Claims

1. An antibody or antigen binding fragment thereof that immunospecifically binds to MHC class I polypeptide-related sequence A (MICA), wherein the antibody comprises

a heavy chain variable region (V_H) CDR1 comprising the amino acid sequence shown in SEQ ID NO: 154,

a V_H CDR2 comprising the amino acid sequence shown in SEQ ID NO: 156, and

a V_H CDR3 comprising the amino acid sequence shown in SEQ ID NO: 158,

or a variant thereof having 5 or fewer conservative amino acid substitutions in V_H CDR1, V_H CDR2 and/or V_H CDR3.

2. The antibody or antigen binding fragment of claim 1, wherein the antibody or antigen binding fragment comprises

a light chain variable region (V_L) CDR1 comprising the amino acid sequence shown in SEQ ID NO: 161,

a V_L CDR2 comprising the amino acid sequence shown in SEQ ID NO: 163, and

a V_L CDR3 comprising the amino acid sequence shown in SEQ ID NO: 165,

or a variant thereof having 5 or fewer conservative amino acid substitutions in V_L CDR1, CDR2, and/or CDR3.

3. The antibody or antigen binding fragment of claims 1 or 2, wherein the V_H region comprises

a V_H CDR1 comprising SEQ ID NO: 154;

a V_H CDR2 comprising SEQ ID NO: 156; and

a V_H CDR3 comprising SEQ ID NO: 158.

4. The antibody or antigen binding fragment of any one of claims 1-3, wherein the V_L region comprises

a V_L CDR1 comprising SEQ ID NO: 161,

a V_L CDR2 comprising SEQ ID NO: 163, and

a V_L CDR3 comprising SEQ ID NO: 165.

5. The antibody or antigen binding fragment of any one of claims 1-4, wherein the FR1, FR2, FR3, FR4 regions of the V_H region comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to the corresponding FR1, FR2, FR3, FR4 regions of the V_H set forth in SEQ ID NO: 150.

6. The antibody or antigen binding fragment of any one of claims 2-5, wherein the FR1, FR2, FR3, FR4 regions of the V_L region comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to the corresponding FR1, FR2, FR3, FR4 of the V_L set forth in SEQ ID NO: 152.

7. The antibody or antigen binding fragment of any one of claims 1-6, wherein the V_H region comprises the amino acid sequence shown in SEQ ID NO: 150, or a variant thereof having 5 or fewer conservative amino acid substitutions in residues that are not within a CDR.

8. The antibody or antigen binding fragment of any one of claims 1-7, comprising a V_L region comprising the amino acid sequence shown in SEQ ID NO: 152, or a variant thereof having 5 or fewer conservative amino acid substitutions in residues that are not within a CDR.

9. The antibody or antigen binding fragment of any one of claims 1-8, comprising a V_H region having the amino acid sequence shown in SEQ ID NO: 150; and a V_L having the amino acid sequence shown in SEQ ID NO: 152.

10. The antibody or antigen binding fragment of any one of claims 1-9, wherein the antibody or antigen binding fragment is human, humanized or chimeric.

11. A pharmaceutical composition comprising the antibody or antigen binding fragment of any one of claims 1-10.

12. The pharmaceutical composition of claim 11, comprising one or more additional agents.

13. The composition of 12, comprising one or more additional agents used for the treatment of cancer selected from the group consisting of chemotherapy, radiation therapy, cytokines, chemokines and other biologic signaling molecules, tumor specific vaccines, cellular cancer vaccines (e.g., GM-CSF transduced cancer cells), tumor specific monoclonal antibodies, autologous and allogeneic stem cell rescue (e.g., to augment graft versus tumor effects), molecular targeted therapies, anti-angiogenic therapy, and gene therapy.

14. The pharmaceutical composition of claim 12, wherein the one or more additional agents comprise: an histone deacetylase inhibitor (HDAC) selected from the group consisting of hydroxamic acid, vorinostat, suberoylanilide hydroxamic acid (SAHA, trichostatin A (TSA), LAQ824, panobinostat (LBH589), belinostat (PXD101), ITF2357 italfarmaco SpA, cyclic tetrapeptide, depsipeptide (romidepsin, FK228), benzamide; entinostat (SNDX-275/MS-275), MGCD0103, short-chain aliphatic acids, valproic acid, phenyl butyrate, AN-9, pivanex, CHR-3996, and CHR-2845; a proteasome inhibitor selected from the group consisting of bortezomib, NPI-0052, carfilzomib (PR-171), CEP 18770, and MLN9708; anti-CTLA-4 antibody or peptide; an anti-PD-1 antibody or peptide; an anti-PDL-1 antibody or peptide; an anti-OX40 antibody or peptide; an anti-GITR antibody or peptide; an anti-LAG-3 antibody or peptide; and an anti-TIM-3 antibody or peptide.

15. The pharmaceutical composition of any one of claims 11-14, for use in the treatment of cancer in a subject.

16. An isolated nucleic acid that encodes the antibody or antigen binding fragment of any one of claims 1-10.

17. The isolated nucleic acid of claim 16, comprising a nucleotide sequence having at least about 75%, 80%, 90%, 95%, 99% or 100% identity to SEQ ID NO: 149.

18. The isolated nucleic acid of claims 16 or 17, comprising a nucleotide sequence having at least about 75%, 80%, 90%, 95%, 99% or 100% sequence identity to SEQ ID NO: 151.

