

What is claimed is:

1. ~~An invention not claimed in any divisional application. A CAR therapy comprising a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR) for use in combination with an inhibitor of a pro-M2 macrophage molecule in treating a subject having a disease associated with expression of a tumor antigen, wherein the CAR comprises a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain.~~
2. ~~A method of treating a subject having a disease associated with expression of a tumor antigen, comprising administering to the subject:~~
 - ~~—— (i) a CAR therapy comprising a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR), wherein the CAR comprises a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain; and~~
 - ~~—— (ii) an inhibitor of a pro-M2 macrophage molecule.~~
3. ~~The CAR therapy for use or the method of claim 1 or 2, wherein the CAR therapy and the inhibitor of a pro-M2 macrophage molecule are administered sequentially.~~
4. ~~The CAR therapy for use or the method of any of claims 1-3, wherein the inhibitor of a pro-M2 macrophage molecule is administered prior to the CAR therapy.~~
5. ~~The CAR therapy for use or the method of any of claims 1-4, wherein the inhibitor of a pro-M2 macrophage molecule and the CAR therapy are administered simultaneously or concurrently.~~
6. ~~The CAR therapy for use or the method of any of claims 1-5, wherein the CAR therapy is administered as (a) single infusion or (b) multiple infusions (e.g., a single dose split into multiple infusions), and wherein the inhibitor of a pro-M2 macrophage molecule is administered as (a) a single dose, or (b) multiple doses (e.g., a first and second, and optionally one or more subsequent doses).~~

7. The CAR therapy for use or the method of any of claims 1-6, wherein a dose of the CAR therapy is administered after (e.g., at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, or more, after) administration of a first dose of the inhibitor of a pro-M2 macrophage molecule, e.g., but before administration of the second dose of the inhibitor.

8. The CAR therapy for use or the method of claims 1 or 5, wherein a dose of the CAR therapy is administered concurrently with (e.g., within 2 days (e.g., within 2 days, 1 day, 24 hours, 12 hours, 6 hours, 4 hours, 2 hours, or less) of), the administration of a first dose of the inhibitor of a pro-M2 macrophage molecule.

9. The CAR therapy for use or the method of any of claims 6-8, wherein one or more subsequent doses of the inhibitor of a pro-M2 macrophage molecule are administered after a second dose of the inhibitor of a pro-M2 macrophage molecule.

10. The CAR therapy for use or the method of any of claims 1-9, wherein the inhibitor of a pro-M2 macrophage molecule is administered in more than one dose, and the doses are administered twice a day (BID), once a day, once a week, once every 14 days, or once every month.

11. The CAR therapy for use or the method of any of claims 1-10, wherein the administering of the inhibitor of a pro-M2 macrophage molecule comprises multiple doses comprising a duration of at least 7 days, e.g., at least 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, or more.

12. The CAR therapy for use or the method of any of claims 1-11, wherein the CAR therapy is administered at a dose comprising at least about 5×10^6 , 1×10^7 , 1.5×10^7 , 2×10^7 , 2.5×10^7 , 3×10^7 , 3.5×10^7 , 4×10^7 , 5×10^7 , 1×10^8 , 1.5×10^8 , 2×10^8 , 2.5×10^8 , 3×10^8 , 3.5×10^8 , 4×10^8 , 5×10^8 , 1×10^9 , 2×10^9 , or 5×10^9 cells, e.g., CAR positive cells.

~~13. The CAR therapy for use or the method of any of claims 1-12, wherein the inhibitor of a pro-M2 macrophage molecule is an IL-13 inhibitor, an IL-4 inhibitor, an IL-13R α 1 inhibitor, an IL-4R α inhibitor, an IL-10 inhibitor, a CSF-1 inhibitor, a TGF beta inhibitor, a JAK2 inhibitor, a cell surface molecule, an iron oxide, a small molecule inhibitor, a PI3K inhibitor, an HDAC inhibitor, an inhibitor of the glycolytic pathway, a mitochondria-targeted antioxidant, or combinations thereof.~~

~~14. The CAR therapy for use or the method of claim 13, wherein the inhibitor of a pro-M2 macrophage molecule is a small molecule, an antibody or antigen-binding fragment thereof, a protein (e.g., a fusion protein), a nucleic acid (e.g., an shRNA or siRNA), or a gene editing system.~~

