des Sel 26(10):663-670; WO2009036379; WO2010105256; and WO2012009568, all of which are incorporated herein by reference in their entireties). For the first two rounds of selection, a magnetic bead sorting technique utilizing the Miltenyi MACS system was performed, as previously described (see e.g., Siegel et al. (2004) J Immunol Methods 286(1-2):141-153, which is incorporated herein by reference in its entirety).

Briefly, yeast cells ($\sim 10^{10}$ cells/library) were incubated with 3 ml of 100 nM biotinylated antigen (recombinant human IL-27; R&D Systems) for 30 min at 30°C in wash buffer (phosphate-buffered saline (PBS)/0.1% bovine serum albumin (BSA)). After washing once with 40 ml ice-cold wash buffer, the cell pellet was resuspended in 20 mL wash buffer, and Streptavidin MicroBeads (500 μ l) were added to the yeast and incubated for 15 min at 4°C. Next, the yeast cells were pelleted, resuspended in 20 mL wash buffer, and loaded onto a Miltenyi LS column. After the 20 mL was loaded, the column was washed 3 times with 3 ml wash buffer. The column was then removed from the magnetic field, and the yeast cells were eluted with 5 mL of growth media and then grown overnight. The following rounds of selection were performed using flow cytometry. Approximately 2×10^7 yeast cells were pelleted, washed three times with wash buffer, and incubated at 30°C with either decreasing concentrations of biotinylated antigen (100 to 1 nM) under equilibrium conditions, 30 nM biotinylated antigens of different species in order to obtain species cross-reactivity, or with a poly-specificity depletion reagent (PSR) to remove non-specific antibodies from the selection. For the PSR depletion, the libraries were incubated with a 1:10 dilution of biotinylated PSR reagent.

Yeast cells were then washed twice with wash buffer and stained with LC-FITC (diluted 1:100) and either SA-633 (diluted 1:500) or EAPE (diluted 1:50) secondary reagents for 15 min at 4°C. After washing twice with wash buffer, the cell pellets were resuspended in 0.3 mL wash buffer and transferred to strainer-capped sort tubes. Sorting was performed using a FACS ARIA sorter (BD Biosciences) and sort gates were determined to select for antibodies with desired characteristics. Selection rounds were repeated until a population with all of the desired characteristics was obtained. After the final round of sorting, yeast cells were plated and individual colonies were picked for characterization.

Light Chain Diversification

Light chain diversification protocol was used during the primary discovery phase for further discovery and improvement of antibodies.

Light chain batch diversification protocol: Heavy chain plasmids from a naïve selection output were extracted from the yeast via smash and grab, propagated in and subsequently purified from *E. coli* and transformed into a light chain library with a diversity of 5×10^6 . Selections were performed with one round of MACS and four rounds of FACS employing the same conditions as the naïve discovery.

Antibody Optimization

Optimization of antibodies was performed by introducing diversities into the heavy chain and light chain variable regions as described below.

CDRH1 and CDRH2 selection: The CDRH3 of a single antibody was recombined into a premade library with CDRH1 and CDRH2 variants of a diversity of 1×10^8 and selections were performed with one round of MACS and four rounds of FACS as described in the naïve discovery. In the different FACS rounds the libraries were looked at for PSR binding, species cross-reactivity, and affinity pressure by titration or parental Fab pre-complexing, and sorting was performed in order to obtain a population with the desired characteristics.

Antibody production and purification

Yeast clones were grown to saturation and then induced for 48 h at 30°C with shaking. After induction, yeast cells were pelleted and the supernatants were harvested for purification.

IgGs were purified using a Protein A column and eluted with acetic acid, pH 2.0. Fab fragments were generated by papain digestion and purified over KappaSelect (GE Healthcare LifeSciences).

ForteBio K_D measurements

ForteBio affinity measurements were performed on an Octet RED384 generally as previously described (see, e.g., Estep et al, High throughput solution-based measurement of antibody-antigen affinity and epitope binning. *Mabs* 5(2), 270-278 (2013), herein incorporated by reference in its entirety). Briefly, ForteBio affinity measurements were performed by loading IgGs on-line onto AHQ sensors. Sensors were equilibrated off-line in assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded IgGs were exposed to 100 nM antigen for 3 minutes, and afterwards were transferred to assay buffer for 3 min for off-rate measurement. All kinetics were analyzed using the 1:1 binding model. Recombinant Human IL-27 Protein (R&D Systems Cat: 2526-IL) was used as an antigen. Affinity measurements for anti-IL-27 antibodies is shown in **FIG. 1**.

ForteBio Epitope Binning/Ligand Blocking

Epitope binning/ligand blocking was performed using a standard sandwich format cross-blocking assay. Control anti-target IgG was loaded onto AHQ sensors and unoccupied Fc-binding sites on the sensor were blocked with an irrelevant human IgG1 antibody. The sensors were then exposed to 100 nM target antigen followed by a second anti-target antibody or ligand. Additional binding by the second antibody or ligand after antigen association indicates an unoccupied epitope (non-competitor), while no binding indicates epitope blocking (competitor or ligand blocking).

MSD-SET kinetic assay

Equilibrium affinity measurements performed as previously described (Estep *et al.*, 2013). Solution equilibrium titrations (SET) were performed in PBS + 0.1% IgG-Free BSA (PBSF) with antigen held constant at 10-100 pM and incubated with 3-to 5-fold serial dilutions of antibody starting at 5 - 100 nM (experimental condition is sample dependent). Antibodies (20 nM in PBS) were coated onto standard bind MSD-ECL plates overnight at 4°C or at room temperature for 30 min. Plates were then blocked for 30 min with shaking at 700 rpm, followed by three washes with wash buffer (PBSF + 0.05% Tween 20). SET samples were applied and incubated on the plates for

150s with shaking at 700 rpm followed by one wash. Antigen captured on a plate was detected with 250ng/mL sulfotag-labeled streptavidin in PBSF by incubation on the plate for 3 min. The plates were washed three times with wash buffer and then read on the MSD Sector Imager 2400 instrument using 1x Read Buffer T with surfactant. The percent free antigen was plotted as a function of titrated antibody in Prism and fit to a quadratic equation to extract the K_D . To improve throughput, liquid handling robots were used throughout MSD-SET experiments, including SET sample preparation.

Example 3: Binding of Anti-IL-27 Antibodies to Recombinant Human IL-27

The ability of anti-IL-27 antibodies described in Example 2 to bind to recombinant human IL-27 was assessed by ELISA. Briefly, Nunc MaxiSorp ELISA Plates (Affymetrix #44-2404-21) were coated with 100 μ L/well recombinant human IL-27 (R&D Systems #2526-IL/CF) (0.5 μ g/mL diluted in PBS), sealed and incubated overnight at 4°C. Plates were washed 3 times with 100 μ L/well of wash buffer (PBS + 0.01% Tween). Plates were then blocked with 200 μ L/well of blocking buffer (PBS + 0.1% BSA + 0.01% Tween) for 1 hour at room temperature (RT) with shaking. Blocking buffer was decanted and 100 μ L per well of diluted control and anti-IL-27 antibodies were added, as indicated. A 10-point serial dilution was created for each antibody by diluting antibodies 1:10 starting from a top concentration of 1 μ g/mL. Plates were incubated for 1-2 hours at RT with shaking. Plates were washed 3 times with 100 μ L/well of wash buffer. 100 μ L/well of anti-human IgG secondary antibody (SouthernBiotech; Cat. # 2014-05) was added (1:5000 diluted in blocking buffer). Plates were then incubated for 1 hour at RT with shaking. After the 1 hour incubation, plates were washed 3 times with 100 μ L/well of wash buffer. To develop the plates 100 μ L/well TMB Buffer (Life Technologies #00-2023) was added. The development of blue color in the wells of the standard curve was observed and as soon as the highest concentration of diluted control antibodies reached a deep blue (5-10 minutes), 50 μ L/well STOP Solution (Thermo Fisher #SS04) was added (the color will change to yellow). The developed plates were read at 450 nm (minus 570 nm for wavelength correction) within 30 minutes of stopping the reaction.

As shown in **FIG. 2**, anti-IL-27 antibodies bind to recombinant human IL-27. An IgG isotype control antibody (IgG Control) was used as a comparator.

For example, biochemical affinity and specificity studies showed that the anti-IL-27 antibody SRF388 binds to the p28 subunit (but not the EBI3 subunit) of the heterodimeric cytokine IL-27. SRF388 bound to human, nonhuman primate, and rodent recombinant IL-27, and the extent of the binding differed between species. The binding specificity of SRF388 to IL-27 was confirmed by testing against a panel of ~4500 cell surface and soluble molecules, and no off-target binding was observed. The binding specificity of IL-27 for its receptor IL-27RA (WSX-1) was also confirmed; no other cell surface receptor bound human IL-27. The ability of SRF388 to block the interaction between human IL-27 and IL-27RA (WSX-1) was confirmed by Surface Plasmon Resonance.

Binding of the antibodies disclosed herein was assessed in several model systems. Since human IL-27 is biologically active on mouse cells, systemic overexpression of human IL-27 in mice using DNA minicircle delivery was utilized to analyze IL-27-mediated effects *in vivo* by whole-genome microarray analysis, flow cytometry, and serum cytokine analysis. Many of the markers that were modulated by IL-27 *in vivo* were consistent with findings in human cell-based assays. SRF381 was also evaluated in a disseminated B16 tumor model. In that setting, treatment with SRF381 showed results consistent with phenotypes observed in mice deficient for various components of IL-27 ligand (IL-27 p28, EBI3) or receptor (IL-27RA).

Collectively, these studies demonstrate that SRF388 (and its sibling SRF381) can phenocopy IL 27 deficiency in mice, binds specifically and with high affinity to IL-27 and can inhibit its immunosuppressive effects, either alone or in combination with PD-L1 blocking agents.

Example 4: Anti-IL27 Antibodies Inhibit Phosphorylation of STAT1 *In Vitro*

IL-27 signaling through the IL-27 receptor (IL-27R) results in the phosphorylation of the Signal Transducer And Activator Of Transcription 1 (STAT1) polypeptide (pSTAT1). Anti-IL-27 antibodies described in Example 2 were tested for their ability to inhibit IL-27-mediated phosphorylation of STAT1 in human whole blood, human PBMCs, the U937 myeloid cells (histiocytic lymphoma cell line) and HUT-78 T cell lymphoma cells by flow cytometry.

Anti-IL-27 antibodies were tested for their ability to inhibit IL-27-mediated phosphorylation of STAT1 in human whole blood. Briefly, EDTA anticoagulated whole human blood, stored at room temperature, was used in this assay. 45µL blood was distributed into each well of a deep well, round bottom plate (Phenix #850356) and warmed for 30 minutes at 37°C on

a plate warmer (EchoTherm IC20) or in a 37°C incubator. Anti-IL-27 antibodies were diluted to a 10x top concentration in endotoxin-free PBS (Teknova #P0300) in a polypropylene V-bottom plate (Corning #3363). Anti-IL-27 antibodies were serially diluted as desired in endotoxin-free PBS. PBS alone was added to wells for unstimulated and stimulated controls. 5 µL of each dilution was added to a well of 45 µL blood and mixed by shaking on plate shaker 15 seconds 1000 RPM (Eppendorf Mix Mate). The plate was incubated for 60 minutes at 37°C on a plate warmer or in a 37°C incubator.

A 10 µg vial of recombinant human IL-27 (R&D Systems # 2526-IL) was reconstituted to 100 µg/mL by adding 100 µL PBS + 0.1% BSA (made from 10% BSA Sigma #A1595). A working stock of the recombinant hIL-27 (rhIL-27) was prepared by dilution to 200 ng/mL in endotoxin-free PBS. After the 60-minute incubation, 5 µL of 200 ng/mL rhIL-27 was added to each well of stimulated blood. 5 µL PBS was added to unstimulated control wells. The plate was shaken on a plate shaker for 15 seconds at 1000 RPM. The plate was incubated for 30 minutes at 37°C.

After the 30-minute incubation, cells were fixed. Lyse/Fix reagent (BD #558049) was diluted 1:5 in sterile water (Hyclone #SH3052902) and warmed to 37°C in a water bath. 500 µL Lyse/Fix reagent was added to each well of the deep well plate and the plate was mixed on a plate shaker for 15 seconds at 1000 RPM. The plate was incubated for 15 min at 37°C.

After the 15-minute incubation, the plate was centrifuged for 5 minutes at 1500 RPM at room temperature (Eppendorf centrifuge 5810R) and supernatant was discarded by flicking. 1 mL of endotoxin-free PBS was added per well and the plate was shaken on plate shaker for 15 seconds at 1000 RPM. The plate was centrifuged for 5 minutes at 1500 RPM at room temperature (Eppendorf centrifuge 5810R) and supernatant was discarded by flicking. Cell pellets remained in the plate.

Cell pellets were resuspended in 50 µL 1:200 CD14-Pacific Blue (Biolegend #325616) in FACS Buffer (PBS, Gibco #14190-144 /2% FBS, Sigma #F8317/1mM EDTA, Fisher #BP2482) and transferred to U-bottom 96 well plate (Costar #3799). The plate was sealed with plate sealer (VWR #89134-432) and incubated for 30 minutes at room temperature in the dark.

After the 30 minute incubation, 150 µL FACS buffer was added to each well and the plate was centrifuged at 1500 RPM for 5 minutes at room temperature. The cell pellets were then resuspended in 100 µL Perm III (stored at -20°C) (BD #558050) with pipetting and the plate was sealed with plate sealer and lid. The plate was incubated overnight at -20°C or 15 minutes at 4°C.

After the incubation, 150 μ L PBS was added and the plate was centrifuged at 1500 RPM for 5 minutes at room temperature. The supernatant was discarded from the plate by flicking and the plate was resuspended in 50 μ L staining cocktail prepared as described in the **Table 6** below:

Table 6

BD Catalog #	Antibody	Color	Dilution
561807	CD3	FITC	1:10
562069	pSTAT1 Y701	PE	1:100
562071	pSTAT3 Y705	APC	1:20

The plate was incubated for 1 hour at room temperature in the dark. After the 1-hour incubation, 100 μ L of FACS buffer was added and the plate was centrifuged at 1500 RPM for 5 minutes at room temperature. The supernatant was discarded from the plate by flicking and the plate was resuspended in 100 μ L FACS buffer for analysis by flow cytometry.

As shown in **FIG. 3A**, anti-IL-27 antibodies inhibit the phosphorylation of STAT1 in human whole blood. The anti-IL-27 antibody Ab14 inhibited the phosphorylation of STAT1 at an IC₅₀ of 24.7 ng/mL - in human whole blood.

The anti-IL-27 antibodies described in Example 2 were further tested for their ability to inhibit IL-27-mediated phosphorylation of STAT1 in pooled human PBMCs by flow cytometry. Briefly, frozen cryovials of human PBMC's (peripheral blood mononuclear cells), obtained from buffy coats, were removed from liquid nitrogen storage and quickly thawed in a 37°C water bath. The contents of each cryovial was removed with a P1000 pipet and transferred to a 15 mL conical falcon tube. 2-3 mLs of complete RPMI-1640 (Gibco, 61870-036) was slowly added to the thawed cells and cells were gently swirled or flicked to suspend. Conical tubes were topped-off up to 10mLs with complete RPMI-1640 and tubes were inverted to mix. Conical tubes were centrifuged tube at 1400 RPM at room temperature for 8 minutes.

PBMC cells were resuspended at a density of 4 million cells per mL in warm, serum-free RPMI-1640 and plated at a density of 200,000 cells per well (50 μ) in a round bottom 96-well plate (Costar, 3799). Anti-IL-27 antibodies were diluted in serum-free RPMI-1640 in the first row of a 96-well polypropylene plate to a top concentration of 40 μ g/ml (will be 10 μ g/ml final). Serial dilutions as desired (1:2, 1:3, etc...) were made in the remainder of the first 10 rows of the plate.

Fifty microliters (μL) of the antibody stock (4x) was added to the first 10 rows the plate of PBMC cells in the round bottom plate. In rows 11 and 12, 50 μL of serum-free RPMI-1640 cell media was added. The plate was then incubated at 37°C for 2 hours.

After the 2-hour incubation, 100 μL of 50 ng/ml recombinant human IL-27 (R&D Systems, 2526-IL) diluted in serum-free RPMI-1640 cell media was added to each well (*except*, the control wells which included serum-free media alone or antibody alone) for a final concentration of 25 ng/ml. 100 μL serum-free RPMI-1640 cell media was added to control wells or wells with antibody alone. The plate was incubated for 20 minutes at 37°C.

After the 20-minute incubation, 50 μL of 4% PFA (Pierce, 28906) in DI water was added directly to each well and the plate was incubated at 37°C for 5 minutes to fix the cells. The plate was centrifuged at 2000 RPM for 5 minutes. Media was discarded by flicking and plate was washed with 150 μL DPBS. The washing steps were repeated 2 more times. 50 μL ice cold 90% methanol (MeOH) (Sigma, 439193) diluted in H_2O was added quickly to each well using a 12-channel pipette. When adding the MeOH special care was taken to mix each well. The plate was incubated at 20°C for at least 15 minutes. 100 μL of DPBS was added to each well on top of the 90% methanol and the plate was centrifuged at 2000 RPM for 5 minutes. Plate contents were discarded by flicking and the plate was washed 3 times as described previously. After the last wash, cell pellets remained in the wells of the plate.