19. A vector comprising the nucleic acid of any one of claims 16-18.

20. The vector of claim 19, wherein the vector is a plasmid or viral vector.

Claims

1. An antibody or antigen binding fragment thereof that immunospecifically binds to MHC class I polypeptide-related sequence A (MICA), wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), and

complementarity determining region (CDR) 1 (CDR1) of the V_H comprises the amino acid sequence shown in SEQ ID NO: 154,

V_H CDR2 comprises the amino acid sequence shown in SEQ ID NO: 156, and

V_H CDR3 comprises the amino acid sequence shown in SEQ ID NO: 158,

or a variant thereof having 5 or fewer conservative amino acid substitutions in V_H CDR1, V_H CDR2 and/or V_H CDR3.

2. The antibody or antigen binding fragment of claim 1, wherein the light chain variable region (V_L) CDR1 comprises the amino acid sequence shown in SEQ ID NO: 161,

V_L CDR2 comprises the amino acid sequence shown in SEQ ID NO: 163, and

V_L CDR3 comprises the amino acid sequence shown in SEQ ID NO: 165,

or a variant thereof having 5 or fewer conservative amino acid substitutions in V_L CDR1, CDR2, and/or CDR3.

3. The antibody or antigen binding fragment of claims 1 or 2, wherein the V_H region comprises

a V_H CDR1 comprising SEQ ID NO: 154;

a V_H CDR2 comprising SEQ ID NO: 156; and

a V_H CDR3 comprising SEQ ID NO: 158.

4. The antibody or antigen binding fragment of any one of claims 1-3, wherein the V_L region comprises

a V_L CDR1 comprising SEQ ID NO: 161,

a V_L CDR2 comprising SEQ ID NO: 163, and

a V_L CDR3 comprising SEQ ID NO: 165.

5. The antibody or antigen binding fragment of any one of claims 1-4, wherein the FR1, FR2, FR3, FR4 regions of the V_H region comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to the corresponding FR1, FR2, FR3, FR4 regions of the V_H set forth in SEQ ID NO: 150.

6. The antibody or antigen binding fragment of any one of claims 2-5, wherein the FR1, FR2, FR3, FR4 regions of the V_L region comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to the corresponding FR1, FR2, FR3, FR4 of the V_L set forth in SEQ ID NO: 152.

7. The antibody or antigen binding fragment of any one of claims 1-6, wherein the V_H region comprises the amino acid sequence shown in SEQ ID NO: 150, or a variant thereof having 5 or fewer conservative amino acid substitutions in residues that are not within a CDR.

8. The antibody or antigen binding fragment of any one of claims 1-7, comprising a V_L region comprising the amino acid sequence shown in SEQ ID NO: 152, or a variant thereof having 5 or fewer conservative amino acid substitutions in residues that are not within a CDR.

9. The antibody or antigen binding fragment of any one of claims 1-8, comprising a V_H region having the amino acid sequence shown in SEQ ID NO: 150; and a V_L having the amino acid sequence shown in SEQ ID NO: 152.

10. The antibody or antigen binding fragment of any one of claims 1-9, wherein the antibody or antigen binding fragment is human, humanized or chimeric.

11. A pharmaceutical composition comprising the antibody or antigen binding fragment of any one of claims 1-10.

12. The pharmaceutical composition of claim 11, comprising one or more additional agents or therapies.

13. The composition of 12, wherein the one or more additional agents or therapies are selected from the group consisting of chemotherapy, radiation therapy, cytokines, chemokines and other biologic signaling molecules, tumor specific vaccines, cellular cancer vaccines (e.g., GM-CSF transduced cancer cells), tumor specific monoclonal antibodies, autologous and allogeneic stem cell rescue (e.g., to augment graft versus tumor effects), molecular targeted therapies, anti-angiogenic therapy, and gene therapy.

14. The pharmaceutical composition of claim 12, wherein the one or more additional agents comprise: an histone deacetylase inhibitor (HDAC) selected from the group consisting of hydroxamic acid, vorinostat (suberoylanilide hydroxamic acid SAHA), trichostatin A (TSA), LAQ824, panobinostat (LBH589), belinostat (PXD101), ITF2357 italfarmaco SpA, cyclic tetrapeptide, depsipeptide (romidepsin, FK228), benzamide; entinostat (SNDX-275/MS-275), MGCD0103, short-chain aliphatic acids (e.g., valproic acid, phenyl butyrate), AN-9, pivanex, CHR-3996, and CHR-2845; a proteasome inhibitor selected from the group consisting of bortezomib, NPI-0052, carfilzomib (PR-171), CEP 18770, and MLN9708; anti-CTLA-4 antibody or peptide; an anti-PD-1 antibody or peptide; an anti-PDL-1 antibody or peptide; an anti-OX40 antibody or peptide; an anti-GITR antibody or peptide; an anti-LAG-3 antibody or peptide; and an anti-TIM-3 antibody or peptide.

15. The pharmaceutical composition of any one of claims 11-14, for use in the treatment of cancer in a subject.

16. An isolated nucleic acid that encodes the antibody or antigen binding fragment of any one of claims 1-10.

17. The isolated nucleic acid of claim 16, comprising a nucleotide sequence having at least about 75%, 80%, 90%, 95%, 99% or 100% identity to SEQ ID NO: 149.

18. The isolated nucleic acid of claims 16 or 17, comprising a nucleotide sequence having at least about 75%, 80%, 90%, 95%, 99% or 100% sequence identity to SEQ ID NO: 151.

19. A vector comprising the nucleic acid of any one of claims 16-18.

20. The vector of claim 19, wherein the vector is a plasmid or viral vector.