Parkinson's disease, myocardial infarction, stroke, autism, epilepsy, Arthus's phenomenon, anaphylaxis, alcohol addiction, and drug addiction.

BRIEF DESCRIPTION OF THE FIGURES

~~The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.~~

FIG. 1 depicts the binding modes of two different co-crystal structures of human CD40 (SEQ ID NO: 1), one with the dAb BMS3h-56-5 (SEQ ID NO: 321) and one with the Fab' of Chi220 antibody. The BMS3h-56-5 and Chi 220 Fab' molecules are shown as cartoons with β-strands (represented as arrows in the dAb) and non-repetitive secondary structure (represented as loops in th dAb). Complementarity-determing regions (CDRs) are also shown CD40 is also shown as a cartoon with the BMS3h-56-5 epitope residues of human CD40. The Chi220 epitope residues are also shown. Disulfide bonds are also shown The N-terminus (N) and C-terminus (C) of CD40 are labeled.

FIG. 2 depicts a space filling model of BMS3h-56-5 (SEQ ID NO: 321) contacting human CD40 (SEQ ID NO: 1), which is shown as a cartoon. Surface residues of the dAb BMS3h-56-5 that contact CD40 are shown. The BMS3h-56-5 CDR3 region and FR-2 residues Leu45, Arg47, Arg56 and Phe99 are labeled. Kabat numbering (Kabat et al., *Sequences of Immunological Interest,* 5th ed., U.S. Dept. Health & Human Services, Washington, D.C. (1991)) is used in this diagram and differs from sequential numbering in that insertion residues are used to keep the residue numbering of the β-strands identical. Thus for BMS3h-56-5, sequential residue 53 becomes residue 52A, sequential residues 84, 85, and 86 become, respectively, 82A, 82B, 82C and Kabat residue number 100 is missing (it would be between sequential residues 103 and 104); CD40 is also represented as a cartoon with non-repetitive secondary structure and the BMS3h-56-5 epitope. CD40 residues that differ between human and *Macaca fascicularis* (cynomolgus monkey), Ala115, Phe99, Ser126, His162, Leu121, and Trp109, are shown in stick representation. CD40 residues that differ between human and cynomolgus monkey that are part of the BMS3h-56-5 epitope are Trp109, Leu121, and His162.

Å, root mean square angles 1.4°. The real space correlation coefficients are 0.92 for main-chain atoms and 0.80 for side-chain atoms. The final model had 13 water molecules.

Using the model of the C-terminal domain from the C2 crystal form as a guide, the CD40 models in I222 crystal form were further refined. Several more cycles of model building using the COOT program and refinement with the autoBUSTER program led to the following statistics: R-free 0.323, R-work 0.292, root mean square bonds 0.011 Å, root mean square angles 1.5°. The real space correlation coefficients are 0.91 for main-chain atoms and 0.80 for side-chain atoms. The model contained no water molecules.

Overall Structure of the CD40/BMS3h-56-5 complex:

One BMS3h-56-5 dAb binds to one CD40 molecule. As shown in FIG. 1, BMS3h-56-5 binds to an epitope that is distinct from that of the antibody Chi220, which binds in the N-terminal region. ~~CD40 residues (SEQ ID NO: 1) are shown in green, except for epitope residues. CD40 epitope residues for Chi220 are shown in blue; BMS3h-56-5 dAb epitope residues are shown in cyan. Chi220 Fab and BMS3h-56-5 β-~~ strands are shown in red, CDR residues are shown in magenta, and other loops are shown ~~in orange. Disulfide bonds are shown for the CD40, Chi220, and BMS3h-56-5 molecules with the sulfur atoms in yellow.~~

The I222 crystal form contains four crystallographically independent CD40/BMS3h-56-5 complexes, and the C2 crystal for contains three crystallographically independent CD40/BMS3h-56-5 complexes. The CD40 molecule has a certain amount of flexibility, and the domains are arrayed differently in the seven unique versions of the complex, but the overall nature of the interaction is retained in all cases.

