CLAIMS

What is claimed:

1. An isolated antibody or antibody fragment thereof comprising an antigen binding region that binds to a V-domain Ig Suppressor of T cell Activation (VISTA), wherein binding of the antibody or antibody fragment to VISTA modulates or enhances an immune response, and wherein the antibody comprises:

a) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:1,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:2 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:3,

and

b) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:4,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:5 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:6;

or

c) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:13,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:14 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:15,

and

d) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:16,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:17 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:18.

2. The antibody or antibody fragment of claim 1, wherein the antibody fragment is a Fab, $F(ab')_2$, or scFv antibody fragment.

3. The antibody or antibody fragment of claim 1 which comprises an antibody constant region.

4. The antibody or antibody fragment of any one of claims 1-3, comprising at least one heavy chain and at least one light chain.

5. An antibody or antibody fragment according to claim 4, wherein the antibody comprises:

a) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:1,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:2 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:3,

and

b) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:4,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:5 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:6.

6. An antibody or antibody fragment according to claim 4, wherein at least one heavy chain comprises the heavy chain variable region sequence as shown in SEQ ID NO:38, and wherein at least one light chain comprises the light chain variable region sequence as shown in SEQ ID NO:41.

7. The antibody or antibody fragment of any one of claims 1-6, wherein the antibody is a monoclonal antibody.

8. The antibody or antibody fragment of any one of claims 1-7, wherein the antibody is a humanized antibody.

9. The antibody or antibody fragment of any one of claims 1-7, wherein the antibody comprises a human constant region.

10. An antibody or antibody fragment according to any one of claims 1-9, wherein the antibody molecule is specific for an epitope within the amino acid sequence SEQ ID NO: 46.

11. The antibody or antibody fragment of any one of claims 1-10, wherein the modulation of the immune response comprises an increase in CD45+ leukocytes, CD4+ T cells, or CD8+ T cells, or a combination thereof, or a decrease in VISTA-expressing immune cells.

12. The antibody or antibody fragment of any one of claims 1-10, wherein the modulation of the immune response comprises enhanced production of cytokines, enhanced T-cell response, and/or modulates Foxp3 expression.

13. The antibody or fragment thereof of claim 1, wherein the antibody VL domain comprises a human framework region.

14. The antibody or fragment thereof of claim 1, which comprises a whole antibody.

15. The antibody or antibody fragment of claim 10, wherein the epitope is a conformational epitope.

16. The antibody or antibody fragment of claim 15, wherein the conformational epitope comprises or is present within residues 103-111 and 136-146 of SEQ ID NO:46.

17. A composition comprising the antibody or antibody fragment of any one of claims 1-12 and a pharmaceutically acceptable carrier, diluent, or excipient.

18. The use of the antibody or antibody fragment of any one of claims 1-12 in the manufacture of a medicament for tre44ating cancer in an individual in need thereof.

19. The use of the composition of claim 17 in the manufacture of a medicament for treating or preventing cancer in an individual in need thereof.

20. The use of any one of Claims 18-19, wherein the individual is a mammal.

21. The use of any one of Claims 18-19, wherein the individual is a human.

22. The use of a V-domain Ig Suppressor of T cell Activation (VISTA) antagonist antibody or antibody fragment thereof comprising an antigen binding region that binds to VISTA in the manufacture of a medicament for treating a cancer in an individual in need thereof, wherein the antibody comprises:

a) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:1,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:2 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:3,

and

b) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:4,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:5 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:6;

or

c) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:13,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:14 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:15,

and

d) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:16,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:17 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:18.

23. The use of claim 22, wherein the cancer is a leukemia, lymphoma, myelodisplastic syndrome or myeloma, or a combination thereof.

24. The use of claim 23, wherein the leukemia is a lymphocytic leukemia or a myelogenous leukemia.

25. The use of claim 23, wherein the leukemia is acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid (myelogenous) leukemia (AML), chronic myelogenous leukemia (CML); hairy cell leukemia, T-cell prolymphocytic leukemia, large granular lymphocytic leukemia, or adult T-cell leukemia.

26. The use of claim 22, wherein the cancer is an acute myeloid (myelogenous) leukemia (AML).

27. The use of claim 22, wherein the cancer is a chronic myelogenous leukemia (CML).

28. The use of claim 22, wherein the cancer is a solid tumor.

29. The use of claim 28, wherein the solid tumor is surrounded by a tumor stroma comprising myeloid cells, T-cells, or a combination of myeloid cells and T-cells.

