

## Claims

What is claimed is:

1. An antigen-binding protein that binds specifically to an HLA-A2:New York esophageal squamous cell carcinoma 1 peptide (NY-ESO-1 peptide) complex at at least one amino acid corresponding to an amino acid selected from the group consisting of M160, W161, and Q164 of SEQ ID NO: 271.
2. The antigen-binding protein of claim 1, wherein said isolated antigen-binding protein specifically binds to a conformational epitope of the HLA-A2 presented NY-ESO-1 polypeptide.
3. The antigen-binding protein of claim 1 or 2, wherein said at least one amino acid is at least two amino acids.
4. The antigen-binding protein of claim 3, wherein said at least one amino acid is three amino acids.
5. An antigen-binding protein that binds specifically to an HLA-A2:NY-ESO-1 157-165 peptide complex, wherein said isolated antigen-binding protein interacts with amino acids M160, W161, and Q164 of said NY-ESO-1 157-165 peptide as determined by X-ray crystallography at a resolution of 4.0 Å or higher.
6. The antigen-binding protein of claim 5, wherein said resolution is 3.5 Å or higher.
7. The antigen-binding protein of claim 6, wherein said resolution is 3.3 Å or higher.
8. An antigen-binding protein that specifically binds to an HLA-A2:NY-ESO-1 157-165 peptide complex but does not specifically bind to one or more off-target peptides selected from the group consisting of BCL9L 1351-1359 (SEQ ID NO: 273), GRID1 7-15 (SEQ ID NO: 274), ZDHHC1 376-384 (SEQ ID NO: 276), ITCH 807-815 (SEQ ID NO: 277), and URB1 1853-1861 (SEQ ID NO: 280), wherein the ratio of i) said antigen-binding protein binding to cells pulsed with said one or more off-target peptides to ii) unpulsed cells is less than about nine.
9. The antigen-binding protein of claim 8, wherein said ratio is less than about 8.

10. The antigen-binding protein of claim 9, wherein said ratio is less than about 7.
11. The antigen-binding protein of claim 10, wherein said ratio is less than about 6.
12. The antigen-binding protein of claim 11, wherein said ratio is less than about 5.
13. The antigen-binding protein of claim 12, wherein said ratio is less than about 4.
14. The antigen-binding protein of claim 13, wherein said ratio is less than about 3.
15. The antigen-binding protein of claim 14, wherein said ratio is less than about 2.
16. The antigen-binding protein of any one of claims 1-15, wherein said antigen-binding protein binds to a monomeric HLA-A2:NY-ESO-1 157-165 peptide complex with a binding dissociation equilibrium constant ( $K_D$ ) of less than about 1nM as measured in a surface plasmon resonance assay at 25°C.
17. The antigen-binding protein of any one of claims 1-16, wherein said NY-ESO-1 peptide comprises the amino acid sequence of SLLMWITQC (SEQ ID NO: 269) or SLLMWITQV (SEQ ID NO: 291).
18. The antigen-binding protein of any one of claims 1-17, wherein the antigen-binding protein is a full-length antibody, a Fab, a Fab', a (Fab')<sub>2</sub>, an Fv, a single chain Fv (scFv), a T-body construct, or a Chimeric Antigen Receptor (CAR).
19. The antigen-binding protein of claim 19, wherein the antigen-binding protein is a CAR.
20. The CAR of claim 19, wherein the CAR comprises a heavy chain variable region (LCVR), a light chain variable region (LCVR), a hinge region, a transmembrane domain, a costimulatory domain, and a signaling domain.
21. The CAR of claim 20, wherein the costimulatory domain is a 4-1BB costimulatory domain.
22. The CAR of claim 20, wherein the costimulatory domain is a CD28 costimulatory domain.

23. The antigen-binding protein of any one of claims 1-22, wherein the antigen-binding protein is a human monoclonal antibody or an antigen-binding fragment thereof.

24. The antigen-binding protein of any one of claims 1-23, comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences listed in Table 1, and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within any one of the light chain variable region (LCVR) sequences listed in Table 1.

25. The antigen-binding protein of claim 24, wherein said HCVR sequences are selected from the group consisting of SEQ ID NOs: 2, 22, 42, 142, and 250.

26. The antigen-binding protein of claim 24, wherein said LCVR sequences are selected from the group consisting of SEQ ID NOs: 10, 30, 50, 150, and 260.

27. The antigen-binding protein of claim 24, wherein said HCVR/LCVR sequences are selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 62/70, 82/90, 102/110, 122/130, 142/150, 162/170, 180/186, 196/203, 211/219, 230/238, and 250/258.

