## SUMMARY

**[0008]** The disclosure is directed, at least in part, to T-cells expressing an amino acid transporter protein, for example, an arginine transporter protein, and a CAR that specifically binds a cell surface antigen on a target cell. Such CAR-T cells are useful for the treatment of malignancies such as cancer. Genetically modified T-cells and expression vectors described herein may have enhanced robustness and/or survival in a tumor microenvironment and resource-depleted, for example, arginine-depleted, microenvironments, as compared to, for example, T-cell populations not subject to genetic modification. The described genetically modified T-cells and expression vectors are useful for treating cancers and other diseases that require targeting of T-cells to a specific cell population.

**[0008a]** In one aspect, the present disclosure provides a genetically modified T-cell genetically modified to express: a) a recombinant arginine transporter and b) a chimeric antigen receptor having at least one antigen-specific targeting region that specifically binds a cell surface antigen present on a target cell population, a transmembrane domain, and an intracellular signaling domain.

**[0009]** In another example, the disclosure is directed, to genetically modified T-cells expressing an amino acid transporter, for example, an arginine transporter. The amino acid transporter can be the product of a recombinant amino acid transporter nucleotide sequence. T-cells described herein that are genetically modified to express or overexpress an amino acid transporter may have enhanced robustness and/or survival in a tumor microenvironment and resource-depleted, for example, arginine-depleted, microenvironments, as compared to, for example, T-cell populations not genetically modified to express or overexpress the amino acid transporter. The described genetically modified T-cells and expression vectors are useful for treating cancers and other diseases that require targeting of T-cells to a specific cell population or which require enhanced robustness of T-cells in order to survive in a biological environment depleted of one or more amino acids, for example, arginine.

**[0010]** In one example, disclosed herein is a genetically modified T-cell that is genetically modified to express an arginine transporter and a chimeric antigen receptor (CAR). In some examples, the CAR has at least one antigen-specific targeting region that specifically binds a cell surface antigen present on a target cell population, a transmembrane domain, and an intracellular signaling domain. In some examples, the CAR has at least an antigen-specific targeting region that specifically binds a cell surface antigen present on a target cell population, a transmembrane domain, at least one co-stimulatory domain, and an intracellular signaling domain.

**[0011]** Also described herein are expression vectors that include nucleotide sequences encoding a CAR and/or an amino acid transporter, for example, an arginine transporter. In some examples, transcription of expression vectors described herein results in producing a ribonucleic acid (RNA), for example a messenger RNA (mRNA) sequence encoding a CAR and/or an amino acid transporter, for example, an arginine transporter nucleotide sequence. In some examples, expression vectors described herein are capable of expressing a CAR and/or an amino acid transporter, for example, an arginine transporter. In another aspect, described herein is an expression vector comprising an isolated nucleic acid sequence encoding an antigen-specific targeting region, a transmembrane domain, optionally, at least one co-stimulatory domain, an intracellular signaling domain, and an arginine transporter. In some examples described herein is an expression vector comprising an isolated nucleic acid sequence encoding an antigen-specific targeting region, a transmembrane domain, optionally, at least one co-stimulatory domain, and an intracellular signaling domain. In some examples described herein is an expression vector comprising an isolated nucleic acid sequence encoding an arginine transporter. In some examples described herein is an expression vector comprising an isolated nucleic acid sequence encoding an antigen-specific targeting region, a transmembrane domain, optionally at least one co-stimulatory domain, an intracellular signaling domain, and an amino acid transporter. In some examples described herein is an expression vector comprising an isolated nucleic acid sequence encoding an amino acid transporter.

**[0012]** Also described herein are expression vectors that include nucleotide sequences encoding an amino acid transporter, for example, an arginine transporter. In some examples, transcription of expression vectors described herein results in producing a ribonucleic acid (RNA), for example a messenger RNA (mRNA) sequence encoding an amino acid transporter, for example, an arginine transporter nucleotide sequence. In some examples, expression vectors described herein are capable of expressing an amino acid transporter, for example, an arginine transporter. In some examples described herein is an expression vector comprising an isolated nucleic acid sequence encoding an arginine transporter. In some examples described herein is an expression vector comprising an isolated nucleic acid sequence encoding an arginine transporter. In some examples described herein is an expression vector comprising an isolated nucleic acid sequence

encoding an amino acid transporter. In some examples described herein is an expression vector comprising an isolated nucleic acid sequence encoding an amino acid transporter. In examples described herein, a nucleic acid sequence can be, for example, a ribonucleic acid (RNA) sequence, a deoxyribonucleic acid (DNA) sequence, or a mixed DNA and RNA sequence.

**[0013]** In some examples, an expression vector described herein comprises a nucleotide sequence encoding a CAR and an amino acid transporter, wherein the CAR and the amino acid transporter nucleotide sequences are transcribed into separate mRNA transcripts. In some examples, an expression vector described herein comprises a nucleotide sequence encoding a CAR and an amino acid transporter, wherein the CAR and the amino acid transporter nucleotide sequences are transcribed together into a single mRNA transcript. In examples wherein the CAR and the amino acid transporter nucleotide sequences are transcribed together into a single mRNA transcript, the expression vector nucleotide sequence encoding the CAR and the amino acid transporter mRNA transcript can include an internal ribosome entry sequence (IRES). In some examples, the IRES is disposed between the portion of the nucleotide sequence encoding the CAR and the portion of the nucleotide sequence encoding the amino acid transporter. Thus, in examples, a CAR nucleotide sequence and an amino acid transporter nucleotide sequence are separated by an IRES sequence. In examples wherein the CAR and the amino acid transporter nucleotide sequences are transcribed together into a single mRNA transcript, the expression vector nucleotide sequence encoding the CAR and the amino acid transporter mRNA transcript may include a 2A self-cleavage sequence disposed between the portion of the nucleotide sequence encoding the CAR and the portion of the nucleotide sequence encoding the amino acid transporter. Thus, in some examples, a CAR nucleotide sequence and an amino acid transporter nucleotide sequence are separated by a 2A self-cleavage sequence. In some examples, a peptide translated from an mRNA that includes a CAR nucleotide sequence, a 2A self-cleavage sequence, and an amino acid transporter nucleotide sequence, is cleaved after translation at the 2A self-cleavage site.

