CLAIMS

1. Use of an LSD1 inhibitor in the manufacture of a medicament for the treatment of a disease associated with the expression of a tumor antigen in a subject, wherein the medicament and a population of immune effector cells engineered to express a CAR are to be administered to the subject.

2. The use of claim 1, wherein:

a) the medicament is to be administered before the subject is to be administered said population of immune effector cells;

b) the medicament is to be administered concurrently with said population of immune effector cells;

c) the medicament is to be administered after the subject is to be administered said population of immune effector cells; or

d) any combination of a), b) and/or c).

3. The use of claim 2, wherein the medicament is to be administered before the subject is to be administered said population of immune effector cells, and wherein said administration of the medicament is to be continued for a period of time after the administration of said population of immune effector cells, optionally wherein the administration of the medicament is in an amount sufficient to increase an anti-tumor effect of said population of immune effector relative to an equivalent population of said immune effector cells to be administered in the absence of said medicament.

4. Use of an LSD1 inhibitor in the manufacture of a medicament for increasing the therapeutic efficacy of a population of immune effector cells engineered to express a CAR, e.g., a CART19 (e.g., CTL019), said use comprising a step of decreasing the activity or expression of LSD1 in said cells, transiently or permanently, optionally wherein the step of decreasing the activity or expression of LSD1 in said cells comprises contacting the cells with the medicament.

5. The use of any of claims 1-4, wherein the administration or the contacting of the medicament results in:

1) an increase in the proportion of naive T cells, e.g., T_{SCM} cells;

2) an increase in the number of naive T cells, e.g., T_{SCM} cells;

3) a decrease in the number of T_{EM} cells;

4) a decrease in the proportion of T_{EM} cells;

5) an increase in the proportion of CD45RA+CD62L+ T cells;

6) an increase in the number of CD45RA+CD62L+ T cells;

7) an increase in the proportion of CD45RA+CCR7+ T cells;

8) an increase in the number of CD45RA+CCR7+ T cells;

9) a decrease in the proportion of PD-1 positive immune effector cells;

10) an increase in the ratio of PD-1 negative immune effector cells / PD-1 positive immune effector cells;

11) a decrease in the proportion of PD-1+/Lag3+/Tim3+ immune effector cells;

12) an increase in the ratio of PD-1-/Lag3-/Tim3- immune effector cells to PD-1+/Lag3+/Tim3+ immune effector cells;

13) an increase in the proliferation of the immune effector cells;

14) an increase in the production of cytokines (e.g., IFNg and/or IL-2) from said population of immune effector cells; or

15) a combination of two or more of the above;

optionally as compared to cells not contacted with the medicament.

6. A method of making a population of immune effector cells comprising:

a) contacting a population of immune effector cells with an LSD1 inhibitor;

thereby making a population of immune effector cells,

wherein the contacting with the LSD1 inhibitor causes one or more of the following to occur:

1) an increase in the proportion of naive T cells, e.g., T_{SCM} cells;

2) an increase in the number of naive T cells, e.g., T_{SCM} cells;

3) a decrease in the number of T_{EM} cells;

4) a decrease in the proportion of T_{EM} cells;

5) an increase in the proportion of CD45RA+CD62L+ T cells;

6) an increase in the number of CD45RA+CD62L+ T cells;

7) an increase in the proportion of CD45RA+CCR7+ T cells;

8) an increase in the number of CD45RA+CCR7+ T cells;

9) a decrease in the proportion of PD-1 positive immune effector cells;

10) an increase in the ratio of PD-1 negative immune effector cells / PD-1 positive immune effector cells;

11) a decrease in the proportion of PD-1+/Lag3+/Tim3+ immune effector cells;

12) an increase in the ratio of PD-1-/Lag3-/Tim3- immune effector cells to PD-1+/Lag3+/Tim3+ immune effector cells;

13) an increase in the proliferation of the immune effector cells;

14) an increase in the production of cytokines (e.g., IFNg and/or IL-2) from said population of immune effector cells; or

15) a combination of two or more of the above;

as compared to a non-contacted population of immune effector cells.

7. The method of claim 6, further comprising the step of b) inserting nucleic acid that encodes the CAR into cells of the population of immune effector cells, optionally wherein said contacting of step a) occurs

1) prior to;

2) concurrently with;

3) after; or

4) any combination of two or more of 1) to 3) above;

said inserting of step b), optionally wherein the contacting of step a), and optionally the inserting of step b), is *ex vivo*.

