

IL-23 BINDING PROTEIN COMPOSITIONS AND METHODS OF USE**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/550,110, filed February 6, 2024, U.S. Provisional Application No. 63/550,233, filed February 6, 2024, U.S. Provisional Application No. 63/550,382, filed February 6, 2024, U.S. Provisional Application No. 63/573,721, filed April 3, 2024, U.S. Provisional Application No. 63/573,741, filed April 3, 2024, U.S. Provisional Application No. 63/573,893, filed April 3, 2024, U.S. Provisional Application No. 63/574,165, filed April 3, 2024, U.S. Provisional Application No. 63/697,429, filed September 20, 2024, and U.S. Provisional Application No. 63/706,462, filed October 11, 2024, the entire contents of each of which are incorporated herein by reference.

SEQUENCE LISTING

[0002] This application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. The XML copy, created on February 4, 2025, is titled 220703-010909_PCT_SL.xml and is 191,676 bytes in size.

BACKGROUND

[0003] Interleukin-23 (IL-23) is a key inflammatory cytokine that promotes the differentiation of T helper 17 cells, leading to production of other cytokines such as interleukin-17. IL-23 plays a role in inflammatory diseases, and disorders such as inflammatory bowel disease (IBD).

[0004] IBD affects the digestive system but can also cause problems in other parts of the body. One type of IBD is Crohn's disease, which can cause symptoms anywhere in the digestive system. The other main form of IBD, ulcerative colitis, affects the large intestine (colon). IBD can be managed with a combination of medications, surgery, and lifestyle changes, but there is no known cure.

[0005] Current treatments for IBD include biologics such as IL-23 antibodies. Due to the importance of IL-23 in mediating pro-inflammatory responses, a need remains for development of additional inhibitors targeting IL-23. Additionally, dosing regimens for many currently used biologics typically include frequent dosing, requiring an injection every couple weeks (e.g., every four to eight weeks). A need remains for improved methods of treatment of IBD.

SUMMARY

[0006] The present disclosure addresses this need with the provision of IL-23 binding proteins, such as anti-IL-23 antibodies, and with methods of treating conditions such as inflammatory bowel disease (IBD), ulcerative colitis and/or Crohn's disease.

[0007] In one aspect, the disclosure provides an IL-23 binding protein comprising a heavy chain variable domain (VH) comprising complementarity-determining regions (CDRs): CDR-H1 comprising the amino acid sequence of SEQ ID NO: 3; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 5. In some embodiments, the VH comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 1. In some embodiments, the IL-23 binding protein further comprising a light chain variable domain (VL) comprising complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, the VL comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 2.

[0008] In another aspect, the disclosure provides an IL-23 binding protein comprising (i) a heavy chain variable domain (VH) comprising complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 3; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 5; and (ii) a light chain variable domain (VL) comprising complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, the disclosure provides an IL-23 binding protein comprising a heavy chain variable domain comprising an amino acid sequence according to SEQ ID NO: 1 and a light chain variable domain comprising an amino acid sequence according to SEQ ID NO: 2.

[0009] In some embodiments, the IL-23 binding protein is an anti-IL-23 antibody comprising a heavy chain comprising an amino acid sequence according to SEQ ID NO: 165, and a light chain comprising an amino acid sequence according to SEQ ID NO: 166.

[0010] In certain embodiments, the IL-23 binding protein is capable of inhibiting activation of STAT3 in human embryonic kidney (HEK) cells expressing IL-23R at a relative IC₅₀ of less than 0.90, less than 0.80, less than 0.70, or less than 0.65 or at a relative IC₅₀ of from about 0.6 to about 0.65. In some embodiments, the IL-23 binding protein is capable of inhibiting phosphorylation of STAT3 in DB cells at a relative IC₅₀ reference of less than 0.80, less than 0.70, less than 0.60, or less than 0.58, or at a relative IC₅₀ of from about 0.55 to about 0.6.

[0011] In one aspect, the disclosure provides an IL-23 binding protein comprising a heavy chain variable domain (VH) comprising complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21. In some embodiments, the VH comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 18.

[0012] In certain embodiments, the IL-23 binding protein further comprises a light chain variable domain (VL) comprising complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, the VL comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 2.

[0013] In one aspect, the disclosure provides an IL-23 binding protein comprising (i) a heavy chain variable domain (VH) comprising complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21; and (ii) a light chain variable domain (VL) comprising complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.

[0014] In some embodiments, the disclosure provides an IL-23 binding protein comprising a heavy chain variable domain comprising an amino acid sequence according to SEQ ID NO: 18 and a light chain variable domain comprising an amino acid sequence according to SEQ ID NO: 2.

[0015] In some embodiments, the IL-23 binding protein is an anti-IL-23 antibody comprising a heavy chain comprising an amino acid sequence according to SEQ ID NO: 169, and a light chain comprising an amino acid sequence according to SEQ ID NO: 170.

[0016] In some embodiments, the IL-23 binding protein is capable of inhibiting activation of STAT3 in human embryonic kidney (HEK) cells expressing IL-23R at a relative IC₅₀ of less than 0.95, less than 0.90, or less than 0.88, or at a relative IC₅₀ of from about 0.85 to about 0.9. In some embodiments, the IL-23 binding protein is capable of inhibiting phosphorylation of STAT3 in DB cells at a relative IC₅₀ of less than 0.95, less than 0.90, or less than 0.85, or at a relative IC₅₀ of from about 0.75 to about 0.85.

[0017] In one aspect, the disclosure provides an IL-23 binding protein comprising (a) a heavy chain variable domain (VH) comprising (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 28, and (2) an asparagine at position 74 of SEQ ID NO: 28; and (b) a light chain variable domain (VL) comprising: (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 29, and (2) a phenylalanine at position 49 of SEQ ID NO: 29, wherein (i) the VH comprises complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 30; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 31; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 32; and (ii) the VL comprises complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8. In an embodiment, the amino acid at position 27 of SEQ ID NO: 28 is not asparagine. In a further embodiment, the amino acid at position 27 of SEQ ID NO: 28 is a tyrosine. In another embodiment, the amino acid at position 74 of SEQ ID NO: 28 is not lysine. In another embodiment, the amino acid at position 49 of SEQ ID NO: 29 is not a tyrosine.

[0018] In some embodiments, the heavy chain variable domain further comprises one or more of the following: glutamic acid at position 1, leucine at position 5, glutamic acid at position 6, glycine at position 9, glycine at position 10, leucine at position 11, valine at position 12, glutamine at position 13, glycine at position 16, leucine at position 18, arginine at position 19, leucine at position 20, alanine at position 23, valine at position 37, lysine at position 43, arginine at position 67, leucine at position 70, serine at position 71, alanine at position 68, lysine at

position 76, asparagine at position 77, leucine at position 81, glutamine at position 82, methionine at position 83, asparagine at position 84, alanine at position 88, or threonine at position 115 of SEQ ID NO: 28. In some embodiments, the light chain variable domain comprises one or more of the following: glutamic acid at position 1, valine at position 3, alanine at position 9, threonine at position 10, valine at position 13, proline at position 15, glutamic acid at position 17, alanine at position 19, leucine at position 21, serine at position 22, glutamine at position 42, alanine at position 43, arginine at position 45, leucine at position 48, isoleucine at position 58, alanine at position 60, glutamic acid at position 70, serine at position 80, phenylalanine at position 83, valine at position 85, tyrosine at position 87, glycine at position 100 or valine at position 104 of SEQ ID NO: 29.

[0019] In some embodiments, the VH comprises an amino acid sequence that is at least 90% identical to that of SEQ ID NO: 28, and the VL comprises an amino acid sequence that is at least 90% identical to that of SEQ ID NO: 29. In some embodiments, the VH comprises an amino acid sequence that is at least 92.5% identical to that of SEQ ID NO: 28, and the VL comprises an amino acid sequence that is at least 92.5% identical to that of SEQ ID NO: 29. In some embodiments, the VH comprises an amino acid sequence that is at least 95% identical to that of SEQ ID NO: 28, and the VL comprises an amino acid sequence that is at least 95% identical to that of SEQ ID NO: 29. In some embodiments, the VH comprises an amino acid sequence that is at least 98% identical to that of SEQ ID NO: 28, and the VL comprises an amino acid sequence that is at least 98% identical to that of SEQ ID NO: 29. In some embodiments, the disclosure provides an IL-23 binding protein comprising a VH comprising the amino acid sequence of SEQ ID NO: 28, and a VL comprising the amino acid sequence of SEQ ID NO: 29.

[0020] In some embodiments, the IL-23 binding protein is an anti-IL-23 antibody comprising a heavy chain comprising an amino acid sequence according to SEQ ID NO: 171, and a light chain comprising an amino acid sequence according to SEQ ID NO: 172.

[0021] In some embodiments, the IL-23 binding protein is capable of inhibiting activation of STAT3 in human embryonic kidney (HEK) cells expressing IL-23R at a relative IC_{50} of less than 0.9, less than 0.8, less than 0.7, or at a relative IC_{50} of from about 0.6 to about 0.7.

[0022] In another aspect, the disclosure provides an IL-23 binding protein comprising: (a) a heavy chain variable domain (VH) comprising (1) an amino acid sequence that is at least 85%

identical to that of SEQ ID NO: 38 and (2) complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 40; and (b) a light chain variable domain (VL) comprising (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 29; (2) a phenylalanine residue at position 49 of SEQ ID NO: 29, and (3) complementarity-determining regions: (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.

[0023] In some embodiments, the light chain variable domain further comprises one or more of the following: glutamic acid at position 1, valine at position 3, alanine at position 9, threonine at position 10, valine at position 13, proline at position 15, glutamic acid at position 17, alanine at position 19, leucine at position 21, serine at position 22, glutamine at position 42, alanine at position 43, arginine at position 45, leucine at position 48, isoleucine at position 58, alanine at position 60, glutamic acid at position 70, serine at position 80, phenylalanine at position 83, valine at position 85, tyrosine at position 87, glycine at position 100 or valine at position 104 of SEQ ID NO: 29

[0024] In some embodiments, the disclosure provides an IL-23 binding protein comprising a VH comprising the amino acid sequence of SEQ ID NO: 38, and a VL comprising the amino acid sequence of SEQ ID NO: 29.

[0025] In some embodiments, the IL-23 binding protein is an anti-IL-23 antibody comprising a heavy chain comprising an amino acid sequence according to SEQ ID NO: 167; and a light chain comprising an amino acid sequence according to SEQ ID NO: 168.

[0026] In some embodiments, the IL-23 binding protein is capable of inhibiting activation of STAT3 in human embryonic kidney (HEK) cells expressing IL-23R at a relative IC_{50} of less than 0.90, less than 0.80, less than 0.70, less than 0.60, less than 0.50, or less than 0.45, or at a relative IC_{50} of from about 0.35 to about 0.45.

[0027] In some embodiments, an IL-23 binding protein of the disclosure is an antibody or antigen-binding fragment thereof. In some embodiments, the IL-23 binding protein is a human antibody or antigen-binding fragment thereof. In some embodiments, the antigen binding fragment is a Fab, a $F(ab')_2$, a Fab' , a single-chain Fv (scFv), an Fv fragment, a Fd fragment, or

a diabody. In some embodiments, the antibody or antigen binding fragment thereof comprises an Fc region. In some such embodiments, the Fc region is a human IgG1, IgG2, or IgG4 Fc region. In some embodiments, the Fc region is a modified Fc region. For example, in some embodiments, the modified Fc region comprises a half-life extending modification or set of modifications. In some embodiments, the Fc region comprises amino acid modifications that result in an extended half-life are M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).

[0028] In some embodiments, the disclosure provides an isolated nucleic acid encoding an IL-23 binding protein as provided herein. In some embodiments, the disclosure provides an expression vector comprising the isolated nucleic acid. In some embodiments, the disclosure provides a host cell comprising the isolated nucleic acid or the expression vector.

[0029] In some embodiments, the disclosure provides a composition comprising an IL-23 binding protein as provided herein and a pharmaceutically acceptable carrier.

[0030] In some embodiments, the disclosure provides a method of treating a disease or condition in a subject, comprising a step of administering to the subject an effective amount of an IL-23 binding protein or composition as provided herein. In some embodiments, the disease or condition is an inflammatory condition. In some embodiments, the disease or condition is a gastrointestinal inflammatory disease. In some embodiments, the disease or condition is inflammatory bowel disease. In some embodiments, the disease or condition is Crohn's disease. In some embodiments, the disease or condition is ulcerative colitis. In some embodiments, the method comprises administering intravenously or subcutaneously the effective amount of an IL-23 binding protein or composition as provided herein.

[0031] In one aspect, the disclosure provides a method of treating a gastrointestinal inflammatory disease in a subject in need thereof, the method comprising administering to the subject a maintenance dose of an IL-23 binding protein every 8 weeks or more for a period of time sufficient to treat or ameliorate inflammatory bowel disease. In some embodiments, the method comprises administering the maintenance dose every 3 months, every 12-13 weeks, every 6 months, every 24-26 weeks, twice a year, every 12 months, every 48-52 weeks, or once a year.

[0032] In some embodiments, the IL-23 binding protein comprises: (1) a VH comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO: 3; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 5; and (2) a modified Fc region that extends half-life of the IL-23 binding protein as compared to an IL-23 binding protein that does not comprise the modified Fc region. In some embodiments, the Fc region comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS). In some embodiments, the VH comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 1.

[0033] In some embodiments, the IL-23 binding protein further comprises a VL comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, the VL comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 2.

[0034] In some embodiments, the IL-23 binding protein comprises: (1) (i) a heavy chain variable domain (VH) comprising complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 3; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 5; and (ii) a light chain variable domain (VL) comprising complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8; and (2) a modified Fc region that extends half-life of the IL-23 binding protein as compared to an IL-23 binding protein that does not comprise the modified Fc region. In some embodiments, the Fc region comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).

[0035] In some embodiments, the IL-23 binding protein comprises: (1) a heavy chain variable domain (VH) comprising complementarity-determining regions: (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21; and (2) a modified Fc region that extends half-life of the IL-23 binding protein as compared to an IL-23 binding protein that does not comprise the modified Fc region. In some

embodiments, the Fc region comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).

[0036] In some embodiments, the VH comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 18.

[0037] In some embodiments, the IL-23 binding protein further comprises a VL comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.

[0038] In some embodiments, the VL comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 2.

[0039] In some embodiments, the IL-23 binding protein comprising: (1) (i) a VH comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21; and (ii) a VL comprising: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8; and (2) a modified Fc region that extends half-life of the IL-23 binding protein as compared to an IL-23 binding protein that does not comprise the modified Fc region. In some embodiments, the Fc region comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).

[0040] In some embodiments, the IL-23 binding protein comprising: (a) a VH comprising (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 28, and (2) an asparagine residue at position 74 of SEQ ID NO: 28; (b) a VL comprising: (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 29, and (2) a phenylalanine residue at position 49 of SEQ ID NO: 29; and (c) a modified Fc region that extends half-life of the IL-23 binding protein as compared to an IL-23 binding protein that does not comprise the modified Fc region, wherein (1) (i) the VH comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO: 30; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 31; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 32; and (ii) the VL comprises CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8

In some embodiments, the Fc region comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS). In an embodiment, the amino acid at position 27 of SEQ ID NO: 28 is not asparagine. In a further embodiment, the amino acid at position 27 of SEQ ID NO: 28 is a tyrosine. In another embodiment, the amino acid at position 74 of SEQ ID NO: 28 is not lysine. In another embodiment, the amino acid at position 49 of SEQ ID NO: 29 is not tyrosine.

[0041] In some embodiments, the IL-23 binding protein comprising: (a) VH comprising (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 38 and (2) complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 40; (b) a light chain variable domain (VL) comprising (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 29, (2) a phenylalanine residue at position 49 of SEQ ID NO: 29, and (3) complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8; and (c) a modified Fc region that extends half-life of the IL-23 binding protein as compared to an IL-23 binding protein that does not comprise the modified Fc region. In some embodiments, the Fc region comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).

[0042] In certain embodiments, the maintenance dose of IL-23 the binding protein is at least about 150 mg, about 300 mg, about 600 mg, about 900 mg, or about 1200 mg. In some embodiments, prior to the step of administering maintenance doses, the subject has received an induction dose or doses of the IL-23 binding protein. In some embodiments, the induction dose of the IL-23 binding protein contains about twice the amount of IL-23 binding protein as the maintenance dose, and the induction dose is administered one, two, or three times. In some embodiments, the induction dose of the IL-23 binding protein contains two partial doses, each partial dose having the same amount of the IL-23 binding protein as the maintenance dose, and each two partial doses administered four weeks apart from each other. In some embodiments, the method comprises administering to the subject an induction dose as a single dose, two doses or three doses, before the administration of a first maintenance dose, and administering a maintenance dose no more frequently than every 3 months or every 12-13 weeks, wherein the

induction dose contains about twice the amount of IL-23 binding protein as the maintenance dose. In some embodiments, the induction dose is administered as two doses four weeks apart.

[0043] In certain embodiments, the Fc region or modified Fc region is a human IgG1 immunoglobulin region. In some embodiments, the IL-23 binding protein is a humanized IL-23 binding protein. In some embodiments, the step of administering comprises systemic administration of the IL-23 binding protein. In some embodiments, the systemic administration comprises subcutaneous administration of the IL-23 binding protein. In some embodiments, the systemic administration comprises intravenous administration of the IL-23 binding protein. In some embodiments, the subject is a mammal. In certain embodiments, the subject is a primate. In certain embodiments, the subject is a human.

[0044] In another aspect, the disclosure provides the IL-23 binding protein or composition as provided herein for use in treatment of a disease or condition. In another aspect, the disclosure provides use of the IL-23 binding protein or composition as provided herein in a method of treating a disease or condition. In another aspect, the disclosure provides use of the IL-23 binding protein or composition as provided herein in the manufacture of a medicament for treating a disease or condition. In some embodiments, the disease or condition is an inflammatory disease or condition. In some embodiments, the disease or condition is gastrointestinal inflammatory disease. In some embodiments, the disease or condition is inflammatory bowel disease. In some embodiments, the disease or condition is Crohn's disease. In some embodiments, the disease or condition is ulcerative colitis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] **FIG. 1** is a graph of normalized serum concentration (y-axis) plotted against days post-injection (x-axis) in cynomolgus monkeys intravenously administered a single bolus dose (5 mg/kg) of an IL-23p19 binding protein with ("YTE") or without ("reference antibody") Fc YTE mutations (Reference Antibody 1). See Example 7.

[0046] **FIG. 2** is a graph of serum concentration in $\mu\text{g/mL}$ (y-axis) plotted against days post-injection (x-axis) in cynomolgus monkeys subcutaneously administered a single bolus dose (5 mg/kg) of an IL-23p19 binding protein with ("YTE") or without ("reference antibody") Fc YTE mutations (Reference Antibody 1). See Example 7.

[0047] **FIG. 3** is a graph of predicted plasma concentrations in $\mu\text{g/mL}$ (y-axis) plotted against days post-injection (x-axis) for an IL-23p19 binding protein dosing regimen which includes an induction regimen and subsequent dosing every 6 months (*e.g.*, 26 weeks) based on pharmacokinetic modeling and simulation experiments described in Example 8. Shown are the predicted plasma concentration curves for an IL-23p19 binding protein with YTE mutations (“+YTE”) ($t_{1/2}$ = 74 days) dosed at 150 mg at weeks 0 and 4 and every 26 weeks thereafter (“dose regimen 1 (150 mg)”) or at 300 mg at week 0 and every 26 weeks thereafter (“dose regimen 2 (300 mg)”). For comparison, also shown are predicted plasma concentration curves for an IL-23p19 binding protein Reference Antibody 1 (“Reference antibody”) without any half-life extending mutations ($t_{1/2}$ = 28 days) dosed at 150 mg at weeks 0 and 4 and every 12 weeks thereafter.

[0048] **FIG. 4** is a graph of predicted plasma concentrations in $\mu\text{g/mL}$ (y-axis) plotted against days post-injection (x-axis) for an IL-23p19 binding protein dosing regimen which includes an induction regimen and subsequent dosing every year (*e.g.*, 52 weeks) based on pharmacokinetic modeling and simulation experiments described in Example 8. Shown are the predicted plasma concentration curves for an IL-23p19 binding protein with YTE mutations (“+YTE”) ($t_{1/2}$ = 74 days) dosed at 600 mg at week 0 and every 52 weeks thereafter (“dose regimen 1 (600 mg)”) or at 900 mg at week 0 and every 52 weeks thereafter (“dose regimen 2 (900 mg)”). For comparison, also shown are predicted plasma concentration curves for an IL-23p19 binding protein Reference Antibody 1 without any half-life extending mutations (“Reference antibody”) ($t_{1/2}$ = 28 days) dosed at 150 mg at weeks 0 and 4 and every 12 weeks thereafter.

[0049] **FIG. 5A** depicts inhibition of pSTAT signaling by MAb002 and by a reference anti-IL-23 antibody (“Reference Antibody 1”; see Table 3 in Example 1). **FIG. 5B** depicts inhibition of IL-17 release by MAb002 and by Reference Antibody 1.