**[0014]** In another aspect, also described herein is a genetically modified T-cell modified to express a CAR encoded by an expression vector. Also described herein is a genetically modified T-cell modified to express a CAR and an amino acid transporter, for example, an arginine transporter, encoded by an expression vector. Also described herein is a genetically modified T-cell modified to express an

amino acid transporter, for example, an arginine transporter encoded by an expression vector. Also described herein is a genetically modified T-cell modified to express a CAR encoded by a first expression vector and an amino acid transporter, for example, an arginine transporter encoded by a second expression vector. In examples described herein, a CAR encoded by an expression vector can include an antigen-specific targeting region, a transmembrane domain, optionally at least one co-stimulatory domain, and an intracellular signaling domain. A genetically modified T-cell modified to express an amino acid transporter, for example, an arginine transporter, encoded by an expression vector can include a genetically modified T-cell modified to express a recombinant amino acid transporter, for example, a recombinant arginine transporter.

**[0015]** Also described herein is a genetically modified T-cell modified to express a CAR encoded by a virus-derived transgene. Also described herein is a genetically modified T-cell modified to express a CAR and an amino acid transporter, for example, an arginine transporter, encoded by a virus-derived transgene. Also described herein is a genetically modified T-cell modified to express an amino acid transporter, for example, an arginine transporter encoded by a virus-derived transgene. Also described herein is a genetically modified T-cell modified to express a CAR encoded by a first virus-derived transgene and an amino acid transporter, for example, an arginine transporter encoded by a second virus-derived transgene. In examples described herein, a CAR encoded by a virus-derived transgene can include an antigen-specific targeting region, a transmembrane domain, optionally at least one co-stimulatory domain, and an intracellular signaling domain. A genetically modified T-cell modified to express an amino acid transporter, for example, an arginine transporter, encoded by a virus-derived transgene can include a genetically modified T-cell modified to express a recombinant amino acid transporter, for example, a recombinant arginine transporter.

**[0016]** A genetically modified T-cell described herein can express a specific arginine transporter. In some examples, an arginine transporter comprises a single arginine transporter protein. In some examples, an arginine transporter comprises two arginine transporter proteins. For example, a genetically modified T-cell described herein can express an arginine transporter selected from the group consisting of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1, 4F2hc, $y^+$LAT2,

$y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT, rBAT, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$, or a combination thereof.

**[0017]** In some examples, an expression vector described herein comprises an isolated nucleic acid sequence encoding an arginine transporter. In some examples, an expression vector described herein comprises two or more isolated nucleic acid sequences encoding proteins that together comprise an arginine transporter. In some examples, the arginine transporter nucleic acid sequence or sequences is selected from the group consisting of the nucleic acid sequence or sequences of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1, 4F2hc, $y^+$LAT2, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT, rBAT, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$, or a combination thereof.

**[0018]** In some examples, a virus-derived transgene described herein comprises an isolated nucleic acid sequence encoding an arginine transporter. In some examples, a virus-derived transgene described herein comprises two or more isolated nucleic acid sequences encoding proteins that together comprise an arginine transporter. In some examples, the arginine transporter nucleic acid sequence or sequences is selected from the group consisting of the nucleic acid sequence or sequences of selected from the group consisting of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1, 4F2hc, $y^+$LAT2, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT, rBAT, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$, or a combination thereof.

**[0019]** Also described herein are expression vectors that include a nucleic acid sequence encoding an amino acid transporter sequence and genetically modified T-cells comprising a recombinant nucleic acid sequence encoding an amino acid transporter. For example, described herein is an expression vector comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof. Also described herein is an expression vector comprising the nucleotide sequence of any one of SEQ ID NO:220-222 and the nucleotide sequence of any one of SEQ ID NO:227-230. Also described herein is an expression vector comprising the nucleotide sequence of any one of SEQ ID NO:214 and 215 and the nucleotide sequence of any one of SEQ ID NO:227-230. Also described herein is an expression vector comprising the nucleotide sequence of any one of SEQ ID NO:234-236 and the nucleotide sequence of SEQ ID NO:242.

**[0020]** Also described herein is a genetically modified T-cell comprising a recombinant nucleic acid sequence comprising a sequence selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof. Also described herein is a genetically modified T-cell comprising a recombinant nucleic acid comprising the nucleotide sequence of any one of SEQ ID NO:220-222 and the nucleotide sequence of any one of SEQ ID NO:227-230. Also described herein is a genetically modified T-cell comprising a recombinant nucleic acid comprising the nucleotide sequence of any one of SEQ ID NO:214 and 215 and the nucleotide sequence of any one of SEQ ID NO:227-230. Also described herein is a genetically modified T-cell comprising a recombinant nucleic acid comprising the nucleotide sequence of any one of SEQ ID NO:234-236 and the nucleotide sequence of SEQ ID NO:242.

**[0021]** In some examples, a genetically modified T-cell described herein is genetically modified to comprise a recombinant nucleic acid sequence comprising a sequence selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof. For example, in some examples, a genetically modified T-cell described herein is modified to comprise one or more additional copies of a nucleic acid sequence selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof. Also described herein is a genetically modified T-cell comprising an expression vector comprising a nucleic acid sequence selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof. In some examples, an expression vector, a genetically modified T-cell, or a genetically modified T-cell comprising an expression vector described herein comprises a combination of nucleic acid sequences selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof. In some examples described herein, an expression vector, a genetically modified T-cell comprising a recombinant nucleic acid sequence, a genetically modified T-cell that is genetically modified to comprise a recombinant nucleic acid sequence, a genetically modified T-cell that is modified to comprise one or more additional copies of a nucleic acid sequence, or a genetically modified T-cell comprising an

expression vector comprising a nucleic acid sequence, comprises at least two nucleic acid sequences selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof. For example, in some examples described herein, an expression vector, a genetically modified T-cell comprising a recombinant nucleic acid sequence, a genetically modified T-cell that is genetically modified to comprise a recombinant nucleic acid sequence, a genetically modified T-cell that is modified to comprise one or more additional copies of a nucleic acid sequence, or a genetically modified T-cell comprising an expression vector comprising a nucleic acid sequence, comprises one of the following pairs of nucleotide sequences: the nucleotide sequence of any one of SEQ ID NO:220-222 and the nucleotide sequence of any one of SEQ ID NO:227-230; the nucleotide sequence of any one of SEQ ID NO:214 and 215 and the nucleotide sequence of any one of SEQ ID NO:227-230; or the nucleotide sequence of any one of SEQ ID NO:234-236 and the nucleotide sequence of SEQ ID NO:242.