8. A population of immune effector cells, made by the method of claim 6 or 7.

9. A population of immune effector cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein expression and/or function of LSD1 in said cell has been reduced or eliminated, optionally wherein the population of immune effector cells further comprises an LSD1 inhibitor or has been contacted with an LSD1 inhibitor.

10. The use, method, or population of immune effector cells of any of the preceding claims, wherein the population of immune effector cells comprise, e.g., consist of, T cells or NK cells.

11. The use, method, or population of immune effector cells of any of the preceding claims, wherein the CAR comprises an antigen binding domain (which is optionally an antibody or antibody fragment, TCR or TCR fragment), a transmembrane domain, and an intracellular signaling domain (which is optionally an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain), optionally wherein the antigen-binding domain binds to a tumor antigen selected from a group consisting of: TSHR, CD19, CD123, CD22, CD30, CD171, CS-1, CLL-1, CD33, EGFRvIII , GD2, GD3, BCMA, Tn Ag, PSMA, ROR1, FLT3, FAP, TAG72, CD38, CD44v6, CEA, EPCAM, B7H3, KIT, IL-13Ra2, Mesothelin, IL-11Ra, PSCA, PRSS21, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, CD20, Folate receptor alpha, ERBB2 (Her2/neu), MUC1, EGFR, NCAM, Prostase, PAP, ELF2M, Ephrin B2, IGF-I receptor, CAIX, LMP2, gp100, bcr-abl, tyrosinase, EphA2, Fucosyl GM1, sLe, GM3, TGS5, HMWMAA, o-acetyl-GD2, Folate receptor beta, TEM1/CD248, TEM7R, CLDN6, GPRC5D, CXORF61, CD97, CD179a, ALK, Polysialic acid, PLAC1, GloboH, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, WT1, NY-ESO-1, LAGE-1a, MAGE-A1, legumain, HPV E6,E7, MAGE A1, ETV6-AML, sperm protein 17, XAGE1,

Tie 2, MAD-CT-1, MAD-CT-2, Fos-related antigen 1, p53, p53 mutant, prostein, survivin and telomerase, PCTA-1/Galectin 8, MelanA/MART1, Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin B1, MYCN, RhoC, TRP-2, CYP1B1, BORIS, SART3, PAX5, OY-TES1, LCK, AKAP-4, SSX2, RAGE-1, human telomerase reverse transcriptase, RU1, RU2, intestinal carboxyl esterase, mut hsp70-2, CD79a, CD79b, CD72, LAIR1, FCAR, LILRA2, CD300LF, CLEC12A, BST2, EMR2, LY75, GPC3, FCRL5, and IGLL1, optionally wherein the tumor antigen is CD19 or BCMA.

12. The use, method, or population of immune effector cells of claim 11, wherein:

the antigen-binding domain is an antibody or antibody fragment comprising:

(i) the amino acid sequence of a CD19 binding domain according to Tables 6-9, e.g., the amino acid sequence of CTL019 scFv domain according to Table 9 or an amino acid sequence according to SEQ ID NO: 957, or an amino acid sequence at least 95% identical thereto;

(ii) the amino acid sequence of a humanized CD19 binding domain according to Tables 6-9, e.g., the amino acid sequence of CAR2 scFv domain according to Table 9 or an amino acid sequence according to SEQ ID NO: 898, or an amino acid sequence at least 95% identical thereto; or

(iii) the amino acid sequence of a BCMA binding domain according to Tables 11A-11B, e.g., the amino acid sequence of 139109 scFv domain according to Table 11A or an amino acid sequence according to SEQ ID NO: 967, or an amino acid sequence at least 95% identical thereto; or

wherein the CAR comprises:

(i) the amino acid sequence of a CD19 CAR according to Tables 6-9, e.g., the amino acid sequence of CTL019 according to Table 9 or an amino acid sequence according to SEQ ID NO: 956 or an amino acid sequence at least 95% identical thereto;

(ii) the amino acid sequence of a humanized CD19 CAR according to Tables 6-9, e.g., the amino acid sequence of CAR2 according to Table 9 or an amino acid sequence according to SEQ ID NO: 902, or an amino acid sequence at least 95% identical thereto; or

(iii) the amino acid sequence of a BCMA CAR according to Tables 11A-11B, e.g., the amino acid sequence of 139109 CAR according to Table 11A or an amino acid sequence according to SEQ ID NO: 971, or an amino acid sequence at least 95% identical thereto.