28. The antigen-binding protein of claim 24, wherein said HCVR/LCVR sequences are selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 142/150, and 250/258.

29. The antigen-binding protein of any one of claims 1-25, comprising a HCVR having an amino acid sequence selected from the group consisting of the HCVR sequences listed in Table 1.

30. The antigen-binding protein of claim 29, wherein said HCVR sequences are selected from the group consisting of SEQ ID NOs: 2, 22, 42, 142, and 250.

31. The antigen-binding protein of any one of claims 1-30, comprising a LCVR having an amino acid sequence selected from the group consisting of the LCVR sequences listed in Table 1.

32. The antigen-binding protein of claim 31, wherein said LCVR sequences are selected from the group consisting of SEQ ID NOs: 10, 30, 50, 150, and 260.

33. The antigen-binding protein of any one of claims 1-32, comprising: (a) a HCVR having an amino acid sequence selected from the group consisting of the HCVR sequences listed in Table 1; and (b) a LCVR having an amino acid sequence selected from the group consisting of the LCVR sequences listed in Table 1.

34. The antigen-binding protein of claim 33, wherein said HCVR/LCVR sequences are selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 62/70, 82/90, 102/110, 122/130, 142/150, 162/170, 180/186, 196/203, 211/219, 230/238, and 250/258.

35. The antigen-binding protein of claim 34, wherein said HCVR/LCVR sequences are selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 142/150, and 250/258.

36. The antigen-binding protein of any one of claims 1-35, comprising:

- (a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 24, 44, 64, 84, 104, 124, 144, 164, 213, 232, and 252;
- (b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 26, 46, 66, 86, 106, 126, 146, 166, 182, 199, 215, 234, and 254;
- (c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 28, 48, 68, 88, 108, 128, 148, 168, 184, 201, 217, 236, and 256;
- (d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 32, 52, 72, 92, 112, 132, 152, 172, 188, 221, 240, and 260;
- (e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 34, 54, 74, 94, 114, 134, 154, 174, 242, and 262; and
- (f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 36, 56, 76, 96, 116, 136, 156, 190, 205, 224, 244, and 264.

37. The antigen-binding protein of any one of claims 1-28 and 36, wherein said antigen-binding protein comprises an HCVR comprising at least 80% sequence identity to an HCVR sequence listed in Table 1.

38. The antigen-binding protein of claim 37, wherein said antigen-binding protein comprises an HCVR comprising at least 90% sequence identity to an HCVR sequence listed in Table 1.

39. The antigen-binding protein of claim 38, wherein said isolated antigen-binding protein comprises an HCVR comprising at least 95% sequence identity to an HCVR sequence listed in Table 1.

40. The antigen-binding protein of any one of claims 1-28 and 36-39, wherein said antigen-binding protein comprises an LCVR comprising at least 80% sequence identity to an LCVR sequence listed in Table 1.

41. The antigen-binding protein of claim 40, wherein said isolated antigen-binding protein comprises an LCVR comprising at least 90% sequence identity to an LCVR sequence listed in Table 1.

42. The antigen-binding protein of claim 38, wherein said antigen-binding protein comprises an LCVR comprising at least 95% sequence identity to an LCVR sequence listed in Table 1.

43. An antigen-binding protein that competes for binding to an antigen-binding protein of any one of claims 1-42.

44. An antigen-binding protein that binds to the same epitope as an antigen-binding protein of any one of claims 1-42.

45. The antigen-binding protein of any one of claims 1-44, comprising a detectable moiety.

46. A pharmaceutical composition comprising an antigen-binding protein that binds to HLA-A2:NY-ESO-1 according to any one of claims 1-45 and a pharmaceutically acceptable carrier or diluent.

47. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a HCVR of an antigen-binding protein as set forth in any one of claims 1-45.

48. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a LCVR of an antigen-binding protein as set forth in any one of claims 1-45.

49. A vector comprising the polynucleotide molecule of claim 47 or 48.

50. A cell expressing the polynucleotide molecule of claim 47 or 48, or the vector of claim 49.

51. A method of treating a subject having an NY-ESO-1-associated disease or disorder, comprising administering to the subject a therapeutically effective amount of the antigen-binding protein as set forth in any one of claims 1-45 or the pharmaceutical composition of claim 46, or the cell of claim 50, thereby treating the subject.

52. The method of claim 51, wherein the NY-ESO-1-associated disease or disorder is an NY-ESO-1-associated cancer.

53. The method of claim 52, wherein the NY-ESO-associated cancer is selected from the group consisting of: a liposarcoma, a neuroblastoma, a myeloma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, a prostate cancer, a breast cancer, astrocytic tumor, glioblastoma multiforme, anaplastic astrocytoma, brain tumor, fallopian tube cancer, ovarian epithelial cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, melanoma, a sarcoma, myelodysplastic syndrome, acute myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma, synovial sarcoma, metastatic solid tumors, esophageal cancer, rhabdomyosarcoma, advanced myxoid, round cell liposarcoma, metastatic melanoma, or recurrent non-small cell lung cancer.