**[0022]** A genetically modified T-cell described herein can include a recombinant nucleic acid sequence that shares similarity with a nucleic acid sequence of one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246. For example, in some examples, a genetically modified T-cell described herein, comprises a nucleic acid sequence having about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, from about 90% to about 95%, from about 95% to about 99%, or from about 90% to about 99% percent identity to one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246. In some examples, a genetically modified T-cell described herein, comprises a nucleic acid sequence having about 90%, 95%, or 99% percent identity to one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246. In some examples, a genetically modified T-cell described herein, comprises an expression vector that comprises a nucleic acid sequence having about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, from about 90% to about 95%, from about 95% to about 99%, or from about 90% to about 99% percent identity to one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246. In some examples, a genetically modified T-cell described herein, comprises an expression vector that comprises a nucleic acid sequence having about 90%, 95%, or 99% percent

identity to one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246.

**[0023]** In another aspect, described herein is a pharmaceutically acceptable composition comprising a genetically modified T-cell described herein and a pharmaceutically acceptable excipient.

**[0024]** Also described herein is a priming medium comprising L-arginine for priming a genetically modified T-cell, for example, a genetically modified T-cell described herein. A priming medium described herein can increase intracellular arginine concentration in a genetically modified T-cell, for example, a genetically modified T-cell expressing an arginine transporter. A priming medium described herein can prime genetically modified T-cells for treatment. For example, a priming medium described herein can increase intracellular arginine concentration in genetically modified T-cells prior to administration of the genetically modified T-cells to a patient in need thereof, for example, a patient in need of treatment of a cancer. In another aspect, described herein is a priming medium comprising a genetically modified T-cell described herein and L-arginine.

**[0025]** Also described herein are pharmaceutical compositions comprising CAR-T cells. In a further aspect, described herein is a pharmaceutical composition comprising a CAR-T cell which expresses a recombinant arginine transporter and a chimeric antigen receptor protein. In some examples, a pharmaceutical composition of the disclosure comprises a CAR-T cell, wherein the CAR-T cell comprises one or more expression vectors that comprise a nucleic acid sequence encoding an arginine transporter and/or a chimeric antigen receptor protein. In some examples, a pharmaceutical composition described herein comprises a CAR-T cell which expresses an arginine transporter. In some examples, a pharmaceutical composition of the disclosure comprises a CAR-T cell, wherein the CAR-T cell comprises one or more recombinant nucleic acid sequences encoding an arginine transporter and/or a chimeric antigen receptor protein. In some examples, a pharmaceutical composition described herein comprises a CAR-T cell which expresses an arginine transporter, for example, a recombinant protein arginine transporter. In various examples, the arginine transporter is selected from the group consisting of CAT-1,

CAT-2, CAT-3, CAT-4, $y^+$LAT1, 4F2hc, $y^+$LAT2, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT, rBAT, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$, or a combination thereof. In some examples, the one or more nucleic acid sequences encoding an arginine transporter comprises one or more recombinant arginine transporter nucleic acid sequences, for example a recombinant CAT-1 nucleic acid sequence, a recombinant CAT-2 nucleic acid sequence, a recombinant CAT-3 nucleic acid sequence, a recombinant CAT-4 nucleic acid sequence, a recombinant $y^+$LAT1 nucleic acid sequence, a recombinant 4F2hc nucleic acid sequence, a recombinant $y^+$LAT2 nucleic acid sequence, a recombinant $y^+$LAT1 nucleic acid sequence and a recombinant 4F2hc nucleic acid sequence, a recombinant $y^+$LAT2 nucleic acid sequence and a recombinant 4F2hc nucleic acid sequence, a recombinant $b^{0,+}$AT nucleic acid sequence, a recombinant rBAT nucleic acid sequence, a recombinant $b^{0,+}$AT nucleic acid sequence and a recombinant rBAT nucleic acid sequence, or a recombinant $ATB^{0,+}$ nucleic acid sequence. In some examples, the arginine transporter is a recombinant arginine transporter protein, for example, a recombinant CAT-1, a recombinant CAT-2, a recombinant CAT-3, a recombinant CAT-4, a recombinant $y^+$LAT1, a recombinant 4F2hc, a recombinant $y^+$LAT2, a recombinant $y^+$LAT1 and a recombinant 4F2hc, a recombinant $y^+$LAT2 and a recombinant 4F2hc, a recombinant $b^{0,+}$AT, a recombinant rBAT, a recombinant $b^{0,+}$AT and a recombinant rBAT, or a recombinant $ATB^{0,+}$.

**[0026]** In another example, a pharmaceutical composition described herein is packaged as a kit. For example, in some examples, a pharmaceutical composition comprising a CAR-T cell which expresses an arginine transporter and a chimeric antigen receptor protein (for example, a genetically modified CAR-T cell which expresses an arginine transporter and a chimeric antigen receptor protein) is packaged as a kit. In some examples, a pharmaceutical composition comprising a T-cell which expresses an arginine transporter (for example, a genetically modified T-cell which expresses an arginine transporter, for example, a recombinant arginine transporter protein) is packaged as a kit. A kit described herein can include instructions for administering the CAR-T cells to a patient in need of treatment. A kit described herein can include instructions for priming CAR-T cells for administration to a patient in need of treatment. In some examples, the kit may include at least one of buffers (for example, a buffer comprising levels of L-arginine sufficient for priming T-cells), reagents and detailed instructions for producing, administering, and/or priming CAR-T

cells. In some examples, a kit described herein can include agents for producing CAR-T cells, including expression vectors, viral constructs, cells, transfection reagents and media, agents for cell selection (for example, antibodies), and/or growth media.

