

SUMMARY

The present disclosure is based on the development of strategies to divert or re-direct glucose metabolites out of the glycolysis pathway in hematopoietic cells such as immune cells, including those that express a chimeric receptor polypeptide, such as an antibody-coupled T-cells receptor (ACTR) polypeptide, chimeric antigen receptor (CAR) polypeptide or a T Cell Receptor (TCR) polypeptide, for use in cell-based immune therapy. Re-direction of glucose metabolites out of the glycolysis pathway may be achieved by expressing (*e.g.*, over-expressing) in hematopoietic stem cells (HSCs), preferably immune cells (*e.g.*, $\alpha\beta$ or $\gamma\delta$ T cells or NK cells), one or more factors (*e.g.*, proteins or nucleic acids) such as those described herein. Such genetically engineered immune cells are expected to have an enhanced metabolic activity relative to native hematopoietic cells of the same type, for example, in a low glucose, low amino acid, low pH, and/or hypoxic environment (*e.g.*, in the TME). As such, hematopoietic cells such as HSCs or immune cells that co-express one or more factors (*e.g.*, polypeptides or nucleic acids) that redirect glucose metabolites out of the glycolysis pathway in the hematopoietic cells and a chimeric receptor polypeptide would exhibit superior bioactivities (*e.g.*, under low glucose, low amino acid, low pH, and/or hypoxic conditions), for example, cell survival, cell proliferation, maintaining its activated phenotype (*e.g.*, increased cytokine production, *e.g.*, IL-2 or IFN- γ production), cytotoxicity, and/or *in vivo* anti-tumor activity.

Accordingly, described herein are modified (*e.g.*, genetically engineered) hematopoietic cells (*e.g.*, HSCs, preferably immune cells (*e.g.*, $\alpha\beta$ or $\gamma\delta$ T cells, or NK cells) that have altered intracellular regulation of glucose concentrations relative to the wild-type immune cells of the same type. In some examples, the modified immune cells may express or overly express a factor that redirects glucose metabolites, for example, a polypeptide that diverts or redirects glucose metabolites out of the glycolysis pathway. A modified immune cell expressing any of the factor that redirects glucose metabolite refers to a genetically engineered immune cell into which an exogenous nucleic acid encoding the factor is introduced such that the encoded factor is expressed in the resultant modified immune cell, while the unmodified parent cell does not express such a factor. A modified immune cell overly expressing any of the factor that redirects glucose

metabolite refers to a genetically engineered immune cell, which is engineered to enhance the expression level of the factor as relative to the unmodified parent cell. In some instances, the modified immune cell may be engineered to enhance expression of the endogenous gene encoding the factor. Alternatively, the modified immune cell may be engineered to transfect an exogenous nucleic acid encoding the factor for producing additional amount of the factor in the modified immune cell.

The factor that redirects glucose metabolites may divert or redirect substrates out of the glycolysis pathway directly (*e.g.*, glutamine-fructose-6-phosphate aminotransferase 1 (GFPT1)) or indirectly by, for example, decreasing the rate of glucose breakdown in the glycolysis pathway (*e.g.*, TP53-inducible glycolysis and apoptosis regulator (TIGAR), pyruvate kinase muscle isozyme M2 (PKM2), or PKM2 variants). Exemplary polypeptides that redirect glucose metabolites out of the glycolysis pathway include, but are not limited to, pyruvate kinase muscle isozyme M2 (PKM2), glutamine-fructose-6-phosphate aminotransferase 1 (GFPT1), TP53-inducible glycolysis and apoptosis regulator (TIGAR), and functional variants thereof (*e.g.*, PKM2 Y105E, PKM2 Y105D, PKM2 K422R, and PKM2 H391Y). In specific examples, the polypeptide that diverts or directs glucose metabolites is TIGAR.

The modified immune cells may further express a chimeric receptor polypeptide, which may comprise (a) an extracellular target binding domain; (b) a transmembrane domain; and (c) a cytoplasmic signaling domain (*e.g.*, a cytoplasmic domain that comprises an immunoreceptor tyrosine-based activation motif (ITAM)). In one aspect, the present disclosure refers to a genetically engineered immune cell, which has altered glucose metabolism as compared with a native immune cell of the same type, wherein the immune cell: (i) expresses or overly expresses a polypeptide that diverts or redirects glucose metabolites out of a glycolysis pathway, and (ii) a chimeric receptor polypeptide; wherein the chimeric receptor polypeptide comprising (a) an extracellular target binding domain; (b) a transmembrane domain; and (c) a cytoplasmic signaling domain. Any of the chimeric polypeptides disclosed herein may further comprise at least one co-stimulatory signaling domain. In other examples, the chimeric receptor polypeptide may be free of co-stimulatory signaling domains.

