~~What is claimed is:~~CLAIMS

1. An antibody, or antigen binding fragment thereof, that specifically binds to an antigen comprising an NPM1c neoepitope in complex with a class I major histocompatibility complex (MHC class I) protein.

2. The antibody, or antigen binding fragment thereof, of claim 1, which does not bind to, or substantially does not bind to: (a) the MHC class I protein alone, and/or (b) a control peptide in complex with the MHC class I protein, optionally wherein the control peptide is an NY-ESO-1 epitope or influenza virus M1 epitope.

3. The antibody, or antigen binding fragment thereof, of claim 1 or 2, wherein the NPM1c neoepitope comprises an amino acid sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9$, wherein X_1 is selected from A, V, L or I, wherein X_2 is selected from A, T, S, V, L, I, M or Q, wherein X_3 is selected from Q or N, wherein X_4 is selected from D or E, wherein X_5 is selected from L, I, V, M, A or F, wherein X_6 is selected from C, S, or A, wherein X_7 is selected from L, I, V, M, A, or F, wherein X_8 is selected from A, V, L or I, and wherein X_9 is selected from L, I, V, M or A.

~~4. The antibody, or antigen binding fragment thereof, of claim 3, wherein X_1 is selected from A or V, wherein X_2 is selected from V, I, or L, wherein X_3 is selected from Q or N, wherein X_4 is selected from D or E, wherein X_5 is selected from L or I, wherein X_6 is selected from C or S, wherein X_7 is selected from V, L or I, wherein X_8 is selected from A or V, and wherein X_9 is selected from V, I, or L.~~

~~5. The antibody, or antigen binding fragment thereof, of claim 4, wherein X_1 is A, wherein X_2 is selected from V, I, or L, wherein X_3 is Q, wherein X_4 is D, wherein X_5 is L, wherein X_6 is C, wherein X_7 is L, wherein X_8 is A, and wherein X_9 is selected from V, I, or L.~~

~~4~~6. The antibody, or antigen binding fragment thereof, of any one of claims 1-~~3~~4, wherein the NPM1c neoepitope comprises an amino acid sequence selected from: AIQDLCLAV (SEQ ID NO:1) or AIQDLCVAV (SEQ ID NO: 71).

57. The antibody, or antigen binding fragment thereof, of claim 1 or 2, wherein the NPM1c neoepitope comprises an amino acid sequence selected from: CLAVEEVSL (SEQ ID NO:72), VEEVSLRK (SEQ ID NO:73), AVEEVSLR (SEQ ID NO:74), AVEEVSLRK (SEQ ID NO:75), CLAVEEVSLRK (SEQ ID NO:76).

8. The antibody, or antigen binding fragment thereof, of any one of claims 1-6, wherein the neoepitope comprises the amino acid sequence AIQDLCLAV (SEQ ID NO:1).

9. The antibody, or antigen binding fragment thereof, of any one of claims 1-8, wherein the neoepitope is 7, 8, 9, 10, 11, or 12 amino acid residues in length.

10. The antibody, or antigen binding fragment thereof, of any one of claims 1-9, wherein the MHC class I protein is an HLA-A*02 protein or is encoded by the HLA-A*02 allele group.

11. The antibody, or antigen binding fragment thereof, of any one of claims 1-10, wherein the MHC class I protein is encoded by the HLA-A*02:01 allele.

12. The antibody, or antigen binding fragment thereof, of any one of claims 1-11, comprising:

(i) a heavy chain variable region (VH) comprising VH complementarity determining region (CDR)1, VH CDR2 and VH CDR3, said VH CDR1, VH CDR2 and VH CDR3 being the CDRs of a VH that has an amino acid sequence of SEQ ID NO:5, and/or

(ii) a light chain variable region (VL) comprising VL complementarity determining region (CDR)1, VL CDR2 and VL CDR3, said VL CDR1, VL CDR2 and VL CDR3 being the CDRs of a VL that has an amino acid sequence of SEQ ID NO:3.

13. The antibody, or antigen binding fragment thereof, of any one of claims 1-12, comprising a heavy chain variable region (VH) comprising VH complementarity determining region (CDR)1, VH CDR2 and VH CDR3, wherein the VH CDR1 has the amino acid sequence GFTFSSYA (SEQ ID NO:9), the VH CDR2 has the amino acid sequence ISGSGGST (SEQ ID NO:10), and the VH CDR3 has the amino acid sequence ARLGYPTTTLLPFDY (SEQ ID NO:11).