**[0026a]** In a further aspect, the present disclosure provides a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating a solid tumor cancer in a patient in need thereof. In a further aspect, the present disclosure provides a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating a hematological cancer in a patient in need thereof. In a further aspect, the present disclosure provides a use of the pharmaceutical composition as described herein in the manufacture of a medicament for modulating intracellular arginine levels to effect a T cell-mediated immune response in a patient in need thereof. In a further aspect, the present disclosure provides a use of composition comprising a chimeric antigen receptor T cell (CAR-T cell) which expresses a recombinant arginine transporter and a chimeric antigen receptor protein in the manufacture of a medicament for treating a condition in a human patient in need thereof. In a further aspect, the present disclosure provides a use of T-cells that are a) genetically modified to express a chimeric antigen receptor wherein the chimeric antigen receptor comprises: at least one antigen-specific targeting region that specifically binds the cell surface antigen present on the target cell population, a transmembrane domain, an intracellular signaling domain, and b) genetically modified to express a recombinant arginine transporter in the manufacture of a medicament for modulating a T cell-mediated immune response to a target cell population expressing a cell surface antigen in a patient in need thereof. In a further aspect, the present disclosure provides a use of a composition comprising a T cell which expresses a recombinant arginine transporter in the manufacture of a medicament for treating a condition in a human patient in need thereof.

**[0027]** Also described herein are methods of treating cancer using a pharmaceutical composition described herein. For example, described herein is a method of treating a solid tumor cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of a pharmaceutical composition described herein. For example, described herein is a method of treating a solid tumor cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of a pharmaceutical composition comprising a

genetically modified T-cell described herein (for example, a CAR-T cell or a T-cell genetically modified to express an amino acid transporter) and a pharmaceutically acceptable excipient.

**[0028]** Also described herein are methods of treating a hematological cancer using a pharmaceutical composition described herein. For example, described herein is a method of treating a hematological cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of a pharmaceutical composition described herein. For example, described herein is a method of treating a hematological cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of a pharmaceutical composition comprising a genetically modified T-cell described herein (for example, a CAR-T cell or a T-cell genetically modified to express an amino acid transporter) and a pharmaceutically acceptable excipient.

**[0029]** Also described herein are methods of modulating intracellular arginine levels (for example, intracellular T-cell arginine levels) to effect a T cell-mediated immune response in a patient in need of treatment. For example, described herein is a method of modulating intracellular arginine levels to effect a T cell-mediated immune response in a patient in need thereof, the method comprising modulating intracellular arginine levels of a genetically modified T-cell. In some examples, the method of modulating intracellular arginine levels to effect a T cell-mediated immune response in a patient in need thereof further comprises administering to the patient an effective amount of a pharmaceutical composition described herein (*e.g.*, a pharmaceutical

composition comprising a genetically modified T-cell described herein and a pharmaceutically acceptable excipient, wherein the genetically modified T-cell has been subjected to conditions effective to increase intracellular arginine levels). In some examples, the method of modulating intracellular arginine levels to effect a T cell-mediated immune response in a patient in need thereof comprises modulating intracellular arginine levels of a genetically modified T-cell and administering to the patient an effective amount of a pharmaceutical composition comprising the genetically modified T-cells and a pharmaceutically acceptable excipient.

**[0030]** In yet another example, described herein is a method for treating a condition in a human patient in need thereof, the method comprising: administering to the human patient a therapeutically effective amount of a composition comprising a CAR-T cell (for example, a genetically modified CAR-T cell) which expresses an arginine transporter (for example, a recombinant arginine transporter) and a chimeric antigen receptor protein. In some examples, a method for treating a condition in a human patient in need thereof comprises administering to the human patient a therapeutically effective amount of a composition comprising a CAR-T cell described herein, for example, a genetically modified CAR-T cell described herein. For example, in some examples, a method for treating a condition in a human patient in need thereof comprises administering to the human patient a therapeutically effective amount of a composition comprising a CAR-T cell wherein the CAR-T cell comprises one or more recombinant nucleic acid sequences encoding an arginine transporter and/or a chimeric antigen receptor protein. In some examples described herein, a method for treating a condition in a human patient in need thereof comprises administering to the human patient a therapeutically effective amount of a composition comprising a genetically modified T cell that is genetically modified to express or overexpress an amino acid transporter, for example, an arginine transporter.

**[0031]** Also described herein is a method for modulating a T-cell-mediated immune response to a target cell population expressing a cell surface antigen in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of genetically modified T-cells. In some examples the T-cells are: a) genetically modified to express a chimeric antigen receptor, wherein the chimeric antigen receptor comprises: at least one antigen-specific targeting region that specifically binds the cell surface antigen present on the target cell population, a

transmembrane domain, an intracellular signaling domain; and b) genetically modified to express an arginine transporter (for example, a recombinant arginine transporter). In some examples the T-cells are genetically modified to express an arginine transporter (for example, a recombinant arginine transporter). For example, in some examples a T-cell for administering comprises one or more recombinant nucleic acid sequences encoding a chimeric antigen receptor, wherein the chimeric antigen receptor comprises: at least one antigen-specific targeting region that specifically binds the cell surface antigen present on the target cell population, a transmembrane domain, an intracellular signaling domain; and an arginine transporter. In some examples a T-cell for administering comprises a recombinant chimeric antigen receptor protein, wherein the recombinant chimeric antigen receptor protein comprises: at least one antigen-specific targeting region that specifically binds the cell surface antigen present on the target cell population, a transmembrane domain, an intracellular signaling domain; and a recombinant arginine transporter protein. In some examples a T-cell for administering comprises one or more recombinant nucleic acid sequences encoding an arginine transporter. In some examples a T-cell for administering comprises a recombinant arginine transporter protein.

**[0032]** In another example, the disclosure relates to a method of increasing T cell survival in a low arginine environment, the method comprising: administering a T cell comprising a recombinant arginine transporter to a low arginine environment. In certain examples, prior to the administering step, the method comprises transfecting the T cell with a DNA construct comprising a nucleotide sequence encoding the recombinant arginine transporter. In certain examples, the T-cell comprises a chimeric antigen receptor and/or comprises a DNA construct comprising a nucleotide sequence encoding a chimeric antigen receptor. In certain examples, the T cell is a CAR-T cell. In certain examples, prior to the administering step, the method comprises culturing the T cell or the CAR-T cell in a culture medium comprising arginine, for example, until the intracellular arginine level of the T cell or CAR-T cell accumulates to a certain level. In certain examples, the low arginine environment is a cell culture medium. In certain examples, the low arginine environment is a tumor microenvironment.

