

[0006] Provided herein are methods of treatment that involve: (a) administering a T cell therapy to a subject having a disease or condition; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein administration of the tryptophan metabolism and/or kynurenine pathway modulator is started at a time point greater than 1 day prior to initiation of administration of the T cell therapy.

[0006a] In one aspect, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, wherein administration of the tryptophan metabolism and/or kynurenine pathway modulator is started at a time point greater than 1 day prior to initiation of administration of the T cell therapy.

[0007] Provided herein are methods of treatment that involve administering a T cell therapy to a subject having a disease or condition, the subject having been previously administered a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator starting at a time point greater than 1 day prior to initiation of the T cell therapy.

[0008] In some embodiments of any of the methods provided herein, the administration of the tryptophan metabolism and/or kynurenine pathway modulator is started at a time point that is within or within about 2 days, 3 days, 6 days, 12 days, 15 days, 30 days, 60 days or 90 days or more prior to initiation of the administration of the T cell therapy. In some embodiments, the method further includes continuing administration of the tryptophan metabolism and/or kynurenine pathway modulator with or subsequent to initiation of administration of the T cell therapy. In some embodiments, the method further includes administering the tryptophan metabolism and/or kynurenine pathway modulator subsequent to administering the therapy cell therapy.

[0009] Provided herein are methods of treatment that involve: (a) administering a T cell therapy to a subject having a disease or condition; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator subsequent to initiation of administration of the T cell therapy. Also provided are

methods of treatment that involves administering to a subject having cancer a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, the subject having been previously administered a T cell therapy. In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is administered within or within about 1 hour, 2 hours, 6 hours, 12 hours, 24 hours or 48 hours subsequent to initiation of the T cell therapy.

[0009a] In another aspect, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject subsequent to initiation of administration of the T cell therapy.

[0009b] In another aspect, there is provided use of a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to a subject having a disease or condition, the subject is one that has been previously administered a T cell therapy.

[0010] In some embodiments, prior to initiation of administration of the composition comprising T cells, the subject has failed to respond or failed to completely respond to treatment with, relapsed following remission after treatment with, or become refractory to, a prior

administration of a tryptophan metabolism and/or kynurenine pathway modulator, optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

[0011] Provided herein are methods of treatment that involve: (a) administering a T cell therapy to a subject having a disease or condition; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein prior to initiation of administration of the composition comprising T cells, the subject has failed to respond or failed to completely respond to treatment with, relapsed following remission after treatment with, or become refractory to, a prior administration of a tryptophan metabolism and/or kynurenine pathway modulator optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

[0011a] In another aspect, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, wherein prior to initiation of administration of the composition comprising T cells, the subject has failed to respond or failed to completely respond to treatment with, relapsed following remission after treatment with, or become refractory to, a prior administration of a tryptophan metabolism and/or kynurenine pathway modulator, optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

[0012] Provided herein are methods of treatment that involve: administering to a subject having a disease or condition a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator to a subject having been administered a T cell therapy, wherein prior to initiation of administration of the composition comprising T cells, the subject has failed to respond or failed to completely respond to treatment with, relapsed following remission after treatment with, or become refractory to, a prior administration of a tryptophan metabolism and/or kynurenine pathway modulator optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

[0013] In some embodiments, the disease or condition is cancer.

[0014] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) is administered prior to, simultaneously with and/or subsequent to initiation of administration of the T cell therapy. In some embodiments, administration of the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) is started at a time point that is within or within about 2 days, 3 days, 6 days, 12 days, 15 days, 30 days, 60 days or 90 days or more prior to initiation of the administration of the T cell therapy.

[0015] In some embodiments, the methods also involve administering the tryptophan metabolism and/or kynurenine pathway modulator administered in (b) subsequent to initiation of administration of the T cell therapy.

and/or kynurenine pathway modulator of IDO1 is administered at a time in which there is an increase in the expression or activity of IDO1 in a biological sample from the subject compared to prior to initiation of administration of the T cell therapy or compared to a preceding time point after initiation of administration of the T cell therapy.

[0023] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is tryptophan.

[0024] In some embodiments of any of the methods provided herein, the cancer contains a tumor negative for IDO1 and/or the subject is not selected for expression of an IDO1 positive tumor; and/or the cancer contains a tumor negative for TDO and/or the subject is not selected for expression of a TDO positive tumor. In some embodiments, the cancer contains a tumor negative for IDO1 and/or the subject is not selected for expression of an IDO1 positive tumor.

[0025] In some embodiments of any of the methods provided herein, the cancer comprises a tumor negative for IDO1 prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor prior to initiation of administration of the T cell therapy; and/or the cancer comprises a tumor negative for TDO prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of a TDO positive tumor prior to initiation of administration of the T cell therapy. In some embodiments, the cancer comprises a tumor negative for IDO1 prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor prior to initiation of administration of the T cell therapy.

[0026] Provided herein are methods of treatment that involve (a) administering a T cell therapy to a subject having a disease or condition, wherein the cancer comprises a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase (TDO) prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor or a TDO positive tumor prior to initiation of administration of the T cell therapy; and; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator that is an inhibitor of IDO1.

[0026a] In another aspect, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition that is cancer, wherein the cancer comprises a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase (TDO) prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor or a TDO positive tumor prior to initiation of administration of the T cell therapy; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject that is an inhibitor of IDO1.

[0027] Also provided herein are methods of treatment that involve administering to a subject having cancer a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator that is an inhibitor of IDO1, the subject having been administered a T cell

fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-bromo-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-chloro-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 1-cyclohexyl-2-(5H-imidazo[5,1-a]isoindol-5-yl)ethanol (NLG919), GDC-0919, F001287, PF-06840003 or pharmaceutically acceptable salt or prodrug thereof or a combination thereof.

[0037] In some embodiments of any of the embodiments herein, the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat). In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is 1-methyl-D-tryptophan (1-MT) (indoximod). In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is tryptophan.

[0038] Provided herein are methods of treatment that involve: (a) administering a T cell therapy to a subject having a disease or condition; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

[0038a] In another aspect, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

[0039] Also provided herein are methods of treatment that involve administering to a subject having cancer a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat), the subject having been administered a T cell therapy.