30. The use of claim 28 or 29, wherein the solid tumor is infiltrated with myeloid cells, T cells or a combination of myeloid cells and T-cells.

31. The use of claim 22, wherein the cancer is a lung cancer.

32. The use of claim 31, wherein the lung cancer is a non-small cell lung carcinoma (NSCLC).

33. The use of the antibody or antibody fragment of claims 1-12 in the manufacture of a medicament for suppressing tumor growth in an individual in need thereof.

34. The use of any one of claims 18-30 and 33, wherein the medicament is suitable for parenteral or nonparenteral administration.

35. The use of any one of claims 18-30 and 33, wherein the dosage of the composition, antibody or fragment is 0.1-15 mg/kg per administration.

36. The use of any one of claims 18-30 and 33, wherein the medicament is suitable for administering weekly, once every two weeks, once every three weeks, once every month, once every 2 months, or once every 3 months.

37. An isolated nucleic acid which comprises a nucleotide sequence encoding the antibody of claim 1.

38. An expression vector comprising the nucleic acid of claim 37 operably linked to a promoter.

39. A host cell transformed with the expression vector of claim 38.

40. A method of producing antibody or fragment thereof of claim 1, the method comprising culturing host cells according to claim 39 under conditions for production of said antibody or fragment.

41. The method according to claim 40 further comprising isolating said antibody.

42. The use of an antibody or an antibody fragment thereof in the manufacture of a medicament for treating a tumor in an individual in need thereof, wherein the antibody binds V-domain Ig Suppressor of T cell Activation (VISTA) and comprises:

a) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:1,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:2 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:3,

and

b) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:4,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:5 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:6;

or

c) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:13,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:14 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:15,

and

d) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:16,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:17 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:18,

and the antibody fragment comprises an antigen binding region that binds to VISTA.

43. The use of an antibody or an antibody fragment thereof in the manufacture of a medicament for treating cancer in an individual in need thereof, wherein the antibody binds V-domain Ig Suppressor of T cell Activation (VISTA) and comprises:

a) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:1,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:2 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:3,

and

b) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:4,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:5 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:6;

or

c) an antibody VH domain comprising:

i) a VH CDR1 having the amino acid sequence of SEQ ID NO:13,

ii) a VH CDR2 having the amino acid sequence of SEQ ID NO:14 and

iii) a VH CDR3 having the amino acid sequence of SEQ ID NO:15,

and

d) an antibody VL domain comprising:

i) a VL CDR1 having the amino acid sequence of SEQ ID NO:16,

ii) a VL CDR2 having the amino acid sequence of SEQ ID NO:17 and

iii) a VL CDR3 having the amino acid sequence of SEQ ID NO:18,

and the antibody fragment comprises an antigen binding region that binds to VISTA, wherein the antibody or antibody fragment elicits a biological response selected from the group consisting of:

a. activation of monocytes;
b. induction of T-cell proliferation and cytokine secretion;
c. increased survival of monocytes;
d. induction of antibody-dependent cell-mediated cytotoxicity (ADCC) in cells-expressing VISTA; and
e. induction of antibody-dependent cellular phagocytosis (ADCP) in cells-expressing VISTA.

44. An antibody or antibody fragment according to claim 4 or 6, wherein at least one heavy chain comprises the heavy chain sequence as shown in SEQ ID NO:47, and wherein at least one light chain comprises the light chain sequence as shown in SEQ ID NO:48.

45. An antibody or antibody fragment according to claim 4, wherein at least one heavy chain comprises the heavy chain sequence as shown in SEQ ID NO:51, and wherein at least one light chain comprises the light chain sequence as shown in SEQ ID NO:52.

46. The use of any one of claims 22-36, 42 and 43, wherein the antibody comprises the heavy chain variable region sequence as shown in SEQ ID NO:38, and the light chain variable region sequence as shown in SEQ ID NO: 41.

47. The use of any one of claims 22-36 and 42,43 and 46 wherein the antibody comprises the heavy chain sequence as shown in SEQ ID NO:47, and the light chain sequence as shown in SEQ ID NO:48.

48. The use of any one of claims 22-36, 42 and 43, wherein the antibody comprises the heavy chain sequence as shown in SEQ ID NO:51, and the light chain sequence as shown in SEQ ID NO:52.

49. An antibody or antibody fragment according to claim 1, 3, 4, 6, 44 or 45, wherein the heavy chain constant region is an IgG1 heavy chain constant region.

50. The use of any one of claims 22-36, 42, 43 and 46-48 wherein the antibody comprises an IgG1 heavy chain constant region.