**[0033]** In examples described herein, a disclosed method can include a step of culturing T-cells in a culture medium comprising arginine before administering (for example, administering to a

patient in need of treatment). For example, described herein is a method for treating a condition in a human patient in need thereof, the method comprising: culturing T-cells in a culture medium comprising arginine before administering a therapeutically effective amount of a composition comprising the T-cells to the human patient. Also described herein is a method for modulating a T cell-mediated immune response to a target cell population expressing a cell surface antigen in a patient in need thereof, the method comprising: culturing genetically modified T-cells in a culture medium comprising arginine before administering to the patient a therapeutically effective amount of the T-cells.

**[0034]** In a method described herein, the arginine transporter is selected from the group consisting of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1, 4F2hc, $y^+$LAT2, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT, rBAT, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$, or a combination thereof. For example, described herein is a method for treating a condition in a human patient in need thereof, the method comprising: administering to the human patient a therapeutically effective amount of a composition comprising a CAR-T cell which expresses a chimeric antigen receptor protein and an arginine transporter (for example, a recombinant arginine transporter) selected from the group consisting of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1, 4F2hc, $y^+$LAT2, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT, rBAT, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$, or a combination thereof. Also described herein is a method for modulating a T cell-mediated immune response to a target cell population expressing a cell surface antigen in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of T-cells genetically modified to express a chimeric antigen receptor and an arginine transporter (for example, a recombinant arginine transporter) selected from the group consisting of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1, 4F2hc, $y^+$LAT2, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT, rBAT, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$, or a combination thereof. In some examples, the arginine transporter is a recombinant arginine transporter protein, for example a recombinant CAT-1, a recombinant CAT-2, a recombinant CAT-3, a recombinant CAT-4, a recombinant $y^+$LAT1, a recombinant 4F2hc, a recombinant $y^+$LAT2, a recombinant $y^+$LAT1 and a recombinant 4F2hc, a recombinant $y^+$LAT2 and a recombinant 4F2hc, a recombinant $b^{0,+}$AT, a recombinant rBAT, a recombinant $b^{0,+}$AT and a recombinant rBAT, or a recombinant $ATB^{0,+}$. In certain examples, the arginine transporter

comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof. In certain examples, the arginine transporter comprises a nucleic acid expressing a sequence having about 90%, 95%, or 99% percent identity to one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246.

**[0035]** In some examples, the method further comprises administering a second therapeutic agent to the human patient. For example, described herein are methods for treating a condition in a human patient in need thereof, the methods comprising administering a therapeutically effective amount of a composition comprising a CAR-T cell and administering a second therapeutic agent to the human patient. In some examples, a method described herein comprises administering the second therapeutic agent before, during, or after the administering of a composition comprising a CAR-T cell. Also described herein are methods for modulating a T cell-mediated immune response to a target cell population expressing a cell surface antigen in a patient in need thereof, the methods comprising administering to the patient a therapeutically effective amount of genetically modified T-cells and administering a second therapeutic agent to the human patient. In some examples, a method described herein comprises administering the second therapeutic agent before, during or after the administering of a therapeutically effective amount of T-cells.

**[0036]** In some examples, the second therapeutic agent is a checkpoint protein inhibitor, for example, a checkpoint protein inhibitor that inhibits checkpoint protein activity or checkpoint protein signaling, for example, an antibody that inhibits a checkpoint protein or checkpoint protein signaling. For example, in some examples, the second therapeutic agent is an anti-PD-1 antibody, an anti-PD-L1 antibody, or an anti-CTLA-4 antibody. In some examples, the second therapeutic agent is a DNA damage and repair inhibitor. For example, in some examples, the DNA damage and repair inhibitor is an ATM/ATR inhibitor, a PARP inhibitor, a WEE1 inhibitor, a Chk1 inhibitor, a Chk2 inhibitor, or a DNA-dependent protein kinase (DNA-PK) inhibitor.

**[0037]** In examples described herein, a composition comprising CAR-T cells is administered to a human patient once every week, once every 2 weeks, once every 3 weeks, or once every 4 weeks. For example, described herein is a method for treating a condition in a human

patient in need thereof, the method comprising administering to the human patient a therapeutically effective amount of a composition comprising a CAR-T cell once every week, once every 2 weeks, once every 3 weeks, or once every 4 weeks. Also described herein is a method for modulating a T cell-mediated immune response to a target cell population expressing a cell surface antigen in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of genetically modified T-cells once every week, once every 2 weeks, once every 3 weeks, or once every 4 weeks.

**[0038]** In some examples, the methods described herein comprise administering a specified number of CAR-T cells based on the weight of the patient or a specified range of CAR-T cells based on the weight of the patient. In some examples, a method described herein comprises administering about $10^2$, about $10^3$, about $10^4$, about $10^5$, about $10^6$, about $10^7$, about $10^8$, about $10^9$, about $10^{10}$, about $10^{11}$, about $10^{12}$, about $10^{13}$, about $10^{14}$, about $10^{15}$, about $10^{16}$, about $10^{17}$, about $10^{18}$, about $10^{19}$, about $10^{20}$, about $10^{25}$, about $10^{30}$, about $10^{35}$, about $10^{40}$, about $10^{45}$, or about $10^{50}$ CAR-T cells per kilogram of the patient. In some examples, a method described herein comprises administering about $10^2$ to $10^7$, about $10^2$ to $10^{10}$, about $10^3$ to $10^{10}$, about $10^4$ to $10^{10}$, about $10^5$ to $10^{10}$, about $10^6$ to $10^{10}$, about $10^7$ to $10^{10}$, about $10^8$ to $10^{11}$, about $10^9$ to $10^{12}$, about $10^{10}$ to $10^{13}$, about $10^7$ to $10^{15}$, about $10^5$ to $10^{15}$, about $10^{10}$ to $10^{20}$, about $10^{10}$ to $10^{25}$, about $10^{10}$ to $10^{30}$, about $10^7$ to $10^{20}$, about $10^7$ to $10^{25}$, about $10^{10}$ to $10^{50}$, or about $10^7$ to $10^{50}$ CAR-T cells per kilogram of the patient. For example, in some examples, a method described herein comprises administering about $10^7$ to $10^{10}$ CAR-T cells per kilogram of the patient.

