

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 any one of claims 1-3, wherein the NPM1c neoepitope comprises an amino acid sequence selected from: AIQDLCLAV (SEQ ID NO:1) or AIQDLCVAV (SEQ ID NO: 71).
5. 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).
6. The antibody, or antigen binding fragment thereof, of any one of claims 1-5, which is a human, humanized or chimeric antibody.

7. The antibody, or antigen binding fragment thereof, of any one of claims 1-6, 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. The antibody, or antigen binding fragment thereof, of claim 7, 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).

9. The antibody, or antigen binding fragment thereof, of claim 8, 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 ARLGYPTTLLPFDY (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).

10. The antibody, or antigen binding fragment thereof, of any one of claims 1-9, which is an antibody, 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.

11. The antibody, or antigen binding fragment thereof, of claim 10, wherein the antibody is of an IgG1 isotype or IgG4 isotype.

12. The antibody, or antigen binding fragment thereof, of claim 11, wherein the antibody comprises a wild type IgG1 heavy chain constant region or wild type IgG4 heavy chain constant region.

13. The antibody, or antigen binding fragment thereof, of claim 11, wherein the antibody comprises a mutant IgG1 heavy chain constant region or mutant IgG4 heavy chain constant region.
14. The antibody, or antigen binding fragment thereof, of claim 13, 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.
15. The antibody, or antigen binding fragment thereof, of any one of claims 10, 11, 13, 14, wherein the antibody comprises an Fc domain comprising at least one mutation.
16. The antibody, or antigen binding fragment thereof, according to any one of claims 1-15, wherein the antigen is on the surface of a cancer cell.
17. The antibody, or antigen binding fragment thereof, of claim 16, wherein the cancer is Acute Myeloid Leukemia (AML).
18. The antibody, or antigen binding fragment thereof, of any one of claims 1-17, which is a bispecific antibody, or antigen binding fragment thereof, which further specifically binds to a second antigen on an immune effector cell, wherein the effector cell is a T cell, a natural killer cell or a macrophage.
19. The antibody, or antigen binding fragment thereof, of claim 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.
20. 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 1-19.
21. The isolated nucleic acid of claim 20, which comprises the nucleotide sequence of SEQ ID NO:12.

22. An expression vector comprising the nucleic acid of claim 20 or 21.
23. A cell transformed with an expression vector of claim 22.
24. A method for producing the antibody, or antigen binding fragment thereof, of any one of claims 1-19, the method comprising maintaining the cell of claim 23 under conditions permitting expression of the antibody, or antigen binding fragment thereof.
25. A pharmaceutical composition comprising a therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1-19, and a pharmaceutically acceptable carrier.
26. 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 1-9 and 18-19.
27. The CAR polypeptide of claim 26, wherein the transmembrane domain comprises the transmembrane domain of CD3-zeta, CD8, CD28, NKG2D, CD16, NKp44 or NKp46.
28. The CAR polypeptide of any one of claim 26 or 27, 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.
29. The CAR polypeptide of any one of the claims 26-28, wherein the intracellular domain further comprises a self-cleaving peptide sequence and a cytokine, wherein cleavage of the self-cleaving peptide releases the cytokine, wherein the cytokine is IL-12, IL-7, IL-13, IL-15, TNF- α , IFN- γ , or CCL19.
30. An isolated nucleic acid encoding the CAR polypeptide of any one of claims 26-29.

31. The isolated nucleic acid of claim 30, 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.
32. An expression vector comprising the isolated nucleic acid of claim 30 or 31, wherein the expression vector is a viral expression vector or a non-viral expression vector.
33. A cell transformed with the expression vector of claim 32.
34. A cell expressing the CAR polypeptide of any one of claims 26-29.
35. A pharmaceutical composition, comprising the cell of any one of claims 33 or 34, and a pharmaceutically acceptable carrier.
36. A method for producing the cell of any one of claims 33 or 34, 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,
 - (iv) isolating the cell expressing the CAR polypeptide, and
 - (v) optionally, expanding the isolated cell.
37. A method for producing the cell of any one of claims 33 or 34, 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,
 - (iii) isolating the immune effector cell expressing the CAR polypeptide, and
 - (iv) optionally, expanding the isolated immune effector cell.

38. Use of the antibody, or antigen binding fragment thereof, of any one of claims 1-19, the cell of any one of claims 33 or 34, or the pharmaceutical composition of claim 24 or 35, in the preparation of a medicament for treating 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. The use of claim 38, wherein the cancer is acute myeloid leukemia (AML).

40. Use of the antibody, or antigen binding fragment thereof, of any one of claims 1-19, the cell of any one of claims 33 or 34, or the pharmaceutical composition of claim 24 or 35, in the preparation of a medicament for preventing relapse of AML in a subject in remission from AML.

41. The use of any one of claims 38, 39, or 40, comprising, before the subject is to be administered with the antibody, or antigen binding fragment thereof, the cell, or the pharmaceutical composition, 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 administration.