~~14. The antibody, or antigen binding fragment thereof, of claim 13, further comprising a light chain variable region (VL) comprising VL complementarity determining region (CDR)1, VL CDR2 and VL CDR3, wherein the VL CDR1 has the amino acid sequence QSISSY (SEQ ID NO:6), the VL CD2 has the amino acid sequence AAS (SEQ ID NO:7), and the VL CD3 has the amino acid sequence QQSYSTPLT (SEQ ID NO:8).~~

~~15. The antibody, or antigen binding fragment thereof, of any one of claims 1-14, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises an amino acid sequence which is at least 90% identical, or at least 95% identical, to the amino acid sequence of SEQ ID NO:5, and/or wherein the VL comprises an amino acid sequence which is at least 90% identical, or at least 95% identical, to the amino acid sequence of SEQ ID NO:3.~~

~~16. The antibody, or antigen binding fragment thereof, of any one of claims 1-15, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the amino acid sequence of SEQ ID NO:5, and/or wherein the VL comprises the amino acid sequence of SEQ ID NO:3.~~

6~~17~~. The antibody, or antigen binding fragment thereof, of any one of claims 1-5~~16~~, which is a human, humanized or chimeric antibody.

7~~18~~. The antibody, or antigen binding fragment thereof, of any one of claims 1-6~~17~~, which is a single chain Fv (scFv), an Fv fragment, a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment, or a single chain antibody molecule.

8~~19~~. The antibody, or antigen binding fragment thereof, of claim 7~~18~~, which is an scFv, wherein the scFV comprises a Gly-Ser linker selected from the group consisting of (Gly4Ser) (SEQ ID NO:58), (Gly4Ser)2 (SEQ ID NO:59), (Gly4Ser)3 (SEQ ID NO:60), and (Gly4Ser)4 (SEQ ID NO:61).

~~20. The antibody, or antigen binding fragment thereof, of claim 19, wherein the scFv is a human scFv.~~

~~21. The antibody, or antigen binding fragment thereof, of claims 19 or 20, wherein the scFv comprises a linker.~~

~~22. The antibody, or antigen binding fragment thereof, of claim 21, wherein the linker is a peptide linker.~~

~~23. The antibody, or antigen binding fragment thereof, of claim 22, wherein the peptide linker is a Gly-Ser linker.~~

~~24. The antibody, or antigen binding fragment thereof, of claim 23, wherein the Gly-Ser linker is selected from the group consisting of (Gly4Ser) (SEQ ID NO:58), (Gly4Ser)2 (SEQ ID NO:59), (Gly4Ser)3 (SEQ ID NO:60), and (Gly4Ser)4 (SEQ ID NO:61).~~

~~25. The antibody, or antigen binding fragment thereof, of claim 23, wherein the Gly-Ser linker comprises the amino acid sequence SGSSGGSSSG (SEQ ID NO:4).~~

9~~26~~. The antibody, or antigen binding fragment thereof, of claim 8~~any one of claims 19-25~~, wherein the scFv has an amino acid sequence which is at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to the amino acid sequence of SEQ ID NO:2; optionally wherein the scFv comprises: (a) a heavy chain variable region (VH) comprising VH complementarity determining region (CDR)1, VH CDR2 and VH CDR3, wherein the VH CDR1 has the amino acid sequence GFTFSSYA (SEQ ID NO:9), the VH CDR2 has the amino acid sequence ISGSGGST (SEQ ID NO:10), and the VH CDR3 has the amino acid sequence ARLGYPTTTLLPFDY (SEQ ID NO:11); and/or (b) a light chain variable region (VL) comprising VL complementarity determining region (CDR)1, VL CDR2 and VL CDR3, wherein the VL CDR1 has the amino acid sequence QSISSY (SEQ ID NO:6), the VL CD2 has the amino acid sequence AAS (SEQ ID NO:7), and the VL CD3 has the amino acid sequence QQSYSTPLT (SEQ ID NO:8).

~~27. The antibody, or antigen binding fragment thereof, of any one of claims 19-26, wherein the scFv has an amino acid sequence of SEQ ID NO:2.~~

1028. The antibody, or antigen binding fragment thereof, of any one of claims 1-917, which is an antibody, ~~.~~

~~29. The antibody, or antigen binding fragment thereof, of claim 28,~~ wherein the antibody is selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, an IgD, and an IgE antibody isotypes.

1130. The antibody, or antigen binding fragment thereof, of claim 1029, wherein the antibody is of an IgG1 isotype or IgG4 isotype.

1231. The antibody, or antigen binding fragment thereof, of claim 1130, wherein the antibody comprises a wild type IgG1 heavy chain constant region or wild type IgG4 heavy chain constant region.