In some examples, the chimeric receptor polypeptide is an antibody-coupled T cell receptor (ACTR), which comprises an extracellular Fc-binding domain (a). In other examples, the chimeric receptor is a chimeric antigen receptor (CAR), which comprises an extracellular antigen binding domain (a). Alternatively or in addition, the cytoplasmic signaling domain (c) is located at the C-terminus of the chimeric receptor polypeptide. In some examples, the chimeric receptor polypeptide is a T cell receptor (TCR), which comprises an extracellular domain, or portion thereof, of a TCR α chain, a TCR β chain, a TCR γ chain, a TCR δ chain, a CD3 ϵ TCR subunit, a CD3 γ TCR subunit, a CD3 δ TCR subunit, or a CD3 ζ TCR subunit.

In some examples, the chimeric receptor polypeptides described herein (*e.g.*, an ACTR polypeptide, a CAR, or a TCR polypeptide) may further comprise a hinge domain, which is located at the C-terminus of (a) and the N-terminus of (b). In other examples, the chimeric receptor polypeptide may be free of any hinge domain. In yet other example, the chimeric receptor polypeptide, for example, an ACTR polypeptide, may be free of a hinge domain from any non-CD16A receptor. Alternatively, or in addition, the chimeric receptor polypeptide further comprises a signal peptide at its N-terminus. Further in another example, the cytoplasmic signaling domain (c) comprises an immunoreceptor tyrosine-based activation motif (ITAM).

In some examples, the chimeric receptor polypeptide disclosed herein may be an ACTR polypeptide comprising an Fc binding domain (a). In some examples, the Fc binding domain of (a) can be an extracellular ligand-binding domain of an Fc-receptor, for example, an extracellular ligand-binding domain of an Fc-gamma receptor, an Fc-alpha receptor, or an Fc-epsilon receptor. In particular examples, the Fc binding domain is an extracellular ligand-binding domain of CD16A (*e.g.*, F158 CD16A or V158 CD16A), CD32A, or CD64A. In other examples, the Fc binding domain of (a) can be an antibody fragment that binds the Fc portion of an immunoglobulin. For example, the antibody fragment can be a single chain variable fragment (ScFv), a single domain antibody, (*e.g.*, a nanobody). Additionally, the Fc binding domain of (a) can be a naturally-occurring protein that binds the Fc portion of an immunoglobulin or an Fc-binding fragment thereof. For example, the Fc binding domain can be Protein A or Protein G, or an Fc-binding fragment thereof. In further examples, the Fc binding domain of (a) can be a

synthetic polypeptide that binds the Fc portion of an immunoglobulin. Examples include, but are not limited to, a Kunitz peptide, a SMIP, an avimer, an affibody, a DARPin, or an anticalin.

In some examples, the chimeric receptor polypeptide disclosed herein can be a CAR polypeptide comprising an extracellular antigen binding domain (a). In some examples, the
5 extracellular antigen binding domain of (a) is a single chain antibody fragment that binds to a tumor antigen, a pathogenic antigen, or an immune cell specific to an autoantigen. In certain examples, the tumor antigen is associated with a hematologic tumor. Examples include, but are not limited to, CD19, CD20, CD22, Kappa-chain, CD30, CD123, CD33, LeY, CD138, CD5, BCMA, CD7, CD40, and IL-1RAP. In certain examples, the tumor antigen is associated with a
10 solid tumor. Examples include, but are not limited to, GD2, GPC3, FOLR (*e.g.*, FOLR1 or FOLR2), HER2, EphA2, EFGRVIII, IL13RA2, VEGFR2, ROR1, NKG2D, EpCAM, CEA, Mesothelin, MUC1, CLDN18.2, CD171, CD133, PSCA, cMET, EGFR, PSMA, FAP, CD70, MUC16, L1-CAM, B7H3, and CAIX. In certain examples, the pathogenic antigen is a bacterial antigen, a viral antigen, or a fungal antigen, for example, those described herein. In some
15 examples, the cytoplasmic signaling domain of (c) in any of the chimeric receptor polypeptides described herein (*e.g.*, ACTR or CAR polypeptides) can be a cytoplasmic domain of CD3z or FcεR1γ.