[0050] **FIG. 6** depicts reduction of IL-17 release by human PBMCs and by murine splenocytes stimulated with IL-23 and inhibition of pSTAT in DB and HEK cells by Reference Antibody 1 (gray bars) or by MAb002 (white bars).

[0051] **FIG. 7** shows the binding epitopes of Reference Antibody 1 and of MAb002 on IL-23 as determined by cryogenic electron microscopy (cryo-EM).

[0052] **FIG. 8** depicts the half-life of MAb002 (upper curve) and the Reference Antibody 1 (lower curve) in non-human primates (cynomolgus monkeys).

[0053] **FIG. 9** depicts predictive simulations of MAb002 (darker line) and Reference Antibody 1 (lighter line) pharmacokinetics in humans. MAb002 was modeled based on a half-life of 90 days with 1200 mg intravenous administration at weeks 0 and 4 followed by 600 mg subcutaneous administration every 26 weeks (Q26W). Reference Antibody 1 was modeled based on a half-life of 28 days with 1200 mg intravenous administration at weeks 0, 4, and 8 followed by 360 mg subcutaneous administration every 8 weeks (Q8W).

[0054] **FIG. 10A** is a graph showing human half-lives (in days) as predicted by non-human primate (NHP) data for MAb002 and Reference Antibody 1 and based on an average Mab002 half-life that is about 3 times greater than average Reference Antibody 1 half-life. **FIG. 10B** depicts predictive simulations of MAb002 (darker line, intravenous administration at weeks 0 and 4 followed by subcutaneous administration at 12 weeks and every 12 weeks (Q12W)) and Reference Antibody 1 (lighter line, intravenous administration at weeks 0, 4 and 8 followed by subcutaneous administration every 8 weeks (Q8W)) pharmacokinetics in humans based on an average Mab002 half-life that is about 3 times greater than average Reference Antibody 1 half-life. Lines show the simulated median; shaded area shows the IQR. Stochastic simulations: n=2,000 virtual subjects.

DETAILED DESCRIPTION

Definitions

[0055] As used herein, the terms “about,” “approximately,” and “comparable to,” when used herein in reference to a value, refer to a value that is similar to the referenced value in the context of that referenced value. In general, those skilled in the art, familiar with the context, will appreciate the relevant degree of variance encompassed by “about,” “approximately,” and “comparable to” in that context. For example, in some embodiments, the terms “about,” “approximately,” and “comparable to” may encompass a range of values that within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value.

[0056] As used herein, the terms “antagonistic,” “neutralizing” or “blocking,” when used in reference to an antibody or antigen-binding fragment thereof, is intended to refer to an antibody or fragment thereof whose binding to its target results in inhibition of at least some of the biological activity of the target.

[0057] As used herein, “antibody” refers to a polypeptide whose amino acid sequence includes immunoglobulins and fragments thereof which specifically bind to a designated antigen, or fragments thereof. Antibodies in accordance with the present invention may be of any type (*e.g.*, IgA, IgD, IgE, IgG, or IgM) or subtype (*e.g.*, IgA1, IgA2, IgG1, IgG2, IgG3, or IgG4). Those of ordinary skill in the art will appreciate that a characteristic sequence or portion of an antibody may include amino acids found in one or more regions of an antibody (*e.g.*, variable region, hypervariable region, constant region, heavy chain, light chain, and combinations thereof). Moreover, those of ordinary skill in the art will appreciate that a characteristic sequence or portion of an antibody may include one or more polypeptide chains, and may include sequence elements found in the same polypeptide chain or in different polypeptide chains.

[0058] “Antibody-dependent cell-mediated cytotoxicity” or “ADCC” refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (*e.g.* Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies “arm” the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in U.S. Pat. No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.*, in an animal model such as that disclosed in Clynes et al. *PNAS (USA)* 95:652-656 (1998).

[0059] An “antigen-binding fragment” of an antibody, or “antibody fragment” comprises a portion of an intact antibody, which portion is still capable of antigen binding. In some embodiments, the antibody has a function in addition to that of antigen-binding, and an antigen-binding fragment retains that function. Typically, an antigen-binding fragment comprises the variable region of the antibody. Papain digestion of antibodies produce two identical antigen-binding fragments, called “Fab” fragments, and a residual “Fc” fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire light chain along with the variable region domain of the heavy chain (V_H), and the first constant domain of one heavy chain (C_{H1}). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment which roughly corresponds to two disulfide linked Fab fragments having different antigen-binding activity and that is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having a few additional residues at the carboxy terminus of the C_{H1} domain, including one or more cysteines from the antibody hinge region. $Fab'-SH$ designates an Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments having hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0060] As used herein, the term “chimeric antibody” refers to an antibody that has a portion of its heavy and/or light chain identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass.

[0061] A “complementarity determining region” (abbreviated “CDR”) is a region of hypervariability interspersed within regions that are more conserved, termed “framework regions” (abbreviated “FR”). The FR of a variable region generally consists of four FRs: FR1, FR2, FR3, and FR4. For example, the V_H and V_L CDR and FR sequences generally appear in the following sequence: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. In some embodiments, the sequences of the framework regions are identical to the framework regions in human germline sequences. In some embodiments, the sequences of the framework regions are modified with respect to the human germline sequence.

[0062] As used herein, the phrase “complement dependent cytotoxicity” or “CDC” refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, *e.g.*, as described in Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996), may be performed.

[0063] As used herein, the expression “control sequences” refers to DNA sequences necessary or advantageous for the expression of an operably linked coding sequence in a particular host organism. Control sequences that are typically suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

[0064] As used herein, antibody “effector functions” refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and which typically vary with the antibody isotype. Examples of antibody effector functions include, but are not limited to, 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), and B cell activation.

[0065] As used herein, the term “epitope” is an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule, known as the paratope, and which is comprised of the six complementary-determining regions of the antibody. A single antigen may have more than one epitope. Epitopes may be conformational or linear. A conformational epitope is comprised of spatially juxtaposed amino acids from different segments of a linear polypeptide chain. A linear epitope is comprised of adjacent amino acid residues in a polypeptide chain.

[0066] An Fc fragment comprises the carboxy-terminal portions of both heavy chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, the region which is also recognized by Fc receptors (FcR) found on certain types of cells.

[0067] As used herein, the term “humanized,” when used in reference to an antibody, refers to a form of a non-human (*e.g.*, murine) antibody that is chimeric. A “humanized antibody” contains minimal sequences derived from non-human immunoglobulin. Typically, humanized antibodies are human immunoglobulins (recipient or acceptor antibody) in which hypervariable region residues of the recipient are replaced by hypervariable region residues from a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having a desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance such as binding affinity. Generally, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin sequence although the framework regions may include one or more amino acid substitutions that improve binding affinity. In some embodiments, no more than six amino acid substitutions in the heavy chain and no more than three amino acid substitutions are used in the light chain in the framework region. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

[0068] As used herein, an “isolated” nucleic acid molecule is a nucleic acid molecule that is identified and separated from at least one contaminant molecule with which it is ordinarily associated in the natural source of the antibody nucleic acid. An isolated nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from the nucleic acid molecule as they exist in natural cells.

[0069] As used herein, the term “monoclonal antibody” refers to an antibody obtained from a population of substantially homogeneous antibodies, *e.g.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier

“monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, monoclonal antibodies may be made by a hybridoma method, such as that first described by Kohler et al., *Nature* 256:495 (1975), or may be made by recombinant DNA methods (see, *e.g.*, U.S. Pat. No. 4,816,567). “Monoclonal antibodies” may also be isolated from phage antibody libraries, *e.g.*, using techniques described in Clackson et al., *Nature* 352:624-628 (1991) and Marks et al., *J. Mol. Biol.* 222:581-597 (1991).

[0070] As used herein, a nucleic acid is “operably linked” when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is “operably linked” to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is “operably linked” to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is “operably linked” to a coding sequence if it is positioned so as to facilitate translation. Generally, “operably linked” means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking may be accomplished, *e.g.*, by ligation at convenient restriction sites. If such sites do not exist, synthetic oligonucleotide adaptors or linkers may be used in accordance with conventional practice.

[0071] As used herein, “polypeptide,” which may be used interchangeably with “protein,” refers to a string of at least two amino acids attached to one another by a peptide bond. In some embodiments, a polypeptide may include at least 3-5 amino acids, each of which is attached to others by way of at least one peptide bond. Those of ordinary skill in the art will appreciate that polypeptides can include one or more “non-natural” amino acids or other entities that nonetheless are capable of integrating into a polypeptide chain. In some embodiments, a polypeptide may be glycosylated, *e.g.*, a polypeptide may contain one or more covalently linked sugar moieties. In some embodiments, a single “polypeptide” (*e.g.*, an antibody polypeptide) may comprise two or more individual polypeptide chains, which may in some cases be linked to one another, for example by one or more disulfide bonds or other means.

[0072] As used herein, the phrase “reference level” generally refers to a level considered “normal” for comparison purposes, *e.g.*, a level of an appropriate control. For example, in the context of half-life (*e.g.* serum half-life) of a protein (*e.g.*, a binding protein) a reference level may refer to the half-life of a “reference binding protein” which may be, *e.g.*, an immunoglobulin of the same class (*e.g.*, IgG1, IgG2, or IgG4) having a wild-type Fc region or an Fc region lacking a half-life extending mutation. In some embodiments, the reference binding protein comprises the same complementarity-determining regions as those of the binding protein of interest (*e.g.*, an IL-23 binding protein as described herein). In some embodiments, the reference binding protein comprises the same variable regions (*e.g.*, heavy chain and/or light chain variable region) as those of the binding protein of interest (*e.g.*, an IL-23 binding protein as described herein.)

[0073] As used herein, the term “relative IC₅₀” refers to an IC₅₀ value calculated relative to the IC₅₀ of a suitable reference antibody (with the reference antibody’s IC₅₀ value being normalize to 1.000). An IC₅₀ of less than 1.000 indicates increased potency compared to the reference antibody. In some embodiments, the reference antibody is an IL-23 antibody which is capable of binding to an epitope on the p19 subunit of IL-23. In some embodiments, the reference antibody is an IL-23p19 antibody comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 156 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 2.

[0074] As used herein, the phrases “therapeutically effective amount” and “effective amount” are used interchangeably and refer to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary according to factors such as the type of disease (*e.g.*, disease state, age, sex, and/or weight of the individual, and the ability of an antibody (or pharmaceutical composition thereof) to elicit a desired response in the individual. An effective amount may also be an amount for which any toxic or detrimental effects of the antibody or pharmaceutical composition thereof are outweighed by therapeutically beneficial effects.

[0075] As used herein, to “treat” a condition or “treatment” of the condition (*e.g.*, the conditions described herein) is an approach for obtaining beneficial or desired results, such as clinical results. Beneficial or desired results can include, but are not limited to, alleviation or

amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilized (i.e., not worsening) state of disease, disorder, or condition; preventing spread of disease, disorder, or condition; delay or slowing the progress of the disease, disorder, or condition; amelioration or palliation of the disease, disorder, or condition; and remission (whether partial or total), whether detectable or undetectable. "Palliating" a disease, disorder, or condition means that the extent and/or undesirable clinical manifestations of the disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to the extent or time course in the absence of treatment.

METHODS OF TREATMENT

[0076] Provided herein, in certain embodiments, are methods of treating a gastrointestinal inflammatory disease in a patient in need thereof. As used herein, the term "gastrointestinal inflammatory disease" refers to a disease of the gastrointestinal tract that involves inflammatory pathways. For example, the gastrointestinal inflammatory disease includes, but is not limited to, inflammatory bowel disease, ulcerative colitis (with or without exposure to anti-tumor necrosis factor (anti-TNF), Crohn's disease (including fistulizing Crohn's Disease), chronic pouchitis, collagenous gastritis, microscopic or collagenous colitis, colitis (including immune mediated colitis), sclerosing cholangitis (including in subjects with underlying inflammatory bowel disease, celiac enteritis, ileitis. In other aspects of the disclosure, provided herein are methods of treating Intestinal Acute Graft Versus Host Disease (aGVHD) (*e.g.*, in subjects undergoing allogeneic hematopoietic stem cell transplantation (Allo-HSCT)), steroid-refractory acute intestinal graft-versus-host disease (GvHD) (*e.g.* in subjects who have undergone Allo-HSCT), Type 1 diabetes (T1D) (*e.g.*, with or without anti-TNF pre-treatment), immune checkpoint inhibitor-related colitis in subjects with genitourinary cancer or melanoma.

[0077] In some embodiments, the disease is a gastrointestinal inflammatory disease. In some embodiments, the disease is an inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is Crohn's disease. In some embodiments, the inflammatory bowel disease is ulcerative colitis.

[0078] In certain embodiments, provided are methods of treatment which generally comprise a step of administering a therapeutically effective amount of an IL-23 binding protein (or

pharmaceutical composition thereof) of the present disclosure to a mammalian subject (*e.g.*, a human subject) in need thereof.

[0079] In some embodiments, the subject has or is at risk of having an inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is Crohn's disease or ulcerative colitis. In some embodiments, the inflammatory bowel disease is ulcerative colitis. In some embodiments, the inflammatory bowel disease is Crohn's disease.

[0080] In some embodiments, the subject has or is at risk of having an inflammatory disease or condition.

[0081] Therapeutically effective amounts of an IL-23 binding protein (or pharmaceutical composition thereof) may be administered via a single dose or via multiple doses (*e.g.*, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten doses). When administered via multiple doses, any of a variety of suitable therapeutic regimens may be used, including administration of an IL-23 binding protein (or pharmaceutical composition thereof) at regular intervals (*e.g.*, once every other day, once every three days, once every four days, once every five days, thrice weekly, twice weekly, once a week, once every two weeks, once every three weeks, etc.).

[0082] The dosage regimen of an IL-23 binding protein (or pharmaceutical composition thereof) (*e.g.*, amounts of each therapeutic, relative timing of therapies, etc.) that is effective in methods of treatment may depend on the severity of the disease or condition and the weight and general state of the subject. For example, the therapeutically effective amount of a particular composition comprising a therapeutic agent (*e.g.*, an IL-23 binding protein of the present disclosure) applied to mammals (*e.g.*, humans) can be determined by the ordinarily-skilled artisan with consideration of individual differences in age, weight, and the condition of the mammal.

[0083] Also contemplated herein are, in certain embodiments, methods of treating gastrointestinal inflammatory disease, inflammatory bowel disease, ulcerative colitis, and/or Crohn's disease in a subject in need thereof, the method comprising a step of administering to the subject a dose of an IL-23 binding protein (such as an IL-23 binding protein as described herein) at regular intervals for a period of time sufficient to treat or ameliorate the

gastrointestinal inflammatory disease, inflammatory bowel disease, ulcerative colitis, and/or Crohn's disease.

Regular Intervals of Administration of an IL-23 binding protein

[0084] By "regular interval," it is meant that the intervals between doses of an IL-23 binding protein (or pharmaceutical composition thereof) (*e.g.*, maintenance doses) are at least substantially the same but need not be exactly the same, *e.g.*, the durations between intervals may be within 10%, within 9%, within 8%, within 7%, within 6%, within 5%, within 4%, within 3%, within 2%, or within 1% of each other.

[0085] In some embodiments, the regular interval between maintenance doses of an IL-23 binding protein (or pharmaceutical composition thereof) is 8 weeks or more, *e.g.* greater than 8 weeks, greater than 12 weeks, greater than 16 weeks, greater than 20 weeks, or greater than 24 weeks. For example, in some embodiments, the regular interval is about 26 weeks.

[0086] In some embodiments, the regular interval is greater than 26 weeks, greater than 30 weeks, greater than 34 weeks, greater than 38 weeks, greater than 42 weeks, or greater than 48 weeks. For example, in some embodiments, the regular interval is about 52 weeks.

[0087] In some embodiments, the regular interval is greater than two months, greater than three months, greater than four months, or greater than five months. For example, in some embodiments, the regular interval is about three months. In some embodiments, the regular interval is about six months.

[0088] In some embodiments, the regular interval is about twice a year or about once a year.

[0089] In some embodiments, the regular interval is about 12 weeks to about 52 weeks, about 12 weeks to about 50 weeks, about 12 weeks to about 48 weeks, about 12 weeks to about 46 weeks, about 12 weeks to about 44 weeks, about 12 weeks to about 42 weeks, about 12 weeks to about 40 weeks, about 12 weeks to about 38 weeks, about 12 weeks to about 36 weeks, about 12 weeks to about 34 weeks, about 12 weeks to about 32 weeks, about 12 weeks to about 30 weeks, about 12 weeks to about 28 weeks, about 12 weeks to about 26 weeks, about 12 weeks to about 24 weeks, about 12 weeks to about 22 weeks, about 12 weeks to about 18 weeks, or about 12 weeks to about 14 weeks

[0090] In some embodiments, the regular interval is about 16 weeks to about 52 weeks, about 16 weeks to about 50 weeks, about 16 weeks to about 48 weeks, about 16 weeks to about 46 weeks, about 16 weeks to about 44 weeks, about 16 weeks to about 42 weeks, about 16 weeks

to about 40 weeks, about 16 weeks to about 38 weeks, about 16 weeks to about 36 weeks, about 16 weeks to about 34 weeks, about 16 weeks to about 32 weeks, about 16 weeks to about 30 weeks, about 16 weeks to about 28 weeks, about 16 weeks to about 26 weeks, about 16 weeks to about 24 weeks, about 16 weeks to about 22 weeks, or about 16 weeks to about 18 weeks.

[0091] In some embodiments, the regular interval is about 20 weeks to about 52 weeks, about 20 weeks to about 50 weeks, about 20 weeks to about 48 weeks, about 20 weeks to about 46 weeks, about 20 weeks to about 44 weeks, about 20 weeks to about 42 weeks, about 20 weeks to about 40 weeks, about 20 weeks to about 38 weeks, about 20 weeks to about 36 weeks, about 20 weeks to about 34 weeks, about 20 weeks to about 32 weeks, about 20 weeks to about 30 weeks, about 20 weeks to about 28 weeks, about 20 weeks to about 26 weeks, about 20 weeks to about 24 weeks, or about 20 weeks to about 22 weeks.

[0092] In some embodiments, the regular interval is about 24 weeks to about 52 weeks, about 24 weeks to about 50 weeks, about 24 weeks to about 48 weeks, about 24 weeks to about 46 weeks, about 24 weeks to about 44 weeks, about 24 weeks to about 42 weeks, about 24 weeks to about 40 weeks, about 24 weeks to about 38 weeks, about 24 weeks to about 36 weeks, about 24 weeks to about 34 weeks, about 24 weeks to about 32 weeks, about 24 weeks to about 30 weeks, about 24 weeks to about 28 weeks, or about 24 weeks to about 26 weeks.

[0093] In some embodiments, the regular interval is about 26 weeks to about 52 weeks, about 26 weeks to about 50 weeks, about 26 weeks to about 48 weeks, about 26 weeks to about 46 weeks, about 26 weeks to about 44 weeks, about 26 weeks to about 42 weeks, about 26 weeks to about 40 weeks, about 26 weeks to about 38 weeks, about 26 weeks to about 36 weeks, about 26 weeks to about 34 weeks, about 26 weeks to about 32 weeks, about 26 weeks to about 30 weeks, or about 26 weeks to about 28 weeks.

[0094] In some embodiments, the regular interval is about 28 weeks to about 52 weeks, about 28 weeks to about 50 weeks, about 28 weeks to about 48 weeks, about 28 weeks to about 46 weeks, about 28 weeks to about 44 weeks, about 28 weeks to about 42 weeks, about 28 weeks to about 40 weeks, about 28 weeks to about 38 weeks, about 28 weeks to about 36 weeks, about 28 weeks to about 34 weeks, about 28 weeks to about 32 weeks, or about 28 weeks to about 30 weeks.

[0095] In some embodiments, the regular interval is about 30 weeks to about 52 weeks, about 30 weeks to about 50 weeks, about 30 weeks to about 48 weeks, about 30 weeks to about

46 weeks, about 30 weeks to about 44 weeks, about 30 weeks to about 42 weeks, about 30 weeks to about 40 weeks, about 30 weeks to about 38 weeks, about 30 weeks to about 36 weeks, about 30 weeks to about 34 weeks, or about 30 weeks to about 32 weeks.

[0096] In some embodiments, the regular interval is about 32 weeks to about 52 weeks, about 32 weeks to about 50 weeks, about 32 weeks to about 48 weeks, about 32 weeks to about 46 weeks, about 32 weeks to about 44 weeks, about 32 weeks to about 42 weeks, about 32 weeks to about 40 weeks, about 32 weeks to about 38 weeks, about 32 weeks to about 36 weeks, or about 32 weeks to about 34 weeks.

[0097] In some embodiments, the regular interval is about 34 weeks to about 52 weeks, about 34 weeks to about 50 weeks, about 34 weeks to about 48 weeks, about 34 weeks to about 46 weeks, about 34 weeks to about 44 weeks, about 34 weeks to about 42 weeks, about 34 weeks to about 40 weeks, about 34 weeks to about 38 weeks, or about 34 weeks to about 36 weeks.