BMS3h-56-5 dAb epitope residues:

The minimal CD40 epitope for BMS3h-56-5 is defined as CD40 residues containing at least one atom in van der Waals or hydrogen-bond contact with a BMS3h-56-5 atom. The minimal epitope in all the complexes contains the following CD40 residues with reference to SEQ ID NO: 1: Trp109, Leu121, His122, Ser124, Ser156,

Ala157, Phe158, Glu159, and His162. The following additional residues are in van der Waals or hydrogen-bond contact in some complexes: Pro85, Asn86, Leu87, Gly88, Glu106, Glu107, Gly108, His110, Thr112, Cys119, Val120, Gln133, Ile134, Ala135, Thr136, Ser155, Lys160.

A maximal CD40 epitope is defined as residues containing atoms that are buried by a 1.7 Å probe sphere. These residues include all the residues above, plus Val 154 in all complexes. In some complexes, additional buried residues are: Ser118, Arg123, Thr141, Phe151, Asp153, Cys161, and Pro163.

A depiction of the surface of BMS3h-56-5 with contacting residues is shown in FIG. 2. Contacting BMS3h-56-5 residues are shown. Buried residues are.also shown. ~~CD40 is represented as a cartoon with orange representing non-repetitive secondary structure and magenta representing the epitope residues.~~ Also shown as sticks ~~(carbon atoms in cyan)~~ are CD40 residues Trp109, Ala115, Leu121, Ser126, and His162, which are five of the seven residues that differ between human and cynomolgus monkey (*Macaca fascicularis*). Ala115 and Ser126 are on the opposite side of CD40 from the BMS3h-56-5 binding site. Trp109 and Leu121 bind in a cleft of BMS-h-56-5 that lies between CDR-3 and FR-2 (BMS-3h-56-5 residues Leu45 and Arg47). His162 of CD40 interacts with Arg56 of CDR-2 of the BMS3h-56-5 dAb. Mutation of Trp109 considerably reduces or ablates BMS3h-56-5 activity.

Depending on the crystallographically independent complex, 660-740 $Å^2$ of CD40 surface area is buried with between 16-21 contacting residues represented at a finer level with contacting 46-67 atoms. For BMS3h-56-5, 660-780 $Å^2$ of surface area is buried with contacting 14-17 residues represented at a finer level with contacting 48-62 atoms. These contacts yield 3-7 hydrogen bonds and 111-142 van der Waals interactions, depending on the crystallographically independent complex.

Example 11

Identifying dAb Binding Epitopes on CD40

To identify dAb binding epitopes on CD40, dAb binding was tested against seven CD40-Fc fusion proteins containing specific amino acid residue substitutions at residues

What is Claimed Is:

1. An antibody polypeptide comprising a first variable domain, wherein said antibody polypeptide specifically binds an epitope of human CD40, wherein the antibody polypeptide competes with the binding of domain antibody (dAb) BMS3h-56-269 (SEQ ID NO: 417) to CD40, wherein CD40 comprises the amino acid sequence of SEQ ID NO: 1, and wherein the epitope comprises at least one CD40 amino acid residue selected from the group consisting of Trp109, Leu121, His122, Ser124, Ser156, Ala157, Phe158, Glu159, and His162.

2. The antibody polypeptide of claim 1, wherein the first variable domain comprises the amino acid sequence of one of the antibody polypeptides selected from the lineage group consisting of BMS3h-37, BMS3h-38, BMS3h-56, and BMS3h-198, and wherein the first variable domain has an apparent binding constant of 1 pM to 100 nM.

3. The antibody polypeptide of any of claims 1-2, wherein the first variable domain comprises the amino acid sequence of one of the antibody polypeptides selected from the lineage group consisting of BMS3h-37, BMS3h-38, and BMS3h-56, and wherein the first variable domain has a hIZCD40L-driven Human B Cell Proliferation EC50 of 0.01nM to 100.0 nM.

4. The antibody polypeptide of claim 1, wherein the amino acid sequence of the first variable domain comprises

(a) a CDR1 region which differs from the CDR1 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids,

(b) a CDR2 region which differs from the CDR2 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids,

(c) a CDR3 region which differs from the CDR3 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids,

(d) a FR1 region which differs from the FR1 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids,

(e) a FR2 region which differs from the FR2 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids,

(f) a FR3 region which differs from the FR3 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids, and

(g) a FR4 region which differs from the FR4 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids.