The pelleted PBMC's were stained with pSTAT1 PE (BD Phosflow, 526069) 1:100 in FACS buffer (2% FBS, 2mM EDTA in DPBS) for 45 minutes at room temperature in the dark. Special care was taken to mix each well with a 12-channel pipette when adding the stain. After the 45-minute incubation, 100 μL FACS buffer was added into each well and the plate was centrifuged at 2000 RPM for 5 minutes. Supernatant was discarded by flicking and the plate was washed 2 times as described previously. Cells were resuspended in 100 μL FACS buffer and analyzed by flow cytometry.

As shown in **FIG. 3B**, anti-IL-27 antibodies inhibited phosphorylation of STAT1 in human pooled PBMCs. The anti-IL-27 antibody SRF381 inhibited phosphorylation of STAT1 at an average IC_{50} of 140.5 ng/ml ($n=2$) in pooled human PBMCs. The anti-IL-27 antibody SRF388 inhibited phosphorylation of STAT1 at an average IC_{50} of 58.3 ng/ml ($n=3$) in pooled human PBMCs.

Anti-IL-27 antibodies were further tested for their ability to inhibit IL-27-mediated phosphorylation of STAT1 in U937 cells, a cell line known to express Fc receptors, by flow cytometry essentially as described for **FIG. 3B**. As shown in **FIG. 3C**, anti-IL-27 antibodies inhibit the phosphorylation of STAT1 in U-937 cells, as indicated. Antibody SRF381 inhibited the phosphorylation of STAT1 at an average IC₅₀ of 81 ng/ml (n=2) in U937 cells. Antibody SRF388 inhibited the phosphorylation of STAT1 at an average IC₅₀ of 96 ng/ml (n=2) in U937 cells.

Anti-IL-27 antibodies were tested for their ability to inhibit IL-27-mediated phosphorylation of STAT1 in the cutaneous T-cell lymphoma line HUT-78, which does not express cell surface Fc receptors, by flow cytometry essentially as described for **FIG. 3B**. As shown in **FIG. 3D**, anti-IL-27 antibodies inhibited the phosphorylation of STAT1 in HUT-78 cells. Antibody SRF381 inhibited the phosphorylation of STAT1 at an IC₅₀ of 80 ng/ml (n=1) in HUT-78 cells. Antibody SRF388 inhibited the phosphorylation of STAT1 at an IC₅₀ of 95 ng/ml (n=1) in HUT-78 cells.

The present disclosure also assessed IL-27 inhibition by SRF388 across species in a whole blood assay. To characterize SRF388 activity across species, recombinant IL-27 from human, cynomolgus monkey, rat, and mouse was tested to stimulate pSTAT1 signaling in T lymphocytes from whole blood samples obtained from these species (data not shown).

Briefly, whole blood was warmed to 37°C followed by a 60-minute pre-incubation with SRF388, and 20 ng/mL of human IL-27 was added. Samples were incubated for another 30 minutes. White blood cells were fixed, and red blood cells were lysed. After washing, fixed cells were permeabilized and stained with anti-CD3 and anti-phospho-STAT1 (Y701). After a 1-hour incubation, samples were washed and resuspended for flow cytometry. Percent inhibition was calculated using stimulated and unstimulated control wells, and IC₅₀ values were calculated using GraphPad Prism.

Representative data for SRF388 signaling inhibition in human T cells are shown in **FIG. 3E**. Consistent with observations made on the affinity of SRF388 to different species, the potency of IL-27 signaling inhibition by SRF388 was strongest in human, followed by cynomolgus monkey, rat, and mouse (see e.g., **Table 7**).

Table 7: SRF388 IC₅₀ Values in Peripheral Blood T Cells from Different Species

Species	Average IC ₅₀ , ng/mL	Standard Deviation	Number
Human	78.4	35	7
Cynomolgus monkey	118.1	36.4	4
Rat	273.2	133.5	8
Mouse	1721	N/A	1 (pool of 10)

Abbreviations: IC₅₀ = half maximal inhibitory concentration, N/A = not applicable

Example 5: Reduction of IL-27-Mediated Inhibition of CD161 by Anti-IL-27 Antibodies

The C-type lectin CD161 is a marker of T cells whose expression is suppressed by IL-27. Anti-IL-27 antibodies described in Example 2 were tested for their ability to reverse the IL-27-mediated inhibition of CD161 in pooled human PBMC cells by flow cytometry. Briefly, frozen cryovials of pooled human PBMC's (peripheral blood mononuclear cells), obtained from buffy coats, were removed from liquid nitrogen storage and quickly thawed in a 37°C water bath. Contents of each cryovial was removed with a P1000 pipet and transferred to a 15 mL conical falcon tube. 2-3 mLs of complete RPMI-1640 (Gibco, 61870-036) was slowly added to the thawed cells and cells were gently swirled or flicked to suspend. Conical tubes were topped-off up to 10 mLs with complete RPMI-1640 and tubes were inverted to mix. Conical tubes were centrifuged tube at 1400 RPM, room temperature for 8 minutes.

Use of outer walls was avoided to minimize the effects of evaporation during the 5-day assay. Outer wells should be filled with 200 µL per well of DPBS (Gibco, 14190-144). PBMC cells were resuspended at a density of 2 million cells per mL in warm, complete RPMI-1640. Purified human anti-CD3 antibody (Biolegend, UCTH1, #300402) was added at a concentration of 0.5µg/mL (this is 2X the final concentration). Plate 100 µL per well of this cell mixture (200,000 cells per well) in a round bottom 96 well plate (Costar, 3799).

Anti-IL-27 antibodies were diluted in complete RPMI-1640 in the first row of a 96 well polypropylene plate to a top concentration of 40 µg/ml (will be 10ug/ml final). Serial dilutions as desired (1:2, 1:3, etc...) were made in the remainder of the first 10 rows of the plate. 50 µL of the antibody stock (4x) was added to the first 10 rows the plate of PBMC cells in the round bottom plate. In rows 11 and 12, 50 µL of complete RPMI-1640 was added.

After the addition of the anti-IL-27 antibodies, 50 μ l of 100 ng/ml recombinant human IL-27 (R&D Systems, #2526-IL) diluted in complete RPMI-1640 was added to each well (except control wells which included serum free media or antibody alone) for a final concentration of 25 ng/ml. Fifty μ L of complete RPMI-1640 was added to control wells. The plate was incubated for 5 days at 37°C in a tissue culture incubator with minimal interference.

After the 5-day incubation the plate was removed from the incubator and agitated on a plate shaker for 30 seconds at 600 RPM. The plate was centrifuged at 1800 RPM for 5 minutes. Media was removed and set aside for additional assays and the plate was washed with 150 μ L DPBS (Gibco, #14190-144). The washing steps were repeated 2 more times. The cell pellets were stained with 50 μ L per well of staining cocktail as described in the **Table 8** below:

Table 8

Biolegend Catalog #	Antibody Target	Color	Dilution
300532	CD4	BV421	1:100
304204	CD45RO	FITC	1:100
339910	CD161	AF647	1:100
353410	CCR6	PE	1:100

The plate agitated on a plate shaker for 30 seconds at 600 RPM and the plate was incubated for 30 minutes at room temperature in the dark.

After the 30-minute incubation the plate was centrifuged and supernatant was discarded by flicking. The plate was washed 2 times as described previously. After the last wash, cell pellets were fixed by adding 50 μ L 4% PFA (Pierce, 28906) in DI water at room temperature for 10 mins. 100 μ L of FASC buffer was added to each well, and the plate was centrifuged at 1800 RPM for 5 minutes. Cells were resuspended in 100 μ L FACS buffer and read by flow cytometry.

As shown in **FIG. 4**, anti-IL-27 antibodies, as indicated, reduce the IL-27 mediated inhibition of CD161.

Example 6: Enhancement of PD-1-Mediated Secretion of TNF α , IL-6 and other Cytokines by Anti-IL-27 Antibodies, Including Additional In Vitro Characterization of Anti-IL-27 Antibodies

Anti-IL-27 antibodies were tested for their ability to enhance PD-1-mediated secretion of TNF α and IL-6 in human PBMC cells from cancer patients. Human PBMC cells from cancer patients were cultured essentially as described in Example 5 with the addition of wells also receiving anti-PD-1 antibody, as indicated, at 1 μ g/mL. Supernatants from the assay were analyzed for TNF α and IL-6 using Human CBA Th1/Th2/Th17 Kit (BD, 560484). As shown in **FIGS. 5A and 5B**, anti-IL-27 antibodies enhance the PD-1-mediated secretion of TNF α and IL-6 in pooled human PBMC cells.

The techniques herein also show cytokine-inducing activity of SRF388 monotherapy and in combination with anti-PD-1 in human PBMCs. IL-27 is known to negatively regulate the expression of several inflammatory cytokines. To determine the effects of IL-27 blockade on cytokine production, human PBMCs from healthy donors, patients with RCC, and patients with ovarian cancer were activated with anti-CD3 in the presence or absence of SRF388 for several days and tested for levels of secreted cytokines including IL-17, IFN γ , TNF α , and IL-6. Briefly, PBMCs isolated from fresh whole blood from 4 healthy donors, 5 patients with RCC, and 2 patients with ovarian cancer were activated by 0.25 μ g/mL anti-CD3 antibody in the absence or presence of SRF388 (1 μ g/mL), anti PD 1 (pembrolizumab, 1 μ g/mL) or both antibodies. After 5 days, supernatants were collected and tested for levels of TNF α (A) or IFN γ (B) by MSD or CBA. Data shown represent the fold-change in cytokine production compared to anti-CD3 stimulation alone. Statistics were calculated by paired t-test (*p < 0.005).

Anti-PD-1 antibody was used as a control in these assays and the combination of PD-1 and IL-27 blockade was also explored as shown in **FIG. 5C**. SRF388 treatment led to increased TNF α production in 6 of 11 PBMC samples tested (determined by > 2 fold increase) including 2 of 4 healthy donors, 3 of 5 patients with RCC, and 1 of 2 patients with ovarian cancer. When tested in a subset of donors this activity was SRF388 dose dependent (data not shown). Anti-PD-1 (pembrolizumab) treatment showed an increase in TNF α in 2 of the 11 donors tested (1 of 5 RCC and 1 of 2 ovarian cancer) while the combination of SRF388 and anti-PD-1 led to an increase in 10 of 11 donors. The increased TNF α seen in the combination treatment conditions appeared to

be additive in 8 of 10 responders. An additive effect for IFN γ production was observed in these cultures after SRF388 and anti-PD-1 treatment (10 of 11 donors); however, responses to anti-PD-1 treatment alone were more frequently seen (10 of 11 donors) compared to SRF388 (2 of 11 donors). Together, these data suggest that SRF388 increases TNF α levels in activated PBMC cultures from healthy donors and patients with cancer and the combination of SRF388 and anti-PD-1 treatment leads to higher levels of TNF α and IFN γ compared to either treatment alone.

To further explore the role of IL-27 and PD-1 blockade, the same activated PBMC culture system was used to determine whether IL-27 could directly counteract the effect of increased cytokine production caused by PD-1 blockade. Briefly, freshly isolated PBMCs from human whole blood were activated by 0.25 $\mu\text{g/mL}$ anti-CD3 antibody. Cells were treated either control IgG1 (1 $\mu\text{g/mL}$), α PD-1 antibody (pembrolizumab, 1 $\mu\text{g/mL}$) alone, rhIL-27 (25 ng/mL) plus α PD-1 or rhIL-27 plus α PD-1 with SRF388 (1 $\mu\text{g/mL}$) at 37°C for 5 days. Supernatants were collected for CBA detection. The example cytokines (IL-17A and IFN γ) from 4 healthy donors were shown as fold change to control. Mean and standard deviation were depicted. Statistics were calculated by paired t-test (* $p < 0.05$, ** $p < 0.01$). Similar results were also seen in PBMCs from patients with RCC. PD-1 blockade increased both IL-17 and IFN γ in these cultures and IL-27 could completely inhibit this activity, a response that was reversed in the presence of SRF388 as shown in FIG. 5D. These data show that IL-27 can attenuate the effects of anti PD-1 treatment on cytokine production.

Therefore, IL-27 was shown to inhibit anti-PD-1 mediated pro-inflammatory cytokine production in activated human PBMCs, a property that was blocked by SRF388. Moreover, SRF388 in combination with PD-1 blockade led to increased cytokine production in activated PBMCs from healthy donors and patients with RCC. Thus, by blocking IL-27, SRF388 enhances immune cell activation by altering immunoregulatory receptor expression and increasing inflammatory cytokine production.

In additional characterization of individual anti-IL-27 antibodies in the presence of anti-IL-27 antibody (here, SRF388), α PD-1 antibody, or combined anti-IL-27 and α PD-1 antibodies, further characterization of cytokine induction/secretion was performed (**FIG. 5E**, specifically for TNF α , IFN γ , IL-6 and IL-17A). *In vitro* dose-response curves were also obtained across a number of IL-27-mediated signaling effects for SRF405, SRF410, SRF411, SRF414, SRF416, SRF536, SRF543, SRF529, SRF381, SRF388 and Ab7 antibodies (FIGS. 5F-5K, where: **FIG. 5F** shows

inhibition of pSTAT1 signal in U937 (lymphoma) cells across increasing concentrations of anti-IL-27 antibodies; **FIG. 5G** shows inhibition of pSTAT1 signal in PBMCs (peripheral blood mononuclear cells) across increasing concentrations of anti-IL-27 antibodies; **FIG. 5H** shows varying effects upon CD161 signal in PBMCs (peripheral blood mononuclear cells) across increasing concentrations of anti-IL-27 antibodies; **FIG. 5I** shows varying effects upon PD-L1 signal in CD4 T lymphocytes (CD4 cells) across increasing concentrations of anti-IL-27 antibodies; **FIG. 5J** shows varying effects upon PD-L1 signal in monocytes across increasing concentrations of anti-IL-27 antibodies; and **FIG. 5K** shows inhibitory effects of varying degree upon TIM-3 signal in monocytes across increasing concentrations of anti-IL-27 antibodies).

Example 7: Inhibition of IL-27-Mediated Expression of PD-L1 and TIM3 by Anti-IL-27 Antibodies

Anti-IL-27 antibodies described in Examples 1 and 2 were tested for their ability to inhibit IL-27-mediated expression PD-L1 and TIM-3 in pooled human monocytes by flow cytometry.

Fresh Monocytes were isolated from human buffy coats using RosetteSep™ Human Monocyte Enrichment Cocktail (Stemcell #15068).

Use of outer wells was avoided to minimize the effects of evaporation during the 5 day assay. Outer wells should be filled with 200 µL per well of DPBS (Gibco, 14190-144).

Monocytes were resuspended at a density of 2 million cells per mL in warm, complete RPMI-1640. 100 µL per well of this cell mixture was plated (200,000 cells per well) in a round bottom 96-well plate (Costar, 3799).

Anti-IL-27 antibodies were diluted in complete RPMI-1640 in the first row of a 96-well polypropylene plate to a top concentration of 40 µg/ml (10µg/ml final concentration). Serial dilutions as desired (1:2, 1:3, etc...) were made in the remainder of the first 10 rows of the plate. 50 µL of the antibody stock (4x) was added to the first 10 rows the plate of PBMC cells in the round bottom plate. In rows 11 and 12, 1250 µL of complete RPMI-1640 was added.

After the addition of the anti-IL-27 antibodies, 50 µL of 80 ng/ml recombinant human IL-27 (R&D Systems, 2526-IL) diluted in complete RPMI-1640 was added to each well (*except*, control wells which included serum-free media or antibody alone) for a final concentration of 20 ng/ml. 100 µL serum-free RPMI-1640 was added to control wells. The plate was incubated for 3 days at 37°C with minimal interference.

After the 3-day incubation the plate was removed from the incubator and agitated on a plate shaker for 30 seconds at 600 RPM. The plate was centrifuged at 1800 RPM for 5 minutes. Media was discarded by flicking and plate was washed with 150 μ L DPBS (Gibco, 14190-144). The washing steps were repeated twice. The cell pellets were stained with 50 μ L per well of staining cocktail as described in the **Table 9** below:

Table 9

Biolegend Catalog #	Antibody Target	Color	Dilution
345006	TIM3	PE	1:100
301310	CD11b	APC	1:100
329714	PD-L1	BV421	1:100

The plate was agitated on a plate shaker for 30 seconds at 600 RPM and the plate was incubated for 30 minutes 4°C in the dark.

After the 30-minute incubation, the plate was centrifuged and supernatant was discarded by flicking. The plate was washed 2 times as described previously. After the last wash cell pellets were fixed by adding 50 μ L 4% PFA (Pierce, 28906) in deionized (DI) water at room temperature for 10 mins. 100 μ L of FACS buffer was added to each well, and the plate was centrifuged at 1800 RPM for 5 minutes. Cells were resuspended in 100 μ L FACS buffer and analyzed by flow cytometry.

As shown in **FIGS. 6A, 6B and 6C**, anti-IL-27 antibodies potently inhibit the IL-27 mediated expression of PD-L1 and TIM3 in pooled human monocytes.

Anti-IL-27 antibodies were further tested for their ability to inhibit IL-27-mediated expression of PD-L1 in resting T cells (inactivated) essentially as described for **FIGS. 6A, 6B and 6C**. Resting T-cells were isolated from human buffy coats using RosetteSep™ Human T cell Enrichment Cocktail (Stemcell #15061).

At the conclusion of the assay, the cell pellets were stained with 50 μ L per well of staining cocktail as described in the **Table 10** below:

Table 10

Biolegend Catalog #	Antibody Target	Color	Dilution
345006	TIM3	PE	1:100
555349	CD4	APC	1:100
329714	PD-L1	BV421	1:100
555366	CD8	FITC	1:100

The plate was agitated on a plate shaker for 30 seconds at 600 RPM and the plate was incubated for 30 minutes at 4°C in the dark.

