4. SUMMARY

[0006] The present disclosure provides a system that permits the immunogenic contribution of each and every amino acid within an area of interest in a reference antibody to be elucidated. The disclosure provides that an amino acid residue at any, some, or all positions of a reference antibody can be mutated into some or all of the other 19 amino acids and the effect of that mutation on the antibody's immunogenicity evaluated. The effect of the mutations on the antibody's expression level and/or binding to a target molecule can also be evaluated, allowing the identification of antibody variants in which immunogenic regions are eliminated or mitigated yet which retain advantageous properties (*e.g.*, suitable expression levels, binding to target molecule). Accordingly, the present disclosure provides methods for reducing the immunogenicity of an antibody. The methods are based on screening for and identifying antibody variants with reduced binding to anti-idiotypic antibodies. Reduction of binding to anti-idiotypic antibodies correlate with reduced *in vivo* immunogenicity (*see, e.g.*, Nagata and Pastan, 2009, *Advanced Drug Delivery Reviews* 61:977-985).

[0006a] In one aspect, there is provided a variant of a reference anti-TNF-α antibody or a reference anti-TNF-α binding fragment of an antibody, which reference antibody or binding fragment comprises six complementarity determining regions ("CDRs") having amino acid sequences corresponding to SEQ ID NO:5 (CDR-H1), SEQ ID NO:6 (CDR-H2), SEQ ID NO:7 (CDR-H3), SEQ ID NO:8 (CDR-Ll), SEQ ID NO:9 (CDR-L2) and SEQ ID NO:10 (CDR-L3), wherein the variant comprises the substitution Y2K in CDR-H1, wherein the six CDRs altogether have up to 8 amino acid substitutions as compared to CDR sequences of the reference antibody or binding fragment.

[0006b] In one aspect, there is provided a nucleic acid molecule encoding the variant as disclosed herein.

[0006c] In one aspect, there is provided host cell comprising a nucleic acid molecule encoding the variant as disclosed herein.

[0006d] In one aspect, there is provided a pharmaceutical composition comprising the variant as disclosed herein and a pharmaceutically acceptable carrier.

[0006e] In one aspect, there is provided a variant as disclosed herein for use in a method of treating an immune disorder in a human patient, wherein the method comprises administering to the patient a therapeutically effective amount of the variant.

[0007] The methods of the disclosure generally comprise the steps of (a) contacting a host cell library with an anti-idiotypic antibody that specifically binds to the reference antibody, the reference antibody being a monoclonal antibody that binds to a target molecule, the host cell library comprising mammalian host cells that each express on the cell surface an antibody variant differing from the reference antibody by a single amino acid point mutation; (b) identifying a population of cells in said host cell library that express antibody variants that display decreased binding to the anti-idiotypic antibody relative to the reference antibody; and (c) identifying an antibody variant that is enriched in the population, thereby identifying a variant of a reference antibody with reduced immunogenicity. In certain aspects, the methods entail subjecting the host cell library to flow cytometry and sorting the population from the host cell library using, for example, fluorescent activated cell sorting (FACS).

[0008] In certain aspects, the methods further comprise a step of determining whether the antibody variant having reduced immunogenicity binds to the target molecule at a level which is substantially equal to or better than the reference antibody and/or is expressed at a level which is substantially equal to or better than the expression level of the reference antibody. In specific embodiments, binding and expression are determined by flow cytometry, magnetic bead sorting,

CLAIMS

1. A variant of a reference anti-TNF-α antibody or a reference anti-TNF-α binding fragment of an antibody, which reference antibody or binding fragment comprises six complementarity determining regions ("CDRs") having amino acid sequences corresponding to SEQ ID NO:5 (CDR-H1), SEQ ID NO:6 (CDR-H2), SEQ ID NO:7 (CDR-H3), SEQ ID NO:8 (CDR-Ll), SEQ ID NO:9 (CDR-L2) and SEQ ID NO:10 (CDR-L3), wherein the variant comprises the substitution Y2K in CDR-H1, wherein the six CDRs altogether have up to 8 amino acid substitutions as compared to CDR sequences of the reference antibody or binding fragment.