[0098] In some embodiments, the regular interval is about 36 weeks to about 52 weeks, about 36 weeks to about 50 weeks, about 36 weeks to about 48 weeks, about 36 weeks to about 46 weeks, about 36 weeks to about 44 weeks, about 36 weeks to about 42 weeks, about 36 weeks to about 40 weeks, or about 36 weeks to about 38 weeks.

[0099] In some embodiments, the regular interval is about 38 weeks to about 52 weeks, about 38 weeks to about 50 weeks, about 38 weeks to about 48 weeks, about 38 weeks to about 46 weeks, about 38 weeks to about 44 weeks, about 38 weeks to about 42 weeks, about 38 weeks to about 40 weeks, or about 38 weeks to about 38 weeks.

[0100] In some embodiments, the regular interval is about 40 weeks to about 52 weeks, about 40 weeks to about 50 weeks, about 40 weeks to about 48 weeks, about 40 weeks to about 46 weeks, about 40 weeks to about 44 weeks, or about 40 weeks to about 42 weeks.

[0101] In some embodiments, the regular interval is about 42 weeks to about 52 weeks, about 42 weeks to about 50 weeks, about 42 weeks to about 48 weeks, about 42 weeks to about 46 weeks, or about 42 weeks to about 44 weeks.

[0102] In some embodiments, the regular interval is about 44 weeks to about 52 weeks, about 44 weeks to about 50 weeks, about 44 weeks to about 48 weeks, or about 44 weeks to about 46 weeks.

[0103] In some embodiments, the regular interval is about 46 weeks to about 52 weeks, about 46 weeks to about 50 weeks, or about 46 weeks to about 48 weeks.

[0104] In some embodiments, the regular interval is about 48 weeks to about 52 weeks or about 48 weeks to about 50 weeks.

[0105] In some embodiments, the regular interval is about 50 weeks to about 52 weeks.

[0106] In some embodiments, the regular interval is about three months to about twelve months, about three months to about eleven and a half months, about three months to about eleven months, about three months to about ten and a half months, about three months to about ten months, about three months to about nine and a half months, about three months to about nine months, about three months to about eight and a half months, about three months to about eight months, about three months to about seven and a half months, about three months to about seven months, about three months to about six and a half months, about three months to about six months, about three months to about five and a half months, about three months to about five months, about three months to about four and half months, about three months to about four months, or about three months to about three and half months.

[0107] In some embodiments, the regular interval is about three and a half months to about twelve months, about three and a half months to about eleven and a half months, about three and a half months to about eleven months, about three and a half months to about ten and a half months, about three and a half months to about ten months, about three and a half months to about nine and a half months, about three and a half months to about nine months, about three and a half months to about eight and a half months, about three and a half months to about eight months, about three and a half months to about seven and a half months, about three and a half months to about seven months, about three and a half months to about six and a half months, about three and a half months to about six months, about three and a half months to about five and a half months, about three and a half months to about five months, about three and a half months to about four and half months, or about three and a half months to about four months.

[0108] In some embodiments, the regular interval is about four months to about twelve months, about four months to about eleven and a half months, about four months to about eleven months, about four months to about ten and a half months, about four months to about ten months, about four months to about nine and a half months, about four months to about nine months, about four months to about eight and a half months, about four months to about eight months, about four months to about seven and a half months, about four months to about seven months, about four months to about six and a half months, about four months to about six

months, about four months to about five and a half months, about four months to about five months, or about four months to about four and half months.

[0109] In some embodiments, the regular interval is about four and a half months to about twelve months, about four and a half months to about eleven and a half months, about four and a half months to about eleven months, about four and a half months to about ten and a half months, about four and a half months to about ten months, about four and a half months to about nine and a half months, about four and a half months to about nine months, about four and a half months to about eight and a half months, about four and a half months to about eight months, about four and a half months to about seven and a half months, about four and a half months to about seven months, about four and a half months to about six and a half months, about four and a half months to about six months, about four and a half months to about five and a half months, or about four and a half months to about five months.

[0110] In some embodiments, the regular interval is about five months to about twelve months, about five months to about eleven and a half months, about five months to about eleven months, about five months to about ten and a half months, about five months to about ten months, about five months to about nine and a half months, about five months to about nine months, about five months to about eight and a half months, about five months to about eight months, about five months to about seven and a half months, about five months to about seven months, about five months to about six and a half months, about five months to about six months, or about five months to about five and a half months.

[0111] In some embodiments, the regular interval is about five and a half months to about twelve months, about five and a half months to about eleven and a half months, about five and a half months to about eleven months, about five and a half months to about ten and a half months, about five and a half months to about ten months, about five and a half months to about nine and a half months, about five and a half months to about nine months, about five and a half months to about eight and a half months, about five and a half months to about eight months, about five and a half months to about seven and a half months, about five and a half months to about seven months, about five and a half months to about six and a half months, or about five and a half months to about six months.

[0112] In some embodiments, the regular interval is about six months to about twelve months, about six months to about eleven and a half months, about six months to about eleven

months, about six months to about ten and a half months, about six months to about ten months, about six months to about nine and a half months, about six months to about nine months, about six months to about eight and a half months, about six months to about eight months, about six months to about seven and a half months, about six months to about seven months, or about six months to about six and a half months.

[0113] In some embodiments, the regular interval is about six and a half months to about twelve months, about six and a half months to about eleven and a half months, about six and a half months to about eleven months, about six and a half months to about ten and a half months, about six and a half months to about ten months, about six and a half months to about nine and a half months, about six and a half months to about nine months, about six and a half months to about eight and a half months, about six and a half months to about eight months, about six and a half months to about seven and a half months, or about six and a half months to about seven months.

[0114] In some embodiments, the regular interval is about seven months to about twelve months, about seven months to about eleven and a half months, about seven months to about eleven months, about seven months to about ten and a half months, about seven months to about ten months, about seven months to about nine and a half months, about seven months to about nine months, about seven months to about eight and a half months, about seven months to about eight months, or about seven months to about seven and a half months.

[0115] In some embodiments, the regular interval is about seven and a half months to about twelve months, about seven and a half months to about eleven and a half months, about seven and a half months to about eleven months, about seven and a half months to about ten and a half months, about seven and a half months to about ten months, about seven and a half months to about nine and a half months, about seven and a half months to about nine months, about seven and a half months to about eight and a half months, or about seven and a half months to about eight months.

[0116] In some embodiments, the regular interval is about eight months to about twelve months, about eight months to about eleven and a half months, about eight months to about eleven months, about eight months to about ten and a half months, about eight months to about ten months, about eight months to about nine and a half months, about eight months to about nine months, or about eight months to about eight and a half months.

[0117] In some embodiments, the regular interval is about eight and a half months to about twelve months, about eight and a half months to about eleven and a half months, about eight and a half months to about eleven months, about eight and a half months to about ten and a half months, about eight and a half months to about ten months, about eight and a half months to about nine and a half months, or about eight and a half months to about nine months.

[0118] In some embodiments, the regular interval is about nine months to about twelve months, about nine months to about eleven and a half months, about nine months to about eleven months, about nine months to about ten and a half months, about nine months to about ten months, or about nine months to about nine and a half months.

[0119] In some embodiments, the regular interval is about nine and a half months to about twelve months, about nine and a half months to about eleven and a half months, about nine and a half months to about eleven months, about nine and a half months to about ten and a half months, or about nine and a half months to about ten months.

[0120] In some embodiments, the regular interval is about ten months to about twelve months, about ten months to about eleven and a half months, about ten months to about eleven months, or about ten months to about ten and a half months.

[0121] In some embodiments, the regular interval is about ten and a half months to about twelve months, about ten and a half months to about eleven and a half months, or about ten and a half months to about eleven months.

[0122] In some embodiments, the regular interval is about eleven months to about twelve months or about eleven months to about eleven and a half months.

[0123] In some embodiments, the regular interval is about eleven and a half months to about twelve months.

Dose amounts

[0124] In some embodiments, each maintenance dose of the IL-23 binding protein is greater than 75 mg, greater than 100 mg, or greater than 125 mg. For example, in some embodiments, the maintenance dose is about 150 mg.

[0125] In some embodiments, each maintenance dose of the IL-23 binding protein is greater than 150 mg, greater than 200 mg, or greater than 250 mg. For example, in some embodiments, the maintenance dose is about 300 mg.

[0126] In some embodiments, each maintenance dose of the IL-23 binding protein is greater than 300 mg, greater than 400 mg, or greater than 500 mg. For example, in some embodiments, the maintenance dose is about 600 mg.

[0127] In some embodiments, each maintenance dose of the IL-23 binding protein is greater than 600 mg, greater than 700 mg, or greater than 800 mg. For example, in some embodiments, the maintenance dose is about 900 mg.

[0128] In some embodiments, each maintenance dose of the IL-23 binding protein is about 75 mg to about 1 g, about 75 mg to about 950 mg, about 75 mg to about 900 mg, about 75 mg to about 850 mg, about 75 mg to about 800 mg, about 75 mg to about 750 mg, about 75 mg to about 700 mg, about 75 mg to about 650 mg, about 75 mg to about 600 mg, about 75 mg to about 550 mg, about 75 mg to about 450 mg, about 75 mg to about 400 mg, about 75 mg to about 350 mg, about 75 mg to about 300 mg, about 75 mg to about 250 mg, about 75 mg to about 200 mg, or about 75 mg to about 150 mg.

[0129] In some embodiments, each maintenance dose of the IL-23 binding protein is about 150 mg to about 1 g, about 150 mg to about 950 mg, about 150 mg to about 900 mg, about 150 mg to about 850 mg, about 150 mg to about 800 mg, about 150 mg to about 750 mg, about 150 mg to about 700 mg, about 150 mg to about 650 mg, about 150 mg to about 600 mg, about 150 mg to about 550 mg, about 150 mg to about 450 mg, about 150 mg to about 400 mg, about 150 mg to about 350 mg, about 150 mg to about 300 mg, about 150 mg to about 250 mg, or about 150 mg to about 200 mg.

[0130] In some embodiments, each maintenance dose of the IL-23 binding protein is about 200 mg to about 1 g, about 200 mg to about 950 mg, about 200 mg to about 900 mg, about 200 mg to about 850 mg, about 200 mg to about 800 mg, about 200 mg to about 750 mg, about 200 mg to about 700 mg, about 200 mg to about 650 mg, about 200 mg to about 600 mg, about 200 mg to about 550 mg, about 200 mg to about 450 mg, about 200 mg to about 400 mg, about 200 mg to about 350 mg, about 200 mg to about 300 mg, or about 200 mg to about 250 mg.

[0131] In some embodiments, each maintenance dose of the IL-23 binding protein is about 250 mg to about 1 g, about 250 mg to about 950 mg, about 250 mg to about 900 mg, about 250 mg to about 850 mg, about 250 mg to about 800 mg, about 250 mg to about 750 mg, about 250 mg to about 700 mg, about 250 mg to about 650 mg, about 250 mg to about 600 mg, about 250

mg to about 550 mg, about 250 mg to about 450 mg, about 250 mg to about 400 mg, about 250 mg to about 350 mg, or about 250 mg to about 300 mg.

[0132] In some embodiments, each maintenance dose of the IL-23 binding protein is about 300 mg to about 1 g, about 300 mg to about 950 mg, about 300 mg to about 900 mg, about 300 mg to about 850 mg, about 300 mg to about 800 mg, about 300 mg to about 750 mg, about 300 mg to about 700 mg, about 300 mg to about 650 mg, about 300 mg to about 600 mg, about 300 mg to about 550 mg, about 300 mg to about 450 mg, about 300 mg to about 400 mg, or about 300 mg to about 350 mg.

[0133] In some embodiments, each maintenance dose of the IL-23 binding protein is about 350 mg to about 1 g, about 350 mg to about 950 mg, about 350 mg to about 900 mg, about 350 mg to about 850 mg, about 350 mg to about 800 mg, about 350 mg to about 750 mg, about 350 mg to about 700 mg, about 350 mg to about 650 mg, about 350 mg to about 600 mg, about 350 mg to about 550 mg, about 350 mg to about 450 mg, or about 350 mg to about 400 mg.

[0134] In some embodiments, each maintenance dose of the IL-23 binding protein is about 400 mg to about 1 g, about 400 mg to about 950 mg, about 400 mg to about 900 mg, about 400 mg to about 850 mg, about 400 mg to about 800 mg, about 400 mg to about 750 mg, about 400 mg to about 700 mg, about 400 mg to about 650 mg, about 400 mg to about 600 mg, about 400 mg to about 550 mg, or about 400 mg to about 450 mg.

[0135] In some embodiments, each maintenance dose of the IL-23 binding protein is about 450 mg to about 1 g, about 450 mg to about 950 mg, about 450 mg to about 900 mg, about 450 mg to about 850 mg, about 450 mg to about 800 mg, about 450 mg to about 750 mg, about 450 mg to about 700 mg, about 450 mg to about 650 mg, about 450 mg to about 600 mg, about 450 mg to about 550 mg, or about 450 mg to about 500 mg.

[0136] In some embodiments, each maintenance dose of the IL-23 binding protein is about 500 mg to about 1 g, about 500 mg to about 950 mg, about 500 mg to about 900 mg, about 500 mg to about 850 mg, about 500 mg to about 800 mg, about 500 mg to about 750 mg, about 500 mg to about 700 mg, about 500 mg to about 650 mg, about 500 mg to about 600 mg, or about 500 mg to about 550 mg.

[0137] In some embodiments, each maintenance dose of the IL-23 binding protein is about 550 mg to about 1 g, about 550 mg to about 950 mg, about 550 mg to about 900 mg, about 550

mg to about 850 mg, about 550 mg to about 800 mg, about 550 mg to about 750 mg, about 550 mg to about 700 mg, about 550 mg to about 650 mg, or about 550 mg to about 600 mg.

[0138] In some embodiments, each maintenance dose of the IL-23 binding protein is about 600 mg to about 1 g, about 600 mg to about 950 mg, about 600 mg to about 900 mg, about 600 mg to about 850 mg, about 600 mg to about 800 mg, about 600 mg to about 750 mg, about 600 mg to about 700 mg, or about 600 mg to about 650 mg.

[0139] In some embodiments, each maintenance dose of the IL-23 binding protein is about 650 mg to about 1 g, about 650 mg to about 950 mg, about 650 mg to about 900 mg, about 650 mg to about 850 mg, about 650 mg to about 800 mg, about 650 mg to about 750 mg, or about 650 mg to about 700 mg.

[0140] In some embodiments, each maintenance dose of the IL-23 binding protein is about 700 mg to about 1 g, about 700 mg to about 950 mg, about 700 mg to about 900 mg, about 700 mg to about 850 mg, about 700 mg to about 800 mg, or about 700 mg to about 750 mg.

[0141] In some embodiments, each maintenance dose of the IL-23 binding protein is about 750 mg to about 1 g, about 750 mg to about 950 mg, about 750 mg to about 900 mg, about 750 mg to about 850 mg, or about 750 mg to about 800 mg.

[0142] In some embodiments, each maintenance dose of the IL-23 binding protein is about 800 mg to about 1 g, about 800 mg to about 950 mg, about 800 mg to about 900 mg, or about 800 mg to about 850 mg.

[0143] In some embodiments, each maintenance dose of the IL-23 binding protein is about 850 mg to about 1 g, about 850 mg to about 950 mg, or about 850 mg to about 900 mg.

[0144] In some embodiments, each maintenance dose of the IL-23 binding protein is about 900 mg to about 1 g or about 900 mg to about 950 mg.

[0145] In some embodiments, each maintenance dose of the IL-23 binding protein is about 950 mg to about 1 g.

[0146] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this disclosure may be in whatever amount as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0147] The specific dose can be a uniform dose in the amounts mentioned herein. Alternatively, a patient's dose can be tailored to the approximate body weight or surface area of

the patient. Other factors in determining the appropriate dosage can include the disease or condition to be treated or prevented, the severity of the disease, the route of administration, and the age, sex, and medical condition of the patient. Further refinement of the calculations necessary to determine the appropriate dosage for treatment is routinely made by those skilled in the art, especially in light of the dosage information and assays disclosed herein. The dosage can also be determined through the use of known assays for determining dosages used in conjunction with appropriate dose-response data. An individual patient's dosage can be adjusted as the progress of the disease is monitored. Blood levels of the targetable construct or complex in a patient can be measured to see if the dosage needs to be adjusted to reach or maintain an effective concentration. Pharmacogenomics may be used to determine which targetable constructs and/or complexes, and dosages thereof, are most likely to be effective for a given individual (Schmitz *et al.*, *Clinica Chimica Acta* 308: 43-53, 2001; Steimer *et al.*, *Clinica Chimica Acta* 308: 33-41, 2001).

Induction doses

[0148] In certain embodiments, *e.g.*, the subject has received an induction dose of the IL-23 binding protein prior to the administering a first maintenance dose. In some embodiments, a single or more than one induction dose is administered, followed by maintenance doses. An induction dose can be administered intravenously or subcutaneously. The induction dose may be higher than a maintenance dose or more frequent than a maintenance dose, *e.g.*, in case potentially by a factor of 2. The induction dose can be administered at once (*e.g.*, in one day) or split into multiple (*e.g.*, two) doses administered in parts a time period apart. In some embodiments, the amount of the induction dose is the same as the amount of each maintenance dose and is administered at once. In some embodiments, the amount of the induction dose is a multiple of the amount of the maintenance dose and is administered in parts, each part of the induction dose having the same amount of IL-23 binding protein as the amount in each maintenance dose. In embodiments in which the induction dose is administered in parts, the interval between each part may be, *e.g.*, at least one week, at least two weeks, at least three weeks, or at least four weeks. In some embodiments, the induction dose is administered in parts, with an interval of about four weeks between each part.

Subjects

[0149] In certain embodiments, the subject to whom IL-23 binding proteins are administered in accordance with the present disclosure is a mammal, such as a primate. In some embodiments, the subject is human.

[0150] In some embodiments, the subject may be suffering from, exhibits at least one symptom of, is diagnosed with, and/or is identified as at risk of gastrointestinal inflammatory disease. In some embodiments, the subject may be suffering from, exhibits at least one symptom of, is diagnosed with, and/or is identified as at risk of inflammatory bowel disease, such as Crohn's disease and/or ulcerative colitis. Crohn's disease, for example, can be a chronic, long-term disease that causes inflammation in a subject's GI tract, and can affect any part of the GI tract from mouth to anus. Crohn's disease can be considered belong to a larger group of conditions related to inflammatory bowel disease or IBD. IBD affects the digestive system but can also cause problems in other parts of the body. Ulcerative colitis, another form of IBD, affects the large intestine (colon).

Routes of administration

[0151] In certain embodiments, the step of administering comprises systemic administration. In certain embodiments, systemic administration comprises parenteral administration, *e.g.*, intravenous administration, intraarterial administration, intraperitoneal administration, subcutaneous administration, or intradermal administration. In some embodiments, systemic administration comprises enteric administration, *e.g.*, trans-gastroenteric administration or oral administration.

[0152] In some embodiments, the step of administering comprises intravenous administration. In some embodiments, the step of administering comprises subcutaneous administration.

Outcomes

[0153] In many embodiments, methods disclosed herein result in a measurable improvement in the subject, *e.g.*, in amelioration or resolution of symptoms. For example, such improvement may include an improvement in a clinical score or a score from a survey or questionnaire associated with, or suitable for assessing, inflammatory bowel disease (*e.g.*, ulcerative colitis and/or Crohn's disease).

IL-23 BINDING PROTEINS

[0154] In one aspect, provided proteins are capable of binding to IL-23 (“IL-23 binding proteins”). In some embodiments, provided binding proteins are capable of binding to an epitope of human IL-23, *e.g.*, an epitope on the p19 subunit of IL-23 (IL-23A).

[0155] In some embodiments, the binding proteins are antibodies or fragments thereof. In some embodiments, the antibodies or fragments thereof are monoclonal antibodies or fragments thereof. In some embodiments, the antibodies or fragments thereof are chimeric antibodies or fragments thereof. In some embodiments, the antibodies or fragments thereof are humanized antibodies or fragments thereof. In some embodiments, the antibodies or antigen-binding fragments are human antibodies.

[0156] Antigen-binding fragments may be, *e.g.*, an scFv, an Fab, an scFab (single-chain Fab). As used herein, the term “scFv” is used in accordance with its common usage in the art to refer to a single chain in which the V_H domain and the V_L domain from an antibody are joined, typically via a linker. As used herein, the term “Fab fragment” is used in accordance with its common usage in the art. Fab fragments typically comprise an entire light chain (V_L and C_L1 domains), the variable region domain of the heavy chain (V_H), and the first constant domain of one heavy chain (C_H1).

[0157] In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in a table selected from Tables 1A-1D. In some embodiments, IL-23 binding proteins further comprise a light chain variable domain comprising complementarity determining regions CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in the same table of Tables 1A-1D.