1332. The antibody, or antigen binding fragment thereof, of claim 1130, wherein the antibody comprises a mutant IgG1 heavy chain constant region or mutant IgG4 heavy chain constant region.

1433. The antibody, or antigen binding fragment thereof, of claim 1332, wherein the antibody comprises a mutant IgG4 heavy chain constant region, wherein the mutant IgG4 heavy chain constant region comprises any one of the following substitutions: S228P, L235E, L235A, or a combination thereof, according to EU numbering.

1534. The antibody, or antigen binding fragment thereof, of any one of claims 10, 11, 13, 1428-30, 32 or 33, wherein the antibody comprises an Fc domain comprising at least one mutation.

1635. The antibody, or antigen binding fragment thereof, according to any one of claims 1-1534, wherein the antigen is on the surface of a cancer cell.

1736. The antibody, or antigen binding fragment thereof, of claim 1635, wherein the cancer is Acute Myeloid Leukemia (AML).

~~37. The antibody, or antigen binding fragment thereof, of any one of claims 1-36, which binds to an antigen comprising an NPM1c neoepitope in complex with a class I major histocompatibility complex (MHC class I) protein with an equilibrium dissociation constant (Kd) of 100 nM or less, 50 nM or less, 20 nM or less, 10 nM or less, from 0.5 nM to 100 nM, or from 1 nM to 15 nM.~~

1838. The antibody, or antigen binding fragment thereof, of any one of claims 1-1737, which is a bispecific antibody, or antigen binding fragment thereof, which further specifically binds to a second antigen on an immune effector cell.

~~39. The antibody, or antigen binding fragment thereof, of claim 38, ,~~ wherein the effector cell is a T cell, a natural killer cell or a macrophage.

~~40. The antibody, or antigen binding fragment thereof, of claim 38 or 39, wherein the second antigen is CD3.~~

~~41. The antibody, or antigen binding fragment thereof, of claim 40, wherein the CD3 is a human CD3 expressed on T cells.~~

~~42. The antibody, or antigen binding fragment thereof, of claim 38 or 39, wherein the second antigen is NKp46.~~

~~43. The antibody, or antigen binding fragment thereof, of claim 42, wherein the NKp46 is a human NKp46 expressed on NK cells.~~

~~44. The antibody, or antigen binding fragment thereof, of claim 38 or 39, wherein the second antigen is CD16A.~~

~~45. The antibody, or antigen binding fragment thereof, of claim 44, wherein the CD16A is a human CD16A expressed on NK-cells.~~

1946. The antibody, or antigen binding fragment thereof, of claim ~~38 or 39~~18, wherein the second antigen is CD3, NKp46, CD16A, CD40, CD47, 4-1BB, TGF-β, LAG-3, PD-1, TIM-3, CTLA-4, OX40, NKp30, NKG2A, NKG2D or DNAM-1.

~~47. The antibody, or antigen binding fragment thereof, according to any one of claims 1-46, which is purified.~~

2048. An isolated nucleic acid, wherein the nucleic acid comprises a nucleic acid sequence encoding the antibody, or antigen binding fragment thereof, according to any one of claims 1-1946.

2149. The isolated nucleic acid of claim 2048, which comprises the nucleotide sequence of SEQ ID NO:12.

2250. An expression vector comprising the nucleic acid of claim 2048 or 2149.

2351. A cell transformed with an expression vector of claim 2250.

2452. A method for producing the antibody, or antigen binding fragment thereof, of any one of claims 1-1946, the method comprising maintaining the cell of claim 2351 under conditions permitting expression of the antibody, or antigen binding fragment thereof.

~~53. The method of claim 52, further comprising purifying the antibody, or antigen binding fragment thereof.~~

2554. A pharmaceutical composition comprising a therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1-1947, and a pharmaceutically acceptable carrier.

~~55. A chimeric antigen receptor (CAR) polypeptide comprising an intracellular domain, a transmembrane domain and an extracellular binding domain, wherein the extracellular binding domain specifically binds to an antigen comprising an NPM1c neoepitope in complex with a class I major histocompatibility complex (MHC class I) protein.~~

2656. A chimeric antigen receptor (CAR) polypeptide comprising an intracellular domain, a transmembrane domain and an extracellular binding domain, wherein the extracellular binding domain comprises the antibody, or antigen binding fragment thereof, of any one of claims 1-279 and ~~38-46~~ 18-19.

2757. The CAR polypeptide of claim ~~55 or 56~~26, wherein the transmembrane domain comprises the transmembrane domain of CD3-zeta, CD8, CD28, NKG2D, CD16, NKp44 or NKp46.