5. The antibody polypeptide of claim 1, wherein the amino acid sequence of the first variable domain comprises

(a) a CDR1 region which differs from the CDR1 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids,

(b) a CDR2 region which differs from the CDR2 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids,

(c) a CDR3 region which differs from the CDR3 region of BMS3h-56-269 (SEQ ID NO: 417) by up to two amino acids.

6. The antibody polypeptide of claim 1, wherein the amino acid sequence of the first variable domain differs from the amino acid sequence of BMS3h-56-258 (SEQ ID NO: 10) or BMS3h-56-269 (SEQ ID NO: 417) by up to 10 amino acids.

7. The antibody polypeptide of claim 6, wherein the amino acid sequence of the first variable domain differs from the amino acid sequence of BMS3h-56-258 (SEQ ID NO: 10) or BMS3h-56-269 (SEQ ID NO: 417) by up to 5 amino acids.

8. The antibody polypeptide of claim 7, wherein the amino acid sequence of the first variable domain differs from the amino acid sequence of BMS3h-56-258 (SEQ ID NO: 10) or BMS3h-56-269 (SEQ ID NO: 417) by two amino acids.

9. The antibody polypeptide of claim 8, wherein the amino acid sequence of the first variable domain differs from the amino acid sequence of BMS3h-56-258 (SEQ ID NO: 10) or BMS3h-56-269 (SEQ ID NO: 417) by one amino acid.

10. The antibody polypeptide of any of claims 2-3, wherein the antibody polypeptide is selected from the lineage group of BMS3h-56, and wherein the amino acid sequence of the first variable domain further comprises:

(a) a CDR1 region having a sequence X_1-Tyr-Glu-Y_1-Trp (SEQ ID NO: 1274), wherein X_1 is Asp or Gly, and Y_1 is Met or Leu;

(b) a CDR2 region having a sequence Ala-Ile-Asn-Pro-X_2-Gly-Y_2-Z_2-Thr-Tyr-Tyr-Ala-Asp-Ser-Val-A_2-Gly (SEQ ID NO: 1275), wherein X_2 is Gln, Tyr, Pro, Trp, or Ala, Y_2 is Thr, Ser, Asn, Gly, Met, or Gln, Z_2 is Arg, Leu, Tyr, His, or Phe, and A_2 is Lys or Met; and

(c) a CDR3 region having a sequence X_3-Pro-Y_3-Z_3-Phe-A_3-B_3 (SEQ ID NO: 1276), wherein X_3 is Leu or Pro, Y_3 is Phe, Gln, Thr, or Met, Z_3 is Tyr, Pro, Leu, Thr, Ile, Phe, or Met, A_3 is Gln, His, Asp, Ser, Lys, Glu, or Gly, and B_3 is Glu, Asp, or Tyr.

11. The antibody polypeptide of claim 10, wherein the amino acid sequence of the first variable domain comprises:

(a) a FR1 region having a sequence Glu-Val-Gln-Leu-Leu-Glu-Ser-Gly-Gly-Gly--Leu-Val-Gln-Pro-Gly-Gly-Ser-X_1-Arg-Leu-Ser-Cys-Ala-Ala-Ser-Gly-Phe-Thr-Phe-Y_1 (SEQ ID NO: 1277), wherein X_1 is Leu or Arg, and Y_1 isArg or Ala;

(b) a FR2 region having a sequence Trp-Val-Arg-X_2-Ala-Pro-Gly-Y_2-Z_2-Leu-Glu-Arg-Val-Ser (SEQ ID NO: 1278), wherein X_2 is Gln or Arg, Y_2 is Lys or Arg, and Z_2 is Gly or Val;

(c) a FR3 region having a sequence Arg-Phe-Thr-Ile-Ser-Arg-Asp-Asn-Ser-Lys-Asn-X_3-Lys-Tyr-Leu-Gln-Met-Asn-Ser-Leu-Arg-Ala-Y_3-Asp-Thr-Z_3-Val-Tyr-A_3-Cys-B_3-Lys (SEQ ID NO: 1279), wherein X_3 is Thr or Met, Y_3 is Glu or Asp, Z_3 is Ala or Ser, A_3 is Tyr or His, and B_3 is Ala or Thr; and

(d) a FR4 region having a sequence X_4-Gly-Y_4-Gly-Thr-Leu-Val-Thr-Val-Ser-Z_4 (SEQ ID NO: 1280), wherein X_4 is Trp or Arg, Y_4 is Gln or Pro, and Z_4 is Ser or Asn.