[0158] In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1A. In some embodiments, IL-23 binding proteins further comprise a light chain variable domain comprising complementarity determining regions CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in the same table of Table 1A. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-H1 shown in Table 1A, CDR-H2 having an

amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-H2 shown in Table 1A, and CDR-H3 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of CDR-H3 shown in Table 1A. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1B. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-H1 shown in Table 1B, CDR-H2 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-H2 shown in Table 1B, and CDR-H3 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of CDR-H3 shown in Table 1B. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1C. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-H1 shown in Table 1C, CDR-H2 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-H2 shown in Table 1C, and CDR-H3 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of CDR-H3 shown in Table 1C. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1D. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain comprises complementarity determining regions CDR-H1 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-H1 shown in Table 1D, CDR-H2 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-H2 shown in Table 1D, and CDR-H3 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of CDR-H3 shown in Table 1D. In some embodiments, IL-23 binding proteins comprise a light chain variable domain comprises complementarity determining regions CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1A. In some embodiments, IL-23 binding proteins comprise a light

chain variable domain comprises complementarity determining regions CDR-L1 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-L1 shown in Table 1A, CDR-L2 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-L2 shown in Table 1A, and CDR-L3 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of CDR-L3 shown in Table 1A. In some embodiments, IL-23 binding proteins comprise a light chain variable domain comprises complementarity determining regions CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1B. In some embodiments, IL-23 binding proteins comprise a light chain variable domain comprises complementarity determining regions CDR-L1 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-L1 shown in Table 1B, CDR-L2 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-L2 shown in Table 1B, and CDR-L3 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of CDR-L3 shown in Table 1B. In some embodiments, IL-23 binding proteins comprise a light chain variable domain comprises complementarity determining regions CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1C. In some embodiments, IL-23 binding proteins comprise a light chain variable domain comprises complementarity determining regions CDR-L1 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-L1 shown in Table 1C, CDR-L2 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-L2 shown in Table 1C, and CDR-L3 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of CDR-L3 shown in Table 1C. In some embodiments, IL-23 binding proteins comprise a light chain variable domain comprises complementarity determining regions CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1D. In some embodiments, IL-23 binding proteins comprise a light chain variable domain comprises complementarity determining regions CDR-L1 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-L1 shown in Table 1D, CDR-L2 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of the CDR-L2 shown in Table 1D, and CDR-L3 having an amino acid sequence with one or two substitutions as compared to the amino acid sequence of CDR-L3 shown in Table 1D.

[0159] In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain with heavy chain variable sequences as shown in a table selected from Tables 1A-1D. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain which is a variant of the heavy chain variable sequence shown in a table selected from Tables 1A-1D, in that the heavy chain variable domain has (1) CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in a table selected from Tables 1A-1D and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain variable domain sequence shown in the same table of Tables 1A-1D. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain with heavy chain variable sequences as shown in Table 1A. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain which is a variant of the heavy chain variable sequence shown in Table 1A, in that the heavy chain variable domain has (1) CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1A and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain variable domain sequence in Table 1A. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain with heavy chain variable sequences as shown in Table 1B. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain which is a variant of the heavy chain variable sequence shown in Table 1B, in that the heavy chain variable domain has (1) CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1B and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain variable domain sequence in Table 1B. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain with heavy chain variable sequences as shown in Table 1C. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain which is a variant of the heavy chain variable sequence shown in Table 1C, in that the heavy chain variable domain has (1) CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1C and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at

least 98%, or at least 99% identical to the amino acid sequence of the heavy chain variable domain sequence in Table 1C. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain with heavy chain variable sequences as shown in Table 1D. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain which is a variant of the heavy chain variable sequence shown in Table 1D, in that the heavy chain variable domain has (1) CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1D and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain variable domain sequence in Table 1D.

[0160] In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain as described herein and further comprise a light chain variable region which has (1) CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in a table selected from Tables 1A-1D and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the light chain variable domain sequence shown in the same table of Tables 1A-1D. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain as described in Table 1A and further comprise a light chain variable region which has (1) CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1A, and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the light chain variable domain sequence shown in Table 1A. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain as described in Table 1B and further comprise a light chain variable region which has (1) CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1B, and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the light chain variable domain sequence shown in Table 1B. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain as described in Table 1C and further comprise a light chain variable region which has (1) CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1C, and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least

93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the light chain variable domain sequence shown in Table 1C. In some embodiments, IL-23 binding proteins comprise a heavy chain variable domain as described in Table 1D and further comprise a light chain variable region which has (1) CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1D, and (2) an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the light chain variable domain sequence shown in Table 1D.

Table 1A. Exemplary heavy chain variable domain, light chain variable domain, and complementarity-determining region sequences of IL-23 binding proteins

IL-23 binding protein	Heavy chain variable domain	Light chain variable domain
Clone MAb001	QVQLVQSGAEVKKPGSSVKVSKASG YTFTTQTLHWMRQAPGQGLEWIGYIY PRDGSTKYNENFKGKVTITADKSTST AYMELSSLRSEDTAVYYCAIPDRSGY AWFQHWGQGTLVTVSS (SEQ ID NO: 1)	DIQMTQSPSSLSASVGDRVITITCKAS RDVAIAVAWYQQKPGKVPKLLIYWAS TRHTGVPSRFSGSGSRTDFTLTISL QPEDVADYFCHQYSSYPFTFGSGTKL EIK (SEQ ID NO: 2)
	<u>Kabat CDRs</u> CDR-H1: TQTLH (SEQ ID NO: 3)	<u>Kabat CDRs</u> CDR-L1: KASRDVAIAVA (SEQ ID NO: 6)
	CDR-H2: YIYPRDGSTKYNENFKG (SEQ ID NO: 4)	CDR-L2: WASTRHT (SEQ ID NO: 7)
	CDR-H3: PDRSGYAWFQH (SEQ ID NO: 5)	CDR-L3: HQYSSYPFT (SEQ ID NO: 8)
	<u>IMGT CDRs</u> CDR-H1: GYTFTTQT (SEQ ID NO: 9)	<u>IMGT CDRs</u> CDR-L1: RDVAIA (SEQ ID NO: 12)
	CDR-H2: IYPRDGST (SEQ ID NO: 10)	CDR-L2: WAS
	CDR-H3: AIPDRSGYAWFQH (SEQ ID NO: 11)	CDR-L3: HQYSSYPFT (SEQ ID NO: 8)

	<u>Chothia CDRs</u> CDR-H1: GYTFTTQ (SEQ ID NO: 13) CDR-H2: YPRDGS (SEQ ID NO: 14) CDR-H3: DRSGYAWFQ (SEQ ID NO: 15)	<u>Chothia CDRs</u> CDR-L1: SRDVAIA (SEQ ID NO: 16) CDR-L2: WAS CDR-L3: YSSYPF (SEQ ID NO: 17)
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Table 1B. Exemplary heavy chain variable domain, light chain variable domain, and complementarity-determining region sequences of IL-23 binding proteins

IL-23 binding protein	Heavy chain variable domain	Light chain variable domain
Clone MAb003	QVQLVQSGAEVKKPGSSVKVCKASG YFTTSQTMHWMRQAPGQGLEWIGYIY PRDDYPKYNDNFKGKVTITADKSTST AYMELSSLRSEDTAVYYCAIPDRSGY AWFHGWGGTLVTVSS (SEQ ID NO: 18) <u>Kabat CDRs</u> CDR-H1: SQTMH (SEQ ID NO: 19) CDR-H2: YIYPRDDYPKYNDNFKG (SEQ ID NO: 20) CDR-H3: PDRSGYAWFIH (SEQ ID NO: 21) <u>IMGT CDRs</u> CDR-H1: GYTFTSQ (SEQ ID NO: 22) CDR-H2: IYPRDDYP (SEQ ID NO: 23) CDR-H3: AIPDRSGYAWFIH	DIQMTQSPSSLSASVGDRVTITCKAS RDVAIAVAWYQQKPGKVPKLLIYWAS TRHTGVPSRFSGSGSRTDFTLTISL QPEDVADYFCHQYSSYPFTFGSGTKL EIK (SEQ ID NO: 2) <u>Kabat CDRs</u> CDR-L1: KASRDVAIAVA (SEQ ID NO: 6) CDR-L2: WASTRHT (SEQ ID NO: 7) CDR-L3: HQYSSYPFT (SEQ ID NO: 8) <u>IMGT CDRs</u> CDR-L1: RDVAIA (SEQ ID NO: 12) CDR-L2: WAS CDR-L3: HQYSSYPFT

	(SEQ ID NO: 24)	(SEQ ID NO: 8)
	<u>Chothia CDRs</u>	<u>Chothia CDRs</u>
	CDR-H1: GYTFTSQ (SEQ ID NO: 25)	CDR-L1: SRDVAIA (SEQ ID NO: 16)
	CDR-H2: YPRDDY (SEQ ID NO: 26)	CDR-L2: WAS
	CDR-H3: DRSGYAWFI (SEQ ID NO: 27)	CDR-L3: YSSYPF (SEQ ID NO: 17)

Table 1C. Exemplary heavy chain variable domain, light chain variable domain, and complementarity-determining region sequences of IL-23 binding proteins

IL-23 binding protein	Heavy chain variable domain	Light chain variable domain
Clone MAb002	EVQLLESGGGLVQPGGSLRLSCAASG YFTFDQTIHWVRQAPGKGLEWIGYIY PRDDSPKYNENFKGRATLSADNSKNT AYLQMNSLRAEDTAVYYCAIPDRSGY AWFIIYWGQGTTTVTVSS (SEQ ID NO: 28) <u>Kabat CDRs</u> CDR-H1: DQTIH (SEQ ID NO: 30) CDR-H2: YIYPRDDSPKYNENFKG (SEQ ID NO: 31) CDR-H3: PDRSGYAWFIY (SEQ ID NO: 32) <u>IMGT CDRs</u> CDR-H1: GYTFTDQT (SEQ ID NO: 33) CDR-H2: IYPRDDSP (SEQ ID NO: 34)	EIVMTQSPATLSVSPGERATLSCKAS RDVAIAVAWYQQKPGQAPRLLLFWAS TRHTGIPARFSGSGSRTEFTLTISL QSEDFAVYYCHQYSSYPFTFGGGTKV EIK (SEQ ID NO: 29) <u>Kabat CDRs</u> CDR-L1: KASRDVAIAVA (SEQ ID NO: 6) CDR-L2: WASTRHT (SEQ ID NO: 7) CDR-L3: HQYSSYPFT (SEQ ID NO: 8) <u>IMGT CDRs</u> CDR-L1: RDVAIA (SEQ ID NO: 12) CDR-L2: WAS

CDR-H3: AIPDRSGYAWFIY (SEQ ID NO: 35)	CDR-L3: HQYSSYPFT (SEQ ID NO: 8)
<u>Chothia CDRs</u> CDR-H1: GYTFTDQ (SEQ ID NO: 36)	<u>Chothia CDRs</u> CDR-L1: SRDVAIA (SEQ ID NO: 16)
CDR-H2: YPRDDS (SEQ ID NO: 37)	CDR-L2: WAS
CDR-H3: DRSGYAWFI (SEQ ID NO: 27)	CDR-L3: YSSYPF (SEQ ID NO: 17)

Table 1D. Exemplary heavy chain variable domain, light chain variable domain, and complementarity-determining region sequences of IL-23 binding proteins

IL-23 binding protein	Heavy chain variable domain	Light chain variable domain
Clone MAb004	QVQLVQSGAEVKKPGSSVKVSCKASG YFTTAQTMHWMRQAPGGLEWIGYIY PRDGSTKYNNFVKGVITADKSTST AYMELSSLRSEDTAVYYCAIPDRSGY AWFIVWGQGTLLTVSS (SEQ ID NO: 38) <u>Kabat CDRs</u> CDR-H1: AQTMH (SEQ ID NO: 39) CDR-H2: YIYPRDGSTKYNNFVKG (SEQ ID NO: 4) CDR-H3: PDRSGYAWFIV (SEQ ID NO: 40) <u>IMGT CDRs</u> CDR-H1: GYTFTAQT (SEQ ID NO: 41) CDR-H2: IYPRDGST (SEQ ID NO: 10)	EIVMTQSPATLSVSPGERATLSCKAS RDVAIAVAWYQQKPGQAPRLLLFWAS TRHTGIPARFSGSGSRTEFTLTISL QSEDFAVYYCHQYSSYPFTFGGGTKV EIK (SEQ ID NO: 29) <u>Kabat CDRs</u> CDR-L1: KASRDVAIAVA (SEQ ID NO: 6) CDR-L2: WASTRHT (SEQ ID NO: 7) CDR-L3: HQYSSYPFT (SEQ ID NO: 8) <u>IMGT CDRs</u> CDR-L1: RDVAIA (SEQ ID NO: 12) CDR-L2: WAS

CDR-H3: AIPDRSGYAWFIV (SEQ ID NO: 42)	CDR-L3: HQYSSYPFT (SEQ ID NO: 8)
<u>Chothia CDRs</u> CDR-H1: GYTFTAQ (SEQ ID NO: 43)	<u>Chothia CDRs</u> CDR-L1: SRDVAIA (SEQ ID NO: 16)
CDR-H2: YPRDGS (SEQ ID NO: 14)	CDR-L2: WAS
CDR-H3: DRSGYAWFI (SEQ ID NO: 27)	CDR-L3: YSSYPF (SEQ ID NO: 17)

[0161] In some embodiments, IL-23 binding proteins comprise a heavy chain and a light chain as shown in Table 1.1A-Table 1.1D.

Table 1.1 A. Exemplary heavy and light chain amino acid sequences of IL-23 binding proteins

IL-23 binding protein	Heavy chain	Light chain
Clone MAb001	QVQLVQSGAEVKKPGSSVKVSCK ASGYTFTTQTLHWMRQAPGQGLE WIGYIYPRDGSTKYNENFKGKVTI TADKSTSTAYMELSSLRSEDTAVY YCAIPDRSGYAWFQHWGQGLVT VSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLYITREPEV TCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSP GK (SEQ ID NO: 165)	DIQMTQSPSSLSASVGDRVITITCK ASRDVAIAVAWYQQKPGKVPKLL IYWASTRHTGVPSRFGSGSRTDF TLTISSLQPEDVADYFCHQYSSYPF TFGSGTKLEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQ DSKDSTYLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 166)

Table 1.1 B. Exemplary heavy and light chain amino acid sequences of IL-23 binding proteins

IL-23 binding protein	Heavy chain	Light chain
Clone MAb003	QVQLVQSGAEVKKPGSSVKVCSK ASGYTFTSQTMHWMRQAPGQGL EWIGYIYPRDDYPKYNDNFKGKV TITADKSTSTAYMELSSLRSEDTA VYYCAIPDRSGYAWFIHWGQGT LVTSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLYITREP EVTCTVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKV SKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTPP VLDSGDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLS LSPGK (SEQ ID NO: 169)	DIQMTQSPSSLSASVGDRVITITCK ASRDVAIAVAWYQQKPGKVPKLL IYWASTRHTGVPSRFSGSGSRTDF LTISSLQPEDVADYFCHQYSSYPF TFGSGTKLEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQ DSKDSTYLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 170)

Table 1.1 C. Exemplary heavy and light chain amino acid sequences of IL-23 binding proteins

IL-23 binding protein	Heavy chain	Light chain
Clone MAb002	VQLLESGGGLVQPGGSLRLSCAAS GYTFTDQTIHWVRQAPGKGLEWI GYIYPRDDSPKYNNFKGRATLSA DNSKNTAYLQMNSLRAEDTAVY YCAIPDRSGYAWFIYWGQGTITV VSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSV	EIVMTQSPATLSVSPGERATLSCK ASRDVAIAVAWYQQKPGQAPRL LFWASTRHTGIPARFSGSGSRTEFT LTISSLQSEDFAVYYCHQYSSYPFT FGGGTKVEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDS KDYSTYLSSTLTLSKADYEKHKVY

TVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLYITREPEV TCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSP GK (SEQ ID NO: 171)	ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 172)
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Table 1.1 D. Exemplary heavy and light chain amino acid sequences of IL-23 binding proteins

IL-23 binding protein	Heavy chain	Light chain
Clone MA004	FPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGTQTY ICNVNHKPSNTKVDDKVEPKSCD KTHTCPPCPAPEAAGGPSVFLFPP KPKDTLYITREPEVTCVVVDVSH DPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK (SEQ ID NO: 167)	EIVMTQSPATLSVSPGERATLSCK ASRDVAIAVAWYQQKPGQAPRL LFWASTRHTGIPARFSGSGSRTEFT LTISSLQSEDFAVYYCHQYSSYPFT FGGGTKVEIKRTVAAPSVFIFPPSD EQLKSGTASVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEEKHKVY ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 168)

[0162] In some embodiments, IL-23 binding proteins comprise a heavy chain as shown in Table 1.1A and a light chain as shown in Table 1.1A. In some embodiments, IL-23 binding proteins comprise (1) CDR-H1, CDR-H2, and CDR-H3 sequences as shown in Table 1A, and (2) a heavy chain having an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid

sequence of the heavy chain shown in Table 1.1A. In some embodiments, IL-23 binding proteins comprise (1) CDR-L1, CDR-L2, and CDR-L3 sequences as shown in Table 1A, and (2) a light chain having an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain shown in Table 1.1A.

[0163] In some embodiments, IL-23 binding proteins comprise a heavy chain as shown in Table 1.1B and a light chain as shown in Table 1.1B. In some embodiments, IL-23 binding proteins comprise (1) CDR-H1, CDR-H2, and CDR-H3 sequences as shown in Table 1B, and (2) a heavy chain having an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain shown in Table 1.1B. In some embodiments, IL-23 binding proteins comprise (1) CDR-L1, CDR-L2, and CDR-L3 sequences as shown in Table 1A, and (2) a light chain having an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain shown in Table 1.1B.

[0164] In some embodiments, IL-23 binding proteins comprise a heavy chain as shown in Table 1.1C and a light chain as shown in Table 1.1C. In some embodiments, IL-23 binding proteins comprise a heavy chain having an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain shown in Table 1.1C, CDR-H1, CDR-H2, and CDR-H3 with sequences as shown in Table 1C, an amino acid sequence that is at least 85% identical to the amino acid sequence of the heavy chain variable domain sequence in Table 1C and asparagine at position 74 of the heavy chain variable domain sequence. In some embodiments, IL-23 binding proteins comprise a light chain having an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain shown in Table 1.1C, CDR-

L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1C and an amino acid sequence that is at least 85% identical to the amino acid sequence of the light chain variable domain sequence in Table 1C and phenylalanine at position 49 of the light chain variable domain sequence. In an embodiment, the amino acid at position 27 of the heavy chain variable domain in Table 1C is not asparagine. In a further embodiment, the amino acid at position 27 of the heavy chain variable domain in Table 1C is a tyrosine. In another embodiment, the amino acid at position 74 the heavy chain variable domain in Table 1C is not lysine. In another embodiment, the amino acid at position 49 of the light chain variable domain in Table 1C is not tyrosine.

[0165] In some embodiments, IL-23 binding proteins comprise a heavy chain as shown in Table 1.1D and a light chain as shown in Table 1.1D. In some embodiments, IL-23 binding proteins comprise (1) CDR-H1, CDR-H2, and CDR-H3 sequences as shown in Table 1B, and (2) a heavy chain having an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain shown in Table 1.1D. In some embodiments, IL-23 binding proteins comprise a light chain having an amino acid sequence that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the heavy chain shown in Table 1.1D, CDR-L1, CDR-L2, and CDR-L3 with sequences as shown in Table 1C and an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence of the light chain variable domain sequence in Table 1D.

[0166] In some embodiments, the IL-23 binding protein comprises: a heavy chain variable domain (VH) comprising (1) an amino acid sequence that is at least 85% identical to amino acid sequence of SEQ ID NO: 28, (2) asparagine at position 74 of SEQ ID NO: 28; and (3) one or more of glutamic acid at position 1, leucine at position 5, glutamic acid at position 6, glycine at position 9, glycine at position 10, leucine at position 11, valine at position 12, glutamine at position 13, glycine at position 16, leucine at position 18, arginine at position 19, leucine at position 20, alanine at position 23, valine at position 37, lysine at position 43, arginine at position 67, leucine at position 70, serine at position 71, alanine at position 68, lysine at position 76,

asparagine at position 77, leucine at position 81, glutamine at position 82, methionine at position 83, asparagine at position 84, alanine a position 88, or threonine at position 115 of SEQ ID NO: 28, (4) complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 30; CDR-H2 comprising the amino acid sequence of SEQ ID NO: 31; and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 32. In some embodiments, the IL-23 protein further comprises (b) a light chain variable domain (VL) comprising: (1) an amino acid sequence that is at least 85% identical to amino acid sequence of SEQ ID NO: 29, and (2) one or more of glutamic acid at position 1, valine at position 3, alanine at position 9, threonine at position 10, valine at position 13, proline at position 15, glutamic acid at position 17, alanine at position 19, leucine at position 21, serine at position 22, glutamine at position 42, alanine at position 43, arginine at position 45, leucine at position 48, phenylalanine at position 49 isoleucine at position 58, alanine at position 60, glutamic acid at position 70, serine at position 80, phenylalanine at position 83, valine at position 85, tyrosine at position 87, glycine at position 100 or valine at position 104 of SEQ ID NO: 29, (3) complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6; CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; an CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.