[0040] Also provided herein are methods of treatment that involve administering to a subject having cancer a T cell therapy, the subject having been administered a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

[0041] In some embodiments, the disease or condition is cancer.

[0042] In some embodiments of any of the embodiments herein, upon administration to the subject the T cell therapy causes an increase or elevation of the level of IFN-gamma in the subject in the local environment of a tumor or in a serum or plasma sample of the subject compared to the level of IFN-gamma in the subject prior to initiation of the T cell therapy.

[0043] In some embodiments of any of the embodiments herein, the T cell therapy is or includes tumor infiltrating lymphocytic (TIL) therapy or a T cell therapy that includes genetically engineered cells expressing a recombinant receptor that specifically binds to a ligand. In some embodiments, the T cell therapy is or includes genetically engineered cells expressing a recombinant receptor that specifically binds to a ligand.

[0044] In some embodiments of any of the embodiments herein, the genetically engineered cell also includes a modification impacting the expression, presence, or activity of a protein or other factor or molecule associated with one or more activities or outcomes or effects, and/or a nucleic acid encoding such protein or factor. In some embodiments, the activities, outcomes, or effects may include those associated with, involved in sensing of, or promoted by tryptophan deficiencies or tryptophan starvation. In some embodiments, the activities, outcomes, or effects may include those associated with, involved in sensing of, or promoted by increased amounts or concentrations of kynurenine or one or more kynurenine pathway metabolites and/or kynurenine mediated immunosuppression, and/or decreased tryptophan/kynurenine ratios in the cell or environment. In some embodiments, the protein or factor is or includes a protein involved in or associated with the sensing of tryptophan starvation and/or kynurenine mediated immunosuppressive effects, such as those that may limit T cell function, e.g., in the tumor environment. Such effects may include inhibition or dampening of T cell activity or function and/or promotion of Treg function, levels, or activity. In some embodiments, the protein or factor is involved in IDO-induced immunosuppressive effects in the cell and/or neighboring cells.

[0045] Provided herein are methods of treatment that involve administering a genetically engineered T cells to a subject having a disease or condition, wherein the genetically engineered T cell contains (i) a recombinant receptor that specifically binds to a ligand and (ii) modification of expression of a protein involved in or associated with the sensing of tryptophan starvation and/or kynurenine mediated immunosuppressive effects and/or protein associated with IDO-mediated immunosuppressive effects in the cell.

[0046] Also provided herein are methods of treatment that involve administering a genetically engineered T cells to a subject having a disease or condition, wherein the genetically engineered T cell comprise (i) a recombinant receptor that specifically binds to a ligand and (ii) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof. In some embodiments, the methods also include (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator.

[0046a] In another aspect, there is provided use of genetically engineered T cells in the manufacture of a medicament for the treatment of a disease or condition, wherein: genetically engineered T cells are to be administered to a subject having a disease or condition, wherein the genetically engineered T cells comprise (i) a recombinant receptor that specifically binds to a ligand and (ii) modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immunosuppression in the cell; and/or the genetically engineered T cells are to be administered to a subject having a disease or condition, wherein the genetically engineered T cells comprise (i) a recombinant receptor that specifically binds to a ligand and (ii) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

[0047] Provided herein are methods of treatment that involve: (a) administering a genetically engineered T cells to a subject having a disease or condition, wherein the genetically engineered T cell contains (i) a recombinant receptor that specifically binds to a ligand and (ii) a modification of expression of a protein involved in or associated with the sensing of tryptophan starvation and/or kynurenine mediated immunosuppressive effects and/or a protein associated with IDO-mediated immunosuppressive effects in the cell; and (b) administering to the subject a therapeutically effective amount of a tryptophan metabolism and/or kynurenine pathway modulator.

[0047a] In another aspect, there is provided use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein: (a) the T cell therapy is to be administered to a subject having a disease or condition, wherein the genetically engineered T

cell comprises (i) a recombinant receptor that specifically binds to a ligand and (ii) a modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression in the cell; and (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject.

[0048] In some embodiments, the disease or condition is cancer.

[0049] In some embodiments, the subject is selected for having a tumor positive for expression of L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2 (SLC7A8), CD98 heavy chain (4F2hc; CD98hc; SLC3A2) and/or proton-assisted amino-acid transporter 4 (PAT4; SLC36A4), or for having cells in the tumor microenvironment that are positive for expression of LAT1, LAT2, CD98hc and/or PAT4.

[0050] In some embodiments of any of the embodiments herein, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway. In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces catabolism of tryptophan or prevents or reduces synthesis or accumulation of a tryptophan metabolite. In some embodiments, the tryptophan metabolite is selected from kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3-HAA).

[0051] In some embodiments of any of the embodiments herein, the tryptophan metabolism and/or kynurenine pathway modulator is a small molecule, peptide, protein, antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.

nucleic acid sequence and the second nucleic acid sequence(s) are comprised in two polynucleotides. In some embodiments, the first nucleic acid and the second nucleic acid(s) are comprised in one or more vector(s), which optionally are viral vector(s).

[0101] Provided herein are methods of selecting a subject having a disease or condition for administering a tryptophan metabolism and/or kynurenine pathway modulator, that involve: (a) assessing the level of tryptophan or a tryptophan metabolite, the level of expression or activity of IDO1, IDO2 or TDO, or the level of interferon-gamma (IFN γ) in one or more biological samples from the subject, wherein the biological sample is from a subject that is a candidate for treatment with a T cell therapy; and (b) selecting a subject in which: (i) the level of tryptophan in the sample is below a threshold level; (ii) the level of the tryptophan metabolite is above a threshold level; (iii) the level of expression or activity of IDO1, IDO2 or TDO is above a threshold level; or (iv) the level of the IFN γ is above a threshold level.