12. The antibody polypeptide of any of claims 2-3, wherein the first variable domain comprises the amino acid sequence of BMS3h-56-258 (SEQ ID NO: 10) or BMS3h-56-269 (SEQ ID NO:417).

13. The antibody polypeptide of any of claims 2-3, wherein the antibody polypeptide is selected from the lineage group of BMS3h-37, wherein the first variable domain comprises the sequence Glu-Val-Gln-Leu-Leu-Glu-Ser-Gly-Gly-Gly-Leu-Val-X_1-Pro-Gly-Gly-Ser-Leu-Arg-Leu-Ser-Cys-Ala-Ala-Ser-Gly-Phe-Thr-Phe-Glu-Trp-Tyr-Glu-Met-Gln-Trp-Val-Arg-Arg-Ala-Pro-Gly-Lys-Gly-Leu-Glu-Trp-Val-Ser-Ala-Ile-Ser-Gly-Asp-Gly-Tyr-Arg-Thr-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly-Arg-Phe-Thr-Ile-Ser-Arg-Asp-Asn-Ser-Lys-Asn-Thr-Leu-Tyr-Leu-Gln-Met-Asn-Ser-Leu-Arg-Ala-Glu-Asp-Thr-Ala-Val-Tyr-Tyr-Cys-Ala-Lys-Y_1-Leu-Z_1-A_1-Phe-Asp-Tyr-B_1-Gly-Arg-Gly-Thr-Leu-Val-Thr-Val-Ser-Ser (SEQ ID NO: 1281); and

wherein X_1 is Gln or Arg; Y_1 is Glu or Gly; Z_1 is Ala, Leu, or Glu; A_1 is Phe or Tyr; and B_1 is Trp or Arg.

14. The antibody polypeptide of any of claims 2-3, wherein the antibody polypeptide is selected from the lineage group of BMS3h-38, wherein the first variable domain comprises the sequence Glu-Val-Gln-Leu-Leu-Ala-Ser-Gly-Gly-Gly-Leu-Val-Gln-Pro-Gly-Gly-Ser-Leu-Arg-Leu-Ser-Cys-Ala-Ala-Ser-Gly-Phe-X_1-Phe-Glu-Glu-Glu-Glu-Met-Ile-Trp-Val-Arg-Gln-Ala-Pro-Gly-Lys-Gly-Leu-Glu-Trp-Val-Ser-Y_1-Ile-Ser-Z_1-A_1-Gly- B_1-C_1-Thr-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly-Arg-Phe-Thr-Ile-Ser-Arg-Asp-Asn-Ser-Lys-Asn-Thr-Leu-Tyr-Leu-Gln-Met-Asn-Ser-Leu-Arg-Ala-Glu-Asp-Thr-Ala-Val-Tyr-Tyr-Cys-Gly-Lys-Glu-Pro-Phe-D_1-Tyr-Asp-Tyr-Trp-Gly-Gln-Gly-Thr-Leu-Val-Thr-Val-Ser-Ser (SEQ ID NO: 1282); and

wherein X_1 is Thr or Pro; Y_1 is Ala or Ser; Z_1 is Arg or Gly; A_1 is Arg, Ser, Asn, Gln, Gly, His, or Leu; B_1 is Tyr, Phe, Trp, or Gly; C_1 is Ser or Gly; and D_1 is Arg, Met, or Pro.

15. The antibody polypeptide of any of claims 2-3, wherein the antibody polypeptide is selected from the lineage group of BMS3h-198, wherein the first variable domain comprises the sequence Glu-Val-Gln-Leu-Leu-Glu-Ser-Gly-Gly-Gly-Leu-Val-Gln-Pro-Gly-Gly-Ser-Leu-Arg-Leu-Ser-Cys-Ala-Ala-Ser-Gly-Phe-Thr-Phe-Ala-Gly-Try-Glu-X_1-Trp-Trp-Y_1-Arg-Gln-Ala-Pro-Gly-Lys-Gly-Leu-Glu-Arg-Val-Ser-Ala-Ile-Ser-Gly-Ser-Gly-Gly-Ser-Thr-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly-Arg-Phe-Thr-Ile-Ser-Arg-Asp-Z_1-A_1-Lys-Asn-Thr-Leu-Tyr-Leu-Gln-Met-Asn-Ser-Leu-Arg-Ala-Glu-Asp-Thr-Ala-Val-Tyr-B_1-Cys-Ala-C_1-D_1-Pro-Tyr-Ser-E_1-Asp-Tyr-F_1-G_1-H_1-Gly-Thr-Leu-Val-Thr-Val-Ser-Ser (SEQ ID NO: 1283); and