In some examples, the hinge domain of any of the chimeric polypeptides described herein (*e.g.*, ACTR or CAR polypeptides), when applicable, can be of CD28, CD16A, CD8a, IgG, murine
20 CD8α or DAP12. In other examples, the hinge domain is a non-naturally occurring peptide. For example, the non-naturally occurring peptide may be an extended recombinant polypeptide (XTEN) or a (Gly₄Ser)_n polypeptide, in which n is an integer of 3-12, inclusive. In some examples, the hinge domain is a short segment, which may contain up to 60 amino acid residues.

In specific examples, an ACTR polypeptide as described herein may comprise (i) a CD28
25 co-stimulatory domain; and (ii) a CD28 transmembrane domain, a CD28 hinge domain, or a combination thereof. For example, the ACTR polypeptide comprises components (a)-(e) as shown in **Table 4**.

In specific examples, a CAR polypeptide described herein may comprise (i) a CD28 co-stimulatory domain or a 4-1BB co-stimulatory domain; and (ii) a CD28 transmembrane domain, a CD28 hinge domain, or a combination thereof. In further specific examples, a CAR polypeptide described herein may comprise (i) a CD28 co-stimulatory domain or a 4-1BB co-stimulatory domain, (ii) a CD8 α transmembrane domain, a CD8 α hinge domain, or a combination thereof.

The genetically engineered immune cells described herein, expressing the factor (*e.g.*, polypeptide or nucleic acid) that redirects glucose metabolites and optionally the chimeric receptor polypeptide, may be a cell line or hematopoietic stem cell or a progeny thereof. In some examples, the genetically engineered immune cells can be natural killer (NK) cell, monocyte/macrophage, neutrophil, eosinophil, $\alpha\beta$ T or $\gamma\delta$ T cell.

In some examples, the immune cell is a T cell, in which the expression of an endogenous T cell receptor, an endogenous major histocompatibility complex, an endogenous beta-2-microglobulin, or a combination thereof has been inhibited or eliminated. In specific examples, the genetically engineered immune cells (*e.g.*, NK, $\alpha\beta$ T or $\gamma\delta$ T cell) described herein may comprise a nucleic acid or a nucleic acid set, which collectively comprises: (a) a first nucleotide sequence encoding the factor (*e.g.*, polypeptide or nucleic acid) that redirects glucose metabolites; and optionally (b) a second nucleotide sequence encoding the chimeric antigen receptor (CAR) polypeptide. The nucleic acid or the nucleic acid set is a DNA or RNA molecule or a set of DNA or RNA molecules. In some examples, the immune cell comprises the nucleic acid, which comprises both the first nucleotide sequence and the second nucleotide sequence. In some examples, the coding sequence of the factor (*e.g.*, polypeptide or nucleic acid) that redirects glucose metabolites is upstream of that of the CAR polypeptide. In some examples, the coding sequence of the CAR polypeptide is upstream of that of the factor that redirects glucose metabolites. In some examples, the genetically engineered immune cells further may further comprise a third nucleotide sequence located between the first nucleotide sequence and the second nucleotide sequence, wherein the third nucleotide sequence encodes a ribosomal skipping site (*e.g.*, a P2A peptide), an internal ribosome entry site (IRES), or a second promoter.

In some examples, the nucleic acid or the nucleic acid set is comprised within a vector or a set of vectors, which can be an expression vector or a set of expression vectors (*e.g.*, viral

vectors such as lentiviral vectors or retroviral vectors). A nucleic acid set or a vector set refers to a group of two or more nucleic acid molecules or two or more vectors, each encoding one of the polypeptides of interest (*i.e.*, a polypeptide or nucleic acid that redirect glucose metabolites out of the glycolysis pathway and the CAR polypeptide). Any of the nucleic acids described herein is
5 also within the scope of the present disclosure.

In another example, the present disclosure describes a pharmaceutical composition, comprising any of the immune cells described herein and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition, comprising a genetically engineered immune cell as described herein.

Moreover, described herein is a method for inhibiting cells expressing a target antigen (*e.g.*, reducing the number of such cells, blocking cell proliferation, and/or suppressing cell activity) in a subject, the method comprising administering to a subject in need thereof a population of the immune cells described herein, which may co-express the factor (*e.g.*, polypeptide or nucleic acid) that redirects glucose metabolites and the CAR polypeptide. In one aspect, the present disclosure
10 refers to use of a population of genetically engineered immune cells in the manufacture of a medicament for inhibiting cells expressing a target antigen in a subject, wherein the population of the genetically engineered immune cells is as described herein. The subject (*e.g.*, a human patient such as a human patient suffering from a cancer) may have been treated or is being treated with an anti-cancer therapy (*e.g.*, an anti-cancer agent). In some examples, at least some of the cells
15 expressing the target antigen are located in a low-glucose environment, a low-amino acid (*e.g.*, low glutamine) environment, a low-pH environment, and/or a hypoxic environment, for example a tumor microenvironment.