[0101a] In another aspect, there is provided a method of selecting a subject having a disease or condition for administering a tryptophan metabolism and/or kynurenine pathway modulator, the method comprising: (a) assessing the level of tryptophan or a tryptophan metabolite, the level of expression or activity of IDO1, IDO2 or TDO, or the level of interferon-gamma (IFN γ) in one or more biological samples from the subject, wherein the biological sample is obtained from a subject having been administered a T cell therapy; and (b) selecting a subject in which: (i) the level of tryptophan in the sample is below a threshold level or is decreased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy; (ii) the level of the tryptophan metabolite is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy; (iii) the level of expression or activity of IDO1, IDO2 or TDO is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy; or (iv) the level of the IFN γ is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy.

[0102] In some embodiments, the one or more biological sample is obtained prior to administration of the T cell therapy.

[0103] In some embodiments, the methods also involve administering the T cell therapy to the subject. In some embodiments, the methods also involve administering the tryptophan metabolism and/or kynurenine pathway modulator to the selected subject. In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is administered to the selected subject prior to or concurrently with initiation of administration of the T cell therapy. In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is administered subsequent to initiation of administration of the T cell therapy.

[0104] Provided herein are methods of selecting a subject having a disease or condition for administering a tryptophan metabolism and/or kynurenine pathway modulator, that involve: (a) assessing the level of tryptophan or a tryptophan metabolite, the level of expression or activity of IDO1, IDO2 or TDO, or the level of interferon-gamma (IFN γ) in one or more biological samples from the subject, wherein the biological sample is obtained from a subject having been administered a T cell therapy; and (b) selecting a subject in which: (i) the level of tryptophan in the sample is below a threshold level or is decreased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy; (ii) the level of the tryptophan metabolite is above a threshold level or is increased compared to the level assessed at a time point prior to

[0121] In some embodiments of any of the embodiments herein, the genetically engineered receptor that specifically binds to a ligand is a functional non-T cell receptor. In some embodiments, the genetically engineered receptor that specifically binds to a ligand is a chimeric antigen receptor (CAR). In some embodiments, the CAR contains an extracellular antigen-recognition domain that specifically binds to the antigen and an intracellular signaling region that includes an ITAM. In some embodiments, the intracellular signaling region contains an intracellular domain of a CD3-zeta (CD3 ζ) chain.

[0122] In some embodiments of any of the embodiments herein, the CAR also contains a costimulatory signaling region. In some embodiments, the costimulatory signaling region contains a signaling domain of CD28 or 4-1BB or an ICOS or a signaling portion thereof. In some embodiments, the costimulatory signaling region is a signaling domain of a CD28.

[0123] In some embodiments of any of the embodiments herein, the recombinant receptor is a transgenic T cell receptor (TCR). In some embodiments, the recombinant receptor is a chimeric antigen receptor (CAR).

[0124] In some embodiments of any of the embodiments herein, the T cell therapy recognizes or targets an antigen associated with the cancer. In some embodiments, the recombinant receptor binds to, recognizes or targets an antigen associated with the cancer. In some embodiments, the antigen is selected from ROR1, Her2, L1-CAM, CD19, CD20, CD22, mesothelin, CEA, hepatitis B surface antigen, anti-folate receptor, CD23, CD24, CD30, CD33, CD38, CD44, EGFR, EGP-2, EGP-4, EPHA2, ErbB2, ErbB3, ErbB4, FBP, fetal acetylcholine receptor, GD2, GD3, HMW-MAA, IL-22R-alpha, IL-13R-alpha2, kdr, kappa light chain, Lewis Y, L1-cell adhesion molecule, MAGE-A1, mesothelin, MUC1, MUC16, PSCA, NKG2D Ligands, NY-ESO-1, MART-1, gp100, oncofetal antigen, TAG72, VEGF-R2, carcinoembryonic antigen (CEA), prostate specific antigen, PSMA, estrogen receptor, progesterone receptor, ephrinB2, CD123, CS-1, c-Met, GD-2, MAGE A3, CE7, Wilms Tumor 1 (WT-1), and cyclin A1 (CCNA1).

[0125] Provided herein are engineered cells that contain (a) a genetically engineered receptor that specifically binds to a ligand; and (b) a modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling in the cell, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression.

[0125a] In another aspect, there is provided an engineered cell, comprising: (a) a recombinant receptor that specifically binds to a ligand; and (b) a modification in expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression in the cell.

[0126] In some embodiments, the molecule is mTOR or protein kinase C theta (PKC- Θ).

[0127] Provided are engineered cells that include (a) a recombinant receptor that specifically binds to a ligand; and (b) a modification in expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression in the cell.

[0128] In some embodiments, the modification comprises recombinant, engineered and/or ectopic expression in the cell of the molecule or a functional and/or catalytically active portion or variant thereof. In some embodiments, the molecule is mTOR or protein kinase C theta (PKC- Θ).

[0129] In some embodiments, the molecule is an amino acid transporter or a chain thereof or a functional and/or catalytically active portion or variant thereof.

[0130] Also provided are engineered cells that include (a) a recombinant receptor that specifically binds to a ligand; and (b) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

[0130a] In another aspect, there is provided an engineered cell, comprising: (a) a recombinant receptor that specifically binds to a ligand; and (b) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof, optionally wherein the amino acid transporter is a tryptophan transporter.

[0131] In some embodiments, the amino acid transporter is a tryptophan transporter. In some embodiments, T (SLC3A1), CD98 heavy chain (4F2hc; SLC3A2), L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2 (SLC7A8), Asc-type amino acid transporter 1 (Asc-1; SLC7A10), Sodium- and chloride-dependent neutral and basic amino acid transporter B(0+)(ATB0,+; SLC6A14), Sodium-dependent neutral amino acid transporter B(0)AT1 (B(0)AT1; SLC6A19), Monocarboxylate transporter 10 (TAT1; SLC16A10), and proton-assisted amino-acid transporter 4 (PAT4; SLC36A4) or a portion thereof. In some embodiments, the amino acid transporter or a chain thereof comprises CD98 heavy chain (4F2hc; SLC3A2) and L-type Amino Acid Transporter 1 (LAT1; SLC7A5) or a portion thereof.

[0132] In some embodiments, the amino acid transporter or a chain thereof comprises the amino acid sequence selected from any one of SEQ ID NOs: 36-115, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 36-115. In some embodiments, the amino acid transporter or a chain thereof is selected from among one or more of CD98 heavy chain (4F2hc; SLC3A2), L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2

embodiments, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more polynucleotides. In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in two polynucleotides. In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more vector(s), which optionally are viral vector(s).