2858. The CAR polypeptide of any one of claim~~s~~ 26 or 27~~55-57~~, wherein the intracellular domain comprises one or more costimulatory domains of one or more costimulatory molecules selected from the group consisting of: CD27, CD28, 4-1BB, OX40, CD30, CD40, PD-1, ICOS, 2B4, DAP10, CD137 and DAP12.

~~59. The CAR polypeptide of any one of the claims 55-58, wherein the intracellular domain comprises a CD3-zeta signaling domain and a 4-1BB costimulatory domain; wherein the transmembrane domain comprises a CD8 transmembrane domain, and wherein the CAR polypeptide further comprises a CD8 hinge region.~~

~~60. The CAR polypeptide of any one of the claims 55-59, wherein the intracellular domain comprises a CD3-zeta signaling domain comprising the amino acid sequence set forth in SEQ ID NO: 27, and a 4-1BB costimulatory domain comprising the amino acid sequence set forth in SEQ ID NO: 26; wherein the CAR polypeptide comprises a CD8 transmembrane domain and a CD8 hinge region, wherein the CD8 transmembrane domain and the CD8 hinge region comprise the amino acid sequence set forth in SEQ ID NO: 25; and wherein the extracellular binding domain comprises the antibody, or antigen binding fragment thereof, and a leading sequence comprising the amino acid sequence set forth in SEQ ID NO: 23.~~

~~61. The CAR polypeptide of any one of claims 55-60, wherein the antibody, or antigen binding fragment thereof, in the extracellular binding domain is an scFv comprising the amino acid sequence set forth in SEQ ID NO:24, or an amino acid sequence which is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to the amino acid sequence of SEQ ID NO:24.~~

2962. The CAR polypeptide of any one of the claims 26-2855-61, wherein the intracellular domain further comprises a self-cleaving peptide sequence and a cytokine, wherein cleavage of the self-cleaving peptide releases the cytokine.~~,~~

~~63. The CAR polypeptide of claim 62,~~ wherein the cytokine is IL-12, IL-7, IL-13, IL-15, TNF-α, IFN-γ, or CCL19.

~~64. The CAR polypeptide of claim 55 or 56, which comprises the amino acid sequence set forth in SEQ ID NO: 22, or an amino acid sequence which is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to the amino acid sequence of SEQ ID NO:22.~~

3065. An isolated nucleic acid encoding the CAR polypeptide of any one of claims 26-2955-~~64~~.

3166. The isolated nucleic acid of claim 3065, which comprises the nucleotide sequence of SEQ ID NO:30, or a nucleotide sequence which is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to the nucleotide sequence of SEQ ID NO:30.

3267. An expression vector comprising the isolated nucleic acid of claim 3065 or 3166, wherein the expression vector is a viral expression vector or a non-viral expression vector.

~~68. The expression vector of claim 67, wherein the expression vector is a viral expression vector, and wherein the viral expression vector is a lentiviral expression vector.~~

3369. A cell transformed with the expression vector of claim 3267 or 68.

3470. A cell expressing the CAR polypeptide of any one of claims 26-2955-64.

~~71. The cell of claim 69 or 70, wherein the cell is an immune effector cell, wherein expression of the CAR polypeptide targets the immune effector cell to a cancer cell expressing an antigen comprising an NPM1c neoepitope in complex with a class I major histocompatibility complex (MHC class I) protein.~~

~~72. The cell of claim 71, wherein the MHC Class I protein is an HLA-A*02 protein or is encoded by the HLA-A*02 allele group.~~

~~73. The cell of claim 71 or 72, wherein the immune effector cell does substantially target and/or induce killing of a cancer cell expressing wild type NPM1.~~

~~74. The cell of any one of claims 69-73, wherein the cell is a T cell.~~

~~75. The cell of claim 74, wherein the T cell is a human $CD8^+$ T cell.~~

~~76. The cell of any one of claims 69-73, wherein the cell is a Natural Killer (NK) cell.~~

~~77. The cell of any one of claims 69-73, wherein the cell is a macrophage.~~

~~78. The cell of any one of claims 71-77, wherein the cancer cell is an acute myeloid leukemia (AML) cell.~~

3579. A pharmaceutical composition, comprising the cell of any one of claims 33 or 3469-78, and a pharmaceutically acceptable carrier.

3680. A method for producing the cell of any one of claims 33 or 3469-78, wherein the method comprises:

(i) purifying a cell from peripheral blood mononuclear cells (PMBC) of a subject,

(ii) optionally, activating the cell with an anti-CD3 antibody or an antigen binding fragment thereof and/or an anti-CD28 antibody or an antigen-binding fragment thereof,

(iii) transducing the cell with an expression vector of claim 32~~67 or 68~~,

(iv) isolating the cell expressing the CAR polypeptide, and

(v) optionally, expanding the isolated cell.