~~15. The CAR therapy for use or the method of claim 13, wherein the inhibitor of a pro-M2 macrophage molecule is an antibody or antigen-binding fragment thereof.~~

~~16. The CAR therapy for use or the method of any of claims 1-15, wherein the tumor antigen binding domain of the CAR binds CD123.~~

~~17. A CAR therapy comprising a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR) for use in combination with a tumor targeting therapy in treating a subject having a disease associated with expression of a tumor antigen, wherein:~~

~~the CAR comprises a tumor antigen binding domain that binds CD123 (CD123 CAR), a transmembrane domain, and an intracellular signaling domain; and~~

~~the tumor targeting therapy comprises a second CAR therapy that comprises a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a CAR comprising a tumor antigen binding domain that binds to a tumor antigen other than CD123 (e.g., a CAR that binds to a solid tumor antigen or a hematologic tumor antigen other than CD123).~~

~~wherein the CD123 CAR is administered in an amount and/or time sufficient to result in inhibition of an M2 macrophage activity.~~

~~18. A method of treating a subject having a disease associated with expression of a tumor antigen, comprising administering to the subject:~~

~~—— (i) a CAR therapy comprising a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR), wherein the CAR comprises a tumor antigen binding domain that binds CD123 (CD123-CAR), a transmembrane domain, and an intracellular signaling domain; and~~

~~—— (ii) a tumor targeting therapy, wherein the tumor targeting therapy comprises a second CAR therapy that comprises a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a CAR comprising a tumor antigen binding domain that binds to a tumor antigen other than CD123 (e.g., a CAR that binds to a solid tumor antigen or a hematologic tumor antigen other than CD123);~~

~~wherein the CD123-CAR is administered in an amount and/or time sufficient to result in inhibition of an M2 macrophage activity.~~

~~7~~

~~19. The CAR therapy for use or the method of claim 17 or 18, wherein the inhibition of the M2 macrophage activity comprises inhibition of polarization of a macrophage to an M2 phenotype, and/or reversal of a phenotype of an M2 macrophage.~~

~~20. The CAR therapy for use of any of claims 17-19, wherein the tumor antigen binding domain of the second CAR therapy binds to CD19, mesothelin, or EGFRviii.~~

~~21. The CAR therapy for use or the method of any of claims 16-20, wherein the tumor antigen binding domain of the CAR that binds to CD123 comprises a heavy chain complementary determining region 1 (HC-CDR1), a heavy chain complementary determining region 2 (HC-CDR2), and a heavy chain complementary determining region 3 (HC-CDR3) of any CD123 heavy chain binding domain amino acid sequence listed in Table 16, Table 18, Table 20, Table 22, Table 24, Table 25, Table 26, Table 27 or Table 28; and~~

~~—— a light chain complementary determining region 1 (LC-CDR1), a light chain complementary determining region 2 (LC-CDR2), and a light chain complementary determining region 3 (LC-CDR3) of any CD123 light chain binding domain amino acid~~

sequence listed in Table 17, Table 19, Table 21, Table 23, Table 24, Table 25, Table 26, Table 27 or Table 28.

~~22. The CAR therapy for use or the method of any of claims 16-21, wherein the CD123 binding domain comprises a CD123 binding domain (e.g., scFv) amino acid sequence listed in Table 26, Table 27 or Table 28.~~

~~23. The CAR therapy for use or the method of any of claims 16-22, wherein the CAR comprises (e.g., consists of) a CAR amino acid sequence listed in Table 26 or Table 27.~~

~~24. The CAR therapy for use or the method of any of claims 1-15, 17, or 18, wherein the tumor antigen binding domain of the CAR binds mesothelin.~~

~~25. The CAR therapy for use or the method of claim 24, wherein the tumor antigen binding domain of the CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any mesothelin heavy chain binding domain amino acid sequence listed in Table 2, Table 3 or Table 11; and
——— a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any mesothelin light chain binding domain amino acid sequence listed in Table 2, Table 4 or Table 11.~~