[0155] Also provided herein are compositions that include any of the engineered cell described herein. In some embodiments of the compositions, the cells are CD4+ or CD8+ cells. In some embodiments, the compositions also include a pharmaceutically acceptable carrier.

[0155a] In another aspect, there is provided a composition comprising the engineered cell as described herein.

[0156] Also provided herein are combinations that include genetically engineered cells expressing a recombinant receptor that binds to a ligand, wherein the recombinant receptor optionally is a T cell receptor (TCR) or a chimeric antigen receptor (CAR); and a tryptophan metabolism and/or kynurenine pathway modulator.

[0156a] In another aspect, there is provided a combination, comprising: genetically engineered cells expressing a recombinant receptor that binds to a ligand, wherein the recombinant receptor optionally is a chimeric antigen receptor (CAR) or a transgenic T cell receptor (TCR); and a tryptophan metabolism and/or kynurenine pathway modulator.

[0157] Also provided herein are combinations that include any of the engineered cells described herein or any of the compositions described herein, and a tryptophan metabolism and/or kynurenine pathway modulator.

[0157a] In another aspect, there is provided a combination, comprising: the engineered cells as described herein or the composition as described herein; and a tryptophan metabolism and/or kynurenine pathway modulator.

[0158] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway, and/or reduces the kynurenine/tryptophan ratio.

[0159] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces catabolism of tryptophan or prevents or reduces synthesis or accumulation of a tryptophan metabolite. In some embodiments, the tryptophan metabolite is selected from kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3-HAA).

[0160] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is a small molecule, peptide, protein, antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.

[0161] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is an antagonist of the enzyme kynureninase.

[0162] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), an inhibitor of IDO2 and an inhibitor of

[0166] Also provided are methods of engineering immune cells expressing a recombinant receptor, that includes contacting a population of cells comprising immune cells with a tryptophan metabolism and/or kynurenine pathway modulator; and introducing a nucleic acid encoding a recombinant receptor into the population of cells under conditions such that the recombinant receptor is expressed.

[0166a] In another aspect, there is provided a method of engineering immune cells expressing a recombinant receptor, comprising: contacting a population of cells comprising immune cells with a tryptophan metabolism and/or kynurenine pathway modulator; and introducing a nucleic acid encoding a recombinant receptor into the population of cells under conditions such that the recombinant receptor is expressed.

[0167] In some embodiments, the recombinant receptor binds to a ligand, optionally an antigen. In some embodiments, the recombinant receptor is a T cell receptor (TCR) or a chimeric antigen receptor (CAR). In some embodiments, the population of cells is or comprises peripheral blood mononuclear cells. In some embodiments, the population of cells is or comprises T cells. In some embodiments, the T cells are CD4+ and/or CD8+. In some embodiments, the population of cells are isolated from a subject, optionally a human subject.

[0168] In some embodiments, the contacting occurs prior to and/or during the introducing.

[0169] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway. In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces catabolism of tryptophan or prevents or reduces synthesis or accumulation of a tryptophan metabolite. In some embodiments, the tryptophan metabolite is selected from kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3-HAA).

[0170] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is a small molecule, peptide, protein, antibody or antigen-binding fragment thereof, an antibody mimetic, an aptamer, or a nucleic acid molecule.

[0171] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is an antagonist of the enzyme kynureninase.

[0172] In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), an inhibitor of IDO2 and an inhibitor of tryptophan 2,3-dioxygenase (TDO). In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is a dual-acting IDO/TDO inhibitor. In some embodiments, the tryptophan metabolism and/or kynurenine pathway modulator is an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1).

[0176] Also provided are methods of engineering immune cells expressing a recombinant receptor, that includes introducing a first nucleic acid sequence encoding a recombinant receptor into the population of cells under conditions such that the recombinant receptor is expressed; and introducing one or more second nucleic acid sequence(s) encoding a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

[0176a] In another aspect, there is provided a method of engineering immune cells expressing a recombinant receptor, wherein the method is selected from: (A) a method comprising: (i) introducing a first nucleic acid sequence encoding a recombinant receptor into a population of cells under conditions such that the recombinant receptor is expressed; and (ii) introducing one or more second nucleic acid sequence(s) encoding an agent capable of or involved in modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression in the cell into the population of cells under conditions such that the agent is expressed; and/or (B) a method comprising: (i) introducing a first nucleic acid sequence encoding a recombinant receptor into a population of cells under conditions such that the recombinant receptor is expressed; and (ii) introducing one or more second nucleic acid sequence(s) encoding a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

[0177] In some embodiments, the modification comprises recombinant, engineered and/or ectopic expression of the molecule or a functional and/or catalytically active chain, portion or variant thereof. In some embodiments, the modification comprises reduced expression of the molecule. In some embodiments, the method comprises an inhibitory nucleic acid or a genetic disruption that reduces expression of the molecule.

[0178] In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more polynucleotides. In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in two polynucleotides. In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence(s) are comprised in one or more vector(s), which optionally are viral vector(s).

[0179] In some embodiments, the combination provided herein is packaged as a kit. In some embodiments, the kit also includes instructions for administration of the engineered cells and tryptophan metabolism and/or kynurenine pathway modulator. In some embodiments, provided are articles of manufacture and/or kits, such as those comprising the tryptophan metabolism and/or kynurenine pathway modulator, e.g., in a therapeutically effective dose. In some embodiments, the articles of manufacture further comprise instructions and/or literature specifying administration of the modulator(s) to a subject having received or that is intended to receive the therapy such as the cell therapy such as an engineered T cell therapy. In some embodiments, the instructions or literature further specify the administration to the subject with a disease or condition, where the disease or condition or associated cells or tissues are or have been confirmed to express IDO—optionally following administration of the therapy—and/or one or more amino acid transporters such as LAT-1. In some embodiments, the instructions or literature do not indicate the expression of IDO and/or do not indicate expression of a transporter or other marker, as a prerequisite for administration of the cell therapy.