13. The use, method, or population of immune effector cells of claim 11 or 12, wherein:

(a) the transmembrane domain comprises:

(i) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 12, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 12; or

(ii) the sequence of SEQ ID NO: 12; and/or

(b) the antigen binding domain is connected to the transmembrane domain by a hinge region, wherein said hinge region comprises SEQ ID NO: 2 or SEQ ID NO: 6, or a sequence with 95-99% identity thereof.

14. The method or population of immune effector cells of any of claims 11-13, wherein:

(a) the intracellular signaling domain comprises a primary signaling domain and/or a costimulatory signaling domain, wherein the primary signaling domain comprises a functional signaling domain of a protein chosen from CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, common FcR gamma (FCER1G), FcR beta (Fc Epsilon R1b), CD79a, CD79b, Fcgamma RIIa, DAP10, or DAP12;

(b) the primary signaling domain comprises:

(i) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20; or

(ii) the amino acid sequence of SEQ ID NO:18 or SEQ ID NO: 20; and/or

(c) the intracellular signaling domain comprises a costimulatory signaling domain, or a primary signaling domain and a costimulatory signaling domain, wherein the costimulatory signaling domain comprises a functional signaling domain of a protein selected from the group consisting of CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46, and NKG2D.

15. The use, method, or population of immune effector cells of any of claims 11-14, wherein:

(a) the costimulatory signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:14 or SEQ ID NO: 16, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:14 or SEQ ID NO: 16;

(b) the costimulatory signaling domain comprises a sequence of SEQ ID NO: 14 or SEQ ID NO: 16;

(c) the intracellular domain comprises the sequence of SEQ ID NO: 14 or SEQ ID NO: 16, and the sequence of SEQ ID NO: 18 or SEQ ID NO: 20, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain; and/or

(d) the CAR comprises a leader sequence comprising, e.g., consisting of, SEQ ID NO: 2.

16. The use, method, or population of immune effector cells of any of the preceding claims, wherein the LSD1 inhibitor is: (1) a gene editing system targeted to one or more sites of the LSD1 gene, or its corresponding regulatory elements; (2) a nucleic acid (e.g., an siRNA or shRNA, or antisense oligonucleotide) comprising sequence complementary to a target sequence of the LSD1 gene; (3) a protein (e.g., a dominant negative LSD1, e.g., catalytically inactive LSD1, or a dominant negative binding partner of LSD1); (4) a small molecule; (5) a nucleic acid encoding any of (1)-(3); or (6) any combination of (1) –(5), optionally wherein:

(a) the LSD1 inhibitor is an shRNA or siRNA comprising sequence complementary to a target sequence of the LSD1 gene listed in Table 1, e.g., selected from SEQ ID NO: [43] to SEQ ID NO: [82];

(b) the LSD1 inhibitor is an shRNA encoded by nucleic acid comprising any sequence encoding an anti-LSD1 shRNA of Table 1, e.g., encoded by nucleic acid comprising a sequence selected from SEQ ID NO: [83] to SEQ ID NO: [122]; or

(c) the LSD1 inhibitor is nucleic acid comprising any sequence encoding an anti-LSD1 shRNA of Table 1, e.g., a sequence selected from SEQ ID NO: [83] to SEQ ID NO: [122].

17. The method or population of immune effector cells of claim 16, wherein said nucleic acid is disposed on a vector, optionally wherein the vector is a retroviral vector, a lentiviral vector, an adenoviral vector, an adeno-associated viral (AAV) vector, a herpes simplex virus (HSV) vector, a plasmid, a minicircle, a nanoplasmid, or an RNA vector, and/or wherein the vector further comprises a sequence encoding a CAR.

18. The method or population of immune effector cells of claim 16, wherein the LSD1 inhibitor is a genome editing system specific for a sequence of the LSD1 gene (KDM1A) or its regulatory elements selected from a CRISPR genome editing system, a zinc finger nuclease genome editing system, a TALEN genome editing system and a meganuclease genome editing system, optionally wherein the LSD1 inhibitor is a CRISPR genome editing system comprising a gRNA molecule comprising a targeting domain complementary to a sequence of the LSD1 gene (KDM1A) or its regulatory elements, e.g., comprising any one of SEQ ID NO: [132] to [862].