2. The variant of claim 1, wherein the variant further comprises at least one of the heavy chain substitutions (i) T6V in CDR-H3, and (ii) V1G in CDR-H3 and T6V in CDR-H3.

3. The variant of claims 1 or 2, wherein the variant further comprises at least one of the light chain substitutions (i) G5S in CDR-L1 and A11S in CDR-L1, (ii) R7I in CDR-L1, (iii) G5S in CDR-L1, R7T in CDR-L1 and A11S in CDR-L1, and (iv) G5S in CDR-L1, R7I in CDR-L1 and A11S in CDR-L1.

4. The variant of claim 1, wherein the variant further comprises at least one of the light chain substitutions (i) R7I in CDR-L1 and (ii) R7T in CDR-L1.

5. The variant of claim 1, wherein the variant further comprises at least one of the light chain substitutions (i) G5S in CDR-L1, R7T in CDR-L1 and A11S in CDR-L1 and (ii) G5S in CDR-L1, R7I in CDR-L1 and A11S in CDR-L1.

6. The variant of any preceding claim, wherein the reference anti-TNF-α antibody or reference anti-TNF-α binding fragment comprises a variable heavy chain fragment having an amino acid sequence corresponding to SEQ ID NO:2 and a variable light chain fragment having an amino acid sequence corresponding to SEQ ID NO:4.

7. A nucleic acid molecule encoding the variant of any one of claims 1-6.

8. A host cell comprising a nucleic acid molecule encoding the variant of any one of claims 1-6.

9. A pharmaceutical composition comprising the variant of any one of claims 1-6 and a pharmaceutically acceptable carrier.

10. A variant according to any one of claims 1-6 for use in a method of treating an immune disorder in a human patient, wherein the method comprises administering to the patient a therapeutically effective amount of the variant.

11. The variant for use according to claim 10, wherein the immune disorder is selected from rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis and axial spondyloarthritis.

WHAT IS CLAIMED IS:

1. A method of identifying a variant of a reference antibody with reduced immunogenicity, comprising the steps of:

(a) contacting a host cell library with an anti-idiotypic antibody that specifically binds to a reference antibody, said reference antibody being a monoclonal antibody that binds to a target molecule, said host cell library comprising mammalian host cells that each express on the cell surface an antibody variant differing from the reference antibody by a single amino acid point mutation;

(b) identifying a population of cells in said host cell library that express antibody variants that display decreased binding to the anti-idiotypic antibody relative to the reference antibody; and

(c) identifying an antibody variant that is enriched in said population,

thereby identifying a variant of a reference antibody with reduced immunogenicity.

2. The method of claim 1, wherein step (b) comprises subjecting the host cell library to flow cytometry and sorting said population from the host cell library.

3. The method of claim 2, wherein the flow cytometry is fluorescent activated cell sorting (FACS).

4. The method of any one of claims 1-3, which further comprises (d) determining whether the antibody variant retains its ability to bind to the target molecule.

5. The method of claim 4, wherein step (d) comprises assaying the level of binding of the antibody variant to the target molecule by flow cytometry, magnetic bead sorting, BIAcore, FACS, ELISA, AlphaLisa, and KinExA.

6. The method of claim 5, wherein step (d) comprises assaying the level of binding of the antibody variant to the target molecule by flow cytometry, in a method comprising the steps of (i) contacting cells of the host cell library or said population with a fluorescently labeled target molecule; (ii) subjecting said cells to flow cytometry; (iii) sorting the cells into

subpopulations by amount of bound fluorescently labeled target molecule; and (iv) determining if the antibody variant is enriched in a subpopulation of cells that express antibody variants which bind to the target molecule substantially equally to or better than the reference antibody, thereby determining whether the antibody variant retains the ability to bind to the target molecule.

7. The method of claim 6, wherein steps (d)(i) to (d)(iii) are carried out before, simultaneously with, or after step (b).

8. The method of any one of claims 6-7, wherein step (d)(iv) is carried out before, simultaneously with, or after step (c).