After the 30-minute incubation, the plate was centrifuged and supernatant was discarded by flicking. The plate was washed 2 times as described previously. After the last wash cell pellets were fixed by adding 50 µL 4% PFA (Pierce, 28906) in DI water at room temperature for 10 mins. 100 µL of FACS buffer was added to each well, and the plate was centrifuged at 1800 RPM for 5 minutes. Cells were resuspended in 100 µL FACS buffer and read by flow cytometry. As shown in **FIG. 6D**, anti-IL-27 antibodies potently inhibit the IL-27-mediated expression of PD-L1 in pooled human resting T cells.

Example 8: *In Vivo* Efficacy of an Anti-IL-27 Antibody in a Disseminated B16F10 Model of Melanoma

A model of melanoma lung metastasis was used to assess the antitumor activity of IL-27 blockade using the clinical candidate SRF388. The growth of disseminated B16F10 lung metastases is known to be significantly reduced in EBI3 and Il27ra (Wsx-1)-deficient mice (Sauer et al., *J. Immunology* 181: 6148-6157). Since lung nodule size and growth kinetics are dependent on the number of B16F10 cells transferred and can proceed variably and rapidly, the combination of anti-PD-1 and anti-CTLA-4 was studied as a benchmark for therapeutic activity. SRF388 pre-treatment resulted in a significant reduction in overall tumor burden. To evaluate the anti-tumor efficacy of an anti-IL-27 antibody in vivo, the effect of Ab14 on tumor growth in a B16F10 melanoma tumor model was evaluated.

Briefly, six to eight-week-old female C57BL/6 mice (n=10/group) were inoculated intravenously (i.v.) with either 2.5×10^5 B16F10 cells or 1×10^5 B16-Luc cells via the tail vein in

200 μ L phosphate-buffered saline (PBS). Animals were injected intraperitoneally (i.p.) with SRF388 (1 mg dose) (Wuxi; lot 2108SD170316K01X01I01) or polyclonal human IgG isotype control (1 mg dose) (Bioxcell; BE0092; lot 658417D1). Antibodies were dosed once weekly beginning 7 days before tumor injection for a total of four doses (days -7, 0, 7, and 14). For visual enumeration of lung metastases, B16F10 tumor bearing mice were euthanized by CO₂ asphyxiation 18 days-post tumor cell injection and lungs were perfused with PBS via cardiac puncture, removed, and fixed in 10% neutral buffered formalin for 24 hours. Fixed lungs were then transferred to 70% ethanol and surface lung metastases were counted visually. For immunohistochemical analysis, formalin fixed lungs (n=5/group) were paraffin embedded, sectioned and stained with hematoxylin and eosin for quantification of total tumor area as a percentage of total tissue area in each section. For *in vivo* tumor imaging of lung metastases, B16-Luc tumor-bearing animals were injected i.v. via the tail vein with 3 mg of VivoGlo D-luciferin in 200 μ l PBS (Promega) twice weekly. Five minutes after luciferin injection animals were anesthetized and bioluminescent imaging was performed using an IVIS Lumina LT Series III imager. Images were analyzed using Living Image (version 4.5.5) software and represented as total flux measurements in photons/second.

As shown in **FIGS. 7A-7D**, treatment of B16F10 tumor-bearing mice with the anti-IL-27 antibody SRF388 resulted in a significant reduction in overall tumor burden as measured by both total counts of surface lung metastases (# pulmonary nodules, **FIG. 7A**), and by a reduction of tumor area in lung tissue sections by immunohistochemistry (IHC) analysis (**FIG. 7C** and **FIG. 7D**). Blockade of p28 with SRF388 resulted in a 42% reduction in the number of pulmonary B16 nodules compared to isotype control treatment. SRF388 treatment significantly inhibited (p=0.0079) the growth of B16F10 lung metastases compared to isotype control (21.6 $\pm$ 8.4 versus 37.6 $\pm$ 10.9 lung nodules, respectively). SRF388 treatment resulted in an 83% reduction in overall lung tumor metastasis area as measured by IHC (16.43 $\pm$ 1.39% in the isotype control group versus 2.83 $\pm$ 1.45% in the SRF388 treatment group). Similarly, bioluminescent imaging revealed that SRF388 treatment significantly (p=0.0062) delayed the growth of B16-Luc lung metastases (**FIG. 7B**). A similar reduction in surface lung metastasis number and total tumor area was observed with IL-27RA (WSX-1) mediated antibody blockade and with anti-PD-1 + anti-CTLA-4 combination therapy, as shown in **FIG. 7D**. These data are from 2 independent experiments in which anti-PD-1 and anti-CTLA-4 benchmark combination demonstrated antitumor activity. B16F10 cells (2.5 x 10⁵) were injected intravenously in C57BL/6 mice (n = 10/group). Mice were treated IP with 1 mg

of either SRF388, anti-IL-27RA (WSX-1), or human IgG isotype control antibody (Days -7, 0, 7, 14). Some animals were treated IP with anti-PD-1 and anti-CTLA-4 (Days 0, 4, 7, and 11). Lungs were collected from animals (n=5/group) bearing B16F10 lung metastases treated as described above were sectioned and stained with H&E. B16F10 tumor tissue was delineated from normal lung tissue in H&E stained lung sections from treated animals (**FIG. 7A**). Tumor area was calculated as a percentage of total lung area (**FIG. 7D**). Statistics were calculated by t-test. Collectively, these data indicate that SRF388 can phenocopy IL27ra (WSX-1) and EBI3 deficiency in a tumor model and shows similar activity to combined blockade of PD-1 and CTLA-4.

These data demonstrate that treatment with an anti-IL-27 antibody (SRF388) results in anti-tumor effects, reducing both tumor growth and metastasis to a greater extent than treatment with an isotype control antibody that does not bind IL-27.

Example 9: Gene Expression Profiling of Murine Splenocytes from Mice Hydrodynamically Transfected with Human IL-27 Minicircles

To examine the effect of IL-27 on T cell phenotype *in vivo*, DNA minicircles encoding IL-27 were used to overexpress IL-27 in mice and T cell responses were assessed by RNA-Seq and flow cytometry. Human IL-27 is known to be species cross-reactive and can induce pSTAT1 signaling and PD L1 in murine splenocytes *in vitro*. This species cross-reactivity was used to study the effects of human IL-27 overexpression in mice and its inhibition by SRF388. To do this, DNA plasmid minicircles encoding human IL-27 (p28 tethered to EBI3 by a glycine serine linker) were administered to mice by hydrodynamic transfection, as described below, which resulted in high systemic levels of IL-27.

Hydrodynamic Transfection of Human IL-27 Minicircles

Six-week-old female BALB/c mice were injected with 20 µg of either empty vector or linked human IL-27 minicircle DNA (System Biosciences, Palo Alto, CA) in 2 mL 0.9% normal saline via the tail vein over the course of 5 seconds. Injected animals were transferred to an empty cage with a heating pad to recover for 5 minutes. Whole blood was collected into K2-EDTA tubes for plasma separation 24 hours after minicircle injection and plasma IL-27 levels were confirmed by ELISA. PBMCs and total splenocytes were collected 5 days after transfection and cells were stained and analyzed by flow cytometry. Expression of the indicated markers were analyzed on CD4⁺ T cells and CD8⁺ T cells. Analysis was performed using FlowJo software.

Gene expression profiling

Mouse splenocytes were prepared by mechanical dissociation of whole spleens, followed by ACK lysis of red blood cells. Total RNA was extracted from splenocytes with the RNeasy[®] Mini Kit (Qiagen, Cat. No: 74104) and adjusted to 20 ng/ul in nuclease free water (Qiagen, Cat. No: 19101). Gene expression profiling was performed on Affymetrix GeneChip[™] Mouse Gene 2.0 ST Arrays (Applied Biosystems, Cat. No: 902118). Processing of RNA samples, hybridization and array scanning were carried out using standard Affymetrix GeneChip[™] protocols at the Boston University Microarray and Sequencing Resource (BUMSR). All CEL files were normalized by Robust Multi-array Average (RMA) (Irizarry et al., 2003) and gene expression data were preprocessed by removing unexpressed probes and discarding transcripts with high inter-replicate coefficient of variance. Subsequent analyses (mean expression, fold change, t test) were performed in R.

Flow cytometric analysis

Whole blood and spleens were collected from mice five days after minicircle injection. Splenocytes were collected from IL 27-expressing mice 5 days after transfection and analyzed by Affymetrix GeneChip Mouse Gene 2.0 ST Array. Single cell splenocyte suspensions were prepared by mechanical dissociation through a 40 µm nylon cell strainer followed by red blood cell lysis in ACK buffer. Whole blood cells were stained directly followed by red blood cell lysis and fixation in BD Phosflow Lyse/Fix Buffer according to the manufacturer's instructions (BD Biosciences, San Jose, CA). FcγRIII/II was blocked by preincubating cells with rat anti-mouse CD16/CD32 mAb (1 µg per million cells; Biolegend, San Diego, CA) in PBS with 2% FBS and 2mM EDTA. Cells were stained with APC-, PE-, Brilliant Violet 510-, and Brilliant Violet 711-conjugated mAbs against murine CD4 (clone GK1.5), CD8 (53-6.7), PD-L1 (10F.9G2), TIM3 (RMT3-23), LAG3 (C9B7W), and TIGIT (1G9) (Biolegend). Cell-associated fluorescence was measured using an LSRFortessa X-20 flow cytometer (BD Biosciences), and analysis was performed using FlowJo software (Tree Star, Ashland, OR).

Statistical Analysis

Statistical significance was determined using GraphPad Prism software, using a paired, unpaired, or ratio Student's t test, as indicated. When the ratio t test was used, 0.1 was added to zero values to make them non-zero. P values less than 0.05 were considered significant.

IL-27 promotes expression of inhibitory receptors by T cells in vivo

Over 400 genes were changed by ≥ 1.0 fold in response to administration of IL-27, as shown in **FIG. 8A**. A subset of these genes is shown in **Table 11**. Among these genes were those that encode immune inhibitory receptors that play key roles in the immune response. As shown in **FIG. 8B**, *Ly6a* (encodes Sca-1), *Lag3*, *Tigit* and *Il10* were upregulated on splenocytes in response to IL-27. There was also a trend toward IL-27-mediated upregulation of *Ctla4* and *Cd274* (encodes PD-L1) that was less than 1-fold induction (data not shown). To validate the expression data, flow cytometry was utilized to assess the protein expression of PD-L1, LAG-3, TIGIT and TIM-3 on T cells from these mice. Administration of IL-27 minicircles led to upregulation of PD-L1, LAG-3 and TIGIT in splenic (Spleen) and peripheral blood (PBMC) CD4⁺ T cells. In CD8⁺ T cells, IL-27 minicircles upregulated PD-L1, LAG-3, TIGIT, and TIM-3. As shown in **FIG. 8C**, administration of IL-27 minicircles led to upregulation of PD-L1, Lag-3, and Tigit in splenic and peripheral blood CD4⁺ T cells. In CD8⁺ T cells, IL-27 minicircles upregulated PD-L1, Lag-3, Tigit, and Tim-3. These data suggest that IL-27 can play a key role in driving immunoregulatory receptor expression in vivo.

To investigate the ability of SRF388 to block minicircle-derived human IL-27 in vivo, both target engagement by enzyme-linked immunosorbent assay (ELISA) and immunoregulatory receptor expression in splenocytes were studied. Five days after IL-27 transfection and treatment with SRF388 (50 mg/kg), plasma was collected from mice to analyze IL-27 heterodimer and EBI3 levels by Meso Scale Discovery (MSD). The IL-27 heterodimer assay utilizes a p28 capture antibody that cross blocks SRF388 and a human specific EBI3 detection antibody; therefore, if SRF388 is bound to IL-27 then its detection will be masked. The EBI3 assay utilizes both capture and detection antibodies specific for 2 distinct epitopes of human EBI3 and since the minicircle derived IL-27 is a tethered heterodimer this assay allows for detection of total IL 27 irrespective of SRF388 binding.

Briefly, Six-week-old female Balb/c mice were injected with empty vector (control) or human IL-27. Mice were treated with 1 mg of either SRF388 or anti-DNP IgG1 isotype control

antibody 7 days before and on the day of minicircle transfection (Day -7 and 0). Whole blood was collected, and plasma was analyzed for IL-27 (**FIG. 8D**) by Meso Scale Discovery. **FIG. 8D** shows that SRF388 treatment completely inhibits IL-27 detection in plasma by MSD. Similar data were seen when a dose of 25 mg/kg of SRF388 was tested. These data suggest that SRF388 at a dose of 25 mg/kg or higher can completely saturate minicircle derived IL-27 *in vivo*. This complete target engagement was also confirmed in a pSTAT1 functional assay.

To assess the ability of SRF388 to block the activity of IL-27 *in vivo*, the expression of PD L1, Tim-3, Lag-3, and Tigit were analyzed in murine PBMCs and splenocytes by flow cytometry. SRF388 significantly blocked IL 27-induced PD-L1 and Lag 3 expression in CD4+ PBMCs and PD-L1, Tim-3, Lag-3, and Tigit expression in CD8+ PBMCs. SRF388 treatment also blocked IL 27 induced PD-L1, Lag-3, and Tigit expression in CD4+ splenocytes and PD-L1 and Lag 3 expression in CD8+ splenocytes. These data suggest that SRF388 can both engage and block the activity of human IL-27 *in vivo*.

These results demonstrate that ectopic expression of IL-27 *in vivo* leads to upregulation of multiple inhibitory receptors by T cells, and several other molecules with immunomodulatory activity in splenocytes. These data suggest that IL-27 antagonism (e.g., by treatment with an anti-IL-27 antibody) would decrease the expression of inhibitor receptors on T cells, thereby increasing immune responses.

Table 11: Genes Upregulated in Response to Administration of IL-27

Gene Symbol	Fold Change	p value
GM4841	3.824228667	0.012331653
LY6A	3.568709	0.000991642
IIGP1	3.294783	0.000455248
TUBB1	3.145617	0.002782618
MPO	3.112051333	0.026667968
CTSG	2.954178333	0.018177934
PPBP	2.878417333	0.006623845
ELANE	2.845762333	0.024770656
MT2	2.757525667	0.004548988
MUC13	2.696042667	0.018195326

F830016B08RIK	2.603319667	0.011330985
GM4951	2.583066667	0.01529863
APOL11B	2.565688667	0.006885943
GZMB	2.515642667	0.004012308
PRTN3	2.450033	0.028785527
CLCA3A1	2.345778333	0.018175529
GM11505	2.331628667	0.023451392
IL10	2.324278	0.008857442
GBP11	2.307386	0.005204674
PF4	2.270045	0.016210658
IRG1	2.269440667	0.003861367
CES2G	2.252403333	0.033921335
OASL2	2.243393	0.00470682
LAG3	2.203067	0.002539095
HIST1H2AG	2.197938	0.03499933
OAS1G	2.184084667	0.007645573
MFSD2B	2.179382333	0.030664254
RHAG	2.146212667	0.072130267
TIGIT	2.145155	0.005421349
SLC6A4	2.121439	0.009945773
SHCBP1	2.092208667	0.038685767
BC023105	2.079652	0.002582842
PKLR	2.045597333	0.053459171
TFR2	2.037887333	0.033394313
F13A1	2.010803333	0.010612157
HIST1H2AB	2.002687333	0.025241
SERPINA3F	1.991916	0.002220854
ERMAP	1.940590333	0.042680673
MCPT8	1.930212667	0.018921256
SLC26A1	1.926420667	0.025126602

PRKAR2B	1.924056667	0.016881189
BIRC5	1.914826333	0.032959509
FADS2	1.91223	0.013830993
TOP2A	1.88339	0.034852729
NCAPG	1.881082333	0.036612626
A730089K16RIK	1.870258667	0.061491704
MNS1	1.860366	0.014834618
GP9	1.859234333	0.002956835
GFI1B	1.852962	0.0291761
NUF2	1.850953	0.032872517
CHIL3	1.848470667	0.001494932
KIF11	1.83252	0.040535377
ALOX12	1.823174	0.006931665
ADGRG7	1.822065	0.017542834
KLF1	1.820262333	0.060689421
E2F8	1.817455333	0.069143254
ATP1B2	1.811274333	0.024016123
KIF2C	1.811223333	0.061246458
FADS3	1.803859667	0.050197663
MS4A6D	1.801871667	0.01036878
SLC25A21	1.801518667	0.048282826
HIST1H1B	1.800434	0.037242995
CKAP2L	1.783850333	0.061646634
SAMD14	1.782388333	0.02384128
CAR1	1.770098667	0.025511071
DEPDC1A	1.765839667	0.03875749
CENPE	1.765095667	0.039288425
ASPM	1.753558	0.054145246
CCNB2	1.751291667	0.036336189
RYK	1.749673	0.035413093

MMP14	1.747348667	0.010510984
BUB1	1.738322667	0.02139336
MYO1D	1.734508	0.006655486
PARVB	1.733820333	0.010799396
GM5593	1.728317	0.008578526
CCNA2	1.724975667	0.026630845
PRR11	1.724352667	0.04875805
AQP1	1.719081667	0.064562051
CASP3	1.709594333	0.009087444
KIF15	1.708689667	0.026782535
ASNS	1.708074333	0.037928738
CPOX	1.706113	0.030298001
MT1	1.699002667	0.010159345
CDC6	1.694586667	0.049970924
GBP2B	1.694018	0.000929009
GBP2	1.689558667	0.004961011
HMMR	1.687253333	0.063769534
KIF20A	1.686718333	0.020639142
GSTM5	1.681807333	0.04316743
REEP6	1.677204667	0.056071877
GM12250	1.675485	0.003251181
GBP10	1.673458	0.009333312
ATP7B	1.671614	0.029798535
GM22973	1.663495667	0.004472758
CASC5	1.659578	0.044333895
ADD2	1.659553667	0.053938067
CAMP	1.659111667	0.066745225
CLEC5A	1.654882667	0.00665055