**[0039]** Another aspect of the disclosure includes a method of making a genetically modified CAR-T cell that expresses a recombinant arginine transporter, the method comprising: transfecting a T-cell with a DNA construct comprising a nucleotide sequence for a specific chimeric antigen receptor and for an arginine transporter thereby producing a genetically modified CAR-T cell that expresses both the chimeric antigen receptor and the arginine transporter; and culturing the genetically modified CAR-T cell in a culture medium comprising arginine. Examples described herein also include a method of making a genetically modified CAR-T cell that expresses an arginine transporter, the method comprising: transducing a T-cell with a virus that includes a nucleotide construct comprising a nucleotide sequence for a specific chimeric antigen receptor and for an arginine

transporter thereby producing a genetically modified CAR-T cell that expresses both the chimeric antigen receptor and the arginine transporter; and culturing the genetically modified CAR-T cell in a culture medium comprising arginine. In yet another aspect, the present disclosure provides a genetically modified T-cell genetically modified to express a recombinant arginine transporter. In yet another aspect, the present disclosure provides a pharmaceutical composition comprising a T cell which expresses a recombinant arginine transporter protein. In some examples, the genetically modified CAR-T cell expresses a recombinant arginine transporter nucleotide sequence. In some examples, the genetically modified CAR-T cell expresses a recombinant arginine transporter protein. In some examples, culturing comprises culturing the genetically modified CAR-T cell in the culture medium until the intracellular arginine level of the CAR-T cell accumulates to a certain level. In some examples, the intracellular arginine level of the CAR-T cell is an intracellular arginine level that allows the CAR-T cell to survive in a tumor microenvironment. For example, in some examples, culturing comprises culturing the genetically modified CAR-T cell in the culture medium until the intracellular arginine level of the CAR-T cell is about 500 μM, about 600 μM, about 700 μM, about 800 μM, about 900 μM, about 1,000 μM, about 1,100 μM, about 1,200 μM, about 1,300 μM, about 1,400 μM, about 1,500 μM, about 1,600 μM, about 1,700 μM, about 1,800 μM, about 1,900 μM, about 2,000 μM, about 2,500 μM, about 3,000 μM, about 3,500 μM, or about 4,000 μM. In some examples, culturing comprises culturing the genetically modified CAR-T cell in the culture medium until the intracellular arginine level of the CAR-T cell is about 500 μM to about 1,000 μM, about 800 μM to about 1,200 μM, about 1,000 μM to about 1,500 μM, about 1,000 μM to about 2,000 μM, about 1,500 μM to about 2,000 μM, about 700 μM to about 900 μM, about 900 μM to about 1,100 μM, about 900 μM to about 1,200 μM, or about 1,300 μM to about 1,500 μM.

**[0040]** Examples described herein also include a method of making a genetically modified T cell that expresses an arginine transporter, the method comprising: transfecting a T-cell with a DNA construct comprising a nucleotide sequence for an arginine transporter thereby producing a genetically modified T cell that expresses the arginine transporter; and culturing the genetically modified T cell in a culture medium comprising arginine. Examples described herein also include a method of making a genetically modified T cell that expresses an arginine transporter, the method comprising: transducing a T-cell with a virus that includes a nucleotide construct comprising a nucleotide sequence for an arginine transporter thereby producing a genetically modified T cell that expresses the arginine transporter; and culturing the genetically modified T cell

in a culture medium comprising arginine. In some examples, culturing comprises culturing the genetically modified T cell in the culture medium until the intracellular arginine level of the T cell accumulates to a certain level. In some examples, the intracellular arginine level of the T cell is an intracellular arginine level that allows the T cell to survive in a tumor microenvironment or an arginine-depleted environment. For example, in some examples, culturing comprises culturing the genetically modified T cell in the culture medium until the intracellular arginine level of the T cell is about 500 μM, about 600 μM, about 700 μM, about 800 μM, about 900 μM, about 1,000 μM, about 1,100 μM, about 1,200 μM, about 1,300 μM, about 1,400 μM, about 1,500 μM, about 1,600 μM, about 1,700 μM, about 1,800 μM, about 1,900 μM, about 2,000 μM, about 2,500 μM, about 3,000 μM, about 3,500 μM, or about 4,000 μM. In some examples, culturing comprises culturing the genetically modified T cell in the culture medium until the intracellular arginine level of the T cell is about 500 μM to about 1,000 μM, about 800 μM to about 1,200 μM, about 1,000 μM to about 1,500 μM, about 1,000 μM to about 2,000 μM, about 1,500 μM to about 2,000 μM, about 700 μM to about 900 μM, about 900 μM to about 1,100 μM, about 900 μM to about 1,200 μM, or about 1,300 μM to about 1,500 μM.

**[0040a]** In yet another aspect, the present disclosure provides a method of making a genetically modified T cell that expresses a recombinant arginine transporter, comprising: transfecting a T-cell with a DNA construct comprising a nucleotide sequence for an arginine transporter thereby producing a genetically modified T cell that expresses the arginine transporter; and culturing the genetically modified T cell in a culture medium comprising arginine.

**[0040b]** In yet another aspect, the present disclosure provides an *in vitro* method of increasing T cell survival in a low arginine environment, the method comprising: administering a T cell comprising a recombinant arginine transporter to a low arginine environment.

**[0040c]** In yet another aspect, the present disclosure provides a use of a T cell comprising a recombinant arginine transporter in the manufacture of a medicament for increasing T cell survival in a low arginine environment, comprising that the T cell is to be administered to a low arginine environment.

## BRIEF DESCRIPTION OF THE FIGURES

**[0041]** **FIG. 1** is a map of the pBCTex01G expression vector. FIG. 1 discloses "(G4S)3" as SEQ ID NO: 30.

**[0042]** **FIG. 2** is a map of the pBCTex02mini expression vector.

**[0043]** **FIG. 3A** is a schematic showing transfection and arginine depletion steps of the experiment described in Example 1.

**[0044]** **FIG. 3B** is a schematic showing cell filtering and counting steps of the experiment described in Example 1.