9. The method of any one of claims 1-8, which further comprises (e) determining the expression level of the variant as compared to the expression level of the reference antibody.

10. The method of claim 9, wherein step (e) comprises assaying the level of expression of the antibody variant by flow cytometry, magnetic bead sorting, BIAcore, FACS, ELISA, AlphaLisa, and KinExA.

11. The method of claim 10, wherein step (e) comprises assaying the level of expression of the antibody variant by flow cytometry, in a method comprising the steps of (i) contacting cells of the host cell library or said population with a fluorescently labeled antibody that binds to an epitope conserved among the antibody variants and the reference antibody; (ii) subjecting said cells to flow cytometry; (iii) sorting the cells into subpopulations by amount of bound fluorescently labeled antibody; and (iv) determining if the antibody variant is enriched in a subpopulation of cells which bind to the fluorescently labeled antibody at a level substantially equal to or better than cells that express the reference antibody, thereby determining whether the antibody variant is expressed at a level substantially equal to or better than the reference antibody.

12. The method of claim 11, wherein said epitope is in a constant region of the antibody variants and the reference antibody.

13. The method of any one of claims 11-12, wherein steps (e)(i) to (e)(iii) are carried out before, simultaneously with, or after step (b).

14. The method of any one of claims 11-12, wherein step (e)(iv) is carried out before, simultaneously with, or after step (c).

15. The method of any one of claims 1-14, wherein the anti-idiotypic antibody is fluorescently labeled.

16. The method of any one of claims 1-15, wherein step (c) comprises massively parallel sequencing nucleic acids obtained from the population.

17. The method of any one of claims 6-8, wherein step (d)(iv) comprises massively parallel sequencing nucleic acids obtained from the subpopulation of cells that express antibody variants which bind to the target molecule substantially equally to or better than the reference antibody.

18. The method of any one of claims 11-14, wherein step (e)(iv) comprises massively parallel sequencing nucleic acids obtained from the subpopulation of cells which bind to the fluorescently labeled antibody at a level substantially equal to or better than cells that express the reference antibody.

19. The method of any one of claims 1-16, wherein the host cell library has fewer than 10,000 unique members.

20. The method of claim 17, wherein the host cell library has about 50 to about 10,000 unique members.

21. The method of claim 20, wherein the host cell library has about 1,000 to about 1,300 unique members.

22. The method of any one of claims 1-21, wherein the host cells are 293c18 cells.

23. The method of any one of claims 1-22, wherein the antibody variants are expressed from vectors comprising the Epstein-Barr virus replication origin and nuclear antigen

and wherein the antibody variable domains are displayed as part of a full length IgG-transmembrane anchor fusion protein on the surface of the cell.

24. The method of any one of claims 1-23, wherein the reference antibody comprises two antibody variable domains and wherein the antibody variants comprise antibody variable domains at least one of which has a single point mutation relative to the variable domains in the reference antibody.

25. The method of claim 24, wherein the single amino acid substitutions are in the complimentary determining regions (CDRs) of the two antibody variable domains.

26. The method of claim 25, wherein about 50 to about 60 amino acid positions in the CDRs of the two antibody variable domains are substituted with each of the naturally occurring amino acids.

27. The method of any one of claims 1-26, wherein the host cell library is constructed using NNK mutagenesis.

28. A variant of a reference anti-TNF-α antibody or a reference anti-TNF-α binding fragment of an antibody, which reference antibody or binding fragment comprises six complementarity determining regions ("CDRs") having amino acid sequences corresponding to SEQ ID NO:5 (CDR-Hl), SEQ ID NO:6 (CDR-H2), SEQ ID NO:7 (CDR-H3), SEQ ID NO:8 (CDR-Ll), SEQ ID NO:9 (CDR-L2) and SEQ ID NO:10 (CDR-H3), wherein the variant comprises at least one substitution selected from G5F in CDR-L1, G5I in CDR-L1, G5V in CDR-L1, G5W in CDR-L1, G5Y in CDR-L1, R7I in CDR-L1, R7T in CDR-L1, R7V in CDR-L1, N8A in CDR-L1, N8D in CDR-L1, N8E in CDR-L1, N8G in CDR-L1, N8L in CDR-L1, N8M in CDR-L1, N8Q in CDR-L1, N8R in CDR-L1, N8T in CDR-L1, A1I in CDR-L2, A1T in CDR-L2, A1V in CDR-L2, T4D in CDR-L2, R2G in CDR-L3, N4F in CDR-L3, N4M in CDR-L3, N4W in CDR-L3, N4Y in CDR-L3, R5L in CDR-L3, R5N in CDR-L3, R5W in CDR-L3, R5Y in CDR-L3, T9Y in CDR-L3, D1S in CDR-H1, Y2A in CDR-H1, Y2C in CDR-H1, Y2K in CDR-H1, Y2M in CDR-H1, Y2R in CDR-H1, Y2S in CDR-H1, Y2V in CDR-H1, H5C in CDR-H1, H5D in CDR-H1, H5E in CDR-H1, H5S in CDR-H1, H5T in CDR-H1, T3A in CDR-H2, T3G in CDR-H2, T3N in CDR-H2, W4A in CDR-H2, W4F in CDR-H2, W4H in CDR-H2,

W4L in CDR-H2, W4M in CDR-H2, W4V in CDR-H2, N5G in CDR-H2, S6D in CDR-H2, S6L in CDR-H2, I9K in CDR-H2, D10L in CDR-H2, Y11A in CDR-H2, Y11C in CDR-H2, Y11E in CDR-H2, Y11F in CDR-H2, Y11G in CDR-H2, Y11H in CDR-H2, Y11I in CDR-H2, Y11K in CDR-H2, Y11L in CDR-H2, Y11M in CDR-H2, Y11N in CDR-H2, Y11Q in CDR-H2, Y11R in CDR-H2, Y11S in CDR-H2, Y11V in CDR-H2, Y11W in CDR-H2, A12Y in CDR-H2, D13N in CDR-H2, V15D in CDR-H2, V15L in CDR-H2, V15M in CDR-H2, V15Q in CDR-H2, V15T in CDR-H2, E16F in CDR-H2, E16H in CDR-H2, E16K in CDR-H2, E16R in CDR-H2, E16T in CDR-H2, E16W in CDR-H2, G17A in CDR-H2, G17C in CDR-H2, G17E in CDR-H2, G17H in CDR-H2, G17I in CDR-H2, G17K in CDR-H2, G17L in CDR-H2, G17M in CDR-H2, G17N in CDR-H2, G17P in CDR-H2, G17Q in CDR-H2, G17R in CDR-H2, G17S in CDR-H2, G17T in CDR-H2, G17Y in CDR-H2, V1G in CDR-H3, V1R in CDR-H3, V1W in CDR-H3, L4T in CDR-H3, L4V in CDR-H3, T6V in CDR-H3, S9K in CDR-H3, S9W in CDR-H3, S9Y in CDR-H3, and D11V in CDR-H3,

wherein the six CDRs altogether have up to 8 amino acid substitutions as compared to CDR sequences of the reference antibody or binding fragment.

29. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from G5F in CDR-L1, G5I in CDR-L1, G5Y in CDR-L1, R7I in CDR-L1, R7T in CDR-L1, R7V in CDR-L1, N8A in CDR-L1, N8D in CDR-L1, N8E in CDR-L1, N8G in CDR-L1, N8L in CDR-L1, N8M in CDR-L1, N8Q in CDR-L1, N8R in CDR-L1, N8T in CDR-L1, A1V in CDR-L2, R2G in CDR-L3, N4F in CDR-L3, N4M in CDR-L3, N4W in CDR-L3, R5L in CDR-L3, R5N in CDR-L3, R5W in CDR-L3, and R5Y in CDR-L3.

30. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from R2G in CDR-L3, R5L in CDR-L3, R5N in CDR-L3, and R5Y in CDR-L3.

31. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from G5F in CDR-L1, G5I in CDR-L1, G5Y in CDR-L1, R7I in CDR-L1, N4M in CDR-L3, and R5W in CDR-L3.

32. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from N8D in CDR-L1 and N8E in CDR-L1.

33. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from R7T in CDR-L1, R7V in CDR-L1, N8A in CDR-L1, N8G in CDR-L1, N8L in CDR-L1, N8M in CDR-L1, N8Q in CDR-L1, N8R in CDR-L1, N8T in CDR-L1, A1V in CDR-L2, N4F in CDR-L3, and N4W in CDR-L3.

34. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from G5F in CDR-L1, G5I in CDR-L1, G5V in CDR-L1, G5W in CDR-L1, G5Y in CDR-L1, R7I in CDR-L1, R7T in CDR-L1, R7V in CDR-L1, N8A in CDR-L1, N8G in CDR-L1, N8L in CDR-L1, N8M in CDR-L1, N8Q in CDR-L1, N8R in CDR-L1, N8T in CDR-L1, A1I in CDR-L2, A1T in CDR-L2, A1V in CDR-L2, T4D in CDR-L2, N4F in CDR-L3, N4M in CDR-L3, N4W in CDR-L3, and R5W in CDR-L3.

35. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include the substitution G5V in CDR-L1.

36. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from G5W in CDR-L1, A1I in CDR-L2, A1T in CDR-L2, and T4D in CDR-L2.

37. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from G5W in CDR-L1, R7T in CDR-L1, R7V in CDR-L1, N8A in CDR-L1, N8D in CDR-L1, N8E in CDR-L1, N8L in CDR-L1, N8M in CDR-L1, N8Q in CDR-L1, N8R in CDR-L1, A1I in CDR-L2, A1T in CDR-L2, A1V in CDR-L2, T4D in CDR-L2, N4F in CDR-L3, N4W in CDR-L3, N4Y in CDR-L3 and T9Y in CDR-L3.

38. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from N4Y in CDR-L3 and T9Y in CDR-L3.

39. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from D1S in CDR-H1, Y2A in CDR-H1, Y2C in CDR-H1, Y2K in CDR-H1, Y2M in CDR-H1, Y2R in CDR-H1, Y2S in CDR-H1, Y2V

in CDR-H1, H5C in CDR-H1, H5D in CDR-H1, H5E in CDR-H1, H5S in CDR-H1, H5T in CDR-H1, T3A in CDR-H2, T3G in CDR-H2, T3N in CDR-H2, W4A in CDR-H2, W4F in CDR-H2, W4H in CDR-H2, W4L in CDR-H2, W4M in CDR-H2, W4V in CDR-H2, D10L in CDR-H2, V1G in CDR-H3, V1R in CDR-H3, V1W in CDR-H3, L4T in CDR-H3, L4V in CDR-H3, T6V in CDR-H3, S9K in CDR-H3, and D11V in CDR-H3.

40. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from N5G in CDR-H2, S6D in CDR-H2, S6L in CDR-H2, I9K in CDR-H2, Y11A in CDR-H2, Y11C in CDR-H2, Y11E in CDR-H2, Y11F in CDR-H2, Y11G in CDR-H2, Y11H in CDR-H2, Y11I in CDR-H2, Y11K in CDR-H2, Y11L in CDR-H2, Y11M in CDR-H2, Y11N in CDR-H2, Y11Q in CDR-H2, Y11R in CDR-H2, Y11S in CDR-H2, Y11V in CDR-H2, Y11W in CDR-H2, A12Y in CDR-H2, V15D in CDR-H2, V15L in CDR-H2, V15M in CDR-H2, V15Q in CDR-H2, V15T in CDR-H2, E16F in CDR-H2, E16H in CDR-H2, E16K in CDR-H2, E16R in CDR-H2, E16T in CDR-H2, E16W in CDR-H2, G17A in CDR-H2, G17C in CDR-H2, G17E in CDR-H2, G17H in CDR-H2, G17I in CDR-H2, G17K in CDR-H2, G17L in CDR-H2, G17M in CDR-H2, G17N in CDR-H2, G17P in CDR-H2, G17Q in CDR-H2, G17R in CDR-H2, G17S in CDR-H2, G17T in CDR-H2, G17Y in CDR-H2, S9W in CDR-H3, and S9Y in CDR-H3.

41. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from N5G in CDR-H2, S6D in CDR-H2, S6L in CDR-H2, Y11M in CDR-H2, Y11Q in CDR-H2, A12Y in CDR-H2, E16H in CDR-H2, G17H in CDR-H2, S9W in CDR-H3, and S9Y in CDR-H3.

42. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from I9K in CDR-H2, Y11A in CDR-H2, Y11C in CDR-H2, Y11E in CDR-H2, Y11F in CDR-H2, Y11G in CDR-H2, Y11H in CDR-H2, Y11I in CDR-H2, Y11K in CDR-H2, Y11L in CDR-H2, Y11N in CDR-H2, Y11R in CDR-H2, Y11S in CDR-H2, Y11V in CDR-H2, Y11W in CDR-H2, V15D in CDR-H2, V15L in CDR-H2, V15M in CDR-H2, V15Q in CDR-H2, V15T in CDR-H2, E16F in CDR-H2, E16K in CDR-H2, E16R in CDR-H2, E16T in CDR-H2, E16W in CDR-H2, G17A in CDR-H2, G17C in CDR-H2, G17E in CDR-H2, G17I in CDR-H2, G17K in CDR-H2, G17L in CDR-H2, G17M in CDR-H2,

G17N in CDR-H2, G17P in CDR-H2, G17Q in CDR-H2, G17R in CDR-H2, G17S in CDR-H2, G17T in CDR-H2, and G17Y in CDR-H2.

43. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include at least one substitution selected from I9K in CDR-H2, Y11A in CDR-H2, Y11C in CDR-H2, Y11E in CDR-H2, Y11F in CDR-H2, Y11G in CDR-H2, Y11H in CDR-H2, Y11I in CDR-H2, Y11K in CDR-H2, Y11L in CDR-H2, Y11N in CDR-H2, Y11R in CDR-H2, Y11S in CDR-H2, Y11V in CDR-H2, Y11W in CDR-H2, D13N in CDR-H2, V15D in CDR-H2, V15L in CDR-H2, V15M in CDR-H2, V15Q in CDR-H2, V15T in CDR-H2, E16F in CDR-H2, E16K in CDR-H2, E16R in CDR-H2, E16T in CDR-H2, E16W in CDR-H2, G17A in CDR-H2, G17C in CDR-H2, G17E in CDR-H2, G17I in CDR-H2, G17K in CDR-H2, G17L in CDR-H2, G17M in CDR-H2, G17N in CDR-H2, G17P in CDR-H2, G17Q in CDR-H2, G17R in CDR-H2, G17S in CDR-H2, G17T in CDR-H2, and G17Y in CDR-H2.

44. The anti-TNF-α antibody or anti-TNF-α binding fragment of claim 28, wherein the CDRs include the substitution D13N in CDR-H2.

45. The anti-TNF-α antibody or anti-TNF-α binding fragment of any one of claims 28-44, wherein the reference anti-TNF-α antibody or reference anti-TNF-α binding fragment comprises a variable heavy chain fragment having an amino acid sequence corresponding to SEQ ID NO:2 and a variable light chain fragment having an amino acid sequence corresponding to SEQ ID NO:4.

46. A nucleic acid molecule encoding the anti-TNF-α antibody or anti-TNF-α binding fragment of any one of claims 28-45.

47. A host cell comprising a nucleic acid molecule encoding the anti-TNF-α antibody or anti-TNF-α binding fragment of any one of claims 28-45.

48. A pharmaceutical composition comprising the anti-TNF-α antibody or anti-TNF-α binding fragment of any one of claims 28-45 and a pharmaceutically acceptable carrier.

49. A method of treating a human patient suffering from an immune disorder comprising administering to the human patient a therapeutically effective amount of the anti-TNF-α antibody or anti-TNF-α binding fragment of any one of claims 28-45.

50. The method of claim 49, wherein the immune disorder is selected from rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis and axial spondyloarthritis.