Table 12: SEQUENCE LISTING

SEQ ID NO	Description	Sequence
		SRF529-A
51	HCDR1 (IMGT)	GFTFSSYS
52	HCDR2 (IMGT)	ISSSSSYI
53	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
54	HCDR1 (NT)	FTFSSYSMN
55	HCDR2 (NT)	SISSSSSYIYYADSVKG
56	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
57	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGTLVTVSS
58	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCA GTAGCTATAGCATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCA
59	LCDR1 (IMGT)	QSVLFSSNNKNY
60	LCDR2 (IMGT)	WAS
61	LCDR3 (IMGT)	QQHASAPPT
62	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
63	LCDR2 (NT)	WASTRES
64	LCDR3 (NT)	QQHASAPPT
65	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIK
66	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA

67	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQCSVMHEA LHNHYTQKSLSLSPGK
68	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGCTATAGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGT TTCTGTTTCCGCCGAAACCGAAAGATACCCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAAC GACCAAAAACCGAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACCTATAAAACCAACCCCGCCGGTGCTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
69	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK

		SGTASVVCLLNNFYPBREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
70	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTGAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTCATCTTCCCACCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCCTGCTGAACAACCTTCTACCC TCGCGAGGCCAAAGTGCAAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCCAGGAATCCGTACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		SRF529-B
71	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKG LEWVSSISSSSSSYIYYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDLMISRTP VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG
72	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGCTATAGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCCTGGAACCTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCTG CCCTGCCCTGAGTTCTTGGGCGGACCTTCCGTGTTCTGTTCCTG CTCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA

		GTGACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF381-A
73	HCDR1 (IMGT)	GFTFRSYG
74	HCDR2 (IMGT)	ISSSSSYI
75	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
76	HCDR1 (NT)	FTFRSYGMN
77	HCDR2 (NT)	SISSSSSYIYYADSVKG
78	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
79	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSS
80	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCC GGAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAGAAG GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCA
81	LCDR1 (IMGT)	QSVLFSSNNKNY
82	LCDR2 (IMGT)	WAS
83	LCDR3 (IMGT)	QQHASAPPT
84	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
85	LCDR2 (NT)	WASTRES
86	LCDR3 (NT)	QQHASAPPT

87	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIK
88	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTGAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
89	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
90	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCC GGAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACCCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGT TTCTGTTTCCGCCGAAACCGAAAGATACCCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT

		GACCAAAAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACCTATAAAACCACCCCGCCGGTGCTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
91	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFIFFPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
92	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTCATCTTCCCACCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTCGTGTGCCTGCTGAACAACCTTCTACCC TCGCGAGGCCAAAGTGCAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCCAGGAATCCGTCACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		SRF381-B
93	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG
94	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCC GGAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAGAAGC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC

		AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCCTGGAACCTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCTG CCCTGCCCTGAGTTCTTGGGCGGACCTTCCGTGTTCTGTTC CTCCAAAGCCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF382-A
95	HCDR1 (IMGT)	GFTFSRTG
96	HCDR2 (IMGT)	ISSSSSYI
97	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
98	HCDR1 (NT)	FTFSRTGMN
99	HCDR2 (NT)	SISSSSSYIYYADSVKG
100	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
101	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRTGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSS
102	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCA GTAGGACTGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAATGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAGAAG GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCA
103	LCDR1 (IMGT)	QSVLFSSNNKNY

104	LCDR2 (IMGT)	WAS
105	LCDR3 (IMGT)	QQHASAPPT
106	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
107	LCDR2 (NT)	WASTRES
108	LCDR3 (NT)	QQHASAPPT
109	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIK
110	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTGAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
111	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRTGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMSHEA LHNHYTQKSLSLSPGK
112	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCA GTAGGACTGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAATGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACCCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTCTGGGCGGCCCCGAGCGTGT TTCTGTTTCCGCGCAACCGAAAGATACCCTGATGATTAGCCGC

		ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT GACCAAAAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAAC TATAAAACCACCCCGCCGGTGCTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAAC T GACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
113	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFI FPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
114	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATT CAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTCATCTTCCCACCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCCTGCTGAACA ACTTCTACCC TCGCGAGGCCAAAGTG CAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCCAGGAATCCGTCACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		SRF382-B
115	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRTGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGV HTFPAVLQSSGLYSLSSVTV PSSSLGTKTYTCNV DHKPSNTKV DKRVESKYGPPCPSCPAP EFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG

116	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGACTGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAATGGGTCTCATCCATTAGTAGTAGTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAGAAGC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTTGGAACTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAACTCTAAGTACGGCCCTCCCTGCCCTTCCTG CCCTGCCCTGAGTTCTTGGGCGGACCTTCCGTGTTCTCTGTTCC CTCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCCGAGAACAAC TACAAGACCACCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF384-A
117	HCDR1 (IMGT)	GFTFSRYG
118	HCDR2 (IMGT)	ISSSSAYI
119	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
120	HCDR1 (NT)	FTFSRYGMN
121	HCDR2 (NT)	SISSSSAYILYADSVKG
122	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
123	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYGMNWVRQAPGKG LEWVSSISSSSAYILYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSS
124	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG

		CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTGCTTACATACT GTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCA
125	LCDR1 (IMGT)	QSVLFSSNNKNY
126	LCDR2 (IMGT)	WAS
127	LCDR3 (IMGT)	QQHASAPPT
128	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
129	LCDR2 (NT)	WASTRES
130	LCDR3 (NT)	QQHASAPPT
131	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIK
132	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTCAAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
133	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYGMNWVRQAPGKG LEWVSSISSSSAYILYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQCSVMHEA LHNHYTQKSLSLSPGK
134	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTGCTTACATACT GTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACCAGCGGCGG

		CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTGTGGGCGGCCCGAGCGTGT TTCTGTTTCCGCCGAAACCGAAAAGATACCCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT GACCAAAAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACCTATAAAACCACCCCGCCGGTGTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
135	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFI FPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
136	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTGAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTCATCTTCCCACCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCCTGCTGAACAACCTTCTACCC TCGCGAGGCCAAAGTGCAAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCCAGGAATCCGTACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		SRF384-B
137	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYGMNWVRQAPGKG LEWVSSISSSSAYILYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV

		HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDPHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG
138	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCA GTAGGTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTAGTAGTGCTTACATACT GTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCCTGGAACCTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACGTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCTG CCCTGCCCCTGAGTTCCCTGGGCGGACCTTCCGTGTTCCCTGTTCC CTCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF386-A
139	HCDR1 (IMGT)	GFTFASYG
140	HCDR2 (IMGT)	ISSSSSYI
141	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
142	HCDR1 (NT)	FTFASYGMN
143	HCDR2 (NT)	SISSSSSYIYYADSVKG

144	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
145	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFASYGMNWVRQAPGKG LEWVSSISSSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGTLVTVSS
146	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCG CTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTTCTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCA
147	LCDR1 (IMGT)	QSVLFSSNNKNY
148	LCDR2 (IMGT)	WAS
149	LCDR3 (IMGT)	QQHASAPPT
150	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
151	LCDR2 (NT)	WASTRES
152	LCDR3 (NT)	QQHASAPPT
153	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLA WYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTIS SLQAEDVAVYYCQQHASAPPTFGGGTKVEIK
154	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
155	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFASYGMNWVRQAPGKG LEWVSSISSSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEA LHNHYTQKSLSLSPGK
156	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCG CTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG

		CTGGAGTGGGTCTCATCCATTAGTAGTTCTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGT TTCTGTTTCCGCCGAAACCGAAAGATACCCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT GACCAAAAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACATATAAAACCAACCCCGCCGGTGCTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCCGGG CAAA
157	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
158	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTGAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTCATCTTCCCACCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTGCTGTGCCTGCTGAACAACCTTCTACCC TCGCGAGGCCAAAGTGCAAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCCAGGAATCCGTACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGA

		CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		SRF386-B
159	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFASYGMNWVRQAPGKG LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG
160	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCG CTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATCCATTAGTAGTTCTAGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTGGAACCTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACGTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCTG CCCTGCCCCCTGAGTTCCTGGGCGGACCTTCCGTGTTCTGTTC CTCAAAGCCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGACACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAAC TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF388-A

161	HCDR1 (IMGT)	GFTRSYG
162	HCDR2 (IMGT)	ISSSGSYI
163	HCDR3 (IMGT)	ARDGGRTSYTATAHNWFDP
164	HCDR1 (NT)	FTFRSYGMN
165	HCDR2 (NT)	GISSSGSYIYYADSVKG
166	HCDR3 (NT)	ARDGGRTSYTATAHNWFDP
167	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSGISSSGSYIYYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGTLVTVSS
168	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCC GTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCAGGTATTAGTAGTAGTGGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAAGAAC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCA
169	LCDR1 (IMGT)	QSVLFSSNNKNY
170	LCDR2 (IMGT)	WAS
171	LCDR3 (IMGT)	QQHASAPPT
172	LCDR1 (NT)	KSSQSVLFSSNNKNYLA
173	LCDR2 (NT)	WASTRES
174	LCDR3 (NT)	QQHASAPPT
175	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIK
176	DNA VL	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC CCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
177	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSGISSSGSYIYYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV

		DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
178	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCC GTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCAGGTATTAGTAGTAGTGGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAGAAGC GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCG AGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACCAGCGGCGG CACCGCGGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAAC CGGTGACCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCT GAGCAGCGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGA CCTATATTTGCAACGTGAACCATAAACCAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTG CCCGCCGTGCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGT TTCTGTTTCCGCCGAAACCGAAAGATACCCTGATGATTAGCCGC ACCCCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGA TCCGGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGC ATAACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACC TATCGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCT GAACGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGC CGGCGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCG CGCGAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACT GACCAAAAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTT ATCCGAGCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCG GAAAACAACATATAAAACCACCCCGCCGGTGTGGATAGCGATGG CAGCTTTTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCT GGCAGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCG CTGCATAACCATTTATACCCAGAAAAGCCTGAGCCTGAGCCCGGG CAAA
179	Light Chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQHASAPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
180	DNA Light Chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCT GGGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTT TATTCAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAG AAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTAC

		CCGGGAATCCGGGGTCCCTGACCGATTTCAGTGGCAGCGGGTCTG GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTCAGCAGCACGCCAGTGCCCCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCCG CTCCCTCCGTGTTTCATCTTCCCACCCTCCGACGAGCAGCTGAAG TCCGGCACCGCCTCCGTCGTGTGCCTGCTGAACAACCTTCTACCC TCGCGAGGCCAAAGTGCAGTGGAAAGTGGACAACGCCCTGCAGT CCGGCAACTCCCAGGAATCCGTCACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGA CTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGC
		SRF388-B
181	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYGMNWVRQAPGKG LEWVSGISSSGSYIYYADSVKGRFTISRDNANKNSLYLQMNSLRA EDTAVYYCARDGGRTSYTATAHNWFDPWGQGLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPSCPAPFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG
182	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCC GTAGCTATGGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTCTCAGGTATTAGTAGTAGTGGTAGTTACATATA CTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGGTGGAGAAG GTCCTACACCGCCACAGCCCACAATTGGTTCGACCCCCTGGGGAC AGGGTACATTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCC TCCGTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTC TACCGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGC CCGTGACCGTGTCTGGAACCTCTGGCGCCCTGACCTCCGGCGTG CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCT GTCCAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGA CCTACACCTGTAACTGGACCACAAGCCCTCCAACACCAAAGTG GACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCTG CCCTGCCCTGAGTTCCTGGGCGGACCTTCCGTGTTCTCTGTTCC CTCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAA GTGACCTGCGTGGTGGTGGACGTGTCCAGGAAGATCCCGAAGT CCAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA AGAGTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCC

		CAAGTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAA TCAAGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCG ATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCCGAGAACAAC TACAAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTGTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAG GCAACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAAGTCCCTGTCCCTGTCTCTGGGC
		SRF410-A
185	HCDR1 (IMGT)	GGTFSAYA
186	HCDR2 (IMGT)	I I P I F G T A
187	HCDR3 (IMGT)	ARSYSSRWYHYMDV
188	HCDR1 (NT)	GTFSAYAIS
189	HCDR2 (NT)	G I I P I F G T A N Y A Q K F Q G
190	HCDR3 (NT)	ARSYSSRWYHYMDV
191	VH	QVQLVQSGAEVKKPGSSVKVSKASGGTFSAYAISWVRQAPGQG LEWMGGI I P I F G T A N Y A Q K F Q G R V T I T A D E S T S T A Y M E L S S L R S E D T A V Y Y C A R S Y S S R W Y H Y Y M D V W G K G T T V T V S S
192	DNA VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCA GCGCTTATGCGATCAGCTGGGTGCGACAGGCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAA CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCA
193	LCDR1 (IMGT)	QGISSW
194	LCDR2 (IMGT)	AAS
195	LCDR3 (IMGT)	QQADDLPLT
196	LCDR1 (NT)	RASQGISSWLA
197	LCDR2 (NT)	AASNLQS
198	LCDR3 (NT)	QQADDLPLT
199	VL	DIQMTQSPSSVSASVGDRVITICRASQGISSWLAWYQQKPGKAP KLLIYAASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQADDLPLTFGGGTKVEIK
200	DNA VL	GACATCCAGATGACACAGTCTCCATCTTCCGTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTA GCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCC ATCAAGGTTCAAGCGCAGTGGATCTGGGACAGATTTCACTCTCA

		CCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGT CAGCAGGCAGACGACCTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAA
201	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSAYAI SWVRQAPGQG LEWMGGI IPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARSYYSSRWHYYYYMDVWGKGTTVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCTVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALH NHYTQKSLSLSPGK
202	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCA GCGCTTATGCGATCAGCTGGGTGCGACAGGCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAA CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCGAGCGTG TTTCCGCTGGCGCCGAGCAGCAAAAGCACCCAGCGGCGGCACCGC GGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAACCGGTGA CCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTGCATACC TTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCTGAGCAG CGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGACCTATA TTTGCAACGTGAACCATAAACCAGCAACACCAAAGTGGATAAA AAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTGCCCGCC GTGCCCGGCGCCGGAAGTGTGGGCGGCCCGAGCGTGTTTCTGT TTCCGCGCGAAACCGAAAGATACCCTGATGATTAGCCGCACCCCG GAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGATCCGGA AGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGCATAACG CGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACCTATCGC GTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCTGAACGG CAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGCCGGCGC CGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCGCGCGAA CCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACTGACCAA AAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTTATCCGA GCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCGGAAAAC AACTATAAAACCACCCCGCCGGTGCTGGATAGCGATGGCAGCTT TTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCTGGCAGC AGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCGCTGCAT AACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGGCAAA
203	Light Chain	DIQMTQSPSSVSASVGDRVITICRASQGISSWLAWYQQKPGKAP KLLIYAASNLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYC

		QQADDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
204	DNA Light Chain	GACATCCAGATGACACAGTCTCCATCTTCCGTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTA GCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCC ATCAAGGTTGAGCGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGT CAGCAGGCAGACGACCTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTTCATCT TCCCACCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCCGTC GTGTGCCTGCTGAACAACCTTCTACCCTCGCGAGGCCAAAGTGCA GTGGAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAAT CCGTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGT GTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGTCCTTCAACCGGGGCGAGTGC
		SRF410-B
205	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSKASGGTFSAYAISWVRQAPGQG LEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARSYYSSRWYHYMDVWGKGTITVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQKTYTCNVDPKPSNTKVDK RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHY TQKSLSLSLG
206	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCA GCGCTTATGCGATCAGCTGGGTGCGACAGGCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAA CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCCTCCGTG TTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTCTACCGC CGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCCGTGA CCGTGTCCTGGAACCTCTGGCGCCCTGACCTCCGGCGTGCACACC TTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCAG CGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGACCTACA CCTGTAACGTGGACCACAAGCCCTCCAACACCAAAGTGGACAAG CGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCCTGCCCTGC CCCTGAGTTCCTGGGCGGACCTTCCGTGTTCCCTGTTCCCTCCAA

		AGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAAGTGACC TGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGTCCAGTT CAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCA AGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTA CAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCCCAAGTG TACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAATCAAGT GTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCGATATCG CCGTGGAGTGGGAGTCCAACGGCCAGCCCCGAGAACAACACTACAAG ACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTGTA CTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAGGCAACG TCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTAC ACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF411-A
207	HCDR1 (IMGT)	GGTFESYT
208	HCDR2 (IMGT)	IAPIFGTA
209	HCDR3 (IMGT)	ARSYYSSRWHYYYYMDV
210	HCDR1 (NT)	GTFESYTIS
211	HCDR2 (NT)	GIAPIFGTAHYAQKFQG
212	HCDR3 (NT)	ARSYYSSRWHYYYYMDV
213	VH	QVQLVQSGAEVKKPGSSVKVSKASGGTFESYTISWVRQAPGQG LEWMGGIAPIFGTAHYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARSYYSSRWHYYYYMDVWGKGTTVTVSS
214	DNA VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCG AGAGCTATACGATCAGCTGGGTGCGACAGGCCCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCGCGCCTATCTTTGGTACAGCACA TTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCA
215	LCDR1 (IMGT)	QGISSW
216	LCDR2 (IMGT)	AAS
217	LCDR3 (IMGT)	QQADDLPLT
218	LCDR1 (NT)	RASQGISSWLA
219	LCDR2 (NT)	AASNLQS
220	LCDR3 (NT)	QQADDLPLT