CLAIMS

WHAT IS CLAIMED:

1. Use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein:

- (a) the T cell therapy is to be administered to a subject having a disease or condition; and
- (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject subsequent to initiation of administration of the T cell therapy.

2. Use of a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to a subject having a disease or condition, the subject is one that has been previously administered a T cell therapy.

3. Use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein:

- (a) the T cell therapy is to be administered to a subject having a disease or condition; and
- (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, wherein administration of the tryptophan metabolism and/or kynurenine pathway modulator is started at a time point greater than 1 day prior to initiation of administration of the T cell therapy.

4. Use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein:

- (a) the T cell therapy is to be administered to a subject having a disease or condition; and
- (b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, wherein prior to initiation of

administration of the composition comprising T cells, the subject has failed to respond or failed to completely respond to treatment with, relapsed following remission after treatment with, or become refractory to, a prior administration of a tryptophan metabolism and/or kynurenine pathway modulator, optionally wherein such prior administration was carried out in combination with an immunomodulatory agent, optionally a checkpoint inhibitor.

5. The use of claim 3 or claim 4, wherein administration of the tryptophan metabolism and/or kynurenine pathway modulator is started at a time point that is within or within about 2 days, 3 days, 6 days, 12 days, 15 days, 30 days, 60 days or 90 days or more prior to initiation of the administration of the T cell therapy.

6. Use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein:

(a) the T cell therapy is to be administered to a subject having a disease or condition that is cancer, wherein the cancer comprises a tumor negative for indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase (TDO) prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor or a TDO positive tumor prior to initiation of administration of the T cell therapy; and

(b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject that is an inhibitor of IDO1.

7. Use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein:

(a) the T cell therapy is to be administered to a subject having a disease or condition; and

(b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject, wherein the tryptophan metabolism and/or kynurenine pathway modulator is or comprises 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

8. Use of genetically engineered T cells in the manufacture of a medicament for the treatment of a disease or condition, wherein:

genetically engineered T cells are to be administered to a subject having a disease or condition, wherein the genetically engineered T cells comprise (i) a recombinant receptor that specifically binds to a ligand and (ii) modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression in the cell; and/or

the genetically engineered T cells are to be administered to a subject having a disease or condition, wherein the genetically engineered T cells comprise (i) a recombinant receptor that specifically binds to a ligand and (ii) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

9. Use of a combination comprising a T cell therapy and a tryptophan metabolism and/or kynurenine pathway modulator in the manufacture of a medicament for the treatment of a disease or condition, wherein:

(a) the T cell therapy is to be administered to a subject having a disease or condition, wherein the genetically engineered T cell comprises (i) a recombinant receptor that specifically binds to a ligand and (ii) a modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression in the cell; and

(b) a therapeutically effective amount of the tryptophan metabolism and/or kynurenine pathway modulator is to be administered to the subject.

10. The use of any of claims 1-9, wherein the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces the formation, concentration, availability, metabolism and/or effect of an enzyme and/or a metabolite of the kynurenine pathway; and/or the tryptophan metabolism and/or kynurenine pathway modulator prevents or reduces catabolism

of tryptophan, prevents or reduces synthesis or accumulation of a tryptophan metabolite or decreases the kynurenine to tryptophan ratio.

11. The use of any of claims 1-6 and 8-10, wherein the tryptophan metabolism and/or kynurenine pathway modulator is selected from among: an antagonist of the enzyme kynureninase; an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), IDO2 and tryptophan 2,3-dioxygenase (TDO); tryptophan; an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) and/or a dual-acting IDO/TDO inhibitor.

12. The use of any of claims 1-6 and 8-11, wherein the tryptophan metabolism and/or kynurenine pathway modulator is selected from 1-methyl-D-tryptophan (1-MT) (indoximod), 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat), 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-chloro-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl} amino)-N'-hydroxy-N-[3-(trifluoromethyl)phenyl]-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-cyano-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-bromo-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-chloro-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 1-cyclohexyl-2-(5H-imidazo[5,1-a]isoindol-5-yl)ethanol (NLG919), GDC-0919, F001287, PF-06840003 or pharmaceutically acceptable salt or prodrug thereof or a combination thereof.

13. The use of any of claims 1-6 and 8-12, wherein the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

14. The use of any one of claims 1-5 and 7-13, wherein:

the disease or condition is a cancer, and the cancer comprises a tumor negative for IDO1 prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of an IDO1 positive tumor prior to initiation of administration of the T cell therapy; and/or

the disease or condition is a cancer, and the cancer comprises a tumor negative for TDO prior to initiation of administration of the T cell therapy and/or the subject is not selected for expression of a TDO positive tumor prior to initiation of administration of the T cell therapy.

15. The use of any of claims 3-14, wherein:

the tryptophan metabolism and/or kynurenine pathway modulator is to be administered from or from about 0 to 96 hours, 0 to 72 hours, 0 to 48 hours, 0 to 24 hours, 0 to 12 hours or 0 to 6 hours or 0 to 2 hours prior to initiation of administration of the T cell therapy; or

the tryptophan metabolism and/or kynurenine pathway modulator is to be administered no more than 96 hours, 72 hours, 48 hours, 24 hours, 12 hours, 6 hours, 2 hours or 1 hour prior to initiation of the T cell therapy.

16. The use of any of claims 1-15, wherein upon administration to the subject the T cell therapy causes an increase or elevation of the level of interferon-gamma (IFN γ) in the subject in the local environment of a tumor or in a serum or plasma sample of the subject compared to the level of IFN-gamma in the subject prior to initiation of the T cell therapy.

17. The use of claim 16, wherein the increase or elevation of the level of IFN γ in the subject results in an increase or elevation of expression of IDO1 in cells present in the local environment of a tumor, optionally tumor cells.