~~26. The CAR therapy for use or the method of claim 24 or 25, wherein the mesothelin binding domain comprises a mesothelin binding domain (e.g., scFv) amino acid sequence listed in Table 2 or Table 11.~~

~~27. The CAR therapy for use or the method of any of claims 24-26, wherein the CAR comprises (e.g., consists of) a CAR amino acid sequence listed in Table 11.~~

~~28. The CAR therapy for use or the method of any of claims 1-15, 17, or 18, wherein the tumor antigen binding domain of the CAR binds EGFRvIII.~~

~~29. The CAR therapy for use or the method of claim 28, wherein the tumor antigen binding domain of the CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any EGFRvIII heavy chain binding domain amino acid sequence listed in Table 5; and~~

~~———— a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any EGFRvIII light chain binding domain amino acid sequence listed in Table 5.~~

~~30. The CAR therapy for use or the method of claim 28 or 29, wherein the EGFRvIII binding domain comprises a EGFRvIII binding domain (e.g., scFv) amino acid sequence listed in Table 5.~~

~~31. The CAR therapy for use or the method of any of claims 28-30, wherein the CAR comprises (e.g., consists of) a CAR amino acid sequence listed in Table 30.~~

~~32. The CAR therapy for use or the method of claims 1-15, 17, or 18, wherein the tumor antigen binding domain of the CAR binds CD19.~~

~~33. The CAR therapy for use or the method of claim 32, wherein the tumor antigen binding domain of the CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any CD19 heavy chain binding domain amino acid sequence listed in Table 6, Table 7, or Table 9; and~~

~~———— a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary~~

determining region 3 (LC CDR3) of any CD19 light chain binding domain amino acid sequence listed in Table 6, Table 8, or Table 9.

34. The CAR therapy for use or the method of claim 32 or 33, wherein the CD19 binding domain comprises a CD19 binding domain (e.g., scFv) amino acid sequence listed in Table 6 or Table 9.

35. The CAR therapy for use or the method of any of claims 32-34, wherein the CD19 binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 83; SEQ ID NO: 84, SEQ ID NO: 85; SEQ ID NO: 86; SEQ ID NO: 87; SEQ ID NO: 88; SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 112.

36. The CAR therapy for use or the method of any of the preceding claims, wherein the tumor antigen binding domain of the CAR binds a solid tumor antigen.

37. The CAR therapy for use or the method of any of the preceding claims, wherein the tumor antigen binding domain of the CAR binds an antigen expressed on a tumor associated with tumor-associated macrophages (TAMs) and/or myeloid derived suppressor cells (MDSCs).

38. The CAR therapy for use or the method of claim 36 or 37, wherein the solid tumor antigen or the antigen expressed on a tumor associated with tumor-associated macrophages (TAMs) and/or myeloid derived suppressor cells (MDSCs) is CD123, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O Glycopeptides, sTn-O Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3,

PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR α 4, or a peptide of any of these antigens presented on MHC.

39. The CAR therapy for use or the method of any of the preceding claims, wherein the intracellular signaling domain comprises a primary signaling domain comprising a CD3-zeta stimulatory domain.

40. The CAR therapy for use or the method of any of the preceding claims, wherein the intracellular signaling domain comprises a costimulatory domain which is an intracellular domain of a costimulatory protein selected from the group consisting of CD27, CD28, 4-1BB (CD137), OX40, GITR, CD30, CD40, ICOS, BAFFR, HVEM, ICAM-1, lymphocyte function-associated antigen-1 (LFA-1), CD2, CDS, CD7, CD287, LIGHT, NKG2C, NKG2D, SLAMF7, NKp80, NKp30, NKp44, NKp46, CD160, B7-H3, and a ligand that specifically binds with CD83.

41. The CAR therapy for use or the method of claim 40, wherein the costimulatory domain comprises an intracellular domain of 4-1BB.

42. The CAR therapy for use or the method of claim 40, wherein the costimulatory domain comprises an intracellular domain of CD28.

43. The CAR therapy for use or the method of any of claims 40-42, wherein the intracellular signaling domain comprises two costimulatory domains, e.g., a 4-1BB costimulatory domain and a CD28 costimulatory domain.

44. The CAR therapy for use or the method of any of the preceding claims, wherein the disease associated with expression of a tumor antigen is cancer.