221	VL	DIQMTQSPSSVSASVGDRVITITCRASQGISSWLAWYQQKPGKAP KLLIYAASNLSQGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQADDLPLTFGGGTKVEIK
222	DNA VL	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTA GCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCC ATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGT CAGCAGGCAGACGACCTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAA
223	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSKASGGTFESYTI SWVRQAPGQG LEWMGGIAPIFGTAHYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARSYYSSRWYHYMDVWGKGTTVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCTVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK
224	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCG AGAGCTATACGATCAGCTGGGTGCGACAGGCCCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCGCGCCTATCTTTGGTACAGCACA TTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCGAGCGTG TTTCCGCTGGCGCCGAGCAGCAAAAGCACCCAGCGGCGGCACCGC GGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAACCGGTGA CCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTGCATACC TTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCTGAGCAG CGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGACCTATA TTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAA AAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTGCCCGCC GTGCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGTTTCTGT TTCCGCGCGAAACCGAAAGATAACCTGATGATTAGCCGCACCCCG GAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGATCCGGA AGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGCATAACG CGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACCTATCGC GTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCTGAACGG CAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGCCGGCGC CGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCGCGCGAA CCGCAGGTGTATACCCTGCCGCGGAGCCGCGATGAACTGACCAA

		AAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTTATCCGA GCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCGGAAAAC AACTATAAAACCACCCCGCCGGTGCTGGATAGCGATGGCAGCTT TTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCTGGCAGC AGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCGCTGCAT AACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGGCAAA
225	Light Chain	DIQMTQSPSSVSASVGRVTITCRASQGISSWLAWYQQKPGKAP KLLIYAASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQADDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
226	DNA Light Chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTA GCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCC ATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGT CAGCAGGCAGACGACCTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTTCATCT TCCCACCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCCGTC GTGTGCCTGCTGAACAACCTTCTACCCTCGCGAGGCCAAAGTGCA GTGGAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAAT CCGTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGT GTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGTCCTTCAACCGGGGCGAGTGC
		SRF411-B
227	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSKASGGTFESYTIWVRQAPGQG LEWMGGIAPIFGTAHYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARSYYSSRWYHYMDVWGKGTITVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQKTYTCNVDPKPSNTKVDK RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHY TQKSLSLSLG
228	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCG AGAGCTATACGATCAGCTGGGTGCGACAGGCCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCGCGCCTATCTTTGGTACAGCACA TTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCCTCCGTG

		TTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTCTACCGC CGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCCGTGA CCGTGTCCTGGAACCTCTGGCGCCCTGACCTCCGGCGTGCACACC TTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCAG CGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGACCTACA CCTGTAACGTGGACCACAAGCCCTCCAACACCAAAGTGGACAAG CGGGTGGAAATCTAAGTACGGCCCTCCCTGCCCTTCCTGCCCTGC CCCTGAGTTCCTGGGCGGACCTTCCGTGTTCTGTTCCTCCAA AGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAAGTGACC TGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGTCCAGTT CAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCA AGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTA CAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCCCAAGTG TACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAATCAAGT GTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCGATATCG CCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAACACTACAAG ACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTGTA CTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAGGCAACG TCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTAC ACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF543-A
229	HCDR1 (IMGT)	GGSFSDYE
230	HCDR2 (IMGT)	IDWSGIT
231	HCDR3 (IMGT)	ARLPMYYYDSSVSTGSVDV
232	HCDR1 (NT)	GSFSDYEWS
233	HCDR2 (NT)	EIDWSGITNYNPSLKS
234	HCDR3 (NT)	ARLPMYYYDSSVSTGSVDV
235	VH	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYEWSWIRQPPGKG LEWIGEIDWSGITNYNPSLKS RVTISVDTSKNQFSLKLSSVTAA DTAVYYCARLPMYYYDSSVSTGSVDVWGQGTMTVTVSS
236	DNA VH	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTGATTATGAGTGGAGTTGGATTCGTCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACTGGTCAGGCATTACTAACTA CAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGACTTCCTATGTACTACTA CGACAGCAGCGTCTCAACCGGAAGCGTAGACGTATGGGGTCAGG GTACAATGGTCACCGTCTCCTCA
237	LCDR1 (IMGT)	QSVSSY

238	LCDR2 (IMGT)	DSS
239	LCDR3 (IMGT)	QQDSDHPIT
240	LCDR1 (NT)	RASQSVSSYLA
241	LCDR2 (NT)	DSSNRAT
242	LCDR3 (NT)	QQDSDHPIT
243	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRL LLIYDSSNRATGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYCQQDSDHPITFGGGTKVEIK
244	DNA VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCC AGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTA GCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATTCATCCAACAGGGCCACTGGCATCCC AGCCAGGTTCAAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCA CCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGT CAGCAGGACAGTGACCACCCTATCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAA
245	Heavy Chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYEW SWIRQPPGKGLEWIGEIDWSGITNYP SLKSRVTISVDTSKNQFSLKLSSVTAA DTAVYYCARLPMYYDSSVSTGSVDVWGQGT MVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVH TTPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKHTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPSSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSQSVSMHEALHNHYTQKS LSLSPGK
246	DNA Heavy Chain	CAAGTACAATTACAACAGTGGGGAGCTGGTTTAT TAAAGCCTTCAGAACTTTAAGTTTGACCTGTG CTGTTTACGGTGGATCATTTTCTGATTATGAG TGGAGTTGGATTCGTCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACTGGTCAGGC ATTACTAATACTCAATCCAAGTTTAAAATCCAG GGTTACTATCTCCGTAGACACGTCCAAGAACC AGTTCTCCCTGAAGCTGAGTTCTGTGACCGCC GCA GACACGGCGGTGTACTACTGCGCCAGACT TCCTATGTACTACTACGACAGCAGCGTCTCAAC CGGAAGCGTAGACGTATGGGGTCAGGTACAAT GGTCACCGTCTCCTCAGCGAGCACCAAAGGCC CCGAGC GTGTTTCCGCTGGCGCCGAGCAGCAA AAGCACCGCGGCACCGCGGCTGGGCTGCCTGG TGAAAGATTATTTTCCGGAACCGGTGACCGGT GAGCTGGAACAGCGGCGCGCTGACCAGCGGCG TGCATACCTTTCCGGCGGTGCTGCAGAGCAGC GGCCTGTATAGCCTGAGCAGCGTGGTGACCGT GCCGAGCAGCCTGGGCACCCAGACCTATATTT GCAACGTGAACCATAAACCGAGCAACACCAA AGTGGATAAAAAGTGGAACCGAAAAGCTGCG ATAAAACCCATACCTGCCCCCGCGTGGCCG GCGGAACTGCTGGGCGGCCCGAGCGTGTTTC TGTTTCCGCCGAAACCGAAAGATACCCTGAT GATTAGCCGCACC

		CCGGAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGATCC GGAAGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGCATA ACGCGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACCTAT CGCGTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCTGAA CGGCAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGCCGG CGCCGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCGCGC GAACCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACTGAC CAAAAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTTATC CGAGCGATATTGCGGTGGAATGGGAAAGCAACGGGCCAGCCGGAA AACAACTATAAAACCACCCCGCCGGTGCTGGATAGCGATGGCAG CTTTTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCTGGC AGCAGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCGCTG CATAACCATTTATACCCAGAAAAGCCTGAGCCTGAGCCCGGGCAA A
247	Light Chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAP RLLIYDSSNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQDS DHPITFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
248	DNA Light Chain	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCC AGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTA GCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATTCATCCAACAGGGCCACTGGCATCCC AGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCA CCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGT CAGCAGGACAGTGACCACCCTATCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTTCATCT TCCCACCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCCGTC GTGTGCCTGCTGAACAACCTTCTACCCTCGCGAGGCCAAAGTGCA GTGGAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAAT CCGTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGT GTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGTCCTTCAACCGGGGCGAGTGC
		SRF543-B
249	Heavy Chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYEW SWIRQPPGKG LEWIGEIDWSGITNYNPSLKS RVTISVDTSKNQFSLKLSSVTAA DTAVYYCARLPMYYDSSSVSTGSVDVWGQGTMTVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVD KRVESKYGPPCPSCPAP EFLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQ VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH YTQKSLSLSLG

250	DNA Heavy Chain	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTGATTATGAGTGGAGTTGGATTTCGTCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACTGGTCAGGCATTACTAACTA CAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGACTTCCTATGTACTACTA CGACAGCAGCGTCTCAACCGGAAGCGTAGACGTATGGGGTCAGG GTACAATGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCCCTCC GTGTTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTCTAC CGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCCG TGACCGTGTCTGGAAGTCTGGCGCCCTGACCTCCGGCGTGCAC ACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTC CAGCGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGACCT ACACCTGTAAAGTGGACCACAAGCCCTCCAACACCAAAGTGGAC AAGCGGGTGGAAATCTAAGTACGGCCCTCCCTGCCCTTCCTGCCC TGCCCCCTGAGTTCCTGGGCGGACCTTCCGTGTTCTCTGTTCCCTC CAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAAGTG ACCTGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGTCCA GTTCAATTGGTACGTGGACGGCGTGGAAAGTGCAACAACGCCAAGA CCAAGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTGGTG TCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGA GTACAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCATCG AAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCCCAA GTGTACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAATCA AGTGTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCGATA TCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAACACTAC AAGACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCT GTACTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAGGCA ACGTCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCAC TACACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF414-A
251	HCDR1 (IMGT)	GSFSRYY
252	HCDR2 (IMGT)	IDYSGST
253	HCDR3 (IMGT)	ARDGVYYDSSDLGFDI
254	HCDR1 (NT)	GSFSRYYWS
255	HCDR2 (NT)	SIDYSGSTEYNPSLKS
256	HCDR3 (NT)	ARDGVYYDSSDLGFDI
257	VH	QVQLQQWGAGLLKPSETLSLTCAVYGGSFYSRYYSWIRQPPGKG LEWIGSIDYSGSTEYNPSLKSRTVISVDTSKNQFSLKLSSVTAA DTAVYYCARDGVYYDSSDLGFDIWGQGTMVTVSS
258	DNA VH	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTCGTTATTACTGGAGTTGGATTTCGTCAACCACCAGGCAAAGGA

		TTGGAGTGGATCGGTAGTATAGACTATTCAGGCTCCACTGAGTACAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGAGATGGTGTGTACTACGACAGCAGCGACTTGGGATTCGACATATGGGGTCAGGGTACAATGGTCACCGTCTCCTCA
259	LCDR1 (IMGT)	QDISNY
260	LCDR2 (IMGT)	DAS
261	LCDR3 (IMGT)	QQYDDLPIIT
262	LCDR1 (NT)	QASQDISNYLN
263	LCDR2 (NT)	DASNLET
264	LCDR3 (NT)	QQYDDLPIIT
265	VL	DIQMTQSPSSLSASVGRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQYDDLPIITFGGGTKVEIK
266	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTA GCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGAAACAGGGGTCCC ATCAAGGTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCA CCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGT CAGCAGTACGACGACCTCCCTATCACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA
267	Heavy Chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSTRYYWSWIRQPPGKGLEWIGSIDYSGSTEYNPSLKSRTVISVDTSKNQFSLKLSSVTAA DTAVYYCARDGVYYDSSDLGFDIWGQGTMVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVKDKV EPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMSHEALHNHYTQKSLSLSPGK
268	DNA Heavy Chain	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTCAGAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTTCTCGTTATTACTGGAGTTGGATTCGTCAACCACCAGGCAAAGGAT TTGGAGTGGATCGGTAGTATAGACTATTCAGGCTCCACTGAGTACAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGAGATGGTGTGTACTACGACAGCAGCGACTTGGGATTCGACATATGGGGTCAGGGTACAATGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCGAGCGTGTTTCCGCTGGCGCCGAGCAGCAAAAGCACACGCGGCGGACCGCGGCGCT

		GGGCTGCCTGGTGAAAGATTATTTTCCGGAACCGGTGACCGTGA GCTGGAACAGCGGCGCGCTGACCAGCGGCGTGCATACCTTTCCG GCGGTGCTGCAGAGCAGCGGCCTGTATAGCCTGAGCAGCGTGGT GACCGTGCCGAGCAGCAGCCTGGGCACCCAGACCTATATTTGCA ACGTGAACCATAAACCAGAGCAACACCAAAGTGGATAAAAAAGTG GAACCGAAAAGCTGCGATAAAACCCATACCTGCCCCGCCGTGCCC GGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGTTTCTGTTTCCGC CGAAACCGAAAGATACCCTGATGATTAGCCGCACCCCGGAAGTG ACCTGCGTGGTGGTGGATGTGAGCCATGAAGATCCGGAAGTGAA ATTTAACTGGTATGTGGATGGCGTGGAAGTGCATAACGCGAAAA CCAAACCGCGCGAAGAACAGTATAACAGCACCTATCGCGTGGTG AGCGTGCTGACCGTGCTGCATCAGGATTGGCTGAACGGCAAAGA ATATAAATGCAAAGTGAGCAACAAAGCGCTGCCGGCGCCGATTG AAAAAACCATTAGCAAAGCGAAAGGCCAGCCGCGCGAACCGCAG GTGTATACCCTGCCGCCGAGCCGCGATGAACTGACCAAAAACCA GGTGAGCCTGACCTGCCTGGTGAAAGGCTTTTATCCGAGCGATA TTGCGGTGGAATGGGAAAGCAACGGCCAGCCGGAAAACAACCTAT AAAACCACCCCGCCGGTGCTGGATAGCGATGGCAGCTTTTTTCT GTATAGCAAACCTGACCGTGATAAAAGCCGCTGGCAGCAGGGCA ACGTGTTTAGCTGCAGCGTGATGCATGAAGCGCTGCATAACCAT TATACCCAGAAAAGCCTGAGCCTGAGCCCGGGCAA
269	Light Chain	DIQMTQSPSSLSASVGDRVITTCQASQDISNYLNWYQQKPGKAP KLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQYDDLPIITFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
270	DNA Light Chain	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTA GCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTACGATGCATCCAATTTGGAAACAGGGGTCCC ATCAAGGTTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCA CCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGT CAGCAGTACGACGACCTCCCTATCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTTCATCT TCCCACCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCCGTC GTGTGCCTGCTGAACAACCTTCTACCCTCGCGAGGCCAAAGTGCA GTGGAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAAT CCGTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGT GTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGTCCTTCAACCGGGGCGAGTGC
		SRF414-B
271	Heavy Chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSTRYYWSWIRQPPGKG LEWIGSIDYSGSTEYNPSLKSRTVISVDTSKNQFSLKLSSVTAA DTAVYYCARDGVYYDSSDLGFDIWGQGTMTVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV

		ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSEFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLG
272	DNA Heavy Chain	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTCGTTATTACTGGAGTTGGATTCTGTCACACCACAGGCAAAGGA TTGGAGTGGATCGGTAGTATAGACTATTCAGGCTCCACTGAGTA CAATCCAAGTTTAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGAGATGGTGTGTACTACGA CAGCAGCGACTTGGGATTCGACATATGGGGTCAGGGTACAATGG TCACCGTCTCCTCAGCTTCCACCAAGGGCCCCCTCCGTGTTCCCT CTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTCTACCGCCGCTCT GGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGT CCTGGAACCTCTGGCGCCCTGACCTCCGGCGTGCACACCTTCCCT GCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCAGCGTCGT GACCGTGCCCTCCTCCAGCCTGGGCACCAAGACCTACACCTGTA ACGTGGACCACAAGCCCTCCAACACCAAAGTGGACAAGCGGGTG GAATCTAAGTACGGCCCTCCCTGCCCTTCCTGCCCTGCCCTGA GTTCCCTGGGCGGACCTTCCGTGTTCCCTGTTCCCTCCAAAGCCCA AGGACACCCTGATGATCTCCCGGACCCCTGAAGTGACCTGCGTG GTGGTGGACGTGTCCCAGGAAGATCCCGAAGTCCAGTTCAATTG GTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCCA GAGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTG CAAAGTGTCCAACAAGGGCCTGCCCTCCAGCATCGAAAAGACCA TCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCCCAAGTGTACACC CTGCCTCCCAGCCAGGAAGAGATGACCAAGAATCAAGTGTCCCT GACTTGTCTGGTCAAGGGCTTCTACCCCTCCGATATCGCCGTGG AGTGGGAGTCCAACGGCCAGCCCGAGAACAACACTACAAGACCACC CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCTCG GCTGACCGTGGACAAGTCCCGGTGGCAGGAAGGCAACGTCTTCT CCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG AAGTCCCTGTCCCTGTCTCTGGGC
		SRF557-A
273	HCDR1 (IMGT)	GGTFSSYA
274	HCDR2 (IMGT)	I I P I F G T A
275	HCDR3 (IMGT)	ARLGGRGYADEGWYFDL
276	HCDR1 (NT)	GTFSSYAIS
277	HCDR2 (NT)	GI I P I F G T A N Y A Q K F Q G
278	HCDR3 (NT)	ARLGGRGYADEGWYFDL