18. The use of any of claims 1, 2, 4 and 6-17, wherein tryptophan metabolism and/or kynurenine pathway modulator is to be administered at a time in which:

there is a decrease in tryptophan levels, an increase in kynurenine levels and/or an increase in expression or activity of IDO1, IDO2 or TDO in a biological sample from the subject compared to prior to initiation of administration of the T cell therapy or compared to a preceding time point after initiation of administration of the T cell therapy;

at a time before the number of cells of the T cell therapy detectable in the blood from the subject is decreased compared to in the subject at a preceding time point after initiation of administration of the T cell therapy;

at a time before T cells exhibit manifestations of prolonged tryptophan starvation, exhaustion, reduction of effector function, expression of inhibitory receptors and/or loss of proliferative capacity;

at a time before a peak or maximum level of the cells of the T cell therapy are detectable in the blood of the subject; and/or

the level of interferon-gamma (IFN γ) is increased in a biological sample from the subject compared to prior to initiation of administration of the T cell therapy or compared to a preceding time point after initiation of administration of the T cell therapy.

19. The use of any of claims 1, 2, 4 and 6-18, wherein the tryptophan metabolism and/or kynurenine pathway modulator is to be administered within or within about 1 hour, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, 7 days, 14 days, 21 days, 28 days subsequent to initiation of the T cell therapy.

20. The use of any of claims 1-19, wherein the T cell therapy is or comprises tumor infiltrating lymphocytic (TIL) therapy or a T cell therapy comprising genetically engineered cells expressing a recombinant receptor that specifically binds to a ligand.

21. The use of claim 20, wherein the genetically engineered cell further comprises a modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression in the cell.

22. The use of claim 21, wherein the modification comprises recombinant, engineered and/or ectopic expression of the molecule or a functional and/or catalytically active chain, portion or variant thereof.

23. The use of claim 21 or claim 22, wherein the molecule is selected from among one or more selected from:

mTOR or protein kinase C theta (PKC- Θ);

rBAT (SLC3A1), CD98 heavy chain (4F2hc; SLC3A2), L-type Amino Acid Transporter 1 (LAT1; SLC7A5), LAT2 (SLC7A8), Asc-type amino acid transporter 1 (Asc-1; SLC7A10), Sodium- and chloride-dependent neutral and basic amino acid transporter B(0+)(ATB0,+; SLC6A14), Sodium-dependent neutral amino acid transporter B(0)AT1 (B(0)AT1; SLC6A19), Monocarboxylate transporter 10 (TAT1; SLC16A10) or proton-assisted amino-acid transporter 4 (PAT4; SLC36A4) or a portion thereof; and

GCN2 kinase, BLIMP-1, aryl hydrocarbon receptor (AHR), AHR nuclear transporter (ARNT), eukaryotic translation initiation factor 2 α (eIF2 α), activating transcription factor 4 (ATF4), CCAAT/enhancer binding protein-homologous protein (CHOP), Gadd45 α , Herp, 4E-BP1, eIF4G, JAK1, NF κ B-2, FK506-BP8 or IFN γ -R2.

24. The use of claim 21, wherein:

the modification comprises introducing an inhibitory nucleic acid, optionally wherein the inhibitory nucleic acid comprises an RNA interfering agent that reduces expression of the molecule; or

the modification comprises introducing a genetic disruption in the gene encoding the molecule that reduces expression of the molecule, optionally wherein the disruption comprises introducing an agent into the cell comprising a zinc finger nuclease (ZFN), a TAL-effector nuclease (TALEN), or a CRISPR-Cas9 combination that specifically binds to, recognizes, or hybridizes to the gene encoding the molecule.

25. The use of any of claims 1-24, wherein the T cell comprises a recombinant receptor that specifically binds to a ligand, optionally wherein the recombinant receptor is a chimeric antigen receptor (CAR) or a transgenic T cell receptor (TCR).

26. The use of claim 25, wherein the recombinant receptor is a CAR and the CAR comprises an extracellular antigen-recognition domain that specifically binds to the antigen and

an intracellular signaling region comprising an ITAM, optionally wherein the intracellular signaling region comprises an intracellular domain of a CD3-zeta (CD3ζ) chain.

27. The use of claim 26, wherein the CAR further comprises a costimulatory signaling region, optionally wherein the costimulatory signaling region comprises a signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof.

28. The use of any of claims 1-5, 7-13 and 15-27, wherein the disease or condition is cancer.

29. The use of claim 6, claim 14 or claim 28, wherein the recombinant receptor binds to, recognizes or targets an antigen associated with the cancer.

30. The use of claim 29, wherein the antigen is selected from ROR1, Her2, L1-CAM, CD19, CD20, CD22, mesothelin, CEA, hepatitis B surface antigen, anti-folate receptor, CD23, CD24, CD30, CD33, CD38, CD44, EGFR, EGP-2, EGP-4, EPHA2, ErbB2, ErbB3, ErbB4, FBP, fetal acetylcholine e receptor, GD2, GD3, HMW-MAA, IL-22R-alpha, IL-13R-alpha2, kdr, kappa light chain, Lewis Y, L1-cell adhesion molecule, MAGE-A1, mesothelin, MUC1, MUC16, PSCA, NKG2D Ligands, NY-ESO-1, MART-1, gp100, oncofetal antigen, TAG72, VEGF-R2, carcinoembryonic antigen (CEA), prostate specific antigen, PSMA, estrogen receptor, progesterone receptor, ephrinB2, CD123, CS-1, c-Met, GD-2, MAGE A3, CE7, Wilms Tumor 1 (WT-1), and cyclin A1 (CCNA1).

31. The use of any of claims 6, 14 and 28-30, wherein the cancer is a myeloma, lymphoma, leukemia, optionally wherein the cancer is non-Hodgkin lymphoma (NHL), an acute lymphoblastic leukemia (ALL), a chronic lymphocytic leukemia (CLL), diffuse large B-Cell lymphoma (DLBCL), or myeloma.

32. The use of any of claims 6, 14 and 28-30, wherein the cancer is a non-hematological cancer or is a solid tumor.

33. The use of claim claim 6, claim 14, 28 or claim 29, wherein the cancer does not express a B cell antigen or is not a B cell malignancy, optionally wherein the cancer does not express CD19 and/or the T cell therapy does not comprise a recombinant receptor that specifically binds CD19 and/or the T cell therapy is a CAR-T cell therapy that does not comprise an anti-CD19 antigen-binding domain.