45. The method of claim 44, wherein the cancer is Hodgkin lymphoma.

46. The method of claim 44, wherein the cancer is a solid cancer.

~~47. The CAR therapy for use or the method of any of the preceding claims, wherein the cell comprising a CAR comprises a nucleic acid encoding the CAR.~~

~~48. The CAR therapy for use or the method of claim 47, wherein the nucleic acid encoding the CAR is a lentiviral vector.~~

~~49. The CAR therapy for use or the method of claim 47 or 48, wherein the nucleic acid encoding the CAR is introduced into the cells by lentiviral transduction.~~

~~50. The CAR therapy for use or the method of any of claims 47-49, wherein the nucleic acid encoding the CAR is an RNA, e.g., an in vitro transcribed RNA.~~

~~51. The CAR therapy for use or the method of any of claims 47-50, wherein the nucleic acid encoding the CAR is introduced into the cells by electroporation.~~

~~52. The CAR therapy for use or the method of any of claims 1-51, wherein the cell is a T cell or an NK cell.~~

~~53. The CAR therapy for use or the method of claim 52, wherein the T cell is an autologous or allogeneic T cell.~~

~~54. The CAR therapy for use or the method of any of claims 1-53, wherein the subject is a mammal, e.g., a human.~~

~~55. The CAR therapy for use or the method of claims 17-54, wherein the CD123 CAR therapy and the tumor targeting therapy are administered sequentially, simultaneously, or concurrently.~~

~~56. The CAR therapy for use or the method of claims 17-55, wherein the CD123 CAR therapy is administered prior to the tumor targeting therapy.~~

57. The CAR therapy for use or the method of claim 56, wherein the CD123 CAR therapy is administered at least 5 days, at least 7 days, at least 10 days, at least 15 days, at least 20 days, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months or at least 10 months, prior to administration of the tumor targeting therapy.

58. The CAR therapy for use or the method of claims 17-57, wherein the CD123 CAR therapy is administered as (a) a single infusion or (b) multiple infusions (e.g., a single dose split into multiple infusions), and wherein the tumor targeting therapy is administered as (a) a single dose, or (b) multiple doses (e.g., a first and second, and optionally one or more subsequent doses).

59. The CAR therapy for use or the method of claims 17-58, wherein the CAR therapy or the tumor targeting therapy is administered at a dose comprising at least about 5×10^6 , 1×10^7 , 1.5×10^7 , 2×10^7 , 2.5×10^7 , 3×10^7 , 3.5×10^7 , 4×10^7 , 5×10^7 , 1×10^8 , 1.5×10^8 , 2×10^8 , 2.5×10^8 , 3×10^8 , 3.5×10^8 , 4×10^8 , 5×10^8 , 1×10^9 , 2×10^9 , or 5×10^9 cells, e.g., CAR positive cells.

60. The CAR therapy for use or the method of claims 17-60, wherein the CAR therapy and the tumor targeting therapy are formulated in a pharmaceutical composition.

61. A pharmaceutical composition comprising (i) a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR), wherein the CAR comprises a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain; and (ii) an inhibitor of a pro-M2 macrophage molecule.

62. A pharmaceutical composition comprising (i) a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR), wherein the CAR comprises a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain; and (ii) an inhibitor of a pro-M2 macrophage molecule for use in treating a disease or disorder.

~~63. — A method for stimulating a T cell-mediated immune response to a solid tumor cell in a mammal, the method comprising administering to a mammal an effective amount of the composition of claim 61.~~

~~64. — A method of providing an anti-solid tumor immunity in a mammal, comprising administering to the mammal an effective amount of the composition of claim 61.~~

~~65. — A method of treating a mammal having a disease associated with expression of a solid tumor antigen, said method comprising administering an effective amount of the composition of claim 61.~~

~~66. The method of any of claims 63-65, wherein the cell, e.g., the population of immune effector cells, and the inhibitor of a pro-M2 macrophage molecule are provided for separate administration (e.g., in two separate compositions).~~

~~67. The method of any of claims 63-65, wherein the cell, e.g., the population of immune effector cells, and the inhibitor of a pro-M2 macrophage molecule are provided for simultaneous administration (e.g., in one composition).~~