Fc regions

[0167] IL-23 binding proteins suitable for use in accordance with the present disclosure typically comprise an Fc region, which typically comprises one or more Fc chains. An IgG Fc chain typically contains two constant heavy domains (CH2 and CH3) and a hinge region connected to the CH2 domain. Typical Fc regions comprise two Fc chains which dimerize with one another; however, an Fc region may have a single chain or more than two Fc chains, *e.g.*, as may be present in some antibody formats. In certain embodiments, an Fc region may have one or more modifications (*e.g.*, changes such as deletions, additions, or substitutions to one or more amino acid residues), such as provided herein (*see, e.g.*, Table 2). In some such embodiments, a modification changes a function of an Fc region (*e.g.*, by changing binding affinity to an Fc receptor, *etc.*).

[0168] In some embodiments, IL-23 binding proteins comprise an IgG1 Fc region (*e.g.*, human IgG1 Fc region), that is, except for having particular residue(s) at certain positions as noted herein, the Fc region has an amino acid sequence that is substantially similar to that of the Fc region within a wild type IgG1 Fc. In some embodiments, the wild type IgG1 Fc is a human

IgG1 Fc, in which each Fc chain has an amino acid sequence of SEQ ID NO: 44. In some embodiments, IL-23 binding proteins comprise an Fc region, each Fc chain of which has an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to that of an Fc chain within a wild-type IgG1 Fc.

[0169] In some embodiments, IL-23 binding proteins comprise an IgG2 Fc region (*e.g.*, human IgG2 Fc region), that is, except for having particular residue(s) at certain positions as noted herein, the Fc region has an amino acid sequence that is substantially similar to that of the Fc region within a wild type IgG2 Fc. In some embodiments, the wild type IgG2 Fc is a human IgG2 Fc, in which each Fc chain has an amino acid sequence of SEQ ID NO: 45. In some embodiments, IL-23 binding proteins comprise an Fc region, each Fc chain of which has an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to that of an Fc chain within a wild-type IgG2 Fc.

[0170] In some embodiments, IL-23 binding proteins comprise an IgG4 Fc region (*e.g.*, human IgG4 Fc region), that is, except for having particular residue(s) at certain positions as noted herein, the Fc region has an amino acid sequence that is substantially similar to that of the Fc region within a wild type IgG4 Fc. In some embodiments, the wild type IgG4 Fc is a human IgG4 Fc, in which each Fc chain has an amino acid sequence of SEQ ID NO: 46. In some embodiments, IL-23 binding proteins comprise an Fc region, each Fc chain of which has an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to that of an Fc chain within a wild-type IgG4 Fc.

[0171] In some embodiments, the one or more modifications modify binding to Fc-gamma receptors, *e.g.*, by promoting selective binding, reducing binding, or enhancing binding thereto.

[0172] In some embodiments, an IL-23 binding protein is an anti-IL-23 antibody with an improvement comprising modification of the Fc portion to increase half-life in humans compared to that antibody without such modification, *e.g.*, substitutions corresponding to M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS), for example an increase by a factor of at least two, or at least three, or at least four. In some embodiments the half-life extension modification

is or comprises the YTE modification. In some embodiments the half-life extension modification is or comprises the LS modification.

[0173] In some embodiments, an IL-23 binding protein is an anti-IL-23 antibody with an improvement comprising modification of the framework region (FR) sequence of the heavy chain. In some embodiments, the modification comprises one or more modifications of FR1, FR2, FR3 and FR4 of the heavy chain. In some embodiments, the modification comprises one or more modifications of FR1, FR2, FR3 and FR4. In some embodiments, the modification can comprise non-conservative and/or conservative modifications such as amino acid substitutions. Conservative substitutions of one amino acid for another generally retain side-chain properties. In some cases, conservative substitutions retain the shape or size of the original residue. In some embodiments, the modifications comprise conservative substitutions of one or more of amino acid sequence of FR1, FR2, FR3 and FR4, for example FR1, FR2 and FR3. In some embodiments, the one or modifications comprise asparagine at position 74. In some embodiments, the modification results in a heavy chain variable region sequence of SEQ ID NO: 28. In some embodiments an IL-23 binding protein is an anti-IL-23 antibody with an improvement comprising modification of the complementarity determining region (CDR) of the heavy chain. In some embodiments, the modification results in heavy chain CDR sequences corresponding to CDRs 1, 2, and 3 in Tables 1A, 1B, and 1D.

[0174] In some embodiments, the anti-IL-23 antibody has improved binding affinity to IL-23, more effective inhibition of IL-23-induced activation of STAT3 and/or more effective inhibition of IL-23-induced phosphorylation of STAT3, as compared to a reference antibody (e.g. Reference Antibody 1). In some embodiments, the anti-IL-23 binding antibody is capable of inhibiting activation of STAT3 at a relative IC₅₀ of less than 0.90. In some embodiments, the IL-23 binding protein is capable of inhibiting phosphorylation of STAT3 at a relative IC₅₀ reference of less than 0.80. In some embodiments an IL-23 binding protein comprises modification of the framework region (FR) sequence of the heavy chain and/or light chain, and/or modification of the complementarity determining region (CDR) of the heavy chain as compared to a reference antibody (e.g. Reference Antibody 1).

[0175] In some embodiments, an IL-23 binding protein is means for binding IL-23 with a Fc portion modified to increase half-life in humans compared to that antibody without such modification, *e.g.*, M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS), for

example an increase by a factor of at least two, or at least three, or at least four. In some embodiments the half-life extension modification is the YTE modification. In some embodiments the half-life extension modification is the LS modification.

[0176] In some embodiments, provided is an IL-23 binding protein comprising a means for binding IL-23 with a modified framework region (FR) sequence of the heavy chain. In some embodiments, the modification results in a heavy chain variable region sequence of SEQ ID NO: 28.

[0177] In some embodiments, provided is an IL-23 binding protein comprising a means for binding IL-23 with a modified complementarity determining region (CDR) of the heavy chain. In some embodiments, the modification results in heavy chain CDR sequences corresponding to CDRs 1, 2, and 3 in Tables 1A, 1B, and 1D.

[0178] Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991.

[0179] Amino acid sequences of exemplary Fc sequences are provided in Table 2.

Table 2. Exemplary Fc Sequences

Name	SEQ ID NO	Fc chain sequence
hIgG1	44	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFSVMSVHEALHNHYTQKSLSLSPG
IgG2	45	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVNHHKPSNTKV DKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV

		VVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSDGS FFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSP
hIgG4	46	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDG SFFLYSRLTVDKSRWQEGNVFCSCVMHEALHNHYTQKSLSLGLGK
IgG4-SP (S228P)	47	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDG SFFLYSRLTVDKSRWQEGNVFCSCVMHEALHNHYTQKSLSLGLGK
IgG4-SPLE (S228P/ L235E)	48	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKV DKRVESKYGPPCPPCPAPEELGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDG SFFLYSRLTVDKSRWQEGNVFCSCVMHEALHNHYTQKSLSLGLGK
hIgG1- N297A	49	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL

		PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- D265A	50	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALA (L234A/ L235A)	51	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LAGA (L235A/ G237A)	52	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALAGA (L234A/ L235A/ G237A)	53	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG

hIgG1- LALAPG (L234A/ L235A/ P329G)	54	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1-YTE (M252Y/ S254T/ T256E)	55	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- N297A/YTE	56	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- D265A/YTE	57	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPE VTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- LALA/YTE	58	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPE

		VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LAGA/YTE	59	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLYITREPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALAGA/Y TE	60	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLYITREPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALAPG/Y TE	61	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYITREPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1-LS (M428L/ N434S)	62	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP

		PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPG
hIgG1- N297A/LS	63	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPG
hIgG1- D265A/LS	64	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPG
hIgG1- LALA/LS	65	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPG
hIgG1- LAGA/LS	66	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSVLHEALHSHYTQKSLSLSPG

hIgG1- LALAGA/L S	67	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCSVLHEALHSHYTQKSLSLSPG
hIgG1- LALAPG/LS	68	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCSVLHEALHSHYTQKSLSLSPG
hIgG1-DHS (L309D/ Q311H/ N434S)	69	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVDHHDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHSHYTQKSLSLSPG
hIgG1- N297A/DHS	70	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVDHHDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHSHYTQKSLSLSPG
hIgG1- D265A/DHS	71	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE

		VTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVDHHDWLNQKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHSHYTQKSLSLSPG
hlgG1- LALA/DHS	72	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVDHHDWLNQKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHSHYTQKSLSLSPG
hlgG1- LAGA/DHS	73	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVDHHDWLNQKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHSHYTQKSLSLSPG
hlgG1- LALAGA/D HS	74	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVDHHDWLNQKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHSHYTQKSLSLSPG
hlgG1- LALAPG/D HS	75	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVDHHDWLNQKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLTP

		PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHSHYTQKSLSLSPG
hIgG4-YTE	76	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTCTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFFLYSRLTVDKSRWQEGNVFCSCVMHEALHNHYTQKSLSLSLGK
hIgG4- SP/YTE	77	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTCTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFFLYSRLTVDKSRWQEGNVFCSCVMHEALHNHYTQKSLSLSLGK
hIgG4- SPLE/YTE	78	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTCTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEELGGPSVFLFPPKPKDTLYITREPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFFLYSRLTVDKSRWQEGNVFCSCVMHEALHNHYTQKSLSLSLGK
hIgG4-LS	79	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTCTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFFLYSRLTVDKSRWQEGNVFCSCVLHEALHSHYTQKSLSLSLGK

hIgG4-SP/LS	80	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDG SFFFLYSRLTVDKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLGK
hIgG4- SPLE/LS	81	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKV DKRVESKYGPPCPPCPAPEELGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDG SFFFLYSRLTVDKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLGK
hIgG4-DHS	82	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV DHHDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDG SFFFLYSRLTVDKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLGK
hIgG4- SP/DHS	83	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV DHHDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDG SFFFLYSRLTVDKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLGK
hIgG4- SPLE/DHS	84	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKV DKRVESKYGPPCPPCPAPEELGGPSVFLFPPKPKDTLMISRTPEVTC

		VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV DHHDWLNKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMEALHSHYTQKSLSLSLGK
hlgG2-YTE	85	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKV DKTVERKCCVECPPEPPVAGPSVFLFPPKPKDTLYITREPEVTCV VVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HQDWLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSP
hlgG2-LS	86	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKV DKTVERKCCVECPPEPPVAGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HQDWLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSP
hlgG2-DHS	87	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKV DKTVERKCCVECPPEPPVAGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HHHDWLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMEALHSHYTQKSLSLSP
IgG4-SP	88	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ

		EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPG
hIgG1-LA	89	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHAHYTQKSLSLSPG
hIgG1- N297A/LA	90	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHAHYTQKSLSLSPG
hIgG1- D265A/LA	91	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHAHYTQKSLSLSPG
hIgG1- LALA/LA	92	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHAHYTQKSLSLSPG

hIgG1- LAGA/LA	93	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAELAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHAHYTQKSLSLSPG
hIgG1- LALAGA/L A	94	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHAHYTQKSLSLSPG
hIgG1- LALAPG/L A	95	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHAHYTQKSLSLSPG
hIgG1- N434A	96	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHAHYTQKSLSLSPG

hIgG1- N297A/ N434A	97	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHAHYTQKSLSLSPG
hIgG1- D265A/ N434A	98	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHAHYTQKSLSLSPG
hIgG1- LALA/ N434A	99	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHAHYTQKSLSLSPG
hIgG1- LAGA/ N434A	100	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHAHYTQKSLSLSPG

hIgG1- LALAGA/ N434A	101	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHAHYTQKSLSLSPG
hIgG1- LALAPG/ N434A	102	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHAHYTQKSLSLSPG
hIgG1- N434W	103	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHWHYTQKSLSLSPG
hIgG1- N297A/ N434W	104	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHWHYTQKSLSLSPG

hIgG1- D265A/ N434W	105	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHWHYEQKSLSLSPG
hIgG1- LALA/ N434W	106	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHWHYEQKSLSLSPG
hIgG1- LAGA/ N434W	107	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHWHYEQKSLSLSPG
hIgG1- LALAGA/ N434W	108	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHWHYEQKSLSLSPG

hIgG1- LALAPG/ N434W	109	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHWHYTQKSLSLSPG
hIgG1/DQ (T256D/ T307Q)	110	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- N297A/DQ	111	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LQVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- D265A/DQ	112	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- LALA/DQ	113	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV

		DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPG
hIgG1- LAGA/DQ	114	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPG
hIgG1- LALAGA/D Q	115	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPG
hIgG1- LALAPG/D Q	116	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVHLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPG
hIgG1/DW (T256D/ T307W)	117	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LWVHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF

		PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hlgG1- N297A/DW	118	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LWVLHQDWLNKGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hlgG1- D265A/DW	119	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LWVLHQDWLNKGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hlgG1- LALA/DW	120	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LWVLHQDWLNKGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hlgG1- LAGA/DW	121	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAELAGAPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LWVLHQDWLNKGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG

hIgG1- LALAGA/D W	122	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LWVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- LALAPG/D W	123	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LWVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1/YD (M252Y/T25 6D)	124	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- N297A/YD	125	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- D265A/YD	126	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV

		DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYISRDE VTCVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALA/YD	127	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYISRDE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LAGA/YD	128	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLYISRDE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALAGA/Y D	129	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLYISRDE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALAPG/Y D	130	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLYISRDE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL

		PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1/QVV (T307Q/ Q311V/ A378V)	131	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVLEHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- N297A/QVV	132	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LQVLEHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- D265A/QVV	133	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVLEHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALA/QVV	134	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVLEHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG

hIgG1- LAGA/QVV	135	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVLHVDWLNNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALAGA/Q VV	136	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVLHVDWLNNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1- LALAPG/Q VV	137	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LQVLHVDWLNNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
hIgG1/DDR VV (T256D/ N286D/ T307R/ Q311V/ A378V)	138	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVDNAKTKPREEQYNSTYRVVSV LRVLHVDWLNNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG

hIgG1- N297A/DDR VV	139	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVDNAKTKPREEQYASTYRVVSV LRVLHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- D265A/DDR VV	140	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRDPE VTCVVVAVSHEDPEVKFNWYVDGVEVDNAKTKPREEQYNSTYRVVSV LRVLHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- LALA/DDR VV	141	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVDNAKTKPREEQYNSTYRVVSV LRVLHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
hIgG1- LAGA/DDR VV	142	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVDNAKTKPREEQYNSTYRVVSV LRVLHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG

hIgG1- LALAGA/D DRVV	143	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVDNAKTKPREEQYNSTYRVVSV LRVLHVDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDII VVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPG
hIgG1- LALAPG/D DRVV	144	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRDPE VTCVVVDVSHEDPEVKFNWYVDGVEVDNAKTKPREEQYNSTYRVVSV LRVLHVDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDII VVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPG
hIgG1- Q311R/M42 8L	145	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHRDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNV FSCSV LHEALHNHYTQKSLSLSPG
hIgG4- Q311R/M42 8L	146	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNV DHKPSNTKV DKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHRDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNV FSCSV LHEALHNHYTQKSLSLSPG

IgG4- SP/Q311R/M 428L	147	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHRDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVLHEALHNHYTQKSLSLSPG
IgG4- SPLE/Q311 R/M428L	148	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPHKPSNTKV DKRVESKYGPPCPPCPAPEELGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHRDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSVLHEALHNHYTQKSLSLSPG
IgG2- Q311R/M42 8L	149	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKV DKTVERKCCVECPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVV HRDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVLHEALHNHYTQKSLSLSP
hIgG1- N297A/Q311 R/M428L	150	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKHTCTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHRDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHNHYTQKSLSLSPG

hIgG1- D265A/Q311 R/M428L	151	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVAVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHRDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHNHYTQKSLSLSPG
hIgG1- LALA/Q311 R/M428L	152	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHRDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHNHYTQKSLSLSPG
hIgG1- LAGA/Q311 R/M428L	153	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHRDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHNHYTQKSLSLSPG
hIgG1- LALAGA/Q 311R/M428L	154	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHRDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHNHYTQKSLSLSPG

hIgG1- LALAPG/Q3 11R/M428L	155	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHRDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVVFSCSVLHEALHNHYTQKSLSLSPG
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[0180] In some embodiments, the IL-23 binding protein comprises an Fc region comprising one or more modifications in SEQ ID NO: 44. In some embodiments, the IL-23 binding protein comprises an Fc region comprising one or more modifications in SEQ ID NO: 45. In some embodiments, the IL-23 binding protein comprises an Fc region comprising one or more modifications in SEQ ID NO: 46. In some embodiments, the Fc region comprises an Fc chain whose amino acid sequence has at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity with the amino acid sequence according to any one of SEQ ID NOs: 44-46. In some embodiments, the Fc region comprises an Fc chain whose amino acid sequence is according to any one of SEQ ID NOs: 44-46.

[0181] In certain embodiments, IL-23 binding proteins comprise an Fc region ("modified Fc region") with at least one amino acid modification relative to a wild-type Fc region. IL-23 binding proteins with a modified Fc region may comprise mutations in one Fc chain, or in multiple Fc chains (*e.g.*, when two or more Fc chains are present). Within an IL-23 binding protein with modifications in multiple Fc chains, the modifications on each Fc chain may be the same or different. In some embodiments the modified Fc region comprises a half-life extending mutation or set of mutations, *e.g.*, M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).

[0182] In some embodiments, the modified Fc region comprises a modification selected from the group consisting of: S298A, E333A, K334A, K326A, F243L, R292P, Y300L, V305I, P396L, F243L, R292P, Y300L, L235V, P396L, F243L, S239D, I332E, A330L, S267E, L328F, D265S, S239E, K326A, A327H, G237F, K326E, G236A, D270L, H268D, S324T, L234F, N325L, V266L, S267D, and combinations thereof. In some embodiments, the modified Fc region comprises a modification selected from the group consisting of S228P, M252Y, S254T, T256E,

T256D, T250Q, H285D, T307A, T307Q, T307R, T307W, L309D, Q411H, Q311V, A378V, E380A, M428L, N434A, N434S, N297A, D265A, L234A, L235A, N434W, and combinations thereof.

[0183] In some embodiments, the modified Fc region comprises a specific combination of amino acid substitutions selected from the group consisting of: L234A/L235A; V234A/G237A; L235A/G237A/E318A; S228P/L236E; H268Q/V309L/A330S/A331S; C220S/C226S/C229S/P238S; C226S/C229S/E3233P/L235V/L235A; L234F/L235E/P331S; C226S/P230S; L234A/G237A; L234A/L235A/G237A; Q311R/M428L; L234A/L235A/P329G; and combinations thereof.

[0184] In some embodiments, the modified Fc region comprises a specific combination of amino acid substitutions selected from the group consisting of M428L/N434S (LS); M252Y/S254T/T256E (YTE); T250Q/M428L; T307A/E380A/N434A; T256D/T307Q (DQ); T256D/T307W (DW); M252Y/T256D (YD); T307Q/Q311V/A378V (QVV); T256D/H285D/T307R/Q311V/A378V (DDRVV); L309D/Q311H/N434S (DHS); S228P/L235E (SPLE); L234A/L235A (LALA); M428L/N434A (LA); L234A/G237A (LAGA); L234A/L235A/G237A (LALAGA); L234A/L235A/P329G (LALAPG); N297A/YTE; D265A/YTE; LALA/YTE; LAGA/YTE; LALAGA/YTE; LALAPG/YTE; N297A/LS; D265A/LS; LALA/LS; LAGA/LS; LALAGA/LS; LALAPG/LS; N297A/DHS; D265A/DHS; LALA/DHS; LAGA/DHS; LALAGA/DHS; LALAPG/DHS; SP/YTE; SPLE/YTE; SP/LS; SPLE/LS; SP/DHS; SPLE/DHS; N297A/LA; D265A/LA; LALA/LA; LAGA/LA; LALAGA/LA; LALAPG/LA; N297A/N434A; D265A/N434A; LALA/N434A; LAGA/N434A; LALAGA/N434A; LALAPG/N434A; N297A/N434W; D265A/N434W; LALA/N434W; LAGA/N434W; LALAGA/N434W; LALAPG/N434W; N297A/DQ; D265A/DQ; LALA/DQ; LAGA/DQ; LALAGA/DQ; LALAPG/DQ; N297A/DW; D265A/DW; LALA/DW; LAGA/DW; LALAGA/DW; LALAPG/DW; N297A/YD; D265A/YD; LALA/YD; LAGA/YD; LALAGA/YD; LALAPG/YD; N297A/QVV; D265A/QVV; LALA/QVV; LAGA/QVV; LALAGA/QVV; LALAPG/QVV; N297A/DDRVV; D265A/DDRVV; LALA/DDRVV; LAGA/DDRVV; LALAGA/DDRVV; LALAPG/DDRVV; SP/Q311R/M428L; SPLE/Q311R/M428L; N297A/Q311R/M428L; D265A/Q311R/M428L; LALA/Q311R/M428L; LAGA/Q311R/M428L; LALAGA/Q311R/M428L; LALAPG/Q311R/M428L; and combinations thereof. In some embodiments, the modified Fc region comprises a specific combination of

amino acid substitutions selected from the group consisting of M428L/N434S (LS) and M252Y/S254T/T256E (YTE). In some embodiments, the modified Fc region comprises M428L/N434S (LS) (*e.g.*, SEQ ID NO: 62, SEQ ID NO: 79, SEQ ID NO: 86) modifications. In some embodiments, the modified Fc region comprises M252Y/S254T/T256E (YTE) (*e.g.*, SEQ ID NO: 55, SEQ ID NO: 76, SEQ ID NO: 85) modifications.