34. The use of any of claims 1-33, wherein the T cell therapy or genetically engineered T cells results in an increase in tryptophan levels and/or a decrease in kynurenine levels in the tumor or in a biological sample from the subject, optionally a serum, plasma or tumor sample, compared to a use of the T cell therapy but in the absence of the tryptophan metabolism and/or kynurenine pathway modulator.

35. The use of any of claims 1-34, wherein the use results in:
increased or prolonged expansion and/or persistence of T cells of the T cell therapy in the subject as compared to a use in which the T cell therapy is to be administered to the subject in the absence of the tryptophan metabolism and/or kynurenine pathway modulatory or a use in which a similar T cell is to be administered but in which the T cells do not comprise modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression; and/or
reduced expression or level of CD25 on the surface of the cells of the T cell therapy following said administration to the subject as compared to the expression or level in a use in which the T cell therapy is to be administered to the subject in the absence of the tryptophan metabolism and/or kynurenine pathway modulator or a use in which a similar T cell therapy is to be administered but in which the T cells do not comprise modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immuno-suppression.

36. The use of any of claims 1-35, wherein the tryptophan metabolism and/or kynurenine pathway modulator is formulated for administration in an amount from or from about

2.5 mg to about 5000 mg, 2.5 mg to 2000 mg, 2.5 mg to 1000 mg, 2.5 mg to 500 mg, 2.5 mg to 200 mg, 2.5 mg to 100 mg, 2.5 mg to 50 mg, 2.5 mg to 25 mg, 2.5 mg to 10 mg, 25 mg to 5000 mg, 25 mg to 2000 mg, 25 mg to 1000 mg, 25 mg to 500 mg, 25 mg to 200 mg, 25 mg to 100 mg, 25 mg to 50 mg, 50 mg to 5000 mg, 50 mg to 2000 mg, 50 mg to 1000 mg, 50 mg to 500 mg, 50 mg to 200 mg, 50 mg to 100 mg, 100 mg to 5000 mg, 100 mg to 2000 mg, 100 mg to 1000 mg, 100 mg to 500 mg, 100 mg to 200 mg, 200 mg to 5000 mg, 200 mg to 2000 mg, 200 mg to 1000 mg, 200 mg to 500 mg, 500 mg to 5000 mg, 500 mg to 2000 mg, 500 mg to 1000 mg or 1000 mg to 2000 mg, each inclusive; and/or at a total daily dosage amount of at least or at least about 5 mg/day, 10 mg/day, 25 mg/day, 50 mg/day, 100 mg/day, 200 mg/day, 400 mg/day, 500 mg/day, 600 mg/day, 800 mg/day, 1000 mg/day, 1200 mg/day, 1600 mg/day, 2000 mg/day, 5000 mg/day or 10000 mg/day.

37. The use of any of claims 1-36, wherein the use results in:
- an increase in tryptophan levels, a decrease in kynurenine levels and/or an decrease in expression or activity of IDO1, IDO2 or TDO in a biological sample from the subject compared to just prior to administration of the tryptophan metabolism and/or kynurenine pathway modulator or compared to just prior to initiation of administration of the T-cell therapy;
 - an increase in the number of cells of the T cell therapy detectable in the blood from the subject compared to in the subject at a preceding time point just prior to administration of the tryptophan metabolism and/or kynurenine pathway modulator or compared to a preceding time point after administration of the T-cell therapy;
 - the number of cells of the T cell therapy detectable in the blood being within 2.0-fold (greater or less) of the peak or maximum number of the cells of the T cell therapy detectable in the blood of the subject after initiation of administration of the T cell therapy;
 - the number of cells of the T cell therapy detectable in the blood from the subject being greater than or greater than about 10%, 15%, 20%, 30%, 40%, 50%, or 60% of total peripheral blood mononuclear cells (PBMCs) in the blood of the subject;
 - the concentration or number of engineered cells in the blood of the subject being (i) at least at or about 10 engineered cells per microliter, (ii) at least 20%, 30%, 40% or 50 % of the total number of peripheral blood mononuclear cells (PBMCs), (iii) at least or at least about 1 x

10^5 engineered cells; or (iv) the blood of the subject contains at least 5,000 copies of recombinant receptor-encoding DNA per micrograms DNA;

at day 90 following the initiation of the T cells, CAR-expressing cells are detectable in the blood or serum of the subject; and/or

at day 90 following the initiation of the T cells, the blood of the subject contains at least 20 % CAR-expressing cells, at least 10 CAR-expressing cells per microliter or at least 1×10^4 CAR-expressing cells.

38. The use of any of claims 1-37, wherein the T cell therapy comprises T cells that are CD4+ or CD8+, optionally wherein the cells are autologous to the subject or allogeneic to the subject.

39. The use of any of claims 1-38, wherein the T cell therapy or genetically engineered T cells are formulated for administration of a dose of recombinant receptor-expressing cells comprising between at or about 1×10^6 and at or about 3×10^8 , at or about 1×10^7 and at or about 2×10^8 total recombinant receptor-expressing cells, optionally 1×10^7 , 5×10^7 , 1×10^8 or 1.5×10^8 total recombinant receptor-expressing cells, or the range between any two of the foregoing values.

40. A method of selecting a subject having a disease or condition for administering a tryptophan metabolism and/or kynurenine pathway modulator, the method comprising:

(a) assessing the level of tryptophan or a tryptophan metabolite, the level of expression or activity of IDO1, IDO2 or TDO, or the level of interferon-gamma (IFN γ) in one or more biological samples from the subject, wherein the biological sample is obtained from a subject having been administered a T cell therapy; and

(b) selecting a subject in which:

(i) the level of tryptophan in the sample is below a threshold level or is decreased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy;

(ii) the level of the tryptophan metabolite is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy;

(iii) the level of expression or activity of IDO1, IDO2 or TDO is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy; or

(iv) the level of the IFN γ is above a threshold level or is increased compared to the level assessed at a time point prior to initiation of administration of the T cell therapy or a preceding time point after initiation of administration of the T cell therapy.

41. The method of claim 40, wherein the disease or condition is cancer.

42. The method of claim 40 or claim 41, wherein the T cell therapy comprises genetically engineered T cells comprising a recombinant receptor, optionally wherein the recombinant receptor is a chimeric antigen receptor (CAR) or a transgenic T cell receptor (TCR).