37~~81~~. A method for producing the cell of any one of claims 33 or 34~~69-78~~, wherein the method comprises:

(i) inducing a pluripotent stem cell (iPSC) to differentiate into an immune effector cell,

(ii) transducing the immune effector cell with an expression vector of claim 32~~67 or 68~~,

(iii) isolating the immune effector cell expressing the CAR polypeptide, and

(iv) optionally, expanding the isolated immune effector cell.

~~82. The method of claim 81, wherein the immune effector cell is a NK cell.~~

~~83. The method of claim 81, wherein the immune effector cell is a macrophage.~~

38~~84~~. ~~A method of treating a cancer in a subject in need thereof, wherein the cell surface of cells comprising the cancer displays an NPM1c neoepitope in complex with a class I major histocompatibility complex (MHC class I) protein, the method comprising administering to the subject~~ Use of the antibody, or antigen binding fragment thereof, of any one of claims 1-19~~47~~, the cell of any one of claims 33 or 34~~69-78~~, or the pharmaceutical composition of claim 24~~54~~ or 35~~79~~, in the preparation of a medicament for treating ~~an amount sufficient to treat the~~ cancer in a subject, wherein the cell surface of cells comprising the cancer displays an NPM1c neoepitope in complex with a class I major histocompatibility complex (MHC class I) protein.

39~~85~~. The ~~method~~ use of claim 38~~84~~, wherein the cancer is acute myeloid leukemia (AML).

~~86. The method of claim 84 or 85, wherein the method of treating cancer is a method of reducing cancer burden or a method of increasing survival in the subject.~~

~~87. A method of treating acute myeloid leukemia (AML) in a subject in need thereof, the method comprising administering to the subject the antibody, or antigen binding fragment thereof, of any one of claims 1-47, the cell of any one of claims 69-78, or the pharmaceutical composition of claim 54 or 79, in an amount sufficient to treat AML.~~

~~88. The method of any one of claims 85-87, wherein the AML is a relapsed AML or a refractory AML.~~

4089. ~~A method of preventing relapse of AML in a subject in remission from AML, the method comprising administering to the subject~~ Use of the antibody, or antigen binding fragment thereof, of any one of claims 1-191~~-47~~, the cell of any one of claims 33 or 34~~69-78~~, or the pharmaceutical composition of claim 24 or 35~~54 or 79~~, in the preparation of a medicament for preventing relapse of AML in a subject in remission from AML.

4190. The ~~method~~ use of any one of claims 38, 39, or 40~~84-89~~, comprising, before the subject is to be administered with the antibody, or antigen binding fragment thereof, the cell, or the pharmaceutical composition~~administering step~~, detecting whether the subject expresses NPM1c or whether the subject has an *NPM1c* mutation in the *NPM1* gene, and if the subject expresses NPM1c or has an *NPM1c* mutation proceeding with the ~~administering step~~administtration.

~~91. The method of any one of claims 84-90, wherein the administering is intravenous, intrathecal, intraosseous, or into the spinal cord.~~

~~92. The method of any one of claims 84-91, wherein the method further comprises administering one or more additional therapeutic agents or procedures.~~

~~93. The method of claim 92, wherein the additional therapeutic agent is an inhibitor of an immune checkpoint molecule; optionally wherein the immune checkpoint molecule is TIM-3, PD-1, PD-L1 or CTLA-4; optionally wherein the inhibitor is an antibody.~~

~~94. Use of the antibody, or antigen binding fragment thereof, of any one of claims 1-47, the CAR polypeptide of any one of claims 55-64, the cell of any one of claims 69-78, or the pharmaceutical composition of claim 54 or 79, in the manufacture of a medicament for treating a cancer in a subject, wherein the cell surface of cells comprising the cancer displays an NPM1c neoepitope in complex with a class I major histocompatibility complex (MHC class I) protein; optionally wherein the use is in combination with one or more additional therapeutic agents or procedures.~~

~~95. The method of any of claims 84-93 or the use of claim 94, wherein the subject is a human.~~

~~96. A kit comprising one or more containers comprising: (i) the antibody, or antigen binding fragment thereof, of any one of claims 1-47, the CAR polypeptide of any one of claims 55-64, the cell of any one of claims 69-78, or the pharmaceutical composition of claim 54 or 79; (ii) optionally, one or more additional therapeutic agents, and (iii) instructions for use in treating cancer in a subject.~~