[0185] In some embodiments, IL-23 binding proteins described herein include modifications to improve their ability to mediate effector function. Such modifications are known in the art and include afucosylation, or engineering of the affinity of the Fc region towards an activating receptor, mainly FCGR3a for antibody-dependent cellular cytotoxicity (ADCC), and towards C1q for complement-dependent cytotoxicity (CDC).

[0186] In some embodiments, the Fc region comprises one or more amino acid substitutions, wherein the one or more substitutions result in a decrease in one or more of ADCC activity, ADCP activity, or CDC activity compared with the Fc without the one or more substitutions.

[0187] In some aspects, an antibody provided herein comprises an Fc region (*e.g.*, an IgG1 Fc region) with reduced fucose content at position Asn 297 (EU numbering) compared to a naturally occurring Fc region. Such Fc regions are known to confer improved ADCC activity to the binding proteins which comprise them. In some aspects, such binding proteins do not comprise any fucose at position Asn 297.

[0188] In some embodiments, IL-23 binding proteins described herein comprise an Fc region with one or more amino acid substitutions which improve ADCC, such as a substitution at one or more of positions 298, 333, and 334 of an Fc chain. In some embodiments, an antibody provided herein comprises an Fc region with one or more amino acid substitutions at positions 239, 332, and 330.

[0189] In some embodiments, the Fc region comprises an Fc chain whose amino acid sequence has at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity with the amino acid sequence according to any one of SEQ ID NOs: 44-155. In some embodiments, the Fc region comprises an Fc chain whose amino acid sequence is according to any one of SEQ ID NOs: 44-155.

[0190] In some embodiments, IL-23 binding proteins described herein comprise an Fc region with at least one galactose residue in the oligosaccharide attached to the Fc region. Such antibody variants may have improved CDC function.

[0191] In some embodiments, IL-23 binding proteins described herein comprise one or more alterations that improve or diminish C1q binding and/or CDC.

[0192] In certain embodiments, IL-23 binding proteins comprise an Fc region with one or more amino acid substitutions, wherein the one or more substitutions result in an increase in antibody half-life, and a decrease in one or more of ADCC activity, ADCP activity, or CDC activity compared with a comparable IL-23 binding protein whose Fc region lacks the one or more substitutions. In certain embodiments, the one or more amino acid substitutions results in increased binding protein half-life at pH 6.0 compared to binding protein comprising a wild-type Fc region. In certain embodiments, the antibody has an increased half-life that is about 10,000-fold, 1,000-fold, 500-fold, 100-fold, 50-fold, 20-fold, 10-fold, 9-fold, 8-fold, 7-fold, 6-fold, 5-fold, 4.5-fold, 4-fold, 3.5-fold, 3-fold, 2.5-fold, 2-fold, 1.95-fold, 1.9-fold, 1.85-fold, 1.8-fold, 1.75-fold, 1.7-fold, 1.65-fold, 1.6-fold, 1.55-fold, 1.50-fold, 1.45-fold, 1.4-fold, 1.35-fold, 1.3-fold, 1.25-fold, 1.2-fold, 1.15-fold, 1.1-fold, or 1.05-fold longer compared to an antibody comprising a wild-type Fc region.

[0193] In certain embodiments, IL-23 binding proteins comprise an Fc region which comprise one or more amino acid substitutions, wherein the one or more substitutions result in a decrease in one or more of ADCC activity, ADCP activity, or CDC activity compared comparable IL-23 binding protein whose Fc region lacks the one or more substitutions.

[0194] In certain embodiments, the Fc region binds an Fc γ Receptor selected from the group consisting of: Fc γ RI, Fc γ RIIa, Fc γ RIIb, Fc γ RIIc, Fc γ RIIIa, and Fc γ RIIIb. In certain embodiments, the Fc region binds an Fc γ Receptor with higher affinity at pH 6.0 compared to an antibody comprising a wild-type Fc region.

[0195] In some embodiments, the IL-23 binding proteins comprise an extended half-life (i.e., serum half-life), *e.g.*, in human serum or in humans. In some embodiments, the IL-23 binding proteins comprise a half-life of at least about 14, 28, 42, 56, 70, 84, 96, or more than 96 weeks. In some embodiments, the IL-23 binding proteins comprise a half-life in a range of about 14 days to about 96 days, about 14 days to about 84 days, about 14 days to about 70 days, about 14 days to about 56 days, about 14 days to about 42 days, about 14 days to about 28 days, of about 28 days to about 96 days, about 28 days to about 84 days, about 28 days to about 70 days, about 28 days to about 56 days, about 28 days to about 42 days, of about 42 days to about 96 days, about 42 days to about 84 days, about 42 days to about 70 days, or about 42 days to about 56

days. In some embodiments, the IL-23 binding proteins comprise a half-life in a range of about 42 days to about 56 days. In some embodiments, the IL-23 binding proteins comprise a half-life in a range of about 74 days to about 93 days. In some embodiments, the IL-23 binding proteins comprise a half-life of at least about 50 days, at least about 55 days, at least about 60 days, at least about 65 days, at least about 70 days, at least about 75 days, at least about 80 days, at least about 85 days, at least about 90 days, or at least about 93 days. In some embodiments, the IL-23 binding proteins comprise a half-life of about 50 days, about 55 days, about 60 days, about 65 days, about 70 days, about 75 days, about 80 days, about 85 days, about 90 days, about 93 days or about 100 days. Methods of measuring half-life are known in the art. In some embodiments, the half-life is measured in a non-human primate. In some embodiments, the half-life is measured in a human. In some embodiments, the half-life is measured following intravenous administration. In some embodiments, the half-life is measured following subcutaneous administration.

[0196] In some embodiments, IL-23 binding proteins described herein have a half-life that is at least 20% longer than a reference binding protein. In some embodiments, the half-life of IL-23 binding proteins described herein is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% longer than the half-life of the reference binding protein. In some embodiments, the half-life of the IL-23 binding proteins described herein is longer than the half-life of the reference binding protein by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, or at least 10 fold.

Antibody fragments

[0197] In certain embodiments, provided are antibody fragments, rather than whole antibodies.

[0198] Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, *e.g.*, Morimoto et al., *Journal of Biochemical and Biophysical Methods* 24:107-117 (1992); and Brennan et al., *Science*, 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the production of large amounts of these fragments. Antibody fragments can be isolated from, *e.g.*, antibody phage libraries. Alternatively or additionally, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled

to form F(ab')₂ fragments (Carter et al., Bio/Technology 10:163-167 (1992)). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')₂ fragment with increased in vivo half-life comprising a salvage receptor binding epitope residues are described, *e.g.*, in U.S. Pat. No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner.

[0199] In some embodiments, the antigen-binding fragment is a single chain Fv fragment (scFv). See, *e.g.*, WO 93/16185; U.S. Pat. No. 5,571,894; and U.S. Pat. No. 5,587,458. Fv and scFv are species with intact combining sites that are devoid of constant regions; thus, these fragments may be suitable for reduced nonspecific binding during in vivo use. scFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an scFv. See, *e.g.*, Antibody Engineering, ed. Borrebaeck. An antigen-binding antibody fragment may also be a "linear antibody", *e.g.*, as described in U.S. Pat. No. 5,641,870.

VECTORS, HOST CELLS AND RECOMBINANT METHODS

[0200] Also provided are isolated nucleic acids encoding IL-23 binding proteins (*e.g.*, antibodies and antigen-binding fragments), vectors and host cells comprising the nucleic acid, and recombinant techniques for the production of the antibody.

[0201] For recombinant production of the antibody or antigen-binding fragment, a nucleic acid encoding the antibody or antigen-binding fragment may be isolated and inserted into a replicable vector for further cloning (amplification of the DNA) or for expression. DNA encoding the monoclonal antibody can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). Many vectors are available. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence.

PHARMACEUTICAL COMPOSITIONS

[0202] The present disclosure also includes pharmaceutical compositions that contain therapeutically effective amounts of the IL-23 binding proteins or methods using such pharmaceutical compositions.

[0203] In certain embodiments, provided antibodies are incorporated together with one or more pharmaceutically acceptable carriers into a pharmaceutical composition suitable for administration to a subject. As used herein, “pharmaceutically acceptable carrier” refers to any of a variety of solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include, but are not limited to, water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof.

[0204] In some embodiments, pharmaceutical compositions comprise one or more tonicity agents or stabilizers. Non-limiting examples of such tonicity agents or stabilizers include sugars (*e.g.*, sucrose), polyalcohols (*e.g.*, mannitol or sorbitol), and sodium chloride.

[0205] In some embodiments, pharmaceutical compositions comprise one or more bulking agents and/or lyoprotectants (*e.g.*, mannitol or glycine), buffers (*e.g.*, phosphate, acetate, or histidine buffers), surfactants (*e.g.*, polysorbates), antioxidants (*e.g.*, methionine), and/or metal ions or chelating agents (*e.g.*, ethylenediaminetetraacetic acid (EDTA)).

[0206] In some embodiments, pharmaceutical compositions comprise one or more auxiliary substances such as wetting or emulsifying agents, preservatives (*e.g.*, benzyl alcohol) or buffers, which may enhance the shelf life and/or effectiveness of antibodies disclosed herein.

[0207] A detergent or surfactant may also be added to a pharmaceutical composition. Exemplary detergents include nonionic detergents such as polysorbates (*e.g.*, polysorbates 20, 80 etc.) or poloxamers (*e.g.*, poloxamer 188). The amount of detergent added is such that it reduces aggregation of the formulated antibody and/or minimizes the formation of particulates in the formulation and/or reduces adsorption. In some embodiments, the formulation may include a surfactant which is a polysorbate. In some embodiments, the formulation may contain the detergent polysorbate 80 or Tween 20. Tween 20 is a term used to describe polyoxyethylene (20) sorbitanmonooleate (*see* Fiedler, *Lexikon der Hilfsstoffe*, Editio Cantor Verlag Aulendorf, 4th edi., 1996).

[0208] Pharmaceutical compositions may be provided in any of a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. Suitability of certain forms may depend on the intended mode of administration and therapeutic application.

[0209] In some embodiments, the pharmaceutical composition is a liquid composition. In some embodiments, the pharmaceutical composition is formulated for subcutaneous administration. In some embodiments, the pharmaceutical composition is formulated for intravenous administration. In some embodiments, the liquid composition contains at least about 100 mg/mL, at least about 125 mg/mL or at least about 150 mg/mL of an IL-23 binding antibody.

[0210] In some embodiments, pharmaceutical compositions are in the form of injectable or infusible solutions. In some embodiments, the injectable or infusible solution is suitable for intravenous injection or infusion. In some embodiments, the injectable or infusible solution is suitable for subcutaneous injection or infusion.

[0211] In some embodiments, the injectable dosage form comprises at least about 100 mg/mL, at least 125 mg/mL or at least about 150 mg/mL of an IL-23 binding antibody. For example, the injectable dosage form comprises from at least about 100 mg/mL to at least 110 mg/mL, from at least about 110 mg/mL to at least 120 mg/mL, from at least about 120 mg/mL to at least 130 mg/mL, from at least about 130 mg/mL to at least 140 mg/mL, from at least about 140 mg/mL to at least 150 mg/mL of the IL-23 binding antibody.

[0212] Pharmaceutical compositions are typically sterile and stable under conditions of manufacture, transport, and storage. Pharmaceutical compositions may be formulated as, for example, a solution, microemulsion, dispersion, liposome, or other ordered structure. In some embodiments, a pharmaceutical composition is formulated as a structure particularly suitable for high drug concentration. For example, sterile injectable solutions can be prepared by incorporating a therapeutic agent (*e.g.*, antibody) in a desired amount in an appropriate solvent with one or a combination of ingredients enumerated herein, optionally followed by sterilization (*e.g.*, filter sterilization). Generally, dispersions may be prepared by incorporating an antibody into a sterile vehicle that contains a basic dispersion medium and other ingredient(s) such as those additional ingredients mentioned herein. In the case of sterile powders for the preparation of sterile injectable solutions, examples of preparation methods include vacuum drying and freeze-drying to yield a powder of the antibody and any additional desired ingredient(s), *e.g.*, from a previously sterile-filtered solution thereof.

[0213] Proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by maintaining certain particle sizes (*e.g.*, in the case of dispersions), and/or by

using surfactants. Prolonged absorption of injectable compositions can be brought about, *e.g.*, by including in the composition an agent that delays absorption (for example, monostearate salts and/or gelatin).

[0214] The IL-23 binding protein may be lyophilized to produce a lyophilized formulation including the proteins and a lyoprotectant. The lyoprotectant may be sugar, *e.g.*, disaccharides. In some embodiments, the lyoprotectant is sucrose or maltose. The lyophilized formulation may also include one or more of a buffering agent, a surfactant, a bulking agent, and/or a preservative.

METHODS OF PREPARATION

[0215] The IL-23 binding proteins described herein can be made using recombinant DNA technology well known to a skilled person in the art. For example, one or more isolated polynucleotides encoding the IL-23 binding protein can be ligated to other appropriate nucleotide sequences, including, for example, constant region coding sequences, and expression control sequences, to produce conventional gene expression constructs (*i.e.*, expression vectors) encoding the desired IL-23 binding proteins. Production of defined gene constructs is within routine skill in the art.

[0216] Nucleic acids encoding desired IL-23 binding proteins can be incorporated (ligated) into expression vectors, which can be introduced into host cells through conventional transfection or transformation techniques. Exemplary host cells are *E. coli* cells, Chinese hamster ovary (CHO) cells, human embryonic kidney 293 (HEK 293) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and myeloma cells that do not otherwise produce IgG protein. Transformed host cells can be grown under conditions that permit the host cells to express the genes that encode IL-23 binding proteins.

[0217] Specific expression and purification conditions will vary depending upon the expression system employed. For example, if a gene is to be expressed in *E. coli*, it is first cloned into an expression vector by positioning the engineered gene downstream from a suitable bacterial promoter, *e.g.*, Trp or Tac, and a prokaryotic signal sequence. The expressed protein may be secreted. The expressed protein may accumulate in refractile or inclusion bodies, which can be harvested after disruption of the cells by French press or sonication. The refractile bodies can then be solubilized, and the protein may be refolded and/or cleaved by methods known in the art.

[0218] If the engineered gene is to be expressed in eukaryotic host cells, *e.g.*, CHO cells, it is first inserted into an expression vector containing a suitable eukaryotic promoter, a secretion signal, a poly A sequence, and a stop codon. Optionally, the vector or gene construct may contain enhancers and introns. In embodiments involving fusion proteins comprising an IL-23 binding protein or portion thereof, the expression vector optionally contains sequences encoding all or part of a constant region, enabling an entire, or a part of, a heavy or light chain to be expressed. The gene construct can be introduced into eukaryotic host cells using conventional techniques.

[0219] In some embodiments, in order to express an IL-23 binding protein, an N-terminal signal sequence is included in the protein construct. Exemplary N-terminal signal sequences include signal sequences from interleukin-2, CD-5, IgG kappa light chain, trypsinogen, serum albumin, and prolactin.

[0220] After transfection, single clones can be isolated for cell bank generation using methods known in the art, such as limited dilution, ELISA, FACS, microscopy, or Clonepix. Clones can be cultured under conditions suitable for bio-reactor scale-up and maintained expression of the IL-23 binding proteins.

[0221] The IL-23 binding proteins can be isolated and purified using methods known in the art including centrifugation, depth filtration, cell lysis, homogenization, freeze-thawing, affinity purification, gel filtration, ion exchange chromatography, hydrophobic interaction exchange chromatography, and mixed-mode chromatography.

[0222] In some aspects, the disclosure provides a method of treating a patient suffering from a gastrointestinal inflammatory disease by administering an IL-23 binding protein with an Fc domain, the improvement comprising said Fc region having a modification that extends half-life of the IL-23 binding protein as compared to an IL-23 binding protein that does not comprise the modification. In some embodiments the modification comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).

[0223] In some aspects, the disclosure provides a method of treating a patient suffering from a gastrointestinal inflammatory disease by administering an IL-23 binding protein with a heavy chain variable region, the improvement comprising modification of the framework region sequence of the heavy chain that results in the IL-23 binding protein having an improved binding affinity to IL-23 as compared to a reference antibody having a heavy chain variable region

sequence of SEQ ID NO: 156. In some embodiments, the modification results in a heavy chain variable region sequence of SEQ ID NO: 28 and a light chain variable region of SEQ ID NO: 29.

[0224] In some aspects, the disclosure provides a method of treating a patient suffering from a gastrointestinal inflammatory disease by administering an IL-23 binding protein with a heavy chain variable region, the improvement comprising modification of the complementarity determining regions (CDRs) sequences of the heavy chain that results in the IL-23 binding protein inhibiting activation of STAT3 at a relative IC_{50} of less than 0.90 and inhibiting phosphorylation of STAT3 at a relative IC_{50} reference of less than 0.80 as compared to a Reference Antibody 1 having CDRs as set forth in Table 3. In some embodiments, the modification results in heavy chain CDR sequences corresponding to CDRs 1, 2, and 3 in Tables 1A, 1B, and 1D.

[0225] In some aspects, the disclosure provides a method of treating a gastrointestinal inflammatory disease in a subject comprising a step of administering to the subject a means for binding IL-23 with a Fc portion modified to increase half-life in humans compared to that means for binding IL-23 without such modification. In some embodiments, the modification comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS). In some embodiments, the modification increases half-life by a factor of at least two, at least three, or at least four times as compared to the half-life of the IL-23 binding protein without the modification.

[0226] In some aspects, the disclosure provides a method of treating a gastrointestinal inflammatory disease in a subject comprising a step of administering to the subject a means for binding IL-23 with a modified framework region sequence of the heavy chain that improves binding affinity to IL-23 as compared to reference antibody having a heavy chain variable region sequence of SEQ ID NO: 156. Examples of means for binding human IL-23 include the antibodies or fragments described herein, including the IL-23 binding proteins having certain amino acid sequences of immunoglobulin heavy chain and/or light chains as described herein. In some embodiments, the modification results in a heavy chain variable region sequence of SEQ ID NO: 28 and a light chain variable region of SEQ ID NO: 29.

[0227] In some aspects, the disclosure provides a method of treating a gastrointestinal inflammatory disease in a subject comprising a step of administering to the subject a means for

binding IL-23 with a modified complementarity determining region of the heavy chain that inhibits activation of STAT3 at a relative IC₅₀ of less than 0.90 and/or inhibits phosphorylation of STAT3 at a relative IC₅₀ reference of less than 0.85 relative to a reference antibody having CDRs as set forth in Table 3. In some embodiments, the modification results in heavy chain CDR sequences corresponding to CDRs 1, 2, and 3 in Tables 1A, 1B, and 1D.

[0228] In some aspects, the disclosure provides an IL-23 binding protein with an Fc domain, the improvement comprising said Fc region having a modification that extends half-life of the IL-23 binding protein as compared to an IL-23 binding protein that does not comprise the modified Fc region. In some embodiments, the Fc region modification comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS)

[0229] In some aspects, the disclosure provides an IL-23 binding protein with a heavy chain variable region, the improvement comprising modification of the framework region sequence of the heavy chain that results in the IL-23 binding protein having an improved binding affinity to IL-23 as compared to reference antibody having a heavy chain variable region sequence of SEQ ID NO: 156. In some embodiments, the modification results in a heavy chain variable region sequence of SEQ ID NO: 28 and a light chain variable region of SEQ ID NO: 29.

[0230] In some aspects, the disclosure provides an IL-23 binding protein with a heavy chain variable region, the improvement comprising modification of the complementarity determining regions sequences of the heavy chain that results in the IL-23 binding protein inhibiting activation of STAT3 at a relative IC₅₀ of less than 0.90 and/or inducing phosphorylation of STAT3 at a relative IC₅₀ reference of less than 0.85 relative to a reference antibody having CDRs as set forth in Table 3. In some embodiments, the modification results in heavy chain CDR sequences corresponding to CDRs 1, 2, and 3 in Tables 1A, 1B, and 1D.

[0231] In some aspects, the disclosure provides a means for binding IL-23 with a Fc portion modified to increase half-life in humans compared to that means for binding IL-23 without such modification. In some embodiments, the modification comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS). In some embodiments, the modification increases half-life by a factor of at least two, at least three, or at least four.