279	VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAI SWVRQAPGQG LEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARLGGRGYADEGWYFDLWGRGTLVTVSS
280	DNA VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCA GCAGCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAA CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATTGGGCGGACGGGG ATACGCCGACGAGGGCTGGTACTTCGACCTATGGGGGAGAGGTA CCTTGGTCACCGTCTCCTCA
281	LCDR1 (IMGT)	QSVSSSY
282	LCDR2 (IMGT)	GAS
283	LCDR3 (IMGT)	QQYYGSPIT
284	LCDR1 (NT)	RASQSVSSSYLA
285	LCDR2 (NT)	GASSRAT
286	LCDR3 (NT)	QQYYGSPIT
287	VL	EIVLTQSPGTL LSLSPGERATLSCRASQSVSSSYLA WYQQKPGQA PRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYY CQQYYGSPITFGGGTKVEIK
288	DNA VL	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCC AGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTA GCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCT CCCAGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCAT CCCAGACAGGTT CAGTGGCAGTGGGTCTGGGACAGACTTCACTC TCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTAC TGTCAGCAGTACTACGGCAGTCCTATCACTTTTGGCGGAGGGAC CAAGGTTGAGATCAAA
289	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAI SWVRQAPGQG LEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARLGGRGYADEGWYFDLWGRGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCTVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK
290	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCA GCAGCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAA

		CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATTGGGCGGACGGGG ATACGCCGACGAGGGCTGGTACTTCGACCTATGGGGGAGAGGTA CCTTGGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCCGAGCGTG TTTCCGCTGGCGCCGAGCAGCAAAAGCACCCAGCGGCGGCACCGC GGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAACCGGTGA CCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTGATACC TTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCTGAGCAG CGTGGTGACCGTGCCGAGCAGCAGCCTGGGACCCAGACCTATA TTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAA AAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTGCCCCGCC GTGCCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGTCTCTGT TTCCGCCGAAACCGAAAGATAACCCTGATGATTAGCCGCACCCCG GAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGATCCGGA AGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGCATAACG CGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACCTATCGC GTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCTGAACGG CAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGCCGGCGC CGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCGCGCGAA CCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACTGACCAA AAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTTATCCGA GCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCGGAAC AACTATAAAACCACCCCGCCGGTGCTGGATAGCGATGGCAGCTT TTTTCTGTATAGCAAACCTGACCGTGGATAAAAGCCGCTGGCAGC AGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCGCTGCAT AACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCCGGGCAAA
291	Light Chain	EIVLTQSPGTLSSLSPGERATLSCRASQSVSSSYLAWYQQKPGQA PRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYY CQQYYGSPITFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
292	DNA Light Chain	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCC AGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTA GCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCT CCCAGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCAT CCCAGACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTC TCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAAGTGTATTAC TGTCAGCAGTACTACGGCAGTCCTATCACTTTTGGCGGAGGGAC CAAGGTTGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTCA TCTTCCCACCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCC GTCGTGTGCCTGCTGAACAACCTTCTACCCTCGCGAGGCCAAAGT GCAGTGGAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGG AATCCGTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTG TCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAA AGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCG TGACCAAGTCCTTCAACCGGGGCGAGTGC

		SRF557-B
293	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAI SWVRQAPGQG LEWMGGI IPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARLGGRGYADEGWYFDLWGRGTLVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNV DHKPSNTKVDK RVESKYGPPCPSCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHY TQKSLSLSLG
294	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCA GCAGCTATGCTATCAGCTGGGTGCGACAGGCCCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAA CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATTGGGCGGACGGGG ATACGCCGACGAGGGCTGGTACTTCGACCTATGGGGGAGAGGTA CCTTGGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCCCTCCGTG TTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTCTACCGC CGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCCGTGA CCGTGTCCTGGA ACTCTGGCGCCCTGACCTCCGGCGTGCACACC TTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCAG CGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGACCTACA CCTGTAACGTGGACCACAAGCCCTCCAACACCAAAGTGGACAAG CGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCCTGCCCTGC CCCTGAGTTCCTGGGCGGACCTTCCGTGTTCCCTGTTCCCTCCAA AGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAAGTGACC TGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGTCCAGTT CAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCA AGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTA CAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCCCAAGTG TACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAATCAAGT GTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCGATATCG CCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACA ACTACAAG ACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTGTA CTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAGGCAACG TCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTAC ACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF536-A
295	HCDR1 (IMGT)	GGSFSEYY

296	HCDR2 (IMGT)	IDEVGST
297	HCDR3 (IMGT)	ARLPMYYYDSSDLPMDV
298	HCDR1 (NT)	GSFSEYYWA
299	HCDR2 (NT)	EIDEVGSTNYNPSLKS
300	HCDR3 (NT)	ARLPMYYYDSSDLPMDV
301	VH	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSEYYWAWIRQPPGKG LEWIGEIDEVGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAA DTAVYYCARLPMYYYDSSDLPMDVWGQGTTVTVSS
302	DNA VH	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTGAGTATTACTGGGCTTGGATTCGTCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACGAGGTTGGCTCCACTAACTA CAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGACTTCCTATGTACTACTA CGACAGCAGCGACTTGCCAATGGACGTATGGGGCCAGGGAACAA CTGTCACCGTCTCCTCA
303	LCDR1 (IMGT)	QDISNY
304	LCDR2 (IMGT)	DAS
305	LCDR3 (IMGT)	QQYDTLPLT
306	LCDR1 (NT)	QASQDISNYLN
307	LCDR2 (NT)	DASNLAT
308	LCDR3 (NT)	QQYDTLPLT
309	VL	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAP KLLIYDASNLATGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQYDTLPLTFGGGTKVEIK
310	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTA GCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTACGATGCATCCAATTTGGCAACAGGGGTCCC ATCAAGGTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCA CCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGT CAGCAGTACGATACCCTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAA
311	Heavy Chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSEYYWAWIRQPPGKG LEWIGEIDEVGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAA DTAVYYCARLPMYYYDSSDLPMDVWGQGTTVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV

		VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQCSVMHEALHN HYTQKSLSLSPGK
312	DNA Heavy Chain	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTGAGTATTACTGGGCTTGGATTCTGCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACGAGGTTGGCTCCACTAACTA CAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGACTTCCTATGTACTACTA CGACAGCAGCGACTTGCCAATGGACGTATGGGGCCAGGGAACAA CTGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCGAGCGTGTTT CCGCTGGCGCCGAGCAGCAAAAGCACCCAGCGGCGGCACCGCGGC GCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAACCGGTGACCG TGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTGCATACCTTT CCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCTGAGCAGCGT GGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGACCTATATTT GCAACGTGAACCATAAACCAGAGCAACACCAAAGTGGATAAAAAA GTGGAACCGAAAAGCTGCGATAAAACCCATACCTGCCCCGCCGTG CCCCGGCGCCGGAACCTGCTGGGCGGCCCGAGCGTGTTTCTGTTC CGCCGAAACCGAAAGATACCCTGATGATTAGCCGCACCCCGGAA GTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGATCCGGAAGT GAAATTTAACTGGTATGTGGATGGCGTGGAAGTGCATAACGCGA AAACCAAACCGCGCGAAGAACAGTATAACAGCACCTATCGCGTG GTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCTGAACGGCAA AGAATATAAATGCAAAGTGAGCAACAAAGCGCTGCCGGCGCCGA TTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCGCGCGAACCG CAGGTGTATACCCTGCCGCCGAGCCGCGATGAACTGACCAAAAA CCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTTATCCGAGCG ATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCGGAAAACAAC TATAAAACCACCCCGCCGGTGCTGGATAGCGATGGCAGCTTTTT TCTGTATAGCAAACCTGACCGTGATAAAAGCCGCTGGCAGCAGG GCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCGCTGCATAAC CATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGGCAAA
313	Light Chain	DIQMTQSPSSLSASVGRVTITCQASQDISNYLNWYQQKPGKAP KLLIYDASNLATGVPSRFSGSGSGTDFTFTISSQLQPEDIATYYC QQYDTLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
314	DNA Light Chain	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGACATTA GCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTACGATGCATCCAATTTGGCAACAGGGGTCCC ATCAAGGTTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCA CCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTACTGT CAGCAGTACGATACCCTCCCTCTCACTTTTGGCGGAGGGACCAA

		GGTTGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTTCATCT TCCCACCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCCGTC GTGTGCCTGCTGAACAACCTTCTACCCTCGCGAGGCCAAAGTGCA GTGGAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAAT CCGTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGT GTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGTCCTTCAACCGGGGCGAGTGC
		SRF536-B
315	Heavy Chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSEYYWAWIRQPPGKG LEWIGEIDEVGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTAA DTAVYYCARLPMYYDSSDLPMDVWGQGTTVTVSSASTKGPSVF PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDPKPSNTKVKDKR VESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLG
316	DNA Heavy Chain	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTGAGTATTACTGGGCTTGGATTCGTCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACGAGGTTGGCTCCACTAACTA CAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGACTTCCTATGTACTACTA CGACAGCAGCGACTTGCCAATGGACGTATGGGGCCAGGGAACAA CTGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCCCTCCGTGTTC CCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTCTACCGCCGC TCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCCGTGACCG TGTCCTGGAACCTCTGGCGCCCTGACCTCCGGCGTGCACACCTTC CCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCAGCGT CGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGACCTACACCT GTAACGTGGACCACAAGCCCTCCAACACCAAAGTGGACAAGCGG GTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCTGCCCTGCCCC TGAGTTCCTGGGCGGACCTTCCGTGTTTCCCTGTTCCCTCCAAAGC CCAAGGACACCCTGATGATCTCCCGGACCCCTGAAGTGACCTGC GTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGTCCAGTTCAA TTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGC CCAGAGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCCGTG CTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTACAA GTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCATCGAAAAGA CCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCCCAAGTGAC ACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAATCAAGTGTC CCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCGATATCGCCG TGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAACTACAAGACC

		ACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTC TCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAGGCAACGTCT TCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACC CAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF416-A
317	HCDR1 (IMGT)	GGSFSGYY
318	HCDR2 (IMGT)	IDVDGST
319	HCDR3 (IMGT)	ARDGYYYDTSPYDV
320	HCDR1 (NT)	GSFSGYYWS
321	HCDR2 (NT)	EIDVDGSTNYNPSLKS
322	HCDR3 (NT)	ARDGYYYDTSPYDV
323	VH	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKG LEWIGEIDVDGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAA DTAVYYCARDGYYYDTSPYDVWGQGTMTVSS
324	DNA VH	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTGGTTATTACTGGAGTTGGATTCGTCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACGTGGATGGCTCCACTAACTA CAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGAGACGGATACTACTACGA CACCAGTCCATACGACGTATGGGGTCAGGGTACAATGGTCACCG TCTCCTCA
325	LCDR1 (IMGT)	QSVSSY
326	LCDR2 (IMGT)	DAS
327	LCDR3 (IMGT)	QQRDSFPLT
328	LCDR1 (NT)	RASQSVSSYLA
329	LCDR2 (NT)	DASNRAT
330	LCDR3 (NT)	QQRDSFPLT
331	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAQYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQRDSFPLTFGGGTKVEIK
332	DNA VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCC AGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTA GCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCC AGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCA CCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGT CAGCAGAGAGACTCCTTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAA

333	Heavy Chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKG LEWIGEIDVDGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAA DTAVYYCARDGYYYDTSPYDVWGQGTMTVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVSMHEALHNHYT QKSLSLSPGK
334	DNA Heavy Chain	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTGGTTATTACTGGAGTTGGATTCGTCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACGTGGATGGCTCCACTAACTA CAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGAGACGGATACTACTACGA CACCAGTCCATACGACGTATGGGGTCAGGGTACAATGGTCACCG TCTCCTCAGCGAGCACCAAAGGCCCGAGCGTGTTTCCGCTGGCG CCGAGCAGCAAAGCACCAGCGGCGGCACCGCGGCGCTGGGCTG CCTGGTGAAAGATTATTTTCCGGAACCGGTGACCGTGAGCTGGA ACAGCGGCGCGCTGACCAGCGGCGGTGCATACCTTTCCGGCGGTG CTGCAGAGCAGCGGCCTGTATAGCCTGAGCAGCGTGGTGACCGT GCCGAGCAGCAGCCTGGGCACCCAGACCTATATTTGCAACGTGA ACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCG AAAAGCTGCGATAAAACCCATACCTGCCCCGCCGTGCCCGGCCG GGAAGTCTGGGCGGCCCGAGCGTGTTTCTGTTTCCGCCGAAAC CGAAAGATACCCTGATGATTAGCCGCACCCCGGAAGTGACCTGC GTGGTGGTGGATGTGAGCCATGAAGATCCGGAAGTGAAATTTAA CTGGTATGTGGATGGCGTGGAAGTGCATAACGCGAAAACCAAAC CGCGCGAAGAACAGTATAACAGCACCTATCGCGTGGTGAGCGTG CTGACCGTGCTGCATCAGGATTGGCTGAACGGCAAAGAATATAA ATGCAAAGTGAGCAACAAAGCGCTGCCGGCGCCGATTGAAAAAA CCATTAGCAAAGCGAAAGGCCAGCCGCGCGAACCAGGTGTAT ACCCTGCCGCCGAGCCGCGATGAACTGACCAAAAACAGGTGAG CCTGACCTGCCTGGTGAAAGGCTTTTATCCGAGCGATATTGCGG TGGAATGGGAAAGCAACGGCCAGCCGGAACAACTATAAAACC ACCCCGCCGGTGCTGGATAGCGATGGCAGCTTTTTTCTGTATAG CAAAGTACCGTGGATAAAAGCCGCTGGCAGCAGGGCAACGTGT TTAGCTGCAGCGTGATGCATGAAGCGCTGCATAACCATTATACC CAGAAAAGCCTGAGCCTGAGCCCGGGCAA
335	Light Chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAP RLLIYDASNRAITGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQRDSFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

336	DNA Light Chain	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCC AGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTA GCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCC AGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCA CCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGT CAGCAGAGAGACTCCTTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTTATCT TCCCACCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCCGTC GTGTGCCTGCTGAACAACCTTCTACCCTCGCGAGGGCCAAAGTGCA GTGGAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAAT CCGTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGT GTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGTCCTTCAACCGGGGCGAGTGC
		SRF416-B
337	Heavy Chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKG LEWIGEIDVDGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAA DTAVYYCARDGYYYDTSFYDVWGQGTMTVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVTPSSSLGTKTYTCNVDPKPSNTKVDKRVES KYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVTV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTL PSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSFGSFFLYSRLTVDPKSRWQEGNVPFSCSVMEALHNHYTQKS LSLSLG
338	DNA Heavy Chain	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCTTC AGAAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCATTTT CTGGTTATTACTGGAGTTGGATTCGTCAACCACCAGGCAAAGGA TTGGAGTGGATCGGTGAGATAGACGTGGATGGCTCCACTAACTA CAATCCAAGTTTAAAATCCAGGGTTACTATCTCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCCGCA GACACGGCGGTGTACTACTGCGCCAGAGACGGATACTACTACGA CACCAGTCCATACGACGTATGGGGTCAGGGTACAATGGTCACCG TCTCCTCAGCTTCCACCAAGGGCCCCCTCCGTGTTCCCTCTGGCC CCTTGCTCCCGGTCCACCTCCGAGTCTACCGCCGCTCTGGGCTG CCTCGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGA ACTCTGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTG CTGCAGTCCTCCGGCCTGTACTCCCTGTCCAGCGTCGTGACCGT GCCCTCCTCCAGCCTGGGCACCAAGACCTACACCTGTAACGTGG ACCACAAGCCCTCCAACACCAAAGTGGACAAGCGGGTGGAAATCT AAGTACGGCCCTCCCTGCCCTTCCTGCCCTGCCCCCTGAGTTCT GGGCGGACCTTCCGTGTTCTCTGTTCCCTCCAAAGCCCAAGGACA CCCTGATGATCTCCCGGACCCCTGAAGTGACCTGCGTGGTGGTG GACGTGTCCCAGGAAGATCCCGAAGTCCAGTTCAATTGGTACGT GGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCCAGAGAGG

		AACAGTTCAACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTG CTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTGCAAAGT GTCCAACAAGGGCCTGCCCTCCAGCATCGAAAAGACCATCTCCA AGGCCAAGGGCCAGCCCCGCGAGCCCCAAGTGTACACCCTGCCT CCCAGCCAGGAAGAGATGACCAAGAATCAAGTGTCCCTGACTTG TCTGGTCAAGGGCTTCTACCCCTCCGATATCGCCGTGGAGTGGG AGTCCAACGGCCAGCCCCGAGAACAATAAGACCAACCCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCTCGGCTGAC CGTGGACAAGTCCCGGTGGCAGGAAGGCAACGTCTTCTCCTGCT CCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCC CTGTCCCTGTCTCTGGGC
		SRF405-A
339	HCDR1 (IMGT)	GGTFVGYA
340	HCDR2 (IMGT)	I I P I F G I A
341	HCDR3 (IMGT)	ARSYSSRWYHYMDV
342	HCDR1 (NT)	GTFVGYAIS
343	HCDR2 (NT)	G I I P I F G I A N Y A Q K F Q G
344	HCDR3 (NT)	ARSYSSRWYHYMDV
345	VH	QVQLVQSGAEVKKPGSSVKVSKASGGTFVGYAISWVRQAPGQG LEWMGGI I P I F G I A N Y A Q K F Q G R V T I T A D E S T S T A Y M E L S S L R S E D T A V Y Y C A R S Y S S R W Y H Y Y M D V W G K G T T V T V S S
346	DNA VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCG TTGGGTATGCTATCAGCTGGGTGCGACAGGCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTATTGCAAA CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCA
347	LCDR1 (IMGT)	QGISSW
348	LCDR2 (IMGT)	AAS
349	LCDR3 (IMGT)	QQADDLPLT
350	LCDR1 (NT)	RASQGISSWLA
351	LCDR2 (NT)	AASNLS
352	LCDR3 (NT)	QQADDLPLT
353	VL	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAP KLLIYAASNLSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQADDLPLTFGGGTKVEIK

354	DNA VL	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTA GCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCCT AAGCTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCC ATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGT CAGCAGGCAGACGACCTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAA
355	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSKASGGTFVGYAISWVRQAPGQG LEWMGGIIPIFGIANYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARSYYSSRWYHYYYMDVWGKGTITVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCTVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALH NHYTQKSLSLSPGK
356	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCG TTGGGTATGCTATCAGCTGGGTGCGACAGGCCCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTATTGCAAA CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCAGCGAGCACCAAAGGCCCCGAGCGTG TTTCCGCTGGCGCCGAGCAGCAAAAGCACCCAGCGGCGGCACCGC GGCGCTGGGCTGCCTGGTGAAAGATTATTTTCCGGAACCGGTGA CCGTGAGCTGGAACAGCGGCGCGCTGACCAGCGGCGTGCATACC TTTCCGGCGGTGCTGCAGAGCAGCGGCCTGTATAGCCTGAGCAG CGTGGTGACCGTGCCGAGCAGCAGCCTGGGCACCCAGACCTATA TTTGCAACGTGAACCATAAACCAGGCAACACCAAAGTGGATAAA AAAGTGGAACCGAAAAGCTGCGATAAAACCCATACCTGCCCCGCC GTGCCCCGGCGCCGGAAGTGTGGGCGGCCCCGAGCGTGTCTGT TTCCGCCGAAACCGAAAGATAACCCTGATGATTAGCCGCACCCCG GAAGTGACCTGCGTGGTGGTGGATGTGAGCCATGAAGATCCGGA AGTGAAATTTAACTGGTATGTGGATGGCGTGGAAGTGCATAACG CGAAAACCAAACCGCGCGAAGAACAGTATAACAGCACCTATCGC GTGGTGAGCGTGCTGACCGTGCTGCATCAGGATTGGCTGAACGG CAAAGAATATAAATGCAAAGTGAGCAACAAAGCGCTGCCGGCGC CGATTGAAAAAACCATTAGCAAAGCGAAAGGCCAGCCGCGCGAA CCGCAGGTGTATACCCTGCCGCCGAGCCGCGATGAACTGACCAA AAACCAGGTGAGCCTGACCTGCCTGGTGAAAGGCTTTTATCCGA GCGATATTGCGGTGGAATGGGAAAGCAACGGCCAGCCGGAAAC AACTATAAAACCACCCCGCCGGTGCTGGATAGCGATGGCAGCTT

		TTTTCTGTATAGCAAACCTGACCGTGGATAAAAAGCCGCTGGCAGC AGGGCAACGTGTTTAGCTGCAGCGTGATGCATGAAGCGCTGCAT AACCATTATACCCAGAAAAGCCTGAGCCTGAGCCCGGGCAA
357	Light Chain	DIQMTQSPSSVSASVGDRVITITCRASQGISSWLAWYQQKPGKAP KLLIYAASNLSQGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQADDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
358	DNA Light Chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTA GCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTCCC ATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGT CAGCAGGCAGACGACCTCCCTCTCACTTTTGGCGGAGGGACCAA GGTTGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTTCATCT TCCCACCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCCGTC GTGTGCCTGCTGAACAACCTTCTACCCTCGCGAGGCCAAAGTGCA GTGGAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAAT CCGTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGT GTACGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGTCCTTCAACCGGGGCGAGTGC
		SRF405-B
359	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFVGYAISWVRQAPGQG LEWMGGIIPIFGIANYAQKFQGRVTITADESTSTAYMELSSLRS EDTAVYYCARSYYSSRWYHYMDVWGKGTTVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDK RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHY TQKSLSLSLG
360	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCG TTGGGTATGCTATCAGCTGGGTGCGACAGGCCCCCTGGACAAGGG CTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTATTGCAAA CTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACG AATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT GAGGACACGGCGGTGTACTACTGCGCCAGATCTTACTACTCCAG CCGATGGCACTACTACTACTACATGGACGTGTGGGGCAAGGGTA CAACTGTCACCGTCTCCTCAGCTTCCACCAAGGGCCCCCTCCGTG TTCCCTCTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTCTACCGC CGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCCGTGA CCGTGTCCTGGAACCTCTGGCGCCCTGACCTCCGGCGTGCACACC

		TTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCAG CGTCGTGACCGTGCCCTCCTCCAGCCTGGGCACCAAGACCTACA CCTGTAACTGGACCAACAAGCCCTCCAACACCAAAGTGGACAAG CGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTTCCTGCCCTGC CCCTGAGTTCCTGGGCGGACCTTCCGTGTTTCTGTTCCCTCCAA AGCCCAAGGACACCCTGATGATCTCCCGGACCCCTGAAGTGACC TGCGTGGTGGTGGACGTGTCCCAGGAAGATCCCGAAGTCCAGTT CAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCA AGCCCAGAGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTA CAAGTGCAAAGTGTCCAACAAGGGCCTGCCCTCCAGCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCCCAAGTG TACACCCTGCCTCCCAGCCAGGAAGAGATGACCAAGAATCAAGT GTCCCTGACTTGTCTGGTCAAGGGCTTCTACCCCTCCGATATCG CCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAATACTACAAG ACCACCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTGTA CTCTCGGCTGACCGTGGACAAGTCCCGGTGGCAGGAAGGCAACG TCTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTAC ACCCAGAAGTCCCTGTCCCTGTCTCTGGGC
		SRF535-A
361	HCDR1 (IMGT)	GFTFSSYG
362	HCDR2 (IMGT)	IKQDGSEK
363	HCDR3 (IMGT)	ARDAPWDIYDYMDV
364	HCDR1 (NT)	FTFSSYGMS
365	HCDR2 (NT)	NIKQDGSEKYYVDSVKG
366	HCDR3 (NT)	ARDAPWDIYDYMDV
367	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNKNSLYLQMNSLRA EDTAVYYCARDAPWDIYDYMDVWGKGTTVTVSS
368	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTA GTAGCTATGGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTGGCCAACATAAAGCAAGATGGAAGTGAGAAATA CTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGCTCCTTGGGA CATCTACGACTACTACATGGACGTATGGGGCAAGGGTACAACCTG TCACCGTCTCCTCA
369	LCDR1 (IMGT)	QSISSY
370	LCDR2 (IMGT)	AAS

371	LCDR3 (IMGT)	QQSYVPPWT
372	LCDR1 (NT)	RASQSISSYLN
373	LCDR2 (NT)	AASSLQS
374	LCDR3 (NT)	QQSYVPPWT
375	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYVPPWTFGGGTKVEIK
376	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATT GCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCC ATCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGT CAGCAAAGCTACGTCCCCCCTTGGACTTTTGGCGGAGGGACCAA GGTTGAGATCAAA
377	Heavy Chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNKNSLYLQMNSLRA EDTAVYYCARDAPWDIYDYMDVWGKGTITVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNH YTQKSLSLSPGK
378	DNA Heavy Chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTA GTAGCTATGGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGG CTGGAGTGGGTGGCCAACATAAAGCAAGATGGAAGTGAGAAATA CTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGCTCCTTGGGA CATCTACGACTACTACATGGACGTATGGGGCAAGGGTACAACCTG TCACCGTCTCCTCAGCGAGCACCAAAGGCCCGAGCGTGTTTCCG CTGGCGCCGAGCAGCAAAAGCACCAGCGGCGGCACCGCGGCGCT GGGCTGCCTGGTGAAAGATTATTTTCCGGAACCGGTGACCGTGA GCTGGAACAGCGGCGCGCTGACCAGCGGCGTGACATACCTTTCCG GCGGTGCTGCAGAGCAGCGGCCTGTATAGCCTGAGCAGCGTGGT GACCGTGCCGAGCAGCAGCCTGGGCACCCAGACCTATATTTGCA ACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAAGTG GAACCGAAAAGCTGCGATAAAACCCATACCTGCCCCGCGTGCCC GGCGCCGGAAGTCTGGGCGGCCCCGAGCGTGTTTCTGTTTCCGC CGAAACCGAAAGATACCCTGATGATTAGCCGCACCCCGGAAGTG ACCTGCGTGGTGGTGGATGTGAGCCATGAAGATCCGGAAGTGAA ATTTAACTGGTATGTGGATGGCGTGGAAGTGCATAACGCGAAAA

		CTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACA ACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGATGCTCCTTGGGA CATCTACGACTACTACATGGACGTATGGGGCAAGGGTACAACTG TCACCGTCTCCTCAGCTTCCACCAAGGGCCCCCTCCGTGTTCCCT CTGGCCCCCTTGCTCCCGGTCCACCTCCGAGTCTACCGCCGCTCT GGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGT CCTGGAACCTCTGGCGCCCTGACCTCCGGCGTGCACACCTTCCCT GCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCAGCGTCGT GACCGTGCCCTCCTCCAGCCTGGGACACCAAGACCTACACCTGTA ACGTGGACCACAAGCCCTCCAACACCAAGTGGACAAGCGGGTG GAATCTAAGTACGGCCCTCCCTGCCCTTCCTGCCCTGCCCCCTGA GTTCCCTGGGCGGACCTTCCGTGTTCCCTGTTCCCTCCAAAGCCCA AGGACACCCTGATGATCTCCCGGACCCCTGAAGTGACCTGCGTG GTGGTGGACGTGTCCCAGGAAGATCCCGAAGTCCAGTTCAATTG GTACGTGGACGGCGTGGAAAGTGCACAACGCCAAGACCAAGCCCA GAGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTG CAAAGTGTCCAACAAGGGCCTGCCCTCCAGCATCGAAAAGACCA TCTCCAAGGCCAAGGGCCAGCCCCGCGAGCCCCAAGTGTACACC CTGCCTCCCAGCCAGGAAGAGATGACCAAGAATCAAGTGTCCCT GACTTGTCTGGTCAAGGGCTTCTACCCCTCCGATATCGCCGTGG AGTGGGAGTCCAACGGCCAGCCCGAGAACAACACTACAAGACCACC CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCTCG GCTGACCGTGGACAAGTCCCGGTGGCAGGAAGGCAACGTCTTCT CCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG AAGTCCCTGTCCCTGTCTCTGGGC
		SRF538-A
383	HCDR1 (IMGT)	GFTFSSYG
384	HCDR2 (IMGT)	IWYDGSNK
385	HCDR3 (IMGT)	ARGAPEYVDV
386	HCDR1 (NT)	FTFSSYGMH
387	HCDR2 (NT)	VIWYDGSNKYYADSVKG
388	HCDR3 (NT)	ARGAPEYVDV
389	VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKG LEWVAVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCARGAPEYVDVWGQGTMVTVSS
390	DNA VH	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGG GAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCA GTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGG CTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATA CTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACA ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCC

		GAGGACACGGCGGTGTACTACTGCGCCAGAGGGGGCCCCTGAATA TG TAGACGTATGGGGTCAGGGTACAATGGTCAACCGTCTCCTCA
391	LCDR1 (IMGT)	QSVSSY
392	LCDR2 (IMGT)	DSS
393	LCDR3 (IMGT)	QQYSLYPT
394	LCDR1 (NT)	RASQSVSSYLA
395	LCDR2 (NT)	DSSNRAT
396	LCDR3 (NT)	QQYSLYPT
397	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRL LLIYDSSNRATGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYC QQYSLYPTFGGGTKVEIK
398	DNA VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCC AGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTA GCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATTCATCCAACAGGGCCACTGGCATCCC AGCCAGGTTCAAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCA CCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGT CAGCAGTACAGTCTCTACCCTACTTTTGGCGGAGGGACCAAGGT TGAGATCAAA
399	Heavy Chain	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKG LEWVAVIWDGSDNKYYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCARGAPEYVDVWGQGTMVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVTV VDSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDS DGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKS LSLSPGK
400	DNA Heavy Chain	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGG GAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCA GTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGG CTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATA CTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACA ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGGGGGCCCCTGAATA TG TAGACGTATGGGGTCAGGGTACAATGGTCAACCGTCTCCTCAG CGAGCACCAAAGGCCCGAGCGTGTTTCCGCTGGCGCCGAGCAGC AAAAGCACCAGCGGCGGCACCGCGGCGCTGGGCTGCCTGGTGAA AGATTATTTTCCGGAACCGGTGACCGTGAGCTGGAACAGCGGCG CGCTGACCAGCGGCGTGACATACCTTTCCGGCGGTGCTGCAGAGC AGCGGCCTGTATAGCCTGAGCAGCGTGGTGACCGTGCCGAGCAG CAGCCTGGGCACCCAGACCTATATTTGCAACGTGAACCATAAAC

		CGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCTGC GATAAAACCCATACCTGCCCCGCCGTGCCCCGGCGCCGGAAGTCT GGGCGGCCCCGAGCGTGTTTCTGTTTCCGCCGAAACCGAAAGATA CCCTGATGATTAGCCGCACCCCGGAAGTGACCTGCGTGGTGGTG GATGTGAGCCATGAAGATCCGGAAGTGAAATTTAACTGGTATGT GGATGGCGTGGAAGTGCATAACGCGGAAAACCAAACCGCGCGAAG AACAGTATAACAGCACCTATCGCGTGGTGAGCGTGCTGACCGTG CTGCATCAGGATTGGCTGAACGGCAAAGAATATAAATGCAAAGT GAGCAACAAAGCGCTGCCGGCGCCGATTGAAAAAACCATTAGCA AAGCGAAAGGCCAGCCGCGCGAACCGCAGGTGTATACCCTGCCG CCGAGCCGCGATGAACTGACCAAAAACAGGTGAGCCTGACCTG CCTGGTGAAAGGCTTTTATCCGAGCGATATTGCGGTGGAATGGG AAAGCAACGGCCAGCCGGAACAACACTATAAAACCAACCCCGCCG GTGCTGGATAGCGATGGCAGCTTTTTTCTGTATAGCAAAGTAC CGTGGATAAAAGCCGCTGGCAGCAGGGCAACGTGTTTAGCTGCA GCGTGATGCATGAAGCGCTGCATAACCATTTATACCCAGAAAAGC CTGAGCCTGAGCCCGGGCAA
401	Light Chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAP RLLIYDSSNRATGIPARFSGSGSGTDFTLTISILEPEDFAVYYC QQYSLYPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
402	DNA Light Chain	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCC AGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTA GCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGATTTCATCCAACAGGGCCACTGGCATCCC AGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCA CCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGT CAGCAGTACAGTCTCTACCCTACTTTTGGCGGAGGGACCAAGGT TGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTTCATCTTCC CACCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTCCGTCGTG TGCCTGCTGAACAACCTTCTACCCTCGCGAGGCCAAAGTGCAGTG GAAAGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCCG TCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCTTCC ACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGTGTA CGCCTGCGAAGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGTCCTTCAACCGGGGCGAGTGC
		SRF538-B
403	Heavy Chain	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKG LEWVAVIWIYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCARGAPEYVDVWGQGTMTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYG PPCPSCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD

		SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLG
404	DNA Heavy Chain	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGG GAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCA GTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGG CTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATA CTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACA ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCGGTGTACTACTGCGCCAGAGGGGGCCCCTGAATA TGTAGACGTATGGGGTCAGGGTACAATGGTCCACCGTCTCCTCAG CTTCCACCAAGGGCCCCCTCCGTGTTCCCTCTGGCCCCCTTGCTCC CGGTCCACCTCCGAGTCTACCGCCGCTCTGGGCTGCCTCGTGAA GGACTACTTCCCCGAGCCCGTGACCGTGTCTTGGAACTCTGGCG CCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCC TCCGGCCTGTACTCCCTGTCCAGCGTCGTGACCGTGCCCTCCTC CAGCCTGGGACCAAGACCTACACCTGTAACGTGGACCACAAGC CCTCCAACACCAAAGTGGACAAGCGGGTGGAACTTAAGTACGGC CCTCCCTGCCCTTCCTGCCCTGCCCCCTGAGTTCCTGGGCGGACC TTCCGTGTTCTCTGTTCCCTCCAAAGCCCAAGGACACCCTGATGA TCTCCCGGACCCCTGAAGTGACCTGCGTGGTGGTGGACGTGTCC CAGGAAGATCCCGAAGTCCAGTTCAATTGGTACGTGGACGGCGT GGAAGTGCACAACGCCAAGACCAAGCCCAGAGAGGAACAGTTCA ACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAG GACTGGCTGAACGGCAAAGAGTACAAGTGCAAAGTGTCCAACAA GGGCCTGCCCTCCAGCATCGAAAAGACCATCTCCAAGGCCAAGG GCCAGCCCCGCGAGCCCCAAGTGTACACCCTGCCTCCCAGCCAG GAAGAGATGACCAAGAATCAAGTGTCCCTGACTTGTCTGGTCAA GGGCTTCTACCCCTCCGATATCGCCGTGGAGTGGGAGTCCAACG GCCAGCCCCGAGAACAATAACAAGACCACCCCTCCCGTGCTGGAC TCCGACGGCTCCTTCTTCTGTACTCTCGGCTGACCGTGGACAA GTCCCGGTGGCAGGAAGGCAACGTCTTCTCCTGCTCCGTGATGC ACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTG TCTCTGGGC
405	FLAG	DYKDDDDK
406	6-HIS	HHHHHH
407	HA	YPYDVPDYA

Table 13: Fc Sequences (=CH2+CH3)

Name	Alias	Amino Acid Sequence
Human IgG1	1.0	EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK (SEQ ID NO: 702)

Human IgG4	4.0	ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVTVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 703)
Human IgG4 (S228P)	4.1	ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVTVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 704)
Human IgG4 (S228P / L235E)	4.2	ESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVTVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 705)

Example 10: SRF388 Binding Properties and IL-27 Receptor Blockade

The association and dissociation of recombinant human IL-27 at concentrations ranging from 0 to 5.0 $\mu\text{g/mL}$ with an SRF388 concentration of 1 $\mu\text{g/mL}$ were determined. Final binding kinetic parameters are shown in **Table 14** along with binding model fit parameters (R^2 and χ^2) that demonstrate goodness of the model fitting to the data.