In some examples, the immune cells are autologous. In other examples, the immune cells are allogeneic. In any of the methods described herein, the immune cells can be activated,
25 expanded, or both *ex vivo*. In some examples, the immune cells comprise T cells, which are activated in the presence of one or more of anti-CD3 antibody, anti-CD28 antibody, IL-2, phytohemagglutinin, and an engineered artificial stimulatory cell or particle. In other examples, the immune cells comprise natural killer cells, which are activated in the

presence of one or more of 4-1BB ligand, anti-4-1BB antibody, IL-15, anti-IL-15 receptor antibody, IL-2, IL-12, IL-21 and K562 cells, an engineered artificial stimulatory cell or particle.

In some examples, the subject to be treated by the methods described herein may be a human patient suffering from a cancer, for example, carcinoma, lymphoma, sarcoma blastoma,
5 and leukemia. Additional exemplary target cancer includes, but are not limited to, a cancer of B-cell origin, breast cancer, gastric cancer, neuroblastoma, osteosarcoma, lung cancer, skin cancer,

prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, rhabdomyosarcoma, leukemia, mesothelioma, pancreatic cancer, head and neck cancer, retinoblastoma, glioma, glioblastoma, liver cancer, and thyroid cancer. Exemplary cancers of B-cell origin is selected from the group consisting of B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia, and B-cell non-Hodgkin's lymphoma.

5 In one aspect, the present disclosure also refers to a nucleic acid or nucleic acid set, which collectively comprises: (A) a first nucleotide sequence encoding the factor that diverts or redirects glucose metabolites as described herein; and (B) a second nucleotide sequence encoding the chimeric receptor polypeptide (e.g., an ACTR, a CAR or a TCR polypeptide) as described herein. An example is a method for generating modified immune cells *in vivo*, the method comprising administering to a subject in need
10 thereof the nucleic acid or nucleic acid set described herein, which may co-express the factor (e.g., polypeptide or nucleic acid) that redirects glucose metabolites and the CAR polypeptide. In another aspect, the present disclosure refers to use of the nucleic acid or nucleic acid set as disclosed herein in the manufacture of modified immune cells, the use comprising the nucleic acid or nucleic acid set to be administered to a subject in need thereof.

15 Also, examples within the scope of the present disclosure are uses of the genetically engineered immune cells described herein, which co-express a factor (e.g., a polypeptide or a nucleic acid) that redirects glucose metabolites out of the glycolysis pathway and a CAR polypeptide for treating a target disease or disorder such as cancer or an infectious disorder and uses thereof for manufacturing a medicament for the intended medical treatment.

20 The details of one or more examples of the disclosure are set forth in the description below. Other features or advantages of the present disclosure will be apparent from the detailed description of several examples and also from the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

25 The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure, which can be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

Figure 1 is a schematic illustration of exemplary polypeptides (open boxes) that re-direct glucose
30 metabolites out of the glycolysis pathway. TIGAR reduces the activity of PFK. PKM2 and its loss of function (LoF) variants are less active than PKM1. In addition, GFPT1, competes with

WHAT IS CLAIMED IS:

1. A genetically engineered immune cell, which has altered glucose metabolism as compared with a native immune cell of the same type, wherein the immune cell:

(i) expresses or overly expresses a polypeptide that diverts or redirects glucose metabolites out of a glycolysis pathway, and

(ii) a chimeric receptor polypeptide; wherein the chimeric receptor polypeptide comprises:

(a) an extracellular target binding domain;

(b) a transmembrane domain; and

(c) a cytoplasmic signaling domain.

2. The genetically engineered immune cell of claim 1, wherein the polypeptide that diverts or redirects glucose metabolites (i) is selected from the group consisting of TP53-inducible glycolysis and apoptosis regulator (TIGAR)pyruvate kinase muscle isozyme M2 (PKM2), and glutamine-fructose-6-phosphate aminotransferase 1 (GFPT1).