[0232] In some aspects, the disclosure provides a means for binding IL-23 having a modified framework region sequence of a heavy chain that results in improved binding affinity to IL-23 as

compared to reference antibody having a heavy chain variable region sequence of SEQ ID NO: 156. In some embodiments, the modification results in a heavy chain variable region sequence of SEQ ID NO: 28 and a light chain variable region of SEQ ID NO: 29.

[0233] In some aspects, the disclosure provides means for binding IL-23 having a modified complementarity determining region (CDR) of a heavy chain that results in inhibiting activation of STAT3 at a relative IC_{50} of less than 0.90 and/or inhibiting phosphorylation of STAT3 at a relative IC_{50} reference of less than 0.85 relative to a reference antibody having CDRs as set forth in Table 3. In some embodiments, the modification results in heavy chain CDR sequences corresponding to CDRs 1, 2, and 3 in Tables 1A, 1B, and 1D.

[0234] In some aspects, the disclosure provides an IL-23 binding protein comprising a means for binding human IL-23 with higher affinity than a reference antibody comprising a heavy chain variable region sequence of SEQ ID NO: 156 and a light chain variable region and a constant region of SEQ ID NO: 2, and a constant region which has been modified to increase in vivo half-life by at least 1, 2 or 3 fold compared to the same binding protein with an unmodified constant region. In some embodiments, the constant region is a human IgG1 region comprising amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).

[0235] In another aspect, the disclosure provides the IL-23 binding protein or composition as provided herein for use in treatment of a disease or condition. In another aspect, the disclosure provides use of the IL-23 binding protein or composition as provided herein in a method of treating a disease or condition. In another aspect, the disclosure provides use of the IL-23 binding protein or composition as provided herein in the manufacture of a medicament for treating a disease or condition. In some embodiments, the disease or condition is an inflammatory disease or condition. In some embodiments, the disease or condition is gastrointestinal inflammatory disease. In some embodiments, the disease or condition is inflammatory bowel disease. In some embodiments, the disease or condition is Crohn's disease. In some embodiments, the disease or condition is ulcerative colitis.

EXAMPLES

Example 1. Affinity Maturation of anti-IL-23p19 Antibody

[0236] An anti-human IL-23p19 antibody whose sequences are shown in Table 3 below ("Reference Antibody 1") was used as a parental antibody for further CDR diversification to identify clones with improvements in potency, manufacturability, and pharmacokinetics.

Table 3: Reference Antibody 1 - characteristic sequences

CDR sequences shown are according to Kabat.

Heavy chain	Light chain
Full sequence: QVQLVQSGAEVKKPGSSVKVSKASGYTFTDQ TIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYC AIPDRSGYAWFIYWGQGLTVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKRVKPKSCD KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFCFSVMHEALHNHYTQKSLSLSP G (SEQ ID NO: 173) <u>Variable domain (VH)</u> QVQLVQSGAEVKKPGSSVKVSKASGYTFTDQ TIHWMRQAPGQGLEWIGYIYPRDDSPKYNENF KGKVTITADKSTSTAYMELSSLRSEDTAVYYC AIPDRSGYAWFIYWGQGLTVTVSS (SEQ ID NO: 156) CDR-H1: DQTIH (SEQ ID NO: 30) CDR-H2: YIYPRDDSPKYNENFKG (SEQ ID NO: 31) CDR-H3:	Full sequence: DIQMTQSPSSLSASVGDRVTITCKASRDVAIAV AWYQQKPGKVPKLLIYWASTRHTGVPSRFSGSG SRTDFTLTISLQPEDVADYFCHQYSSYPFTFG SGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNFFYPREAKVQWKVDNALQSGNSQESVTE QDSKDYSLSSLTLSKADYEEKHKVYACEVTH QGLSSPVTKSFNREGC (SEQ ID NO: 174) Variable domain (VL) DIQMTQSPSSLSASVGDRVTITCKASRDVAIAV AWYQQKPGKVPKLLIYWASTRHTGVPSRFSGSG SRTDFTLTISLQPEDVADYFCHQYSSYPFTFG SGTKLEIK (SEQ ID NO: 2) CDR-L1: KASRDVAIAVA (SEQ ID NO: 6) CDR-L2: WASTRHT (SEQ ID NO: 7) CDR-L3: HQYSSYPFT

PDRSGYAWFTY (SEQ ID NO: 32)	(SEQ ID NO: 8)
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[0221] Site-directed PCR mutagenesis was employed to generate distinct libraries for heavy chain CDR1/2 and heavy chain CDR3. Additionally, an additional library consisting of naive human kappa light chain CDRs was prepared. This approach resulted in three unique libraries. Individual mutants were displayed as Fabs in a phage display system and within each library, mutants were panned through two or three rounds of selection.

[0222] For the heavy chain mutant libraries, the first round of selection consisted of 0.01 nM biotinylated human IL-23 (hIL-23) while also being washed for 2 hours at room temperature in buffer containing 1 nM unlabeled hIL-23. The output of that round was subsequently split into four distinct secondary rounds of parallel selection consisting of A) 0.01 nM biotinylated hIL-23 while also being washed for 20 hours at room temperature in buffer containing 10 nM of unlabeled hIL-23, B) 0.001 nM biotinylated hIL-23 while also being washed for 20 hours at room temperature in buffer containing 1 nM of unlabeled hIL-23, C) 0.01 nM biotinylated cynomolgus monkey IL-23 (cyIL-23) while also being washed for 20 hours at room temperature in buffer containing 10 nM of unlabeled cyIL-23, and D) 0.001 nM biotinylated cyIL-23 while also being washed for 20 hours at room temperature in buffer containing 1 nM of unlabeled cyIL-23.

[0223] For the light chain mutant libraries, the first round of selection consisted of 10 nM biotinylated hIL-23 while also being washed for 2 hours at room temperature in buffer containing 1000 nM unlabeled hIL-23. The output of that round was subsequently split into two distinct secondary rounds of parallel selection consisting of A) 1 nM biotinylated hIL-23 while also being washed for 16 hours at room temperature in buffer containing 100 nM of unlabeled hIL-23, B) 0.1 nM biotinylated hIL-23 while also being washed for 16 hours at room temperature in buffer containing 10 nM of unlabeled hIL-23. These outputs were then subsequently split into two additional tertiary rounds of parallel selection consisting of A) 0.1 nM biotinylated cyIL-23 while also being washed for 20 hours at room temperature in buffer containing 100 nM of unlabeled cyIL-23 and B) 0.01 nM biotinylated cyIL-23 while also being washed for 20 hours at room temperature in buffer containing 10 nM of unlabeled cyIL-23.

[0224] Mutant clones from the output of each arm of secondary and tertiary selection were analyzed for off rate (kd) as a proxy for binding affinity by using periplasmic extracts of each

mutant clone through surface plasmon resonance (SPR) using a BIACORE™ 8K+ SPR system (Cytiva). Sensor chips (Series S Sensor Chip CM5 – Cytiva) were prepared by immobilizing hIL-23 (Acro Biosciences) and interaction with periplasmic extracts was analyzed in order to determine the *k_d*. Bioinformatic analyses of sequences to identify patterns of enrichment were also employed to characterize mutant clones. Mutants that exhibited no loss or improved binding relative to the reference antibody as well as population enrichment throughout the selection were combined into a single library comprising all mutants in both the heavy and light chain.

[0225] Clones containing a random combinatorial mix of these individual CDR mutants were again screened in a phage display system, with multiple combinations of selection strategies outlined in Table 4. Mutant clones from the output of each arm of secondary selection were once again analyzed for *k_d* as described.

Table 4

Strategy	Round 1 Selection	Round 2 Selection
Strategy 1	Antigen: 0.01 nM biotinylated hIL-23 Wash: 16 hr R.T w/ 1 nM unlabeled hIL-	Antigen: 0.01 nM biotinylated hIL-23 Wash: 48 hr R.T. w/ 1 nM unlabeled hIL-23
Strategy 2	Antigen: 0.01 nM biotinylated hIL-23 Wash: 16 hr R.T w/ 1 nM unlabeled hIL-23	Antigen: 0.001 nM biotinylated hIL-23 Wash: 24 hr R.T. w/ 1 nM unlabeled hIL-23
Strategy 3	Antigen: 0.01 nM biotinylated hIL-23 Wash: 16 hr R.T w/ 1 nM unlabeled hIL-23	Antigen: 0.0001 nM biotinylated hIL-23 Wash: 24 hr R.T. w/ 0.1 nM unlabeled hIL-23
Strategy 4	Antigen: 0.01 nM biotinylated hIL-23 Wash: 16 hr R.T w/ 1 nM unlabeled hIL-23	Antigen: 0.001 nM biotinylated cyIL-23 Wash: 24 hr R.T. w/ 1 nM unlabeled cyIL-23
Strategy 5	Antigen: 0.01 nM biotinylated hIL-23 Wash: 16 hr R.T w/ 1 nM unlabeled hIL-23	Antigen: 0.0001 nM biotinylated cyIL-23 Wash: 24 hr R.T. w/ 0.1 nM unlabeled cyIL-23

[0226] Mutant clones of interest (clones MAb001 and MAb003) were then reformatted to full antibody format. Briefly, the coding sequences for the heavy chain and light chain of the antibody were generated by DNA synthesis and PCR, then subsequently subcloned into plasmids for protein expression in a mammalian cell system. The gene sequences in the expression vectors were confirmed by DNA sequencing. Antibodies were then purified by a two-step affinity chromatography (Protein A) and size-exclusion chromatography process.

Example 2. Humanization of an anti-IL-23p19 Antibody

[0227] Complementarity-determining region (CDR) grafting technology was used to humanize the parental mouse hybridoma sequence of Reference Antibody 1 (see Table 3 above).

[0228] The parental mAb light chain sequence of the mouse hybridoma sequence was compared to a group of human variable region light chain (VK) germline amino acid sequences (Lefranc, M.-P. IMGT, the international ImMunoGeneTics database; Nucleic Acids Res., 29, D207-209 (2001). DOI:10.1093/nar/29.1.207. PMID:11125093). Human germline IGKV3-15 and human germline IGKJ4 were selected.

[0229] The parental mAb heavy chain sequence of the mouse hybridoma sequence was compared to a group of human variable region heavy chain (VH) germline amino acid sequences (Lefranc, M.-P. IMGT, the international ImMunoGeneTics database; Nucleic Acids Res., 29, D207-209 (2001). DOI:10.1093/nar/29.1.207. PMID:11125093). Human germline IGKV3-23 and human germline IGHJ6 were selected.

[0230] The resulting humanized VL and VH were then combined and reformatted to full antibody format, generating clone mAb002. Briefly, the coding sequences for the heavy chain and light chain of the antibody were generated by DNA synthesis and PCR, then subsequently subcloned into plasmids for protein expression in a mammalian cell system. The gene sequences in the expression vectors were confirmed by DNA sequencing. Antibodies were then purified by a two-step affinity chromatography (Protein A) and size-exclusion chromatography process.

Example 3. Affinity Maturation and Humanization of anti-IL-23p19 Antibody

[0231] Reference Antibody 1 (see Table 3 above) was used as a parental antibody for further CDR diversification to identify clones with improvements in potency, manufacturability, and pharmacokinetics.

[0232] Site-directed PCR mutagenesis was employed to generate distinct libraries for heavy chain CDR1/2 and heavy chain CDR3. Additionally, an additional library consisting of naïve human kappa light chain CDRs was prepared. This approach resulted in 3 unique libraries. Individual mutants were displayed as Fabs in a phage display system and within each library, mutants were panned through two or three rounds of selection.

[0233] For the heavy chain mutant libraries, the first round of selection consisted of 0.01 nM biotinylated human IL-23 (hIL-23) while also being washed for 2 hours at room temperature in buffer containing 1 nM unlabeled hIL-23. The output of that round was subsequently split into four distinct secondary rounds of parallel selection consisting of A) 0.01 nM biotinylated hIL-23 while also being washed for 20 hours at room temperature in buffer containing 10 nM of unlabeled hIL-23, B) 0.001 nM biotinylated hIL-23 while also being washed for 20 hours at room temperature in buffer containing 1 nM of unlabeled hIL-23, C) 0.01 nM biotinylated cynomolgus monkey IL-23 (cyIL-23) while also being washed for 20 hours at room temperature in buffer containing 10 nM of unlabeled cyIL-23, and D) 0.001 nM biotinylated cyIL-23 while also being washed for 20 hours at room temperature in buffer containing 1 nM of unlabeled cyIL-23.

[0234] For the light chain mutant libraries, the first round of selection consisted of 10 nM biotinylated hIL-23 while also being washed for 2 hours at room temperature in buffer containing 1000 nM unlabeled hIL-23. The output of that round was subsequently split into two distinct secondary rounds of parallel selection consisting of A) 1 nM biotinylated hIL-23 while also being washed for 16 hours at room temperature in buffer containing 100 nM of unlabeled hIL-23, B) 0.1 nM biotinylated hIL-23 while also being washed for 16 hours at room temperature in buffer containing 10 nM of unlabeled hIL-23. These outputs were then subsequently split into two additional tertiary rounds of parallel selection consisting of A) 0.1 nM biotinylated cyIL-23 while also being washed for 20 hours at room temperature in buffer containing 100 nM of unlabeled cyIL-23 and B) 0.01 nM biotinylated cyIL-23 while also being washed for 20 hours at room temperature in buffer containing 10 nM of unlabeled cyIL-23.

[0235] Mutant clones from the output of each arm of secondary and tertiary selection were analyzed for off rate (kd) as a proxy for binding affinity by using periplasmic extracts of each mutant clone through surface plasmon resonance (SPR) using a BIACORE™ 8K+ SPR system (Cytiva). Sensor chips (Series S Sensor Chip CM5 – Cytiva) were prepared by immobilizing hIL-23 (Acro Biosciences) and interaction with periplasmic extracts was analyzed in order to determine the kd. Bioinformatic analyses of sequences to identify patterns of enrichment were also employed to characterize mutant clones. Mutants that exhibited no loss or improved binding relative to the reference antibody as well as population enrichment throughout the selection were combined into a single library comprising all mutants in both the heavy and light chain.

[0236] Clones containing a random combinatorial mix of these individual CDR mutants were again screened in a phage display system, with multiple combinations of selection strategies outlined in Table 4 in Example 1. Mutant clones from the output of each arm of secondary selection were once again analyzed for kd as described.

[0237] Additionally, complementarity-determining region (CDR) grafting technology was used to rehumanize the light chain output of the mutant clones.

[0238] The light chain sequence was compared to a group of human variable region light chain (VK) germline amino acid sequences (Lefranc, M.-P. IMGT, the international ImMunoGeneTics database; Nucleic Acids Res., 29, D207-209 (2001). DOI:10.1093/nar/29.1.207. PMID:11125093). Human germline IGKV3-15 and human germline IGKJ4 were selected.

[0239] The resulting humanized VL was then combined with the VH with affinity matured heavy chain CDRs reformatted to full antibody format, with the final antibody (antibody clone Mab004) having the VH and VL sequences of SEQ ID NO: 38 and SEQ ID NO: 29, respectively. (See Table 1D.) Briefly, the coding sequences for the heavy chain and light chain of the antibody were generated by DNA synthesis and PCR, then subsequently subcloned into plasmids for protein expression in a mammalian cell system. The gene sequences in the expression vectors were confirmed by DNA sequencing. Antibodies were then purified by a two-step affinity chromatography (Protein A) and size-exclusion chromatography process.

Example 4: Determination of Antibody Affinity to IL-23

[0240] Binding affinities (K_D) of antibodies to human IL-23 (generated as described in Examples 1-3) were determined through surface plasmon resonance (SPR) using a BIACORE™ 8K SPR system (Cytiva). Series S Sensor Chip CM5 (Cytiva) sensor chips were prepared by immobilizing goat anti-human IgG (Jackson ImmunoResearch) and ultimately used to determine the binding kinetic rate and affinity constants at 25°C and in a running buffer of HBS-P+ (10 mM HEPES pH 7.4, 150 mM NaCl, 0.05% Surfactant P20). Anti-IL23 mAb constructs (diluted to 2 µg/mL) were captured onto flow cell 2 (active) for 60 sec at a flow rate of 10 µL/min. Recombinant Human IL-23 was prepared at concentrations of 0, 1.23, 3.7, 11.11, 33.33, 100 nM and injected over flow cell 1 (reference) and flow cell 2 (active) for 180 sec at a flow rate of 50 µL/min. Samples were injected in a multi-cycle manner over freshly captured mAb, by regenerating the capture surfaces with injection of 10 mM glycine, pH 1.5 for 30 sec at a flow rate of 30 µL/min. A 1:1 kinetic binding model was utilized to determine the apparent association (k_a) and dissociation rate constants (k_d). Their ratio provides the apparent equilibrium dissociation constant or affinity constant ($K_D = k_d/k_a$). Results for clones of interest are shown in Table 5.

[0241] Under the conditions tested, the k_d (and thus K_D) of the reference antibody and the tested clones were not able to be determined, as the limit of detection of BIACORE™ 8K SPR is 1×10^{-6} 1/s (both antibodies tested had dissociation rates below this limit).

[0242] The strength of the interaction between the antigen-binding site and the epitope can be measured by the equilibrium association constant, k_a . k_a is the amount of antibody-antigen complex that exists at equilibrium.

[0243] Table 5 shows optimization of affinity of the clones of interest: Mab001 and Mab003 have a comparable k_a as Reference Antibody 1; Mab002 and Mab004 have a higher k_a as Reference Antibody 1.

Table 5

Antibody	hIL-23 k_a (1/Ms)	hIL-23 k_d (1/s)	hIL-23 K_D (nM)
Reference			
Antibody 1	1.67×10^5	$< 1 \times 10^{-6}$	ND
Clone MAb001	1.51×10^5	$< 1 \times 10^{-6}$	ND
Clone MAb003	1.64×10^5	$< 1 \times 10^{-6}$	ND

Clone MAb002	2.66×10^5	$< 1 \times 10^{-6}$	ND
Clone MAb004	2.47×10^5	$< 1 \times 10^{-6}$	ND

Example 5: Inhibition of IL-23-Induced Activation of STAT3 in HEK 293F IL-23R+/IL-12R β 1+ STAT3 Luciferase Reporter Cells

[0244] Inhibition of STAT3 activation in HEK 293F cells expressing IL-23R, IL-12R β 1, and a STAT3-linked luciferase reporter was used to evaluate the functional activity of antibodies (generated as described in Examples 1-3) to block IL-23-induced biological activity. Briefly, reporter cells were seeded into a 96-well plate. A mixture of hIL-23 and purified IL-23 antibodies were allowed to associate for 30 min at room temperature before adding to cells, resulting in a final concentration of 20 ng/mL of hIL-23 and 0-50 nM of antibody. Cells were incubated at 37 °C for 5 hours and subsequently lysed with One-Glo luciferase assay buffer (Promega) at room temperature for 10 min under dark conditions. Luminescence was quantified by a SpectraMax® M5e plate reader (Molecular Devices) and subsequent data were analyzed using GraphPad Prism. IC₅₀ values were determined as the concentration of antibody required to inhibit 50% of the maximum luminescent signal detected with incubation of 20 ng/mL of hIL-23 alone.

[0245] As shown in Table 6, the tested clones demonstrated more effective inhibition of IL-23-induced activation of STAT3 as compared to the Reference Antibody 1.

Table 6

Antibody	Relative IC ₅₀
Reference antibody 1	1.000
Clone MAb001	0.612
Clone MAb003	0.868
Clone MAb002	0.640
Clone MAb004	0.409

Values relative to Reference Antibody 1. <1.000 is more potent.

Example 6. Inhibition of IL-23-Induced Phosphorylation of STAT3 in DB Cells

[0246] Inhibition of STAT3 phosphorylation in DB cells was used to evaluate the functional activity of antibodies to block IL-23-induced biological activity. Briefly, 6×10^5 DB cells were seeded into TC-treated round-bottom 96-well plates. A mixture of hIL-23 and purified IL-23 antibodies were allowed to associate for 1 hr at room temperature before adding to cells, resulting in a final concentration of 25 ng/mL of hIL-23 and 0-10 nM of antibody. Cells were incubated at 37 °C for 1 hr and phosphorylated STAT3 (pSTAT3) was quantified using a pSTAT3 Sandwich ELISA kit (Cell Signaling Technology). Subsequent data were analyzed using GraphPad Prism. IC₅₀ values were determined as the concentration of antibody required to inhibit 50% of the maximum pSTAT levels detected with incubation of 25 ng/mL of hIL-23 alone.

[0247] As shown in Table 7, the affinity matured clones demonstrated more effective inhibition of IL-23-induced phosphorylation of STAT3 as compared to the Reference Antibody 1.

Table 7

Antibody	Relative IC ₅₀
Reference Antibody 1	1.000
Clone MAb001	0.573
Clone MAb003	0.799

Values relative to Reference Antibody 1. <1.000 is more potent.