Human IL-27 displayed the strongest binding affinity for SRF388 of all species tested in this study (3.86 pM). Recombinant rat and cynomolgus monkey IL-27 also showed strong affinities for SRF388 with values of 80.9 and 37.4 pM, respectively, although somewhat weaker than the human protein. Recombinant mouse IL-27 had the weakest affinity for SRF388 by comparison with the human protein, with a value in the nM range (4.43 nM) as indicated by its slower association and faster dissociation rates.

Table 14: Data Summary for IL-27 Binding to SRF388 and Species Cross-Reactivity

Analyte	K_D (M)	k_a (1/Ms)	k_d (1/s)	Full χ^2	Full R^2
Human IL-27	3.86E-12	5.10E+05	1.97E-06	0.4055	0.9991
Mouse IL-27	4.43E-09	5.50E+04	2.44E-04	0.6732	0.9963
Rat IL-27	8.09E-11	2.34E+06	1.89E-04	0.4685	0.9945
Cynomolgus monkey IL-27	3.74E-11	3.18E+05	1.19E-05	1.3431	0.9979

Abbreviations: IL-27 = interleukin 27, k_a = association constant, k_d = dissociation constant, K_D = binding affinity
Note: R^2 values > 0.95 and χ^2 values < 3.0 are demonstrative of a good fit of the model to the data.

Example 11: CDR Sequence Alignments

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

For SRF388, SRF381, SRF382, SRF384, SRF386 and SRF529 antibodies, alignments of the CDR sequences of each of these anti-IL-27 antibodies revealed extensive homology, punctuated by variable residues. In particular, heavy chain CDR1 alignments revealed the following variable residues:

HCDR1 (IMGT)

CLUSTAL O(1.2.4) multiple sequence alignment

1	GFTFRSYG	8	(SEQ ID NO: 161)
5	GFTFRSYG	8	(SEQ ID NO: 73)
4	GFTFASYG	8	(SEQ ID NO: 139)
2	GFTFSRTG	8	(SEQ ID NO: 95)
3	GFTFSRYG	8	(SEQ ID NO: 117)
6	GFTFSSYS	8	(SEQ ID NO: 51)

A consensus heavy chain CDR1 (IMGT) sequence for these homologous antibodies is therefore N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 412) and, accordingly, more generally contemplated herein as a consensus heavy chain CDR1 (IMGT) sequence is N-GFTFXXXX-C (SEQ ID NO: 408), where X is any amino acid residue.

Alignment of the SRF388, SRF381, SRF382, SRF384, SRF386 and SRF529 antibody heavy chain CDR2 (IMGT) sequences revealed the following:

HCDR2 (IMGT)

CLUSTAL O(1.2.4) multiple sequence alignment

10	ISSSGSYI	8	(SEQ ID NO: 162)
11	ISSSSSYI	8	(SEQ ID NO: 140)

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7      ISSSSSYI      8      (SEQ ID NO: 74)
9      ISSSSSYI      8      (SEQ ID NO: 96)
8      ISSSSAYI      8      (SEQ ID NO: 118)
12     ISSSSSYI      8      (SEQ ID NO: 52)
      *****

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A consensus heavy chain CDR2 (IMGT) sequence for these homologous antibodies is therefore N-ISSSS[S/G][S/A]YI-C (SEQ ID NO: 413) and, accordingly, more generally contemplated herein as a consensus heavy chain CDR2 (IMGT) sequence is N-ISSSSXXYI-C (SEQ ID NO: 409), where X is any amino acid residue.

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

HCDR1 (NT)

CLUSTAL O(1.2.4) multiple sequence alignment

```

13     FTFRSYGMN      9      (SEQ ID NO: 76)
16     FTFRSYGMN      9      (SEQ ID NO: 164)
17     FTFASYGMN      9      (SEQ ID NO: 142)
14     FTFSRTGMN      9      (SEQ ID NO: 98)
15     FTFSRYGMN      9      (SEQ ID NO: 120)
18     FTFSSYSMN      9      (SEQ ID NO: 54)
      ***      ***

```

HCDR2 (NT)

CLUSTAL O(1.2.4) multiple sequence alignment

```

23     GISSSGSYIYYADSVKG 17      (SEQ ID NO: 165)
19     SISSSSSYIYYADSVKG 17      (SEQ ID NO: 77)
20     SISSSSSYIYYADSVKG 17      (SEQ ID NO: 99)
22     SISSSSSYIYYADSVKG 17      (SEQ ID NO: 143)
21     SISSSSAYILYADSVKG 17      (SEQ ID NO: 121)
24     SISSSSSYIYYADSVKG 17      (SEQ ID NO: 55)
      .*****.;** *****

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Consensus heavy chain CDR1 (NT) and CDR2 (NT) sequences for these homologous antibodies are therefore N-FTF[S/A/R][S/R][T/Y][G/S]MN-C (SEQ ID NO: 414) and N-[G/S]ISSSS[S/G][S/A]YI[L/Y]YADSVKG-C (SEQ ID NO: 415), respectively. In view of these consensus sequences, more generally contemplated herein are consensus heavy chain CDR1 (NT)

and CDR2 (NT) sequences N-FTFXXXXMN-C (SEQ ID NO: 410) and N-XISSXXYIXYADSVKG-C (SEQ ID NO: 411), respectively, where X is any amino acid residue.

Heavy chain CDR3 (IMGT or NT) and light chain CDRs CDR1 (IMGT or NT), CDR2 (IMGT or NT) and CDR3 (IMGT or NT) were fully conserved between SRF388, SRF381, SRF382, SRF384, SRF386 and SRF529.

Similar CDR sequence alignments performed upon SRF535 and SRF538 monoclonal antibodies revealed the following consensus CDR sequences for these two related antibodies:

Observed variation (IMGT):

HCDR1 (IMGT) – N-GFTFSSYG-C (SEQ ID NO: 361)

HCDR2 (IMGT) – N-I[K/W][Q/Y]DGS[E/N]K-C (SEQ ID NO: 445)

HCDR3 (IMGT) – N-AR[D/G]AP[WDIYDYYM/EYV]DV-C (SEQ ID NO: 446)

LCDR1 (IMGT) – N-QS[I/V]SSY-C (SEQ ID NO: 447)

LCDR2 (IMGT) – N-[A/D][A/S]S-C (SEQ ID NO: 448)

LCDR3 (IMGT) – N-QQ[S/Y][Y/S][V/L][P/Y]P[W/-]T-C (SEQ ID NO: 449)

Consensus (IMGT):

HCDR1 (IMGT) – N-GFTFSSYG-C (SEQ ID NO: 361)

HCDR2 (IMGT) – N-IXXDGSXK-C (SEQ ID NO: 436)

HCDR3 (IMGT) – N-ARXAP[X]_{n=3-8}DV-C (SEQ ID NO: 437)

LCDR1 (IMGT) – N-QSXSSY-C (SEQ ID NO: 438)

LCDR2 (IMGT) – N-XXS-C (SEQ ID NO: 439)

LCDR3 (IMGT) – N-QQXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 440)

Observed variation (NT):

HCDR1 (NT) – N-FTFSSYGM[S/H]-C (SEQ ID NO: 450)

HCDR2 (NT) – N-[N/V]I[K/W][Q/Y]DGS[E/N]KYY[V/A]DSVKG-C (SEQ ID NO: 451)

HCDR3 (NT) – N-AR[D/G]AP[WDIYDYYM/EYV]DV-C (SEQ ID NO: 446)

LCDR1 (NT) – N-RASQS[I/V]SSYL[N/A]-C (SEQ ID NO: 452)

LCDR2 (NT) – N-[AA/D]SS[LQS/NRAT]-C (SEQ ID NO: 453)

LCDR3 (NT) – N-QQ[S/Y][Y/S][V/L][P/Y]P[W/-]T-C (SEQ ID NO: 449)

Consensus (NT):

HCDR1 (NT) – N-FTFSSYGMX-C (SEQ ID NO: 441)

HCDR2 (NT) – N-XIXXDGSXKYYXDSVKG-C (SEQ ID NO: 442)

HCDR3 (NT) – N-ARXAP[X]_{n=3-8}DV-C (SEQ ID NO: 437)

LCDR1 (NT) – N-RASQSXSSYLX-C (SEQ ID NO: 443)

LCDR2 (NT) – N-[X]_{n=1-2}SS[X]_{n=3-4}-C (SEQ ID NO: 444)

LCDR3 (NT) – N-QQXXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 440)

Alignments of CDR sequences were also performed between the entirety of SRF388, SRF381, SRF382, SRF384, SRF386, SRF529, SRF535 and SRF538 antibodies, which resulted in the following observed variation and consensus sequences:

Observed variation (IMGT):

HCDR1 (IMGT) – N-GFTF[S/A/R][S/R][T/Y][G/S]-C (SEQ ID NO: 454)

HCDR2 (IMGT) – N-I[S/K/W][S/Q/Y][S/D][S/G][S/A][Y/E/N][I/K]-C (SEQ ID NO: 455)

HCDR3 (IMGT) – N-AR[DGGRTSYTATAHNWF/DAPWDIYDYYM/GAPEYV]D[P/V]-C (SEQ ID NO: 457)

LCDR1 (IMGT) – N-QS[VLF/I/V]SS[NNKN/-]Y-C (SEQ ID NO: 459)

LCDR2 (IMGT) – N-[W/A/D][A/S]S-C (SEQ ID NO: 461)

LCDR3 (IMGT) – N-QQ[H/S/Y][A/Y/S][S/V/L][A/P/Y]P[P/W/-]T-C (SEQ ID NO: 463)

Consensus (IMGT):

HCDR1 (IMGT) – N-GFTFXXXX-C (SEQ ID NO: 408)

HCDR2 (IMGT) – N-IXXXXXXXXX-C (SEQ ID NO: 456)

HCDR3 (IMGT) – N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 458)

LCDR1 (IMGT) – N-QS[X]_{n=1-3}SS[X]_{n=0-4}Y-C (SEQ ID NO: 460)

LCDR2 (IMGT) – N-XXS-C (SEQ ID NO: 462)

LCDR3 (IMGT) – N-QQXXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 464)

Observed variation (NT):

HCDR1 (NT) – N-FTF[S/A/R][S/R][T/Y][G/S]M[N/S/H]-C (SEQ ID NO: 465)

HCDR2 (NT) – N-[G/S/N/V]I[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)

HCDR3 (NT) – N-AR[D/G][GGRTSYTATAHNWF/APWDIYDYYM/APEYV]D[P/V]-C (SEQ ID NO: 469)

LCDR1 (NT) – N-RASQS[I/V]SSYL[N/A]-C (SEQ ID NO: 471)

LCDR2 (NT) – N-[WA/AA/D]S[TRES/SLQS/SNRAT]-C (SEQ ID NO: 473)

LCDR3 (NT) – N-QQ[H/S/Y][A/Y/S][S/V/L][A/P/Y]P[P/W/-]T-C (SEQ ID NO: 475)

Consensus (NT):

HCDR1 (NT) – N-FTFXXXXMX-C (SEQ ID NO: 466)

HCDR2 (NT) – N-XIXXXXXXXXXXXDSVKG-C (SEQ ID NO: 468)

HCDR3 (NT) – N-AR[X]_{n=6-15}DX-C (SEQ ID NO: 470)

LCDR1 (NT) – N-RASQSXSSYLX-C (SEQ ID NO: 472)

LCDR2 (NT) – N-[X]_{n=1-2}S[X]_{n=4-5}-C (SEQ ID NO: 474)

LCDR3 (NT) – N-QQXXXXP[X]_{n=0-1}T-C (SEQ ID NO: 476)

Alignments of SRF543 and SRF414 were also performed, and yielded the following observed variation and consensus sequences:

Observed variation (IMGT):

HCDR1 (IMGT) – N-GGSFS[R/D]Y[E/Y]-C (SEQ ID NO: 426)

HCDR2 (IMGT) – N-ID[W/Y]SG[I/S]T-C (SEQ ID NO: 427)

HCDR3 (IMGT) – N-AR[D/L][P/G][M/V]YY[-/Y]DSS[VSTGSV/DLGF]D[V/I]-C (SEQ ID NO: 428)

LCDR1 (IMGT) – N-Q[S/D][V/I]S[S/N]Y-C (SEQ ID NO: 429)

LCDR2 (IMGT) – N-D[S/A]S-C (SEQ ID NO: 430)

LCDR3 (IMGT) – N-QQ[D/Y][S/D]D[H/L]PIT-C (SEQ ID NO: 431)

Consensus (IMGT):

HCDR1 (IMGT) – N-GGSFSXYX-C (SEQ ID NO: 416)

HCDR2 (IMGT) – N-IDXSGXT-C (SEQ ID NO: 417)

HCDR3 (IMGT) – N-ARXXXYY[X]_{n=0-1}DSS[X]_{n=4-6}DX-C (SEQ ID NO: 418)

LCDR1 (IMGT) – N-QXXSXY-C (SEQ ID NO: 419)

LCDR2 (IMGT) – N-DXS-C (SEQ ID NO: 420)

LCDR3 (IMGT) – N-QQXXDXPIT-C (SEQ ID NO: 421)

Observed variation (NT):

HCDR1 (NT) – N-GSFS[R/D]Y[E/Y]WS-C (SEQ ID NO: 432)

HCDR2 (NT) – N-SID[W/Y]SG[I/S]T[N/E]YNPSLKS-C (SEQ ID NO: 433)

HCDR3 (NT) – N-AR[D/L][P/G][M/V]YY[-/Y]DSS[VSTGSV/DLGF]D[V/I]-C (SEQ ID NO: 428)

LCDR1 (NT) – N-[Q/R]ASQ[S/D][V/I]S[S/N]YL[N/A]-C (SEQ ID NO: 434)

LCDR2 (NT) – N-D[S/A]SN[R/L][A/E]T-C (SEQ ID NO: 435)

LCDR3 (NT) – N-QQ[D/Y][S/D]D[H/L]PIT-C (SEQ ID NO: 431)

Consensus (NT):

HCDR1 (NT) – N-GSFSXYXWS-C (SEQ ID NO: 422)

HCDR2 (NT) – N-SIDXSGXTXYNPSLKS-C (SEQ ID NO: 423)

HCDR3 (NT) – N-ARXXXYY[X]_{n=0-1}DSS[X]_{n=4-6}DX-C (SEQ ID NO: 418)

LCDR1 (NT) – N-XASQXXSXYLX-C (SEQ ID NO: 424)

LCDR2 (NT) – N-DXSNXXT-C (SEQ ID NO: 425)

LCDR3 (NT) – N-QQXXDXPIT-C (SEQ ID NO: 421)

Example 12: Properties of Selected Monoclonal Antibodies

Selected monoclonal antibodies of the instant disclosure were assessed for various functional properties. The outcome of certain such assessment is tabulated in FIG. 9. Remarkably, a wide array of monoclonal antibodies were identified that exhibited binding to human IL-27 (as determined by surface plasmon resonance (SPR) technology in a BIACORE 2000 instrument, as described above) (“Property (i)”) with an equilibrium dissociation constant (KD) of 15 nM or less, including Ab7, SRF557, SRF536, SRF416, SRF543, SRF414, SRF529, SRF381, SRF388, SRF382, SRF384, SRF386, SRF410, SRF411, SRF405, SRF535 and SRF538.

Unexpectedly, a selection of monoclonal antibodies were identified to be WSX-1 competitive (“Property (ii)”), including Ab7, SRF536, SRF416, SRF543, SRF414, SRF529, SRF381, SRF388, SRF382, SRF384, SRF386, SRF535 and SRF538.

Surprisingly, a selection of monoclonal antibodies were identified that inhibited pSTAT1 U937 (“Property (iii)”), including Ab7, SRF536, SRF416, SRF543, SRF414, SRF529, SRF381, SRF388, SRF382, SRF384, SRF386, SRF410, SRF411, SRF405, SRF535 and SRF538.

Remarkably, a selection of monoclonal antibodies were also identified that inhibited CD161 expression (“Property (iv)”), including Ab7, SRF536, SRF416, SRF543, SRF529, SRF381, SRF388, SRF382, SRF384 and SRF386.

A selection of monoclonal antibodies that, remarkably, inhibited PD-L1 expression in CD4⁺ T cells (“Property (v)”) were also identified, including Ab7, SRF536, SRF416, SRF543, SRF414, SRF529, SRF381, SRF388, SRF382, SRF384, SRF386 and SRF535.

While only tested for a limited number of monoclonal antibodies, variability in the ability of those antibodies tested to enhance PD-1-mediated cytokine secretion (“Property (vi)”) was also observed. Specifically, SRF381 and SRF388 antibodies were remarkably identified to enhance PD-1-mediated cytokine secretion, whereas SRF536 did not.

Monoclonal antibodies possessing each of properties (i)-(vi), as recited above, have therefore been identified herein. Not all antibodies examined were identified to possess each of properties (i)-(vi), and it is therefore expressly contemplated that selections of antibodies can be assembled that possess a sub-selection of these properties. For example, antibodies Ab7, SRF536, SRF416, SRF543, SRF529, SRF381, SRF388, SRF382, SRF384 and SRF386 were identified to possess each of properties (i)-(v). Meanwhile, antibodies Ab7, SRF536, SRF416, SRF543, SRF529, SRF381, SRF388, SRF382, SRF384 and SRF386 were identified to possess each of properties (iii) and (iv). As will be apparent to the skilled artisan, similar sub-selections of antibodies and associated properties are readily assembled from the information presented in FIG. 9.

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 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.

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.