19. The use, method, or population of immune effector cells of claim 16, wherein the LSD1 inhibitor is a reversible small molecule LSD1 inhibitor or an irreversible small molecule LSD1 inhibitor, optionally wherein the LSD1 inhibitor is:

a) GSK2699537;

b) rel- 2-[[(1R,2S)-2-[4-[(4-chlorophenyl)methoxy]phenyl]cyclopropyl]amino]-1-(4-methyl-1-piperazinyl)-ethanone;

c) (R)-4-(5-(pyrrolidin-3-ylmethoxy)-2-(p-tolyl)pyridin-3-yl)benzonitrile;

d) (1S,2R)-N-((2-methoxypyridin-3-yl)methyl)-2-phenylcyclopropan-1-amine;

e) N,N-dimethyl-1-((4-(4-(4-(piperidin-4-yl)phenyl)-1H-indazol-1-yl)phenyl)sulfonyl)piperidin-4-amine;

f) 5-(6-chloro-4'-(methylsulfonyl)-[1,1'-biphenyl]-3-yl)-2-(piperazin-1-yl)-1H-pyrrole-3-carbonitrile;

g) rel- N-[(1R,2S)-2-Phenylcyclopropyl]-4-Piperidinamine;

h) 2-(1R,2S)-2-(4-(Benzyloxy)phenyl)cyclopropylamino)-1-(4-methylpiperazin-1-yl)ethanone;

i) Trans-3-(3-amino-2-methylphenyl)-1-(4-hydroxycyclohexyl)-6-methyl-1H-indole-5-carbonitrile; or

j) a pharmaceutically acceptable salt of any of the foregoing.

20. The use, method, or population of immune effector cells of claim 16, wherein:

(a) the LSD1 inhibitor is a protein, e.g., is a dominant negative binding partner of LSD1 (e.g., a histone deacetylase (HDAC) that interacts with LSD1 or other member of the Co-REST or AR co-activator complex), or nucleic acid encoding said dominant negative binding partner of LSD1; or

(b) the inhibitor of LSD1 is a protein, e.g., is a dominant negative (e.g., catalytically inactive) LSD1, or nucleic acid encoding said dominant negative LSD1.

21. Use of a population of immune effector cells in the manufacture of a medicament for the treatment of a disease associated with the expression of a tumor antigen in a subject, wherein the population of immune effector cells forming the medicament comprises an effective amount of the population of immune effector cells of claim 8 or 9 and the medicament is to be administered to the subject, optionally wherein:

(a) the treatment further comprises LSD1 inhibitor to be administered to said subject;

(b) the subject is to receive a pre-treatment of the LSD1 inhibitor, prior to the administration of the medicament;

(c) the subject is to receive concurrent treatment with an LSD1 inhibitor and the medicament; and/or

(d) the subject is to receive treatment with an LSD1 inhibitor after administration of the medicament.

22. The use, method, or population of immune effector cells of any of claims 1-7 or 10-21, wherein the disease associated with expression of a tumor antigen, is chosen from a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen, optionally wherein the cancer is a hematologic cancer chosen from one or more of chronic lymphocytic leukemia (CLL), acute leukemias, acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, or pre-leukemia, or wherein the cancer is selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers, combinations of said cancers, and metastatic lesions of said cancers.

23. The use, method, or population of immune effector cells of any of the preceding claims, wherein the subject is a human.

24. A compound selected from N,N-dimethyl-1-((4-(4-(4-(piperidin-4-yl)phenyl)-1H-indazol-1-yl)phenyl)sulfonyl)piperidin-4-amine, 5-(6-chloro-4'-(methylsulfonyl)biphenyl-3-yl)-2-(piperazin-1-yl)-1H-pyrrole-3-carbonitrile, or a pharmaceutically acceptable salt thereof.

25. A composition for use in *ex vivo* manufacturing a population of immune effector cells, comprising an LSD1 inhibitor, optionally wherein the population of immune effector cells comprises cells engineered to express a CAR.

26. An LSD1 inhibitor, for use in the treatment of a subject, wherein said subject has received or is about to receive therapy comprising an immune effector cell, e.g., an immune effector cell engineered to express a CAR.

27. An LSD1 inhibitor, for use in the manufacture of an immune effector cell, e.g., an immune effector cell engineered to express a CAR.

28. A method of manufacturing an immune effector cells comprising introducing into said cells nucleic acid encoding a CAR, wherein the nucleic acid integrates into the genome of said cell within the LSD1 gene, such that LSD1 expression and/or function is reduced.