**[0045]** **FIG. 3C** is a set of graphs showing the estimated change in percent of cells transfected with an expression construct (Control, CAT, or ASS) after 72 hours in an arginine-rich (left) or

WHAT IS CLAIMED IS:

1. A genetically modified T-cell genetically modified to express:

a) a recombinant arginine transporter and

b) a chimeric antigen receptor having at least one antigen-specific targeting region that specifically binds a cell surface antigen present on a target cell population, a transmembrane domain, and an intracellular signaling domain.

2. An expression vector comprising an isolated nucleic acid encoding a) an antigen-specific targeting region, b) a transmembrane domain, c) optionally at least one co-stimulatory domain, d) an intracellular signaling domain and e) an arginine transporter.

3. A genetically modified T-cell modified to express a chimeric antigen receptor encoded by the expression vector of claim 2.

4. The genetically modified T-cell of claim 1 or 3, wherein the arginine transporter is selected from the group consisting of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$.

5. The genetically modified T-cell of any one of claims 1, 3, or 4, wherein the genetically modified T-cell comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof.

6. The genetically modified T-cell of claims 1, 3 or 4, wherein the genetically modified T-cell comprises a nucleic acid expressing a sequence having about 90%, 95%, or 99% percent identity to one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246.

7. A pharmaceutically acceptable composition comprising the genetically modified T-cell of any one of claims 1 or 3-6, and a pharmaceutically acceptable excipient.

8. A priming medium comprising the genetically modified T-cell of any one of claims 1 or 3-6, and L-arginine.

9. A pharmaceutical composition comprising a chimeric antigen receptor T cell (CAR-T cell) which expresses a recombinant arginine transporter and a chimeric antigen receptor protein.

10. The pharmaceutical composition of claim 9, wherein the arginine transporter is CAT-1.

11. The pharmaceutical composition of claim 9, wherein the arginine transporter is CAT-2.

12. The pharmaceutical composition of claim 9, wherein the arginine transporter is CAT-3.

13. The pharmaceutical composition of claim 9, wherein the arginine transporter is CAT-4.

14. The pharmaceutical composition of claim 9, wherein the arginine transporter is $y^+$LAT1 and 4F2hc.

15. The pharmaceutical composition of claim 9, wherein the arginine transporter is $y^+$LAT2 and 4F2hc.

16. The pharmaceutical composition of claim 9, wherein the arginine transporter is $b^{0,+}$AT and rBAT.

17. The pharmaceutical composition of claim 9, wherein the arginine transporter is $ATB^{0,+}$.

18. The pharmaceutical composition of claim 9, wherein the pharmaceutical composition is packaged as a kit.

19. Use of the pharmaceutical composition of claim 7 or 9 in the manufacture of a medicament for treating a solid tumor cancer in a patient in need thereof.

20. Use of the pharmaceutical composition of claim 7 or 9 in the manufacture of a medicament for treating a hematological cancer in a patient in need thereof.

21. Use of the pharmaceutical composition of claim 7 or 9 in the manufacture of a medicament for modulating intracellular arginine levels to effect a T cell-mediated immune response in a patient in need thereof.

22. Use of a composition comprising a chimeric antigen receptor T cell (CAR-T cell) which expresses a recombinant arginine transporter and a chimeric antigen receptor protein in the manufacture of a medicament for treating a condition in a human patient in need thereof.

23. Use of T-cells that are a) genetically modified to express a chimeric antigen receptor wherein the chimeric antigen receptor comprises: at least one antigen-specific targeting region that specifically binds the cell surface antigen present on the target cell population, a transmembrane domain, an intracellular signaling domain, and b) genetically modified to express a recombinant arginine transporter in the manufacture of a medicament for modulating a T cell-mediated immune response to a target cell population expressing a cell surface antigen in a patient in need thereof.

24. The use of claim 22 or 23, wherein the T-cells are cultured in a culture medium comprising arginine before they are to be administered.

25. The use according to any one of claims 22-24, wherein the arginine transporter is CAT-1.

26. The use according to any one of claims 22-24, wherein the arginine transporter is CAT-2.

27. The use according to any one of claims 22-24, wherein the arginine transporter is CAT-3.

28. The use according to any one of claims 22-24, wherein the arginine transporter is CAT-4.

29. The use according to any one of claims 22-24, wherein the arginine transporter is $y^+$LAT1 and 4F2hc.

30. The use according to any one of claims 22-24, wherein the arginine transporter is $y^+$LAT2 and 4F2hc.

31. The use according to any one of claims 22-24, wherein the arginine transporter is $b^{0,+}$AT and rBAT.

32. The use according to any one of claims 22-24, wherein the arginine transporter is $ATB^{0,+}$.

33. The use of any one of claims 22-24, comprising that the T-cell of any one of claims 1 and 3-6 is to be administered.

34. The use according to any one of claims 22-32, further comprising that a second therapeutic agent is to be administered to the human patient.

35. The use according to claim 34, wherein the second therapeutic agent is an anti-PD-1, anti-PD-L1, or an anti-CTLA-4 antibody.

36. The use according to claim 34 or 35, wherein the second therapeutic agent is to be administered before, during or after the composition comprising the CAR-T cell.

37. The use according to claim 34 or 35, wherein the second therapeutic agent is to be administered before, during or after the T-cells.

38. The use according to any one of claims 22-37, wherein the composition comprising the CAR-T cells is to be administered to the human patient once every week, once every 2 weeks, once every 3 weeks, or once every 4 weeks.

39. The use according to any one of claims 22-37, comprising that $10^7$ to $10^{10}$ CAR-T cells is to be administered per kilogram of the patient.

40. A method of making a genetically modified CAR-T cell that expresses a recombinant arginine transporter, comprising:

transfecting a T-cell with a DNA construct comprising a nucleotide sequence for a specific chimeric antigen receptor and for an arginine transporter thereby producing a genetically modified CAR-T cell that expresses both the chimeric antigen receptor and the arginine transporter; and

culturing the genetically modified CAR-T cell in a culture medium comprising arginine.

41. The method of claim 40, wherein said culturing comprises culturing the genetically modified CAR-T cell in the culture medium until the intracellular arginine level of the CAR-T cell accumulates to a certain level.

42. A genetically modified T-cell genetically modified to express a recombinant arginine transporter.

43. The genetically modified T-cell of claim 42, wherein the arginine transporter is selected from the group consisting of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$.

44. The genetically modified T-cell of claim 42 or 43, wherein the genetically modified T-cell comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof.