wherein X_1 is Met or Leu; Y_1 is Val or Phe; Z_1 is Asp or Asn; A_1 is Ser or Thr; B_1 is Tyr or His; C_1 is Lys or Arg; D_1 is Asp or Glu; E_1 is Tyr or Phe; F_1 is Trp or Arg; G_1 is Gly or Arg; and H_1 is Gln or His.

16. The antibody polypeptide of any of claims 1-15, wherein the antibody polypeptide is a domain antibody (dAb).

17. The antibody polypeptide of any of claims 1-16, wherein the antibody polypeptide is a fusion polypeptide comprising the first variable domain and an Fc domain.

18. The fusion polypeptide of claim 17, wherein the fusion polypeptide comprises an IgG4 Fc domain.

19. The fusion polypeptide of claim 18, wherein the fusion polypeptide comprises an IgG1 Fc domain.

20. The fusion polypeptide of any of claims 17-19, where the fusion polypeptide comprises the amino acid sequence of one of the antibody polypeptides selected from the lineage group consisting of BMS3h-37, BMS3h-38, and BMS3h-56, and wherein the fusion polypeptide has a hIZCD40L-driven Human B Cell Proliferation EC50 of 0.001nM to 100.0 nM.

21. The antibody polypeptide of any of claims 1-20, wherein the antibody polypeptide further comprises a second variable domain that specifically binds a second antigen, wherein the second antigen is an antigen other than human CD40.

22. The antibody polypeptide of claim 21, wherein the second antigen is a cluster of differentiation (CD) molecule or a Major Histocompatibility Complex (MHC) Class II molecule.

23. The antibody polypeptide of claim 21, wherein the second antigen is serum albumin (SA).

24. A nucleic acid encoding the antibody polypeptide of any one of claims 1-23.

25. A vector comprising the nucleic acid of claim 24.

26. An isolated host cell comprising the vector of claim 25.

27. A pharmaceutical composition comprising a therapeutically-effective amount of the antibody polypeptide of claim 1 and a pharmaceutically acceptable carrier.

28. The pharmaceutical composition of claim 27, further comprising an immunosuppressive/immunomodulatory and/or anti-inflammatory agent.

29. A method of treating an immune disease in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 27.

30. The method of claim 29, wherein the pharmaceutical composition is administered in combination with an immunosuppressive/immunomodulatory and/or anti-inflammatory agent.

31. The method of claim 29, wherein the immune disease is an autoimmune disease or a graft-related disease.

32. The method of claim 29, wherein the immune disease is selected from the group consisting of selected from the group consisting of Addison's disease, allergies, ankylosing spondylitis, asthma, atherosclerosis, autoimmune diseases of the ear, autoimmune diseases of the eye, autoimmune hepatitis, autoimmune parotitis, colitis, coronary heart disease, Crohn's disease, diabetes, including Type 1 and/or Type 2 diabetes, epididymitis, glomerulonephritis, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hemolytic anemia, idiopathic thrombocytopenic purpura, inflammatory bowel disease, immune response to recombinant drug products, systemic lupus erythematosus, male infertility, multiple sclerosis, myasthenia gravis, pemphigus, psoriasis, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, spondyloarthropathies, thyroiditis, transplant rejection, vasculitis, AIDS, atopic allergy, bronchial asthma, eczema, leprosy, schizophrenia, inherited depression, transplantation of tissues and organs, chronic fatigue syndrome, Alzheimer's disease, Parkinson's disease, myocardial infarction, stroke, autism, epilepsy, Arthus's phenomenon, anaphylaxis, alcohol addiction, and drug addiction.