54. The method of any one of claims 51-53, wherein the antigen-binding protein is administered to the subject in combination with a second therapeutic agent.

55. The method of claim 54, wherein the second therapeutic agent is selected from the group consisting of a PD-1 inhibitor, a CTLA-4 inhibitor, an antibody to a tumor specific antigen, an antibody to a virally-infected-cell antigen, a PD-L1 inhibitor, a CD20 inhibitor, a bispecific antibody against CD20 and CD3, a dietary supplement such as an antioxidant, a VEGF antagonist, a chemotherapeutic agent, a cytotoxic agent, surgery, radiation, a NSAID, a corticosteroid, and any other therapy useful for ameliorating at least one symptom associated with the disease or disorder.

56. The method of any one of claims 51-55, wherein the antigen-binding protein is administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially.

57. The method of any one of claims 51-56, wherein the antigen-binding protein is administered at a dose of about 0.1 mg/kg of body weight to about 100 mg/kg of body weight of the subject.

58. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an extracellular binding domain that specifically binds to a conformational epitope of an HLA-A2 presented New York esophageal squamous cell carcinoma 1 peptide (NY-ESO-1 peptide), a transmembrane domain, and an intracellular signaling domain.

59. The isolated nucleic acid molecule of claim 58, wherein the extracellular binding domain is an anti-HLA-A2:NY-ESO-1 antigen-binding protein.

60. The isolated nucleic acid molecule of claim 59, wherein the antigen-binding protein comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences listed in Table 1; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences listed in Table 1.

61. The isolated nucleic acid molecule of any one of claims 58-60, wherein the antigen-binding protein comprises a HCVR having an amino acid sequence selected from the group consisting of the HCVR sequences listed in Table 1.

62. The isolated nucleic acid molecule of any one of claims 58-61, wherein the antigen-binding protein comprises a LCVR having an amino acid sequence selected from the group consisting of the LCVR sequences listed in Table 1.

63. The isolated nucleic acid molecule of any one of claims 58-62, wherein the antigen-binding protein comprises (a) a HCVR having an amino acid sequence selected from the group consisting of HCVR sequences listed in Table 1; and (b) a LCVR having an amino acid sequence selected from the group consisting of LCVR sequences listed in Table 1.

64. The isolated nucleic acid molecule of any one of claims 58-63, wherein the antigen-binding protein comprises

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 24, 44, 64, 84, 104, 124, 144, 164, 213, 232, and 252;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 26, 46, 66, 86, 106, 126, 146, 166, 182, 199, 215, 234, and 254;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 28, 48, 68, 88, 108, 128, 148, 168, 184, 201, 217, 236, and 256;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 32, 52, 72, 92, 112, 132, 152, 172, 188, 221, 240, and 260;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 34, 54, 74, 94, 114, 134, 154, 174, 242, and 262; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 36, 56, 76, 96, 116, 136, 156, 190, 205, 224, 244, and 264.

65. The isolated nucleic acid molecule of any one of claims 58-64, wherein the antigen-binding protein comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 62/70, 82/90, 102/110, 122/130, 142/150, 162/170, 180/186, 196/203, 211/219, 230/238, and 250/258.

66. The isolated nucleic acid molecule of any one of claims 58-65, wherein the antigen-binding protein comprises an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 142/150, and 250/258

67. The isolated nucleic acid molecule of any one of claims 58-66, comprising any one of the sequences listed in Table 2.

68. The isolated nucleic acid molecule of any one of claims 58-67, wherein the antigen-binding protein is an scFv.

69. A vector comprising the isolated nucleic acid molecule of any one of claims 58-68.

70. An isolated immune effector cell comprising the isolated nucleic acid molecule of any one of claims 58-68 or the vector of claim 69.

71. The isolated immune effector cell of claim 70, which is a T-body.

72. The isolated immune effector cell of claim 70 or 71, wherein said cell expresses said CAR.

73. A method of treating a subject having an NY-ESO-1-associated disease or disorder, comprising administering to the subject the immune effector cell of any one of claims 70-72.

74. The method of claim 73, wherein the NY-ESO-1-associated disease or disorder is NY-ESO-1-associated cancer.

75. The method of claim 73 or 74, wherein the antigen-binding protein is administered to the subject in combination with a second therapeutic agent.