3. The genetically engineered immune cell of claim 2, wherein the polypeptide that diverts or redirects glucose metabolites is TIGAR.

4. The immune cell of any one of claims 1 - 3, wherein the chimeric receptor polypeptide comprises one or more of the following features:

(i) the chimeric receptor polypeptide further comprises at least one co-stimulatory signaling domain or is free of co-stimulatory signaling domains;

(ii) the cytoplasmic signaling domain (c) comprises an immunoreceptor tyrosine-based activation motif (ITAM);

(iii) the cytoplasmic signaling domain (c) is located at the C-terminus of the chimeric receptor polypeptide;

(iv) the chimeric receptor polypeptide further comprises a hinge domain, which is located at the C-terminus of (a) and the N-terminus of (b),

(v) the chimeric receptor polypeptide is free of any hinge domain; and

(vi) the chimeric receptor polypeptide further comprises a signal peptide at its N-terminus.

5 5. The genetically engineered immune cell of any one of claims 3 - 4, wherein the chimeric receptor polypeptide is preferably a chimeric receptor antigen (CAR) polypeptide, in which (ii)(a) is an extracellular antigen binding domain.

10 6. The genetically engineered immune cell of claim 5, wherein the extracellular antigen binding domain of (ii)(a) is a single chain variable fragment (scFv) or a single domain antibody that binds to a tumor antigen, a pathogenic antigen, or an immune cell specific to an autoantigen.

15 7. The genetically engineered immune cell of claim 6, wherein the extracellular antigen binding domain of (ii)(a) binds to the tumor antigen, which is associated with a hematologic or solid tumor.

20 8. The genetically engineered immune cell of claim 6, wherein the extracellular antigen binding domain of (ii)(a) binds to the pathogenic antigen, which is a bacterial antigen, a viral antigen, or a fungal antigen.

25 9. The genetically engineered immune cell of any one of claims 1-8, wherein the transmembrane domain is of a membrane protein selected from the group consisting of CD8 α , CD8 β , 4-1BB, CD27, CD28, CD34, CD4, Fc ϵ RI γ , CD16A, OX40, CD3 ζ , CD3 ϵ , CD3 γ , CD3 δ , TCR α , TCR β , TCR ζ , CD32, CD64, CD45, CD5, CD9, CD22, CD37, CD80, CD86, CD40, CD40L/CD154, VEGFR2, FAS, FGFR2B, CD2, IL15, IL15R, IL21, DNAM-1, 2B4, NKG2D, NKp44 and NKp46.

30 10. The genetically engineered immune cell of any one of claims 1-9, wherein the chimeric receptor polypeptide comprises the at least one co-stimulatory signaling domain, which is of a co-stimulatory molecule selected from the group consisting of 4-1BB, CD28, CD8 α , 2B4,

OX40, OX40L, ICOS, CD27, GITR, HVEM, TIM1, LFA1, CD2, DAP10, DAP12, DNAM-1, NKG2D, NKp30, NKp44, NKp46 and JAMAL, or a functional variants thereof.

11. The genetically engineered immune cell of any one of claims claim 1- 10, wherein
5 the at least one co-stimulatory signaling domains is a CD28 co-stimulatory signaling domain or a 4-1BB co-stimulatory signaling domain.

12. The genetically engineered immune cell of any one of claims 1 - 10, wherein the
chimeric receptor polypeptide comprises two co-stimulatory signaling domains.

10 13. The genetically engineered immune cell of claim 12, wherein

(i) one of the co-stimulatory signaling domains is a CD28 co-stimulatory signaling domain;
and wherein the other co-stimulatory domain is selected from the group consisting of a CD8 α , 4-
1BB, 2B4, OX40, OX40L, ICOS, CD27, GITR, HVEM, TIM1, LFA1, CD2, DAP10, DAP12,
15 DNAM-1, NKG2D, NKp30, NKp44, NKp46 and JAMAL co-stimulatory signaling domain;

(ii) one of the co-stimulatory signaling domains is a CD8 α co-stimulatory signaling domain;
and wherein the other co-stimulatory domain is selected from the group consisting of a CD28, 4-
1BB, 2B4, OX40, OX40L, ICOS, CD27, GITR, HVEM, TIM1, LFA1, CD2, DAP10, DAP12,
DNAM-1, NKG2D, NKp30, NKp44, NKp46 and JAMAL co-stimulatory signaling domain' or

20 (iii) one of the co-stimulatory signaling domains is a 4-1BB co-stimulatory signaling domain;
and wherein the other co-stimulatory domain is selected from the group consisting of a CD8 α ,
CD28, 2B4, OX40, OX40L, ICOS, CD27, GITR, HVEM, TIM1, LFA1, CD2, DAP10, DAP12,
DNAM-1, NKG2D, NKp30, NKp44, NKp46 and JAMAL co-stimulatory signaling domain.