What is Claimed Is:

1. An antibody polypeptide comprising a first variable domain, wherein the first variable domain comprises:

(a) a CDR1 region comprising the CDR1 region of BMS3h-56-269 (amino acids 31 to 35 of SEQ ID NO: 417) or differs from the CDR1 region of BMS3h-56-269 by up to two amino acids,

(b) a CDR2 region comprising the CDR2 region of BMS3h-56-269 (amino acids 50 to 66 of SEQ ID NO: 417) or differs from the CDR2 region of BMS3h-56-269 by up to two amino acids,

(c) a CDR3 region comprising the CDR3 region of BMS3h-56-269 (amino acids 99 to 105 of SEQ ID NO: 417) or differs from the CDR3 region of BMS3h-56-269 by up to two amino acids, and

wherein said antibody polypeptide is a domain antibody that binds CD40 and wherein the binding of the antibody polypeptide to CD40 antagonizes CD40 activity.

2. The antibody polypeptide of claim 1, wherein the first variable domain comprises the amino acid sequence of one of the antibody polypeptides of the lineage group of BMS3h-56 selected from the group consisting of SEQ ID NO: 317; SEQ ID NO: 318; SEQ ID NO: 320; SEQ ID NO: 321; SEQ ID NO: 322; SEQ ID NO: 324; SEQ ID NO: 325; SEQ ID NO: 326; SEQ ID NO: 327; SEQ ID NO: 331; SEQ ID NO: 332; SEQ ID NO: 333; SEQ ID NO: 334; SEQ ID NO: 335; SEQ ID NO: 336; SEQ ID NO: 337; SEQ ID NO: 341; SEQ ID NO: 342; SEQ ID NO: 343; SEQ ID NO: 344; SEQ ID NO: 345; SEQ ID NO: 346; SEQ ID NO: 347; SEQ ID NO: 348; SEQ ID NO: 349; SEQ ID NO: 9; SEQ ID NO: 350; SEQ ID NO: 353; SEQ ID NO: 355; SEQ ID NO: 356; SEQ ID NO: 358; SEQ ID NO: 366; SEQ ID NO: 367; SEQ ID NO: 376; SEQ ID NO: 379; SEQ ID NO: 381; SEQ ID NO: 386; SEQ ID NO: 394; SEQ ID NO: 403; SEQ ID NO: 405; SEQ ID NO: 412; SEQ ID NO: 417; and SEQ ID NO: 419.

3. The antibody polypeptide of claims 1-2, wherein:

(a) the CDR1 region comprises the CDR1 region of BMS3h-56-269 (SEQ ID NO: 417),

(b) the CDR2 region comprises the CDR2 region of BMS3h-56-269 (SEQ ID NO: 417), and

(c) the CDR3 region comprises the CDR3 region of BMS3h-56-269 (SEQ ID NO: 417).

4. The antibody polypeptide of claim 1, wherein the first variable domain further comprises:

(a) a FR1 region comprising the FR1 region of BMS3h-56-269 (amino acids 1 to 30 of SEQ ID NO: 417) or differs from FR1 region of BMS3h-56-269 by up to two amino acids,

(b) a FR2 region comprising the FR2 region of BMS3h-56-269 (amino acids 36 to 49 of SEQ ID NO: 417) or differs from the FR2 region of BMS3h-56-269 by up to two amino acids,

(c) a FR3 region comprising the FR3 region of BMS3h-56-269 (amino acids 67 to 98 of SEQ ID NO: 417) or differs from the FR3 region of BMS3h-56-269 by up to two amino acids, and

(d) a FR4 region comprising the FR4 region of BMS3h-56-269 (amino acids 106 to 116 of SEQ ID NO: 417) or differs from the FR4 region of BMS3h-56-269 by up to two amino acids.

5. The antibody polypeptide of claim 4, wherein:

(a) the FR1 region comprises the FR1 region of BMS3h-56-269 (SEQ ID NO: 417),

(b) the FR2 region comprises the FR2 region of BMS3h-56-269 (SEQ ID NO: 417),

(c) the FR3 region comprises the FR3 region of BMS3h-56-269 (SEQ ID NO: 417), and

(d) the FR4 region comprises the FR4 region of BMS3h-56-269 (SEQ ID NO: 417).