45. The genetically modified T-cell of claim 42 or 43, wherein the genetically modified T-cell comprises a nucleic acid expressing a sequence having about 90%, 95%, or 99% percent identity to one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246.

46. A pharmaceutically acceptable composition comprising the genetically modified T-cell of any one of claims 42-45, and a pharmaceutically acceptable excipient.

47. A priming medium comprising the genetically modified T-cell of any one of claims 42-45, and L-arginine.

48. A pharmaceutical composition comprising a T cell which expresses a recombinant arginine transporter protein.

49. The pharmaceutical composition of claim 48, wherein the arginine transporter is CAT-1.

50. The pharmaceutical composition of claim 48, wherein the arginine transporter is CAT-2.

51. The pharmaceutical composition of claim 48, wherein the arginine transporter is CAT-3.

52. The pharmaceutical composition of claim 48, wherein the arginine transporter is CAT-4.

53. The pharmaceutical composition of claim 48, wherein the arginine transporter is $y^+$LAT1 and 4F2hc.

54. The pharmaceutical composition of claim 48, wherein the arginine transporter is $y^+$LAT2 and 4F2hc.

55. The pharmaceutical composition of claim 48, wherein the arginine transporter is $b^{0,+}AT$ and rBAT.

56. The pharmaceutical composition of claim 48, wherein the arginine transporter is $ATB^{0,+}$.

57. The pharmaceutical composition of claim 48, wherein the pharmaceutical composition is packaged as a kit.

58. Use of the pharmaceutical composition of claim 46 or 48 in the manufacture of a medicament for treating a solid tumor cancer in a patient in need thereof.

59. Use of the pharmaceutical composition of claim 46 or 48 in the manufacture of a medicament for treating a hematological cancer in a patient in need thereof.

60. Use of the pharmaceutical composition of claim 46 or 48 in the manufacture of a medicament for modulating intracellular arginine levels to effect a T cell-mediated immune response in a patient in need thereof.

61. Use of a composition comprising a T cell which expresses a recombinant arginine transporter in the manufacture of a medicament for treating a condition in a human patient in need thereof.

62. The use of claim 61, wherein the T-cells are cultured in a culture medium comprising arginine before they are to administered.

63. The use of claim 61 or 62, wherein the arginine transporter is CAT-1.

64. The use of claim 61 or 62, wherein the arginine transporter is CAT-2.

65. The use of claim 61 or 62, wherein the arginine transporter is CAT-3.

66. The use of claim 61 or 62, wherein the arginine transporter is CAT-4.

67. The use of claim 61 or 62, wherein the arginine transporter is $y^{+}LAT1$ and 4F2hc.

68. The use of claim 61 or 62, wherein the arginine transporter is $y^+$LAT2 and 4F2hc.

69. The use of claim 61 or 62, wherein the arginine transporter is $b^{0,+}$AT and rBAT.

70. The use of claim 61 or 62, wherein the arginine transporter is $ATB^{0,+}$.

71. The use of claim 61 or 62, comprising that the T-cell of any one of claims 42-45 is to be administered.

72. The use according to any one of claims 58-71, further comprising that a second therapeutic agent is to be administered to the human patient.

73. The use according to claim 72, wherein the second therapeutic agent an anti-PD-1, anti-PD-L1, or an anti-CTLA-4 antibody.

74. The use according to claim 72 or 73, wherein the second therapeutic agent is to be administered before, during or after the composition comprising the T cell.

75. The use according to claim 72 or 73, wherein the second therapeutic agent is to be administered before, during or after the T-cells.

76. A method of making a genetically modified T cell that expresses a recombinant arginine transporter, comprising:

transfecting a T-cell with a DNA construct comprising a nucleotide sequence for an arginine transporter thereby producing a genetically modified T cell that expresses the arginine transporter; and

culturing the genetically modified T cell in a culture medium comprising arginine.

77. The method of claim 76, wherein said culturing comprises culturing the genetically modified T cell in the culture medium until the intracellular arginine level of the T cell accumulates to a certain level.

78. An *in vitro* method of increasing T cell survival in a low arginine environment, the method comprising: administering a T cell comprising a recombinant arginine transporter to a low arginine environment.

79. Use of a T cell comprising a recombinant arginine transporter in the manufacture of a medicament for increasing T cell survival in a low arginine environment, comprising that the T cell is to be administered to a low arginine environment.

80. The method of claim 78 or the use of claim 79, wherein prior to the administration, the method or the use comprises transfecting the T cell with a DNA construct comprising a nucleotide sequence encoding the recombinant arginine transporter.

81. The method of claim 78 or claim 80, or the use of claim 79 or claim 80, wherein the T-cell comprises a chimeric antigen receptor and/or a DNA construct comprising a nucleotide sequence encoding a chimeric antigen receptor.

82. The method of any one of claims 78 or 80-81, or the use of any one of claims 79-81 wherein prior to the administration, the method or the use comprises culturing the T cell in a culture medium comprising arginine.

83. The method or the use of claim 82, wherein the culturing comprises culturing the T cell in the culture medium until the intracellular arginine level of the T cell accumulates to a certain level.

84. The method of any one of claims 78 or 80-83, or the use of any one of claims 79-83, wherein the arginine transporter is selected from the group consisting of CAT-1, CAT-2, CAT-3, CAT-4, $y^+$LAT1 and 4F2hc, $y^+$LAT2 and 4F2hc, $b^{0,+}$AT and rBAT, and $ATB^{0,+}$.

85. The method of any one of claims 78 or 80-83, or the use of any one of claims 79-83, wherein the DNA construct comprising a nucleotide sequence encoding the recombinant arginine transporter comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NO:180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246, or a fragment or a variant thereof.

86. The method of any one of claims 78 or 80-83, or the use of any one of claims 79-83, wherein the DNA construct comprising a nucleotide sequence encoding the recombinant arginine transporter comprises a nucleic acid expressing a sequence having about 90%, 95%, or 99% percent identity to one of SEQ ID NO: 180, 184-188, 204, 205, 210, 214, 215, 220-222, 227-230, 234-236, 242, and 246.

87. The method of any one of claims 78 or 80-86, wherein the low arginine environment is a cell culture medium.

88. The use of any one of claims 79-85, wherein the low arginine environment is a tumor microenvironment.