Example 7. Pharmacokinetic (PK) Analysis of IL-23p19 Binding Proteins in Cynomolgus Monkeys

[0248] In order to evaluate the impact of half-life extension mutations on IL-23p19 binding protein pharmacokinetics (PK), male cynomolgus monkeys (*Macaca fascicularis*) ranging from 2.4 to 3.4 kg in weight were administered a single bolus dose (5 mg/kg) of the reference antibody described in Example 1 (Reference Antibody 1, see sequences in Table 3 above) containing Fc LALA mutations with and without Fc YTE mutations (see SEQ ID NOs: 51 and 55, respectively in Table 2) by either intravenous (IV) and/or subcutaneous (SC) injection on Day 0. Serum samples were taken regularly through the study.

[0249] Half-life was determined from cynomolgus serum samples for each dose-cohort up to day 56, with average PK curves shown in **FIG. 1** for IV administration and **FIG. 2** for SC

administration. The β -elimination half-life of IL-23p19 binding proteins with Fc YTE mutations was observed to be 30 days and 24 days for IV and SC dosing, respectively. In contrast, the observed half-life of the Reference Antibody 1 (without Fc YTE mutations) was 11 days and 10 days for IV and SC dosing, respectively.

[0250] Scaling of the observed half-life in cynomolgus monkey of IL-23p19 binding protein with YTE modifications led to a human half-life projection of 74-93 days.

[0251] Therefore, the present example demonstrates enhanced half-life of an IL-23p19 binding protein having a half-life extending mutations in the Fc region.

Example 8. Pharmacokinetic Modeling and Simulation of Potential Clinical Dosing

Regimens

[0252] Pharmacokinetic modeling and simulation were utilized in order to identify potential clinical dosing regimens that would maintain serum concentration of IL-23p19 binding proteins above a specific level at a given time during the regimen or at steady state. Achieving these thresholds has been demonstrated to translate into better responses and patient outcomes in relevant indications.

[0253] A two compartment linear model with parameters for central volume of distribution (V_c), peripheral volume of distribution (V_p), clearance from the central volume (CL), first-order absorption rate constant from a subcutaneous depot into the central volume (k_a), and subcutaneous bioavailability (F) relative to the intravenous administration was used to identify dosing regimens. Given the results from the PK analysis in cynomolgus monkey described in Example 4, an IL-23p19 binding protein with YTE may be expected to have a longer serum half-life than normal IgG. Therefore, the effective half-life used in these simulations was 74 days, in line with the lower end of projections based on the cynomolgus monkey PK study.

[0254] In order to achieve optimal patient outcomes, subcutaneous dosing regimens which achieved an average concentration from week 0-16 ($C_{avg, W0-16}$) of 16.0 $\mu\text{g/mL}$ or higher and a trough concentration at steady state ($C_{trough, SS}$) of 2.0 $\mu\text{g/mL}$ or higher were identified (Table 8). Based on these simulations, IL-23p19 binding proteins with a half-life of 74 days can be dosed subcutaneously with a maintenance frequency of every 6 months, *e.g.*, every 26 weeks (**FIG. 3**) or every year (*e.g.*, every 12 months or every 52 weeks) (**FIG. 4**) and maintain clinically relevant serum concentrations.

Table 8

Induction Regimen	Maintenance Frequency	Dose (mg)
Week 0, Week 4	Every 26 weeks	150
Week 0	Every 26 weeks	300
Week 0	Every 52 weeks	600, 900, 1200

Example 9. Characteristics of Anti-IL-23 Antibody MAb002

[0255] The cytokine IL-23 is secreted by activated macrophage and dendritic cells (DC) and promotes the expansion and/or activity of Th17 cells, CD8+ T cells, macrophages, and DCs. Its pathogenic role in IBD is suggested by genetic association and has been confirmed in clinical trials, demonstrating IL-23 antagonism as an effective and safe treatment for Crohn's disease (CD) and ulcerative colitis (UC).

[0256] MAb002 is a novel, extended half-life humanized IgG1 monoclonal antibody (mAb) that binds IL-23. This Example evaluates the characteristics of MAb002. In particular, MAb002 binds specifically to IL-23 with picomolar affinity. It inhibits STAT3 activity and phosphorylation with IC_{50} values < 1 nM, as well as IL-17 secretion in IL-23-stimulated mouse splenocytes and human PBMC. IL-23 binding potency and IC_{50} values for IL-23 antagonism are comparable to those of two different reference antibodies, Reference Antibody 1 (see Table 3 in Example 1), and Reference Antibody 2, whose characteristic sequences are shown in Table 9 below.

Table 9: Reference Antibody 2 - characteristic sequences *CDR sequences shown are according to Kabat.*

Heavy chain variable domain	Light chain variable domain
EVQLVQSGAEVKKPGESLKISCKGSGYSFSNY WIGWVRQMPGKGLEWMGIIDPSNSYTRYSPSF QGQVTISADKSISTAYLQWSSLKASDTAMYYC ARWYYKPFDDVWGQGTLLTVSS (SEQ ID NO: 157)	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGSGY DVHWYQQLPGTAPKLLIYGNSKRPSGVPDRFSG SKSGTSASLAITGLQSEDEADYYCASWTDGLSL VVFGGGTKLTVL (SEQ ID NO: 158)

CDR-H1: NYWIG (SEQ ID NO: 159)	CDR-L1: TGSSSNIGSGYDVH (SEQ ID NO: 162)
CDR-H2: IIDPSNSYTRYSPSFQG (SEQ ID NO: 160)	CDR-L2: GNSKRPS (SEQ ID NO: 163)
CDR-H3: WYKPFDV (SEQ ID NO: 161)	CDR-L3: ASWTDGLSLVV (SEQ ID NO: 164)

[0257] Cryo-EM demonstrates the binding epitope of MAb002 is within IL-23. The half-life of MAb002 is significantly extended in cynomolgus monkeys compared to both Reference Antibody 1 and Reference Antibody 2. Based on allometric scaling of the clearance of Mab002 observed in this study, predictive simulations of MAb002 pharmacokinetics in humans suggest that subcutaneous dosing at intervals once every three months or longer, *e.g.*, between once every three months and once every six months, or even longer intervals (Q3M-Q6M+) will achieve therapeutic exposures in patients across a wide range of body weights and albumin concentrations.

Materials and Methods

[0258] MAb002 was evaluated in multiple *in vitro* and *ex vivo* assays compared to a reference anti-IL-23 antibody. Binding affinity to IL-23 was determined by surface plasmon resonance (SPR) and kinetic exclusion assays (KinExA). Antagonism of IL-23 signaling was measured via a STAT3 reporter cell line and phospho-STAT3 ELISA. Antibody-induced reduction of IL-17 secretion in response to human IL-23 was assessed in mouse splenocytes and human peripheral blood mononuclear cells (PBMC). The binding epitope of the Reference Antibody 1 and MAb002 to IL-23 was determined using cryogenic electron microscopy. Half-life extension was measured via pharmacokinetic analysis in cynomolgus monkeys given a single bolus of MAb002 and Reference Antibody 1 by intravenous and/or subcutaneous (SC) administration.

Results

[0259] MAb002 inhibits STAT3 activity and phosphorylation with IC₅₀ values < 1 nM, as well as IL-17 secretion in IL-23-stimulated mouse splenocytes and human PBMC (**FIG. 5A**). IL-23 binding potency and IC values for IL-23 antagonism are comparable to those of the Reference Antibody 1 (**FIG. 5B**). MAb002 also inhibits IL-17 release after IL-23 stimulation in human PBMC and murine splenocytes about as effectively as the Reference Antibody 1 (**FIG.**

6). In addition, the EC₅₀ for suppression of pSTAT in DB and HEK cells was similar for both MAb002 and the Reference Antibody 1 (FIG. 6).

[0260] Cryo-EM demonstrates that MAb002 binds to a similar epitope on the p19 subunit of IL-23 as Reference Antibody 1 (FIG. 7).

[0261] The half-life of MAb002 is extended in cynomolgus monkeys about 3-times compared to the reference antibody (FIG. 8, about 30 days for Mab002 vs. about 9 days for Reference Antibody 1). Based on allometric scaling of the clearance of MAb002 and the reference antibody observed in this study, predictive simulations of MAb002 PK in humans suggest that Q3M-Q6M+ subcutaneous (SC) dosing will achieve therapeutic exposures in patients across a wide range of body weights and albumin concentrations in comparison to a Q2M dosing frequency of the Reference Antibody 1 (FIG. 9, FIG. 10A, and FIG. 10B).

Conclusions

[0262] MAb002 exhibits high selectivity and affinity for IL-23 and potently inhibits downstream cellular signaling. With an extended half-life in NHP, MAb002 demonstrates therapeutic potential for effective and safe treatment of Crohn's disease and ulcerative colitis with the potential advantage of twice a year subcutaneous dosing. Further preclinical and clinical studies may further demonstrate this potential.

EQUIVALENTS

[0263] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

[0264] The disclosure may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the disclosure described herein.

[0265] Various structural elements of the different embodiments and various disclosed method steps may be utilized in various combinations and permutations, and all such variants are to be considered forms of the disclosure. Scope of the disclosure is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CLAIMS

1. An IL-23 binding protein comprising a heavy chain variable domain (VH) comprising complementarity-determining regions:
 - CDR-H1 comprising the amino acid sequence of SEQ ID NO: 3;
 - CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and
 - CDR-H3 comprising the amino acid sequence of SEQ ID NO: 5.
2. The IL-23 binding protein of claim 1, wherein the VH comprises an amino acid sequence that is at least 85% identical to amino acid sequence of SEQ ID NO: 1.
3. The IL-23 binding protein of claim 1 or claim 2, further comprising a light chain variable domain (VL) comprising complementarity-determining regions:
 - CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6;
 - CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and
 - CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.
4. The IL-23 binding protein of claim 3, wherein the VL comprises an amino acid sequence that is at least 85% identical to amino acid sequence of SEQ ID NO: 2.
5. An IL-23 binding protein comprising:
 - (a) a heavy chain variable domain (VH) comprising complementarity-determining regions:
 - CDR-H1 comprising the amino acid sequence of SEQ ID NO: 3;
 - CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and
 - CDR-H3 comprising the amino acid sequence of SEQ ID NO: 5;
 - and
 - (b) a light chain variable domain (VL) comprising complementarity-determining regions:
 - CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6;
 - CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and
 - CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.

6. An IL-23 binding protein comprising:
 - (a) a heavy chain comprising an amino acid sequence according to SEQ ID NO: 165;and
 - (b) a light chain comprising an amino acid sequence according to SEQ ID NO: 166.
7. The IL-23 binding protein of any of claims 1-6, wherein the IL-23 binding protein is capable of inhibiting activation of STAT3 in human embryonic kidney (HEK) cells expressing IL-23R at a relative IC₅₀ of less than 0.90, less than 0.80, less than 0.70, less than 0.65 or from about 0.6 to about 0.65.
8. The IL-23 binding protein of any of claims 1-7, wherein the IL-23 binding protein is capable of inhibiting phosphorylation of STAT3 in DB cells at a relative IC₅₀ reference of less than 0.80, less than 0.70, less than 0.60, less than 0.58 or from about 0.55 to about 0.6.
9. An IL-23 binding protein comprising a heavy chain variable domain (VH) comprising complementarity-determining regions:
 - CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19;
 - CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20; and
 - CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21.
10. The IL-23 binding protein of claim 9, wherein the VH comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 18.
11. The IL-23 binding protein of claim 9 or claim 10, further comprising a light chain variable domain (VL) comprising complementarity-determining regions:
 - CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6;
 - CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and
 - CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.

12. The IL-23 binding protein of claim 11, wherein the VL comprises an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 2.
13. An IL-23 binding protein comprising:
(a) a heavy chain variable domain (VH) comprising complementarity-determining regions: CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19;
CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20; and
CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21;
and
(b) a light chain variable domain (VL) comprising complementarity-determining regions: CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6;
CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and
CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.
14. An IL-23 binding protein comprising:
(a) a heavy chain comprising an amino acid sequence according to SEQ ID NO: 169;
and
(b) a light chain comprising an amino acid sequence according to SEQ ID NO: 170.
15. The IL-23 binding protein of any of claims 9-14, wherein the IL-23 binding protein is capable of inhibiting activation of STAT3 in human embryonic kidney (HEK) cells expressing IL-23R at a relative IC_{50} of less than 0.95, less than 0.90, less than 0.88 or from about 0.85 to about 0.9.
16. The IL-23 binding protein of any of claims 9-15, wherein the IL-23 binding protein is capable of inhibiting phosphorylation of STAT3 in DB cells at a relative IC_{50} of less than 0.95, less than 0.90, less than 0.85 or from about 0.75 to about 0.85.
17. An IL-23 binding protein comprising:
(a) a heavy chain variable domain (VH) comprising:

- (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 28, and
 - (2) an asparagine at position 74 of SEQ ID NO: 28;
- and
- (b) a light chain variable domain (VL) comprising:
- (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 29; and
 - (2) a phenylalanine at position 49 of SEQ ID NO: 29;
- wherein
- (i) the VH comprises complementarity-determining regions:
 - CDR-H1 comprising the amino acid sequence of SEQ ID NO: 30;
 - CDR-H2 comprising the amino acid sequence of SEQ ID NO: 31; and
 - CDR-H3 comprising the amino acid sequence of SEQ ID NO: 32;
- and
- (ii) the VL comprises complementarity-determining regions:
 - CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6;
 - CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and
 - CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.

18. The IL-23 binding protein of claim 17, wherein the heavy chain variable domain comprises one or more of the following: glutamic acid at position 1, leucine at position 5, glutamic acid at position 6, glycine at position 9, glycine at position 10, leucine at position 11, valine at position 12, glutamine at position 13, glycine at position 16, leucine at position 18, arginine at position 19, leucine at position 20, alanine at position 23, valine at position 37, lysine at position 43, arginine at position 67, leucine a position 70, serine at position 71, alanine at position 68, lysine at position 76, asparagine at position 77, leucine at position 81, glutamine at position 82, methionine at position 83, asparagine at position 84, alanine a position 88, or threonine at position 115 of SEQ ID NO: 28.

19. The IL-23 binding protein of claim 17 or claim 18, wherein the light chain variable domain comprises one or more of the following: glutamic acid at position 1, valine at position 3, alanine at position 9, threonine at position 10, valine at position 13, proline at position 15, glutamic acid at position 17, alanine at position 19, leucine at position 21, serine at position 22, glutamine

at position 42, alanine at position 43, arginine at position 45, leucine at position 48, isoleucine at position 58, alanine at position 60, glutamic acid at position 70, serine at position 80, phenylalanine at position 83, valine at position 85, tyrosine at position 87, glycine at position 100 or valine at position 104 of SEQ ID NO: 29.

20. The IL-23 binding protein of any one of claims 17-19, wherein the VH comprises an amino acid sequence that is at least 90% identical to that of SEQ ID NO: 28, and the VL comprises an amino acid sequence that is at least 90% identical to that of SEQ ID NO: 29.

21. The IL-23 binding protein of any one of claims 17-19, wherein the VH comprises an amino acid sequence that is at least 92.5% identical to that of SEQ ID NO: 28, and the VL comprises an amino acid sequence that is at least 92.5% identical to that of SEQ ID NO: 29.

22. The IL-23 binding protein of any one of claims 17-19, wherein the VH comprises an amino acid sequence that is at least 95% identical to that of SEQ ID NO: 28, and the VL comprises an amino acid sequence that is at least 95% identical to that of SEQ ID NO: 29.

23. The IL-23 binding protein of any one of claims 17-19, wherein the VH comprises an amino acid sequence that is at least 98% identical to that of SEQ ID NO: 28, and the VL comprises an amino acid sequence that is at least 98% identical to that of SEQ ID NO: 29.

24. The IL-23 binding protein of any one of claims 17-19, wherein the VH comprises the amino acid sequence of SEQ ID NO: 28, and the VL comprises the amino acid sequence of SEQ ID NO: 29.

25. An IL-23 binding protein comprising:

- (a) a heavy chain comprising an amino acid sequence according to SEQ ID NO: 171; and
- (b) a light chain comprising of an amino acid sequence according to SEQ ID NO: 172.

26. The IL-23 binding protein of any of claims 17-25, wherein the IL-23 binding protein is capable of inhibiting activation of STAT3 in human embryonic kidney (HEK) cells expressing IL-23R at a relative IC_{50} of less than 0.9, less than 0.8, less than 0.7, or from about 0.6 to about 0.7.

27. An IL-23 binding protein comprising:

(a) a heavy chain variable domain (VH) comprising:

- (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 38 and
- (2) complementarity-determining regions:
 - (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 39;
 - CDR-H2 comprising the amino acid sequence of SEQ ID NO: 4; and
 - CDR-H3 comprising the amino acid sequence of SEQ ID NO: 40; and

(b) a light chain variable domain (VL) comprising:

- (1) an amino acid sequence that is at least 85% identical to that of SEQ ID NO: 29;
- (2) phenylalanine residue at position 49 of SEQ ID NO: 29, and
- (3) complementarity-determining regions:
 - CDR-L1 comprising the amino acid sequence of SEQ ID NO: 6;
 - CDR-L2 comprising the amino acid sequence of SEQ ID NO: 7; and
 - CDR-L3 comprising the amino acid sequence of SEQ ID NO: 8.

28. The IL-23 binding protein of claim 27, wherein the light chain variable domain comprises one or more of the following: glutamic acid at position 1, valine at position 3, alanine at position 9, threonine at position 10, valine at position 13, proline at position 15, glutamic acid at position 17, alanine at position 19, leucine at position 21, serine at position 22, glutamine at position 42, alanine at position 43, arginine at position 45, leucine at position 48, isoleucine at position 58, alanine at position 60, glutamic acid at position 70, serine at position 80, phenylalanine at position 83, valine at position 85, tyrosine at position 87, glycine at position 100 or valine at position 104 of SEQ ID NO: 29..

29. An IL-23 binding protein comprising:

- (a) a heavy chain comprising an amino acid sequence according to SEQ ID NO: 167; and

- (b) a light chain comprising of an amino acid sequence according to SEQ ID NO: 168.

30. The IL-23 binding protein of any one of claims 27-29, wherein the IL-23 binding protein is capable of inhibiting activation of STAT3 in human embryonic kidney (HEK) cells expressing IL-23R at a relative IC₅₀ of less than 0.90, less than 0.80, less than 0.70, less than 0.60, less than 0.50, or less than 0.45 or from about 0.35 to about 0.45.
31. The IL-23 binding protein of any one of claims 1-30, wherein the IL-23 binding protein is a human antibody or antigen-binding fragment thereof.
32. The IL-23 binding protein of any one of claims 1-31, wherein the antibody or antigen binding fragment thereof comprises an Fc region.
33. The IL-23 binding protein of claim 32, wherein the Fc region is a human IgG1, IgG2, or IgG4 Fc region.
34. The IL-23 binding protein of claim 33, wherein the Fc region is a modified Fc region.
35. The IL-23 binding protein of claim 34, wherein the modified Fc region comprises a half-life extending modification or set of modifications.
36. The IL-23 binding protein of claim 35, wherein modified Fc region comprises amino acid modifications M252Y, S254T, and T256E (YTE) and/or M428L and N434S (LS).
37. An isolated nucleic acid encoding an IL-23 binding protein of any one of claims 1-36.
38. An expression vector comprising the isolated nucleic acid of claim 37.
39. A host cell comprising the isolated nucleic acid molecule of claim 37 or the expression vector of claim 38.

40. A composition comprising an IL-23 binding protein of any one of claims 1-36 and a pharmaceutically acceptable carrier.
41. A method of treating a disease or condition in a subject in need thereof, comprising a step of administering to the subject an effective amount of the IL-23 binding protein of any one of claims 1-36 or the composition of claim 40.
42. The method of claim 41, wherein the disease or condition is an inflammatory condition.
43. The method of claim 41, wherein the disease or condition is inflammatory bowel disease.
44. The method of claim 41, wherein the disease or condition is Crohn's disease (CD).
45. The method of claim 41, wherein the disease or condition is ulcerative colitis (UC).
46. The method of any one of claims 41-45, comprising administering subcutaneously or intravenously the effective amount of the IL-23 binding protein or the composition to the subject in need thereof.
47. The IL-23 binding protein of any one of claims 1-36 or the composition of claim 40 for use in treatment of a disease or condition.
48. Use of the IL-23 binding protein of any one of claims 1-36 or the composition of claim 40 in a method of treating a disease or condition.
49. Use of the IL-23 binding protein of any one of claims 1-36 or the composition of claim 40 in the manufacture of a medicament for treating a disease or condition.

50. The IL-23 binding protein or the composition of claim 47, or the use of claims 48 or claim 49, wherein the disease or condition is an inflammatory condition.
51. The IL-23 binding protein or the composition of claim 47, or the use of claims 48 or claim 49, wherein the disease or condition is a gastrointestinal inflammatory disease.
52. The IL-23 binding protein or the composition of claim 47, or the use of claims 48 or claim 49, wherein the disease or condition is inflammatory bowel disease.
53. The IL-23 binding protein or the composition of claim 47, or the use of claims 48 or claim 49, wherein the disease or condition is Crohn's disease.
54. The IL-23 binding protein or the composition of claim 47, or the use of claims 48 or claim 49, wherein the disease or condition is ulcerative colitis.