43. The method of any of claims 42, wherein the T cell therapy comprises T cells that are CD4⁺ or CD8⁺, optionally wherein the cells are autologous to the subject or allogeneic to the subject.

44. The method of any of claims 40-43, wherein the tryptophan metabolism and/or kynurenine pathway modulator is selected from among an antagonist of the enzyme kynureninase; an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), IDO2 and tryptophan 2,3-dioxygenase (TDO); tryptophan; an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) and/or a dual-acting IDO/TDO inhibitor.

45. The method of any of claims 40-44, wherein the tryptophan metabolism and/or kynurenine pathway modulator is selected from 1-methyl-D-tryptophan (1-MT) (indoximod), 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-

oxadiazole-3-carboximidamide (INCB024360, epacadostat), 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-chloro-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N'-hydroxy-N-[3-(trifluoromethyl)phenyl]-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-cyano-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-bromo-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-chloro-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, 1-cyclohexyl-2-(5H-imidazo[5,1-a]isoindol-5-yl)ethanol (NLG919), GDC-0919, F001287, PF-06840003 or pharmaceutically acceptable salt or prodrug thereof or a combination thereof.

46. The method of any of claims 40-45, wherein the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

47. An engineered cell, comprising:
(a) a recombinant receptor that specifically binds to a ligand; and
(b) a modification in expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immunosuppression in the cell.

48. An engineered cell, comprising:
(a) a recombinant receptor that specifically binds to a ligand; and
(b) a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof, optionally wherein the amino acid transporter is a tryptophan transporter.

49. The engineered cell of any of claims 47, wherein:

the engineered cell comprises an inhibitory nucleic acid, optionally wherein the inhibitory nucleic acid comprises an RNA interfering agent that reduces expression of the molecule; or

the engineered cell comprises a genetic disruption in the gene encoding the molecule that reduces expression of the molecule, optionally wherein the disruption comprises introducing an agent into the cell comprising a zinc finger nuclease (ZFN), a TAL-effector nuclease (TALEN), or a CRISPR-Cas9 combination that specifically binds to, recognizes, or hybridizes to the gene encoding the molecule.

50. The engineered cell of any of claims 47-49, wherein the cell is a T cell, optionally wherein the T cell is a CD8⁺ T cell or a CD4⁺ T cell; a natural killer (NK) cell and/or an iPS-derived cell.

51. The engineered cell of any of claims 47-50, wherein the recombinant receptor that specifically binds to a ligand is a chimeric antigen receptor (CAR) or a transgenic T cell receptor (TCR).

52. The engineered cell of claim 51, wherein the recombinant receptor is a CAR and the CAR comprises an extracellular antigen-recognition domain that specifically binds to the antigen and an intracellular signaling region comprising an ITAM, optionally wherein the intracellular signaling region comprises an intracellular domain of a CD3-zeta (CD3 ζ) chain.

53. The engineered cell of claim 52, wherein the CAR further comprises a costimulatory signaling region, optionally wherein the costimulatory signaling region comprises a signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof.

54. A composition comprising the engineered cell of any of claims 47-53.

55. A combination, comprising:

genetically engineered cells expressing a recombinant receptor that binds to a ligand, wherein the recombinant receptor optionally is a chimeric antigen receptor (CAR) or a transgenic T cell receptor (TCR); and

a tryptophan metabolism and/or kynurenine pathway modulator.

56. A combination, comprising:

the engineered cells of any of claims 47-53 or the composition of claim 54; and

a tryptophan metabolism and/or kynurenine pathway modulator.

57. The combination of claim 55 or claim 56, wherein the tryptophan metabolism and/or kynurenine pathway modulator is selected from among an antagonist of the enzyme kynureninase; an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), IDO2 and tryptophan 2,3-dioxygenase (TDO); tryptophan; an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) and/or a dual-acting IDO/TDO inhibitor.

58. The combination of any of claims 55-57, wherein the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).

59. A method of engineering immune cells expressing a recombinant receptor, comprising:

contacting a population of cells comprising immune cells with a tryptophan metabolism and/or kynurenine pathway modulator; and

introducing a nucleic acid encoding a recombinant receptor into the population of cells under conditions such that the recombinant receptor is expressed.

60. A method of engineering immune cells expressing a recombinant receptor, wherein the method is selected from:

(A) a method comprising:

(i) introducing a first nucleic acid sequence encoding a recombinant receptor into a population of cells under conditions such that the recombinant receptor is expressed; and
(ii) introducing one or more second nucleic acid sequence(s) encoding an agent capable of or involved in modification of expression of a molecule associated with IDO-mediated immunosuppressive signaling, associated with sensing or responding to tryptophan starvation or insufficiency and/or associated with sensing or responding to kynurenine-mediated immunosuppression in the cell into the population of cells under conditions such that the agent is expressed; and/or

(B) a method comprising:

(i) introducing a first nucleic acid sequence encoding a recombinant receptor into a population of cells under conditions such that the recombinant receptor is expressed; and
(ii) introducing one or more second nucleic acid sequence(s) encoding a recombinant, engineered and/or ectopically expressed amino acid transporter or chain thereof or a functional and/or catalytically active portion or variant thereof.

61. The method of claim 59 or claim 60, wherein the recombinant receptor is a T cell receptor (TCR) or a chimeric antigen receptor (CAR).

62. The method of any of claims 59-61, wherein the population of cells is or comprises T cells, optionally wherein the T cells are CD4+ and/or CD8+, optionally wherein the population of cells are isolated from a subject, optionally a human subject.

63. The method of any of claims 59-62, wherein the tryptophan metabolism and/or kynurenine pathway modulator is selected from among an antagonist of the enzyme kynureninase; an inhibitor of one or more enzymes selected from the group consisting of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1), IDO2 and tryptophan 2,3-dioxygenase (TDO); tryptophan; an inhibitor of indoleamine-pyrrole 2,3-dioxygenase 1 (IDO1) and/or a dual-acting IDO/TDO inhibitor.

64. The method of any of claims 59-63, wherein the tryptophan metabolism and/or kynurenine pathway modulator is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide (INCB024360, epacadostat).