25 14. The genetically engineered immune cell of any one of claims 1-13, wherein the
cytoplasmic signaling domain of (c) is a cytoplasmic domain of CD3 ζ or Fc ϵ R1 γ .

15. The genetically engineered immune cell of any one of claims 1-14, wherein the
chimeric receptor polypeptide comprises the hinge domain (iv), which is a hinge domain selected
30 from the list of CD28, CD16A, CD8 α , IgG, murine CD8 α , and DAP12.

16. The genetically engineered immune cell of any one of claims 1 - 15, wherein the immune cell is an $\alpha\beta$ T, $\gamma\delta$ T or a natural killer (NK) cell.

17. The genetically engineered immune cell of claim 16, wherein the immune cell is an $\alpha\beta$ T cell, and wherein the chimeric receptor polypeptide is a CAR polypeptide that comprises components as shown in Table 8.

18. The genetically engineered immune cell of claim 16, wherein the immune cell is a NK cell, and wherein the chimeric receptor polypeptide is a CAR polypeptide that comprises components as shown in Table 9.

19. The genetically engineered immune cell of claim 16, wherein the immune cell is a $\gamma\delta$ T cell, and wherein the chimeric receptor polypeptide is a CAR polypeptide that comprises components as shown in Table 10.

20. The genetically engineered immune cell of any one of claims 1 - 19, wherein

- (i) the immune cell is derived from cell lines; or
- (ii) the immune cell is derived from peripheral blood mononuclear cells (PBMC), hematopoietic stem cells (HSCs), cord blood stem cells or induced pluripotent stem cells (iPSCs).

21. The genetically engineered immune cell of any one of claims 1 - 20, wherein the immune cell comprises a nucleic acid or nucleic acid set, which collectively comprises:

(A) a first nucleotide sequence encoding the factor that diverts or redirects glucose metabolites; and

(B) a second nucleotide sequence encoding the chimeric receptor polypeptide.

22. The genetically engineered immune cell of claim 21, wherein the immune cell comprises the nucleic acid, which comprises both the first nucleotide sequence and the second nucleotide sequence.

23. The genetically engineered immune cell of claims 21 - 22, wherein the nucleic acid further comprises a third nucleotide sequence located between the first nucleotide sequence and the second nucleotide sequence, wherein the third nucleotide sequence encodes a ribosomal skipping site, an internal ribosome entry site (IRES), or a promoter.

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24. The genetically engineered immune cell of claim 23, wherein the nucleic acid or nucleic acid set is comprised within one or more viral vectors.

25. A pharmaceutical composition, comprising a genetically engineered immune cell
10 of any one of claims 1 - 24.

26. Use of a population of genetically engineered immune cells in the manufacture of a medicament for inhibiting cells expressing a target antigen in a subject, wherein the population of the genetically engineered immune cells is set forth in any one of claims 1 - 24.

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27. The use of claim 26, wherein the subject is a human patient suffering from a cancer and the target antigen is a tumor antigen; wherein the cancer is selected from the group consisting of carcinoma, lymphoma, sarcoma, blastoma, and leukemia, preferably wherein

(i) the cancer is selected from the group consisting of a cancer of B-cell origin, breast
20 cancer, gastric cancer, neuroblastoma, osteosarcoma, lung cancer, skin cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, rhabdomyosarcoma, leukemia, mesothelioma, pancreatic cancer, head and neck cancer, retinoblastoma, glioma, glioblastoma, liver cancer, and thyroid cancer; or

(ii) the cancer of B-cell origin is selected from the group consisting of B-lineage
25 acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia, and B-cell non-Hodgkin's lymphoma.

28. A nucleic acid or nucleic acid set, which collectively comprises:

(A) a first nucleotide sequence encoding the factor that diverts or redirects glucose
30 metabolites set forth in any one of claims 1 - 3; and

(B) a second nucleotide sequence encoding the chimeric receptor polypeptide set forth in any one of claims 4 - 24.

29. Use of the nucleic acid or nucleic acid set of claim 28 in the manufacture of
5 modified immune cells, the use comprising the nucleic acid or nucleic acid set to be administered to a subject in need thereof.