6. The antibody polypeptide of claim 1, wherein the first variable domain comprises BMS3h-56-269 (SEQ ID NO: 417).

7. The antibody polypeptide of claim 1, wherein:

(a) the CDR1 region consists of a sequence X_1-Tyr-Glu-Y_1-Trp (SEQ ID NO: 1274), wherein X_1 is Asp or Gly, and Y_1 is Met or Leu;

(b) the CDR2 region consists of a sequence Ala-Ile-Asn-Pro-X_2-Gly-Y_2-Z_2-Thr-Tyr-Tyr-Ala-Asp-Ser-Val-A_2-Gly (SEQ ID NO: 1275), wherein X_2 is Gln, Tyr, Pro, Trp, or Ala, Y_2 is Thr, Ser, Asn, Gly, Met, or Gln, Z_2 is Arg, Leu, Tyr, His, or Phe, and A_2 is Lys or Met; and

(c) the CDR3 region consists of a sequence X_3-Pro-Y_3-Z_3-Phe-A_3-B_3 (SEQ ID NO: 1276), wherein X_3 is Leu or Pro, Y_3 is Phe, Gln, Thr, or Met, Z_3 is Tyr, Pro, Leu, Thr, Ile, Phe, or Met, A_3 is Gln, His, Asp, Ser, Lys, Glu, or Gly, and B_3 is Glu, Asp, or Tyr.

8. The antibody polypeptide of any one of claims 1 to 7, wherein the antibody polypeptide is a fusion polypeptide comprising the first variable domain and an Fc domain.

9. The antibody polypeptide of claim 8, wherein the antibody polypeptide comprises the amino acid sequence of the BMS3h-56-269-IgG1* Fc fusion polypeptide (SEQ ID NO: 1286).

10. The antibody polypeptide of claim 8, wherein the antibody polypeptide comprises the amino acid sequence of the BMS3h-56-269-IgG4 Fc fusion polypeptide (SEQ ID NO: 1287).

11. The antibody polypeptide of any one of claims 1 to 10, wherein the antibody polypeptide further comprises a second variable domain that specifically binds a second antigen, wherein the second antigen is an antigen other than human CD40.

12. A nucleic acid encoding the antibody polypeptide of any one of claims 1 to 11.

13. An isolated host cell comprising the nucleic acid of claim 12.

14. A pharmaceutical composition for treating an immune disease comprising a therapeutically-effective amount of the antibody polypeptide of any one of claims 1 to 11 and a pharmaceutically acceptable carrier.

15. Use of an antibody polypeptide of any one of claims 6, 9 and 10 in the manufacture of a medicament to treat an immune disease in a patient in need of such treatment.

16. The use of claim 15, wherein the immune disease is selected from the group consisting of Addison's disease, allergies, ankylosing spondylitis, asthma, atherosclerosis, autoimmune diseases of the ear, autoimmune diseases of the eye, autoimmune hepatitis, autoimmune parotitis, ulcerative colitis, coronary heart disease, Crohn's disease, diabetes, including Type 1 and/or Type 2 diabetes, epididymitis, glomerulonephritis, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hemolytic anemia, idiopathic thrombocytopenic purpura, inflammatory bowel disease, immune response to recombinant drug products, systemic lupus erythematosus, male infertility, multiple sclerosis, myasthenia gravis, pemphigus, psoriasis, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, spondyloarthropathies, thyroiditis, transplant rejection, vasculitis, AIDS, atopic allergy, bronchial asthma, eczema, leprosy, schizophrenia, inherited depression, transplantation of tissues and organs, chronic fatigue syndrome, Alzheimer's disease, Parkinson's disease, myocardial infarction, stroke, autism, epilepsy, Arthus' phenomenon, anaphylaxis, alcohol addiction, and drug addiction.

17. The use of claim 15, wherein the immune disease is selected from the group consisting of ulcerative colitis, Crohn's disease, and inflammatory bowel disease.

18. The use of claim 15, wherein the immune disease is systemic lupus erythematosus.

19. The pharmaceutical composition of claim 14, wherein the immune disease is selected from the group consisting of ulcerative colitis, Crohn's disease, and inflammatory bowel disease.

20. The pharmaceutical composition of claim 14, wherein the immune disease is